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Case Presentation: A 42-year-old woman was referred to the Hypertrophic Cardiomyopathy Clinic. A diagnosis of apical hypertrophic cardiomyopathy had been given 16 years earlier on the basis of echocardiographic findings. Left ventricular systolic function was reportedly at the lower limit of normal 5 years earlier.

The patient gave a 6-month history of mild dyspnea occurring during exertion. Although still active, her exercise tolerance had decreased. She also complained of more frequent and sustained episodes of rapid palpitations associated with shortness of breath. She had occasional episodes of heavy, burning discomfort in the chest during activity and while at rest.

There was no family history of cardiomyopathy, although first degree relatives had not been screened. Her heart rate was 74. Blood pressure was 110/70. Jugular venous pressure was normal. Carotid pulse volume and contour were normal. The first and second heart sounds were normal. There was a presystolic apical impulse and a prominent S4 gallop. There was no S3 gallop. A grade III/VI, harsh, midsystolic murmur was heard best at the upper left sternal border. There was no diastolic murmur.

The ECG showed sinus rhythm, normal QRS duration, and left ventricular hypertrophy with repolarization changes. An echocardiogram demonstrated marked thickening and heavy trabeculation of the apical half of the left ventricle. Color Doppler displayed flow within the deep intertrabecular recesses. The left ventricle was not dilated. There was diffuse left ventricular hypokinesis with an ejection fraction of 20% to 25%. The right ventricle appeared to be more heavily trabeculated than usual. No additional abnormalities were present. The findings were consistent with isolated noncompaction of the ventricular myocardium.

Introduction

Noncompaction of the ventricular myocardium is a cardiomyopathy thought to be caused by arrest of normal embryogenesis of the endocardium and myocardium. This abnormality is often associated with other congenital cardiac defects, but it is also seen in the absence of other cardiac anomalies. Clinical manifestations are highly variable, ranging from no symptoms to disabling congestive heart failure, arrhythmias, and systemic thromboemboli. Echocardiography has been the diagnostic procedure of choice, but the correct diagnosis is often missed or delayed because of lack of knowledge about this uncommon disease and its similarity to other diseases of the myocardium and endocardium.

Embryology and Development

During early embryonic development, the myocardium is a loose network of interwoven fibers separated by deep recesses that link the myocardium with the left ventricular cavity. Gradual "compaction" of this spongy meshwork of fibers and intertrabecular recesses, or "sinusoids," occurs between weeks 5 and 8 of embryonic life, proceeding from the epicardium to endocardium and from the base of the heart to the apex.[1–5] The coronary circulation develops concurrently during this process, and the intertrabecular recesses are reduced to capillaries.[1] The normal process of trabeculation appears to involve secretion of neuregulin growth factors from the endocardium and may also involve angiogenesis factors, such as vascular endothelial growth factor and angiopoietin-1.[6]

Noncompaction of the ventricular myocardium (NVM) is an uncommon finding. It is thought to be caused by arrest of the normal process of endomyocardial morphogenesis.[1–3,6] NVM was first described in association with

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other congenital anomalies, such as obstruction of the right or left ventricular outflow tracts, complex cyanotic congenital heart disease, and coronary artery anomalies.[1,4,7] The abnormal compaction process in these cases is not fully understood, but pressure overload or myocardial ischemia preventing regression of the embryonic myocardial sinusoids has been suggested. This process results in the persistence of deep intertrabecular recesses in communication with both the ventricular cavity and the coronary circulation.[8]

Isolated noncompaction of the ventricular myocardium (INVM), first described by Chin et al[3] in 1990, is characterized by persistent embryonic myocardial morphology found in the absence of other cardiac anomalies to explain the abnormal development. In such cases, the resultant deep recesses communicate only with the ventricular cavity, not the coronary circulation.[9]

The left ventricle is uniformly affected, but biventricular noncompaction has been reported, with right ventricular noncompaction described in less than one-half of patients.[1,6,7] Because of difficulty in distinguishing normal variants in the highly trabeculated right ventricle from the pathological noncompacted ventricle, several authors dispute the existence of right ventricular noncompaction.[8,10] Furthermore, some authors have advocated that the term "left ventricular hypertrabeculation" be used instead of "isolated noncompaction," as coexisting cardiac abnormalities have been described in "isolated" cases, and the latter term suggests that the pathogenesis is proven.[11,12]

Although widely believed to be the mechanism, there has been no proof of an arrest in embryonic endomyocardial morphogenesis. In 1997, Bleyl et al[13] described the absence of characteristic features of noncompaction on fetal echocardiography in 3 infants who were subsequently diagnosed with INVM. It is not clear whether these findings were related to limitations of fetal echocardiography or to the development of the disorder postnatally. These findings called into question the theory of arrested embryonic development as the pathogenesis of left ventricular noncompaction.[11,13]

Histology

Histologically, isolated noncompaction differs from noncompaction 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.[8] There is no specific histological finding in INVM, although fibrosis has been described in multiple reports.[12,14,15] In five individuals with INVM who underwent right ventricular endomyocardial biopsy, Hamamichi et al[16] described interstitial fibrosis in all with endomyocardial thickening and subendocardial fibroelastosis in 3. Several reports have observed necrotic myocytes within the prominent trabeculations of patients with noncompaction.[8,12]

Genetics

Both familial and sporadic forms of noncompaction have been described. In the original report of INVM, which predominantly involved children, familial recurrence was seen in half of patients.[3] Familial recurrence was seen in 18% in the largest reported adult population with INVM,[8] although the authors reported that incomplete screening of siblings may account for the lower percentage compared with the earlier report.

Although genes responsible for the sporadic forms have not been identified, genes responsible for some familial cases of INVM have been described.[6] Bleyl et al[13] reported a family of 6 affected children with INVM and X-linked inheritance. In this family, genetic linkage localized INVM to a mutation in the G4.5 gene of the Xq28 chromosome region, where other myopathies with cardiac involvement have been localized, including Barth syndrome, Emery-Dreifuss muscular dystrophy, and myotubular myopathy.[6,13] Ichida et al[17] reported novel mutations in the G4.5 gene and mutations in the alpha-dystrobrevin gene, which is associated with muscular dystrophy in humans, in patients with noncompaction associated with congenital heart disease. The cardiac-specific gene CSX has been implicated in the development of some cases of INVM. Distal chromosome 5q deletion has been reported to cause a loss of the gene.[18]

Possible genetic loci involved in noncompaction have been described in mice. A mutation in the FKBP12 gene resulted in ventricular septal defects, dilated cardiomyopathy, and noncompaction.[9] Mice lacking the Peg1 gene were found to have alterations in trabeculation similar to those seen in humans with NVM.[19]

Epidemiology and Demographics

In the initial case series of isolated noncompaction,[3] the median age at diagnosis was 7 years (ranging from 11 months to 22 years). Subsequent case reports have described this finding in adults, including the elderly.[1–3,8,9,11,20–22] In the largest series of patients with INVM,[8] the prevalence was 0.014% of patients referred to the echocardiography laboratory. The true prevalence is unclear, as this represented a population referred to a tertiary care hospital for abnormal echocardiographic findings or congestive heart failure, resulting in selection bias. Men appear to be affected more often than women, with males accounting for 56% to 82% of cases in the 4 largest reported series of INVM.[1,3,8,23]

Isolated noncompaction is currently categorized as an unclassified cardiomyopathy by the World Health Organization classification, but a growing body of literature on the characteristic features of INVM has led some to call for its designation as a distinct cardiomyopathy.[8,10,14]

Clinical Features and Pathophysiology

Three major clinical manifestations of noncompaction have been described:

Clinical and Demographic Characteristics of Patients With Noncompaction of the Ventricular Myocardium

	Chin et al[3]	Ritter et al[1]	Ichida et al[23]	Oechslin et al[8]	Stollberger et al[11]
Patients, n	8	17	27	34	62
Males, %	63	82	56	74	70
Median age at diagnosis	7	45	5	40	50 (mean)
Age range, y	0.9 to 22.5	18 to 71	0 to 15	16 to 71	18 to 75
Follow-up, y	≤5	≤6	≤17	≤11	≤6
Facial dysmorphism, %	38	0	33	0	...
Familial occurrence, %	50	12	44	18	...
Localization of noncompacted segments, %					
Apex	Most prominent	100	100	94	98
Inferior wall	...	100	70	84	8
Lateral wall	...	...	41	100	19
Abnormal ECG, %	88	88	88	94	92
Bundle branch block, %	25*	47	15	56	26
Wolff-Parkinson-White syndrome, %	13	0	15	0	3
Ventricular tachycardia, %	38	47	0	41	18
Atrial fibrillation, %	...	29	...	26	5
Left ventricular systolic dysfunction, %	63	76	60	82	58†
Congestive heart failure, %	63	53	30	68	73
Systemic embolism, %	38	24	0	21	...
Pulmonary embolism, %	0	6	7	9	...
Ventricular thrombi, %	25	6	0	9	...
Heart transplantation, %	0	12	4‡	12	...
Neuromuscular disorders, %	...	...	...	...	82§
Deceased, %	38	47	7	35	...
Sudden death, %	13	18	0	18	...

*Left ventricular (intraventricular) conduction defects.
†Fractional shortening ≤24%.
‡One patient was a candidate for heart transplantation.
§Thirteen patients were not investigated for neuromuscular disorders.
Adapted from Rigopoulous et al,[9] with permission from S. Karger AG, Basel.

Heart failure, arrhythmias, and embolic events.[1–3] 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 INVM had symptomatic heart failure.[8] Clinical characteristics of patients from 5 study populations with noncompaction of the ventricular myocardium are presented in the Table.

In the cohort with INVM described in the initial report by Chin et al,[3] depressed ventricular systolic function was noted in 63% of patients. Both systolic and diastolic ventricular dysfunction have been described. Restrictive hemodynamics by cardiac catheterization, as well as an initial presentation of INVM as a restrictive cardiomyopathy, have been described in children with INVM.[23,24] In a population of Japanese children with INVM followed for up to 17 years, left ventricular dysfunction developed in the vast majority, regardless of the presence or absence of symptoms at initial diagnosis.[23]

Diastolic dysfunction in ventricular noncompaction may be related to both abnormal relaxation and restrictive filling caused by the numerous prominent trabeculae.[2] The origin of systolic dysfunction in noncompaction is unclear, but a body of evidence is accumulating that points toward subendocardial hypoperfusion and microcirculatory dysfunction playing roles in ventricular dysfunction and arrhythmogenesis. Chin et al[3] suggested that subendocardial perfusion might be abnormal in INVM despite the absence of epicardial coronary artery disease. Because of the prominent, numerous trabeculae, subendocardial ischemia may result from isometric contraction of the endocardium and myocardium within the deep intertrabecular recesses.

Subendocardial perfusion defects have been described in INVM using cardiac magnetic resonance imaging (MRI).[25] Positron emission tomography (PET)[26] and scintigraphy with thallium-201[23] have demonstrated transmural perfusion defects correlat-

ing with areas of noncompacted myocardium in INVM. The presence of ischemic subendocardial lesions discovered during postmortem analysis of individuals with INVM lends support to the theory that coronary microcirculatory abnormalities may play a key role in its pathophysiology. Diminished coronary flow reserve has been demonstrated by PET in both noncompacted and compacted segments of myocardium in INVM.[27] Epicardial coronary stenosis is unlikely to explain the decreased coronary flow reserve in patients with INVM.[1,3,13,26] Impaired microvascular function may account for the contractile dysfunction. Junga et al[26] suggested that altered perfusion and coronary flow reserve in INVM may be related to failure of the coronary microcirculation to grow with the increasing ventricular mass, compression of the intramural coronary bed by the hypertrophied myocardium, or both processes.

Arrhythmias are common in patients with ventricular noncompaction. Atrial fibrillation has been reported in over 25% of adults with INVM.[1,8] Ventricular tachyarrhythmias have been reported in as many as 47%. Sudden cardiac death accounted for half of the deaths in the larger series of patients with INVM.[1,3,8,9] Although ventricular arrhythmias occurred in nearly 40% of patients in the initial description of INVM by Chin et al,[3] Ichida[23] et al described no cases of ventricular tachycardia or sudden death in the largest series of pediatric patients with INVM. Paroxysmal supraventricular tachycardia and complete heart block have also been reported in patients with INVM.[1,23]

Abnormalities of the resting ECG are found in the majority of patients with NVM but findings are nonspecific and include left ventricular hypertrophy, repolarization changes, inverted T waves, ST segment changes, axis shifts, intraventricular conduction abnormalities, and AV block.[1,3,8,23,28] Oechslin et al[8] described left bundle branch block in 44% of adult patients with INVM, but the reported incidence in children was much lower in another study.[23] Electrocardiographic findings of the Wolff-Parkinson-White syndrome have been described in up to 15% of pediatric patients,[23,29] but it was not observed in the 2 largest series of adults with isolated noncompaction.[1,8]

In 3 groups of patients with isolated NVM, the occurrence of thromboembolic events, including cerebrovascular accidents, transient ischemic attacks, pulmonary embolism, and mesenteric infarction, ranged from 21% to 38%.[1,3,8] Embolic complications may be related to development of thrombi in the extensively trabeculated ventricle, depressed systolic function, or the development of atrial fibrillation.[1,2] Of interest, no systemic embolic events were reported in the largest pediatric series with INVM.[23]

An association between INVM and facial dysmorphisms, including a prominent forehead, low-set ears, strabismus, high-arching palate, and micrognathia, was described by Chin et al.[3] One third of children with INVM in the series by Ichida et al[23] had similar dysmorphic facial features. No associated dysmorphic facial features were observed in 2 adult populations with INVM.[1,8]

An association between noncompaction and neuromuscular disorders has also been described,[11,30] with as many as 82% of patients having some form of neuromuscular disorder.

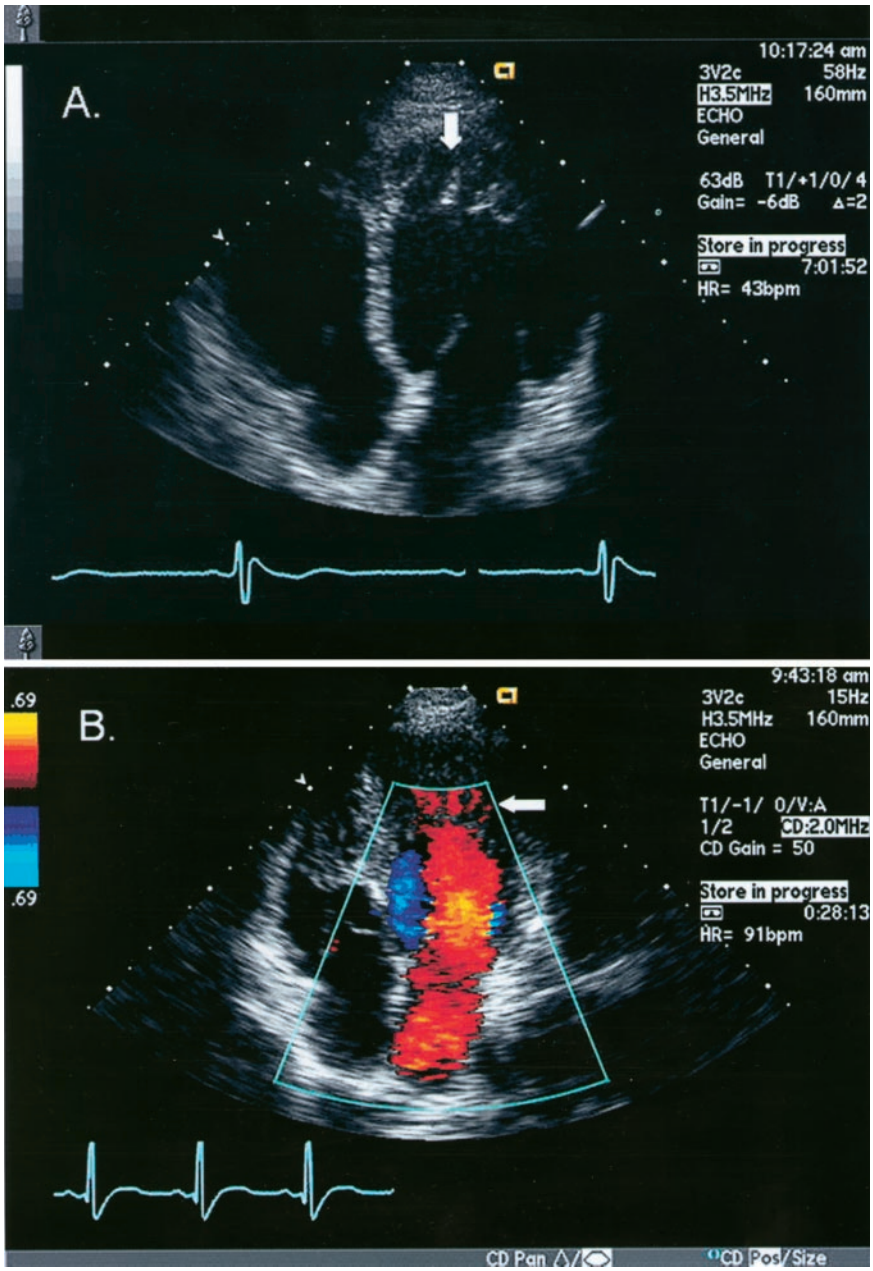
Diagnosis

The diagnosis of noncompaction of the ventricular myocardium can be made by 2-dimensional and color Doppler echocardiography (Figure). Multiple prominent ventricular trabeculations with deep intertrabecular recesses are seen. Color Doppler imaging demonstrates blood flow through these deep recesses in continuity with the ventricular cavity.[2] INVM is diagnosed when the above criteria are satisfied and coexisting cardiac lesions, such as semilunar valve obstruction and coronary artery anomalies, are excluded.

The left ventricular apical and inferior wall segments were involved in all patients in an adult population with INVM studied by echocardiography.[1] The right ventricular apex was involved in 41%. In the largest series of patients with INVM,[8] in addition to the apical and mid-ventricular inferior wall segments, the mid-ventricular lateral wall segment was involved in more than 80% of patients. Depressed left ventricular systolic function was the rule, with a mean calculated ejection fraction of 33% in 28 patients examined. Diastolic function by mitral inflow and pulmonary venous flow Doppler was assessed in 17 patients, with impaired function observed in all, including a restrictive filling pattern in 36%. Hypokinesis was observed occasionally in normally compacted segments as well as in the noncompacted segments of the left ventricle,[8] which may correlate with the observation of microcirculatory dysfunction in both noncompacted and “normal” segments in patients with INVM.

Chin et al[3] described a quantitative approach to diagnose noncompaction using a trabeculation peak to trough ratio, but it has not been used widely in clinical practice.[2,9] Oechslin et al[8] and Jenni et al[10] described the abnormally thickened myocardium as a 2-layered structure, with a normally compacted epicardial layer and a thickened endocardial layer. They proposed a quantitative evaluation for the diagnosis of INVM by determining the ratio of maximal thickness of the noncompacted to compacted layers (measured at end systole in a parasternal short axis view), with a ratio >2 diagnostic of INVM. This technique allowed differentiation of the trabeculations of INVM from that observed with dilated cardiomyopathy or hypertensive cardiomyopathy.[10]

Similarity with other defects, as well as nonspecific clinical manifestations, makes the diagnosis of noncompaction difficult. Ichida et al reported[23] that the diagnosis of INVM was missed in 89% of children. Ritter et al[1] observed a mean time from onset of symptoms to correct diagnosis of more than 3 years in one adult population with INVM.



A, Two-dimensional echocardiogram of a patient with isolated noncompaction of the left ventricular myocardium demonstrating prominent, numerous trabeculations (arrow) in the left ventricular apex with deep intertrabecular recesses. B, Color Doppler echocardiogram of another patient with isolated noncompaction of the left ventricular myocardium demonstrating flow within deep intertrabecular recesses (arrow) in continuity with the left ventricular cavity.

Prominent trabeculations (although virtually always <3 in number in normal variants),[31] apical hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, endocardial fibroelastosis, cardiac metastases, and left ventricular thrombus are important differential diagnostic considerations.[2,11,22,23] Transesophageal echocardiography may be used when transthoracic studies cannot reliably exclude other processes.[22] One report described the use of contrast echocardiography with sonicated albumin in a patient with INVM. Contrast echocardiography may be helpful when standard echocardiographic image quality is limited or the diagnosis is questionable.[32]

Although echocardiography has been the diagnostic test of choice for noncompaction, other modalities have been used for the diagnosis, including contrast ventriculography,[20,21] computed tomography,[16,21] and MRI.[15,25,26] MRI provides good correlation with echo for localization and extent of noncompaction and is useful in cases with poor echocardiographic image quality.[26] In addition, the demonstration of differences in MRI signal intensity in noncompacted myocardium may help identify substrate for potentially lethal arrhythmias.[15]

Invasive electrophysiological studies in patients with INVM have not been widely reported. Signal averaged electrocardiography in 5 children with INVM showed late potentials in 3 and

prolonged QT dispersion in 1.[26] Such findings may help identify individuals at increased risk for ventricular arrhythmias and sudden death.

Management

Treatment for noncompaction 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. Only 6 cases of INVM leading to cardiac transplantation have been published to date.[14] The beneficial effects of the β-blocker carvedilol on left ventricular function, mass, and neurohormonal dysfunction in an infant with INVM have been described.[33] Because of the frequency of ventricular tachycardia and significant risk of sudden cardiac death and systemic embolism, assessment for atrial and ventricular arrhythmias by ambulatory ECG monitoring should be performed annually. As more information is gathered about NVM and risk of sudden cardiac death, implantable defibrillator technology may have an expanded role. Biventricular pacemakers may have a role in the treatment of NVM patients with heart failure, reduced left ventricular function, and prolonged intraventricular conduction.

Prevention of embolic complications is also an important management issue, and several authors have recommended long-term prophylactic anticoagulation for all patients with ventricular noncompaction whether or not thrombus has been found.[1,8]

Because of the familial association described with noncompaction, screening echocardiography of first degree relatives is recommended. Given the high percentage of associated neuromuscular disorders reported in patients with INVM, neurological and musculoskeletal evaluations are also recommended.

Prognosis

Although the prognosis for patients with NVM varies, nearly 60% of patients described in one large series[1] had either died or undergone cardiac transplantation within 6 years of diagnosis. Two of 8 in the initially asymptomatic group of this series died during the follow-up period, both having documented sustained ventricular tachycardia and one with sudden cardiac death. Similarly, in a series of 34 adults with INVM, 47% either died or underwent cardiac transplantation during the follow-up period of 44±39 months.[8] The occurrences of systemic emboli, ventricular arrhythmias, and death were considerably lower in the largest pediatric series with INVM[23] when compared with adults and the initial case series by Chin et al,[3] although nearly 90% of patients followed for up to 10 years developed left ventricular dysfunction. Oechslin et al[8] reported that certain clinical characteristics were observed significantly more frequently in nonsurvivors compared with survivors with INVM, including higher left ventricular end diastolic diameter on presentation, New York Heart Association class III-IV, permanent or persistent atrial fibrillation, and bundle branch block.[8] Patients with these high risk features are candidates for early, aggressive interventions, including consideration of cardioverter-defibrillator implantation and evaluation for transplantation.

Conclusions

The patient used a looping ECG event recorder, which documented multiple episodes of atrial fibrillation with a rapid ventricular response associated with palpitations. There were no ventricular arrhythmias.

Chronic anticoagulation with warfarin was prescribed. Treatment with an angiotensin-converting enzyme inhibitor and carvedilol was begun. Palpitations became infrequent and single. Exercise tolerance improved. The patient has New York Heart Association class II symptoms.

Lacking indications for more aggressive therapy at this time, the patient will return for regular follow-up to include assessment of exercise tolerance, measurement of ventricular size and function, and use of continuous ambulatory electrocardiography. Because of the presence of severely depressed left ventricular function and heart failure, the importance of avoiding pregnancy was stressed. First degree relatives will be screened with echocardiography.

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