Unusual Cardiomyopathies: Ventricular Noncompaction and Takotsubo Cardiomyopathy

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With improved imaging techniques, such as cardiac magnetic resonance imaging and computed tomography, 2 unusual cardiomyopathies have been added to the differential diagnosis of nonischemic dilated cardiomyopathies. Ventricular noncompaction (VNC) classically affects the left ventricle, although right ventricular involvement can also be seen. Symptoms can be absent or can be consistent with varying degrees of heart failure and arrhythmias. VNC can initially present in all age groups, from neonates to the elderly. In takotsubo cardiomyopathy, the characteristic appearance of the left ventricle involves transient regional dysfunction of the apex and mid-ventricle, with hyperkinesis of the basal segments. Classically, it occurs after an emotionally stressful event, and it predominately affects postmenopausal women. This article reviews characteristics of these unique cardiomyopathies.

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In the absence of epicardial coronary artery disease, global or segmental left ventricular dysfunction presents an increasingly difficult diagnostic challenge. The differential diagnosis of the nonischemic dilated cardiomyopathies include molecular and genetic disorders (eg, Duchenne dystrophy, Friedreich ataxia); disorders of contractile proteins (eg, incessant tachycardia, pressure or volume overload states); toxins (eg, alcohol, anthracyclines), infections, and/or inflammation (eg, collagen vascular disorders, human immunodeficiency virus or other viral injury); and idiopathic causes, including peripartum cardiomyopathy.

Restrictive processes result in nonischemic, nondilated, nonhypertrophic cardiomyopathies and include infiltrative diseases (eg, amyloidosis), metabolic storage diseases (eg, Fabry disease and hemachromatosis), sarcoidosis, and radiation. Other unusual myocardial processes occasionally encountered clinically include idiopathic myocardial fibrosis (thought by some to be an abnormality in the calcium-dependent phase of cardiac relaxation), endomyocardial fibrosis (also called tropical eosinophilic fibrosis), and Löffler endocardial fibrosis. With improved imaging techniques, such as cardiac magnetic resonance imaging (CMRI) and computed tomography (CT), 2 unusual cardiomyopathies have been added to the traditional differential. This review will discuss these unique cardiomyopathies: ventricular noncompaction (VNC) and takotsubo cardiomyopathy (TC).

Ventricular Noncompaction

Etiology

Ventricular noncompaction is a rare disorder believed to be an arrest in the normal morphogenesis of the endocardium and myocardium. As our understanding of the embryonic development of the heart increases, however, this explanation is being challenged.[1,2] The characteristic appearance of the myocardium in VNC is that of a spongy meshwork of prominent ventricular trabeculae (Figure 1). The traditional cardiac imaging modality for the diagnosis of VNC is echocardiography. The diagnosis is commonly made according to the characteristic echocardiographic appearance of a thin, compacted epicardial layer and a thick, noncompacted endocardial layer, with numerous prominent trabeculations and deep intertrabecular recesses communicating with the left ventricular cavity.[3] The prominent ventricular trabeculations and deep recesses are well visualized with 2-dimensional echocardiography (Figure 2).

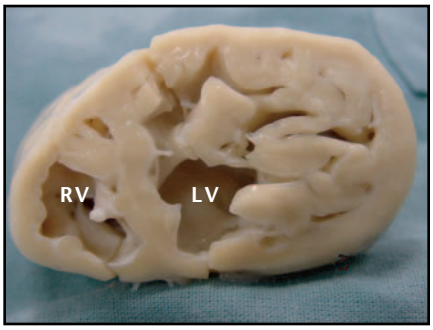


Figure 1. *Pathologic specimen taken from a 6-month-old girl with ventricular noncompaction who underwent cardiac transplantation for severe heart failure. Note the spongy meshwork of prominent ventricular trabeculae. RV, right ventricle; LV, left ventricle.* www.medreviews.com

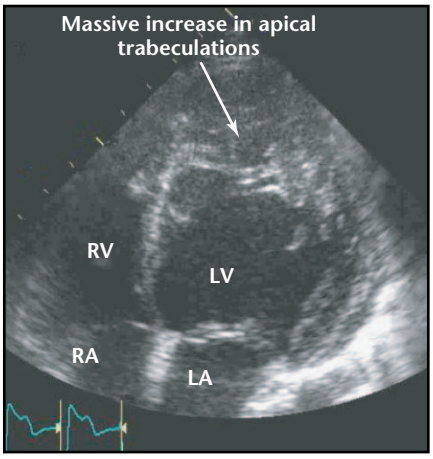


Figure 2. *Four-chamber 2-dimensional echocardiogram of a patient with ventricular noncompaction. Note the massive increase in left ventricular apical trabeculations. RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium.* www.medreviews.com

One important consideration in this diagnosis is that prominent trabeculations are also found in normal hearts. Boyd and colleagues[4] reported the necropsy findings in 474 normal hearts. Discrete muscle bundles more than 2 mm in diameter were observed in 68% of subjects. However, no subject had more than 3 such bundles. In comparison, patients with VNC have numerous prominent trabeculations.[5] Color Doppler echocardiography demonstrates blood flow within the deep intertrabecular recesses in continuity with the left ventricular cavity.[6]

Because the diagnosis of VNC is based on morphologic criteria, CMRI is also beneficial in establishing a diagnosis.[7] Pathology analysis at autopsy showed that both children and adults exhibited various abnormalities, including poorly formed papillary muscles in the left ventricle, a distinct noncompacted zone, and endomyocardial fibroelastosis.[8,9]

In 1995, the World Health Organization defined VNC as an unclassified cardiomyopathy.[10] The incidence of VNC is not well established. In a 10-year retrospective review of over 37,000 echocardiograms at one institution, VNC was present in only 17 cases.[9] However, a recent review of 132 cases of idiopathic cardiomyopathies in Qatar reported an incidence of 6.1% in patients under age 50.[11]

Genetics

There is significant genetic heterogeneity in VNC, and genetic alterations are associated with different age groups. Mutations in the G4.5 gene, located on Xq28, were initially described in Barth syndrome and result in a wide spectrum of X-linked infantile cardiomyopathies, including VNC.[12,13] Ichida and colleagues[14] found that patients with VCN exhibit a novel mutation in the α-dystrobrevin gene that is associated with congenital heart disease. Mutations in this gene are associated with muscular dystrophy in humans,[15] and with skeletal abnormalities and cardiomyopathies in mice models.[16] VNC may be part of the phenotypic spectrum of laminopathies, as well.[17] In a molecular genetic analysis of 25 adults with VNC, mutations in the G4.5 gene were rare.[18] It was postulated that VNC in adults follows an autosomal dominant pattern that is

genetically different from X-linked infantile cases. Kenton and associates[19] performed genetic analysis on 48 patients with VNC and found that gene mutations in G4.5 and α-dystrobrevin were unusual. The age range of these patients, however, was not reported. The genetic influence of the condition was demonstrated in a case report of a pregnant woman diagnosed with VNC at 24 weeks gestation, whose infant also had VNC that was identified by neonatal echocardiography and confirmed by autopsy.[20]

Associated Syndromes

VNC may be associated with other congenital cardiac anomalies,[21-23] however, it has classically been described as an isolated defect.[5] In one study of 113 children with mitochondrial disorders, 40% had cardiac involvement, of which 13% was VNC.[24] There have been cases of VNC in patients with a variety of conditions, including nail-patella syndrome,[25] Melnick-Needles syndrome,[26] Roifman syndrome,[27] Fabry disease,[28] and Patau syndrome.[29]

Pathophysiology

Although these patients do not typically have coronary artery stenoses, ischemia has been demonstrated by numerous imaging modalities. Subendocardial ischemia has been documented with CMRI and positron emission tomography (PET).[30] Microcirculatory dysfunction is evident. Jenni and colleagues[31] found that adenosine administration impaired increased myocardial blood flow, which suggests that coronary artery flow reserve is decreased. In one report, a 12-year-old boy with VNC and normal coronary arteriography had calcification in the basal interventricular septum, which was presumed to be associated with subendocardial infarction secondary to microcirculatory dysfunction.[32] Several reports have described fibrosis in cases of isolated VNC.[33-35]

FKBP12 is an isomerase that modulates calcium release. The cardiac ryanodine receptor binds selectively to FKBP12.6. FKBP12-deficient mice, generated by embryonic stem cell technology, exhibited cardiac morphologic characteristics consistent with those of VNC.[36]

Anatomic Localization

Ventricular noncompaction is classically described as affecting the left ventricle. Histologically, the deep intertrabecular recesses communicate with the left ventricular cavity, and, in cases associated with other congenital lesions, the recesses may communicate with the coronary circulation as well.[37] It is important to recognize that VNC might involve only the left ventricular apex; cases of VNC have been misdiagnosed as apical thrombus, apical hypertrophic cardiomyopathy, and dilated cardiomyopathy.[38]

Right ventricular involvement can also be seen in VNC. Rarely, only right ventricular involvement is present,[21] and VNC must be considered in the differential diagnosis of early postnatal right heart failure.[39] Additionally, right VNC has been described in a child following a Senning atrial switch for D-transposition of the great arteries.[40]

Clinical Presentation

VNC has been suspected prenatally by fetal echocardiography, and confirmed by neonatal death,[20] however, it has also been described with an initial presentation in the elderly.[41] The clinical presentation of VNC varies from asymptomatic patients to patients with varying degrees of heart failure and arrhythmias.[5,9] The majority of patients with VNC have heart failure, but as many as 40% of patients may have normal systolic function.[12] Patients with VNC may also have diastolic dysfunction and restrictive physiology.[6,12]

A number of arrhythmias are commonly associated with VNC, and their occurrence appears to increase with age. In adults, atrial fibrillation has been reported in $>25\%$ of cases.[37] Supraventricular tachycardia and heart block have also been reported.[9,37] Ventricular dysrhythmias are common, occurring in almost half of the cases reported in some series, and left bundle branch block has been reported in 44% of adult patients.[37] Wolff-Parkinson-White syndrome has been documented in up to 15% of children with VNC,[12] however, the associated electrocardiographic findings are not commonly reported in adults. Conduction system abnormalities occur in children with VNC, and the condition has been implicated as a cause of sudden infant cardiac death.[42]

Embolic events appear to be more common in adults with VNC. Events including transient ischemic attacks, cerebral vascular accidents, and pulmonary embolism have been reported in 21% to 38% of adult patients.[5,9,37] Further, a case of superior mesenteric artery embolic occlusion was recently reported in a 40-year-old woman.[43] Patients with VNC may be predisposed to thrombi that develop in the deep ventricular trabeculations and are associated with poor systolic function, or arrhythmias.[6] However, one recent retrospective study evaluating the risk of stroke and peripheral embolism in adults with VNC did not show an increased incidence of events compared to controls matched for age, sex, and left ventricular shortening.[44] Devastating neurologic events have been reported in children, including a fatal cardioembolic stroke in an 18-month-old girl with elevated factor VIII levels.[45] VNC has been

associated with a spectrum of neuromuscular disorders, including muscular dystrophy, Pompe disease, Barth syndrome, Friedreich ataxia, and Charcot-Marie-Tooth disease.[46]

Diagnostic Testing

The echocardiographic criteria established to diagnose VNC remain controversial.[37,47,48] Oschelin and colleagues[37] have described the utility of the ratio of noncompacted myocardium versus compacted myocardium ≥ 2 as diagnostic for isolated VNC, specifying, however, that the criterion is valid only for left ventricular assessment. Stollberger and others[1] propose that the definition rely on the presence of > 3 trabeculations protruding from the left ventricular wall that are apical to the papillary muscles and visible in 1 imaging plane. Color Doppler echocardiography should demonstrate blood flow within the deep intertrabecular recesses. It is important to exclude anomalous coronary artery origins with exuberant collateral flow as a cause of these findings by color Doppler imaging.

Sengupta and colleagues[47] compared the echocardiographic findings of dilated cardiomopathy to those of VNC, and found an exaggerated degree of spherical remodeling in patients with VNC. Various echocardiographic imaging modalities have been described in the characterization of VNC, including contrast echocardiography,[49] 3-dimensional echocardiography,[50] and tissue strain imaging.[51] Cardiac catheterization often reveals globally poor function with massively increased trabeculae in the left ventricular apex (Figure 3).

More recently, CMRI has been used in the diagnosis of VNC (Figure 4).[34] In the T2-weighted and contrast-enhanced CMRI images, the noncompacted myocardium was separated into 2 distinct layers: a subendocardial layer and an endocardial layer. Interestingly, in a reported case of familial, isolated VNC, delayed contrast enhancement imaging did not demonstrate any areas of myocardial fibrosis.[52]

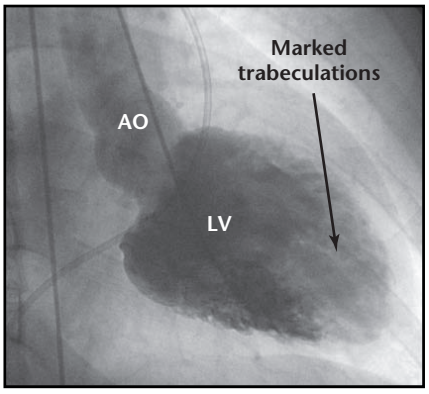


Figure 3. *Angiogram in the right anterior oblique projection in a patient with ventricular noncompaction. AO, aorta; LV, left ventricle.* www.medreviews.com

Management

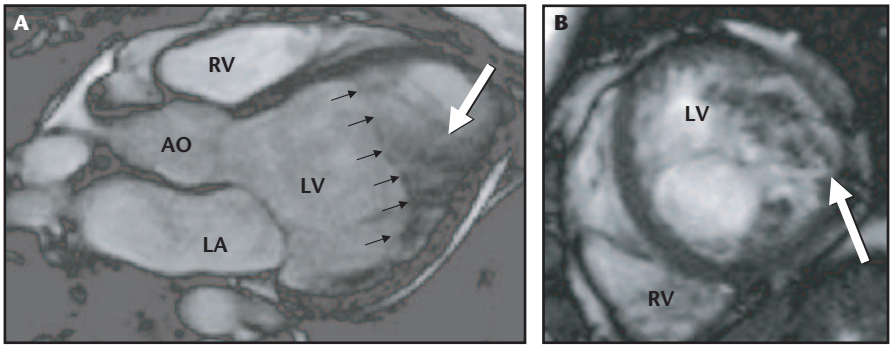
Management strategies are usually focused on the individual patient's symptoms. Because of the rare occurrence of VNC, there are no randomized trials in treatment. Medical treatment of heart failure, such as diuretics, angiotensin-converting enzyme inhibitors, and β-blockers, is warranted.[53,54] Systemic anticoagulation, regardless of whether thrombosis is present, has been proposed by several authors.[9,37] Serial electrocardiographic ambulatory monitoring is recommended because of the high rate of arrhythmias. Implantable cardiac defibrillators have been placed in both adults[55] and children[56] with ventricular arrhythmias associated with VNC. Cardiac transplantation is reserved for cases refractory to medical management.[57]

Prognosis

The prognosis of patients with VNC is widely variable. Characteristics that have been associated with a higher risk of mortality in adults include an elevated left ventricular end diastolic pressure, inclusion in the New York Heart Association Class III-IV, atrial fibrillation, and left bundle branch block.[37]

In children, Wald and colleagues[58] identified several echocardiographic features that were associated with poor outcomes. These included a greater noncompacted to compacted segment ratio and an enlarged left ventricular end-diastolic dimension. In a retrospective study of 36 children with VNC at Texas Children's Hospital, mortality was 14% over a median 3-year follow-up. A certain percentage of children recover normal systolic function, only to have progressive deterioration later in life.[59]

Figure 4. *Cardiac magnetic resonance cine of ventricular noncompaction in the long axis plane* **(A)** *and short axis plane* **(B)**. *White arrows point to areas of marked apical trabeculations. The row of darker arrows indicates the obvious demarcation in the area of increased trabeculations in the left ventricular chamber. RV, right ventricle; AO, aorta; LV, left ventricle; LA, left atrium.* www.medreviews.com



Unresolved Issues

The criteria used to diagnose VNC vary among many of the published reports. Some reports included cases of left ventricular hypertrabeculation, which is a distinct entity.[60] Therefore, the conclusions must be used with caution until larger, detailed, prospective trials are completed.

Takotsubo Cardiomyopathy

Etiology

TC, also known as transient left ventricular apical ballooning syndrome, was first described by Dote and colleagues in 1991.[61] The syndrome, initially reported in the Japanese population, was named after a round-bottomed, narrow-necked fishing pot used for trapping octopus, a takotsubo (Figure 5).

The characteristic appearance of the left ventricle involves transient regional dysfunction of the apex and mid-ventricle, with hyperkinesis of the basal segments.[62] Recently, a report of transient mid-ventricular ballooning was also described.[63] Although the etiology remains unclear, CD36 deficiency, which is thought to be associated with many cardiovascular disease and metabolic abnormalities, was confirmed in a 71-year-old woman with takotsubo cardiomyopathy.[64] Additionally, myocardial scintigraphy in patients with TC has demonstrated a discrepancy of sympathetic innervation between the apical and basal region, which may account for the area's unusual appearance.[65] Another proposed mechanism in TC is coronary microvasculature dysfunction. In a study of 8 patients with TC, subjects had decreased coronary flow velocity reserve and shortened deceleration diastolic times during the acute presentation.[66] These symptoms were improved at subsequent 3-week follow-up.

This rare cardiomyopathy predominately affects postmenopausal women.[67] Classically, it occurs after an emotionally stressful event that presumably would evoke a marked catecholamine response (Table 1). In a recent evaluation of 19 patients presenting with left ventricular dysfunction after sudden emotional stress, exaggerated sympathetic stimulation was documented by plasma catecholamine levels.[68] TC has also been described in a 70-year-old patient with microscopic polyangitis, whose ventricular dysfunction resolved with steroid therapy.[69]

Clinical Presentation

Patients with TC typically present with sudden onset of chest pain or dyspnea that is usually associated with sudden emotional stress. Rarely, patients have presented with syncopal episodes.[70] In the elderly, presentation can mimic acute myocardial infarction, and varying severity of congestive heart failure has been described.[70,71] Patients with TC have also been reported to exhibit ventricular septal defect perforation[72] and left ventricular rupture.[73]

Diagnostic Testing

Admission electrocardiograms commonly reveal ST-segment elevation in the precordial leads.[74] The development of evolutionary T-wave inversions is common. Left and right bundle branch blocks have been reported. Pathologic Q waves are present in about one third of cases. Serum cardiac biomarkers are often increased. Cardiac creatine kinase and troponin levels classically exhibit a rapid rise.[75] Plasma brain natriuretic peptide does not appear to correlate with prognosis.[76]

Angiography of patients with TC exhibits no obstructive coronary artery disease.[74] Ventriculography reveals apical and mid-ventricular regional wall motion abnormalities, with a compensatory hyperkinetic response of the basal portion of the left ventricle (Figure 6). The left ventricular ejection fraction is mildly to moderately depressed (39% to 49%).[74]

Echocardiography characteristically demonstrates the apical ballooning appearance of the left ventricle. It may also show a mid-ventricular gradient[77] or a left ventricular outflow tract gradient.[78]

Figure 5. *A round-bottomed, narrow-necked fishing pot used for trapping octopus, from which the term "takotsubo cardiomyopathy" was derived.*
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Table 1
Events That Have Precipitated the Acute Appearance of the Ampulla-Shaped Left Ventricle (Takotsubo Cardiomyopathy)

- Earthquakes[83,84]
- Pneumothorax[85]
- Stressful episode[86] or documented high catecholamine state[68,87]
- Hypoglycemic attack[88]
- Ventricular tachycardia[89]
- Alcohol withdrawl[90]
- Lightning strike[91]
- Hyperthyroidism[92]
- Subarachnoid hemorrhage[93]
- Surgery (cholecystectomy)[94]

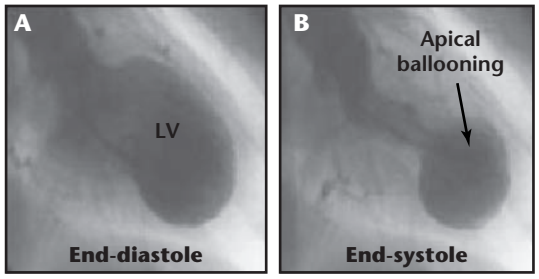

Figure 6. *Angiogram in the right anterior oblique projection at end-diastole* **(A)** *and end-systole* **(B)** *in a patient with takotsubo cardiomyopathy. Arrow indicates area of apical ballooning. LV, left ventricle.* www.medreviews.com

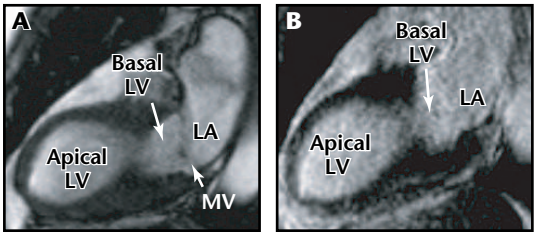

Figure 7. *Cardiac magnetic resonance demonstrating apical ballooning* **(A)** *and gadolinium-delayed enhancement image without areas of hyperenhancement* **(B)***, suggesting no areas of myocardial fibrosis. LV, left ventricle; LA, left atrium; MV, mitral valve.* www.medreviews.com

Cardiac magnetic resonance (CMR) is increasingly being used in the diagnosis of TC (Figure 7). Delayed hyperenhancement on gadolinium-enhanced CMR, which identifies areas of myocardial fibrosis, is usually absent in patients with TC.[79] However, at least 1 case of subendocardial delayed hyperenhancement has been reported.[80]

Other imaging modalities that have been used to evaluate TC include 99mTc-tetrofosmin myocardial single photon emission computed tomography (SPECT),[81] PET,[82] and MIBG (I-123-β-methyl-iodophenyl pentadecanoic acid myocardial scintigraphy).[65]

Management

In the acute presentation phase, TC must be managed as an acute coronary syndrome, with emergent coronary angiography to rule out obstructive coronary artery disease. Subsequent medical management includes aspirin, β-blockers, angiotensin-converting enzyme inhibitors, and diuretics as needed to treat heart failure symptoms.

Prognosis

The overall prognosis for patients with TC is favorable, with complete resolution of the wall motion abnormalities in most cases. However, complications that have been associated with this disorder include left heart failure, pulmonary edema, cardiogenic shock, mitral regurgitation, ventricular arrhythmias, left ventricular thrombus, left ventricular free wall rupture, and, rarely, death.

Conclusion

Rare forms of cardiomyopathy must be considered in patients with left ventricular dysfunction in the absence of obstructive coronary artery disease. Ventricular noncompaction has varying degrees of systolic dysfunction, and may present during childhood or adulthood. The treatment is based on symptomatology, with the goal of relieving heart failure symptoms, controlling arrhythmias, and preventing embolic events.

TC is a rare disorder that predominately affects postmenopausal women following an emotionally stressful event. The presentation mimics an acute coronary syndrome with chest pain, ST-segment elevation, and positive serum cardiac

Main Points

- Unusual forms of cardiomyopathies must be considered in the differential diagnosis of nonischemic left ventricular dysfunction.
- The diagnosis of ventricular noncompaction (VNC) is commonly made according to the characteristic echocardiographic appearance of a thin, compacted epicardial layer and a thick, noncompacted endocardial layer, with numerous prominent trabeculations and deep intertrabecular recesses communicating with the left ventricular cavity.
- VNC may present at any age, and is associated with varying degrees of systolic and/or diastolic dysfunction.
- Takotsubo cardiomyopathy (TC) typically affects postmenopausal women following a stressful event that presumably would evoke a marked catecholamine response.
- In TC patients, noninvasive studies characteristically demonstrate the apical ballooning appearance of the left ventricle. The ballooning typically resolves over time.
- The characteristic appearance of the left ventricle in patients with TC involves transient regional dysfunction of the apex and mid ventricle, with hyperkinesis of the basal segments.

biomarkers. The left ventricle typically has regional wall motion abnormalities of the apical and mid-ventricular walls, with hyperkinesis of the basal segments. The prognosis for TC patients is generally favorable. ■

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