Isolated Ventricular Non-Compaction: An Underdiagnosed Cause of Congestive Heart Failure

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ABSTRACT: Isolated ventricular non-compaction is a frequently underdiagnosed rare congenital cardiomyopathy. The importance of diagnosing this cardiomyopathy lies especially in asymptomatic patients, screening relatives of index cases in order to focus on their follow-up, and searching for criteria warranting prophylactic anticoagulation, implantable cardioverter defibrillator and anti-remodeling drugs such as angiotensin-converting inhibitors. We present the clinical and imaging characteristics of this entity and discuss some of the therapeutic dilemmas involving these patients.

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KEY WORDS: isolated ventricular non-compaction, congestive heart failure, thromboembolism, ventricular tachyarrhythmia

Isolated ventricular non-compaction is a rare congenital cardiomyopathy. Initially described in 1984 by Engberding et al. [1], this condition was long overlooked until the last few years during which an abundance of various publications, series and case reports has been published. Only recently was it classified as a genetic cardiomyopathy by the American Heart Association [2]. On the basis of echocardiographic studies, the prevalence of IVNC in the general population has been estimated at 0.05% [3]. Apparently, this disease continues to be frequently underdiagnosed, mostly due to lack of knowledge of its possible coincidence with dilated or hypertrophic cardiomyopathy. This is often the result of inadequate imaging of the apical segments of the left ventricle [4,5], especially since the left ventricular apex, which is commonly involved in IVNC, is particularly difficult to visualize by echocardiography. We present here the clinical and imaging characteristics of this entity and discuss some of the therapeutic dilemmas involving these patients.

PATHOGENESIS

Currently, the cardiomyopathy of IVNC is believed to be the result of an arrest of the myocardial compaction process in the fetus, during which the primordial trabecular loose meshwork gradually undergoes condensation from the epicardium to the endocardium and from the base of the heart to the apex [6,7]. The result of this congenital defect is an altered myocardial structure consisting of a thick "spongy" non-compacted endocardial layer and a thin compacted myocardium on the epicardial side. The deep intertrabecular recesses in IVNC are continuous with the ventricular cavity without evidence of communication to the epicardial coronary arteries, in contrast to the resembling non-compacted myocardium reported in association with ventricular outflow tract obstruction in which recesses formed by "persisting sinusoids" do communicate with the coronary arteries [8].

IVNC = isolated ventricular non-compaction

GENETICS

The inheritance of IVNC can be either sporadic or familial in up to 44% of patients; therefore, echocardiographic screening of family members is recommended [9]. The pattern of inheritance is generally autosomal dominant. X-linked recessive inheritance has been described with mutations in the G4.5 gene encoding tafazzin, which is involved in maintaining levels of cardiolipin. Mutations in other genes including alpha-dystrobervin, Cypher/ZASP (cytoskeleton proteins), and lamin A/C have been described [10,11]. A recent genetic analysis in a cohort of 63 unrelated adult probands with left ventricular non-compaction and no other congenital heart anomalies revealed heterozygous mutations in 11 patients in genes encoding beta-myosin heavy chain (MYH7), alpha-cardiac actin (ACTC), and cardiac troponin T (TNNT2) [12]. Nine distinct mutations were found: 7 in MYH7, 1 in ACTC, and 1 in TNNT2.

DIAGNOSIS

The diagnosis of IVNC is usually made by echocardiography according to the criteria defined by Jenni et al. [13]: a) absence of coexisting cardiac abnormalities; b) segmental thickening of the left ventricular myocardial wall consisting of two layers: a thin compacted epicardial layer and a much thicker non-compacted endocardial layer having prominent trabeculations and deep recesses bearing an end-systolic ratio of non-compacted to compacted layers of > 2; c) predominant localization of the pathology in the apical and mid-lateral or mid-inferior regions of the left ventricle; and d) color Doppler evidence of deep-

Figure 1. Apical four-chamber view of the left ventricle showing prominent trabeculations with deep intertrabecular recesses in the apex and a ratio of non-compacted ("NC") to compacted ("C") myocardium › 2

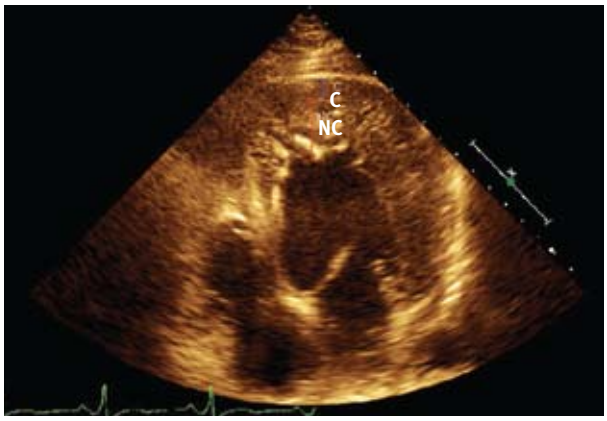


Figure 2. Apical four-chamber color Doppler view of the left ventricle showing blood flow into the deep recesses in the apex in the same patient

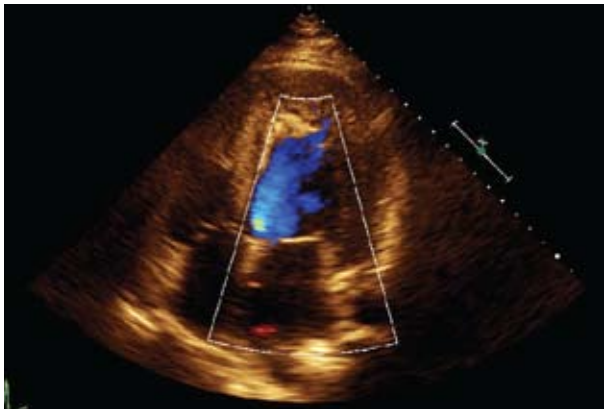
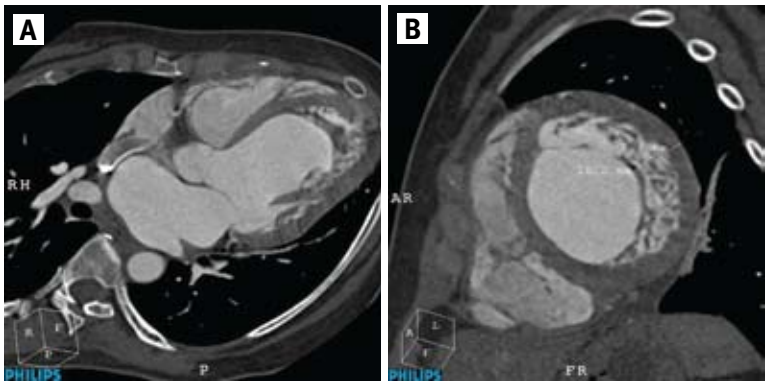


Figure 3. Sixty-four-slice multidetector CT coronary angiography showing enlarged left and right ventricles with a marked increase in the non-compacted layer of myocardium, such that the ratio of compacted to non-compacted myocardium at the apical area was › 3, consistent with LV non-compaction. **[A]** Four-chamber multiplanar reformation, **[B]** Short axis multiplanar reformation



perfused intertrabecular recesses. Figures 1 and 2 demonstrate two typical echocardiographic views of IVNC in a 48 year old patient who presented with fatigue and dyspnea. The ratio of the non-compacted to compacted myocardial layers at the site of maximal wall thickness was 2.5. Color Doppler flow [Figure 2] shows direct blood flow from the ventricular cavity into the spaces between the prominent trabeculations throughout the cardiac cycle.

Other imaging methods including computed tomography and magnetic resonance imaging are employed less frequently and demonstrate prominent trabeculations and intertrabecular recesses, distinguishable from characteristics of the outer compacted layer of the myocardium. They are useful for differentiating IVNC from arrhythmogenic right ventricular dysplasia and endomyocardial fibroelastosis, or apical thrombus especially when echocardiographic windows are limited [14]. When performing MRI, the best distinguishing feature of IVNC from the prominent trabeculations occasionally observed in healthy individuals, patients with hypertrophic cardiomyopathy, and patients with dilated cardiomyopathy was found to be an end-diastolic ratio between non-compacted and compacted myocardium > 2.3 [15]. Figure 3 shows the dramatic CT appearance of IVNC in a 39 year old patient who was admitted to our department with acute heart failure presenting with dyspnea and was found to have dilated cardiomyopathy with severely reduced left ventricular ejection fraction. The CT angiography images demonstrate severe dilation of the left and right ventricles, with heavy trabeculations at the left ventricular wall, which were more than threefold thicker than the adjacent myocardium, most prominent in the apical area, consistent with the diagnosis of IVNC. An additional advantage of the CT examination is that it can exclude coronary artery disease and thus ischemic cardiomyopathy as an alternative etiology of the recently diagnosed dilated cardiomyopathy. In a comparative imaging study, both CT and MRI were superior to echocardiography in recognizing distribution of the non-compacted myocardium in the ventricle, since they revealed the areas of non-compaction to be more prominent in length, more frequent in number, more complex in terms of the trabecular network, and more widely distributed than in dilated cardiomyopathy [14].

Isolated ventricular non-compaction is a rare underdiagnosed distinct congenital cardiomyopathy

CLINICAL PRESENTATION AND THERAPEUTIC CONSIDERATIONS

Several cohort series and registries describing the various clinical manifestations in IVNC series have been published in

recent years [3-5,16-18]. Heart failure is primarily due to systolic dysfunction, and the leading symptom is dyspnea. Other common symptoms include arrhythmias such as ventricular tachycardia and atrial fibrillation, and systemic thromboembolic events. The most frequent electrocardiocardiographic abnormality is left bundle brunch block, reported in up to 56% of cases [16].

In the aforementioned patient series, the reported frequency of ventricular tachycardia ranged from 6% in an Italian follow-up series of 65 patients for a mean of 46 months [18] to 41% in a Swiss series of 32 patients with a mean follow-up of 44 months [16]. In a small retrospective study of 12 patients with IVNC who were treated with an implantable cardioverter defibrillator during a median follow-up of 36 months, 5 patients (42%) presented with appropriate ICD therapy: in 4 of the 8 patients (50%) in whom the ICD was implanted as a secondary prevention and in 1 of the 4 patients (25%) for whom the ICD was implanted for primary prevention [19]. In contrast to these studies, in a large Italian series of 238 consecutive patients with IVNC in whom periodic Holter monitoring was performed every 6 months for 4 years, only 4.2% of patients had documented ventricular arrhythmias, of whom only two had sustained ventricular tachycardia [20]. Thus, until further data are available, the indications for ICD implantation should probably be similar to those for dilated cardiomyopathy. Nevertheless, it should be mentioned that the present ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm do recommend placement of an ICD as a "reasonable strategy" to reduce the risk of sudden cardiac death in IVNC, although they are based on previous observational data only and do not take into account this newer Italian study [21].

Despite previous reports, recent studies suggest that the long-term prognosis is better than initially reported, and treatment principles do not differ significantly from those in other cases of congestive heart failure

The importance of diagnosing this cardiomyopathy lies especially in asymptomatic patients, screening relatives of index cases in order to focus on their follow-up, and searching for criteria warranting prophylactic anticoagulation, ICD and anti-remodeling drugs

Systemic thromboembolic complications can be a serious source of morbidity: cerebrovascular accidents, transient ischemic attacks and mesenteric infarction were described in 24% of the Swiss cohort by Oechslin and co-authors [16] in contrast to only 4% in a study cohort comprising 45 patients during 10 years of follow-up described by Murphy et al. [4]. This discrepancy could be accounted for by a high proportion of patients (60%) receiving long-term oral anticoagulation in Murphy's study. In a retrospective study that assessed the risk of thromboembolism in patients with IVNC matched with control patients with regard to age, gender and left ventricular dysfunction, the number of stroke or embolic events was not increased in the IVNC group [22]. Thus, it would seem that long-term prophylaxis with oral anticoagulants is justified mainly in patients with systolic dysfunction, atrial fibrillation, or a history of previous embolic events.

In the study by Oechslin and team [16], poor prognostic factors included the development of atrial fibrillation, bundle brunch block, dilated LV end-diastolic diameter and New York Heart Association class III-IV. A ratio of non-compacted to compacted myocardium greater than 3 and involvement of three or more segments were found in another study [17] to be associated with poor prognosis [3] and LV dysfunction.

In conclusion, IVNC is a peculiar entity that should be specifically sought for when evaluating patients with heart failure and especially those with dilated or hypertrophic cardiomyopathy. Despite previous reports, recent studies suggest that the long-term prognosis is better than initially reported, and treatment principles do not differ significantly from those in other cases of congestive heart failure. In cases of decreased systolic function, the cornerstone of treatment should include angiotensin-converting enzyme inhibitors and beta-blockers. The additional benefit in diagnosing this cardiomyopathy lies especially in asymptomatic patients, screening relatives of index cases in order to focus on their follow-up, and searching for criteria warranting prophylactic anticoagulation, ICD implantation and anti-remodeling drugs such as ACE inhibitors.

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ICD = implantable cardioverter defibrillator
ACC/AHA/HRS = American College of Cardiology/American Heart Association/Heart Rhythm Society

LV = left ventricular
ACE = angiotensin-converting enzyme

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