Progress in Cardiovascular Diseases 52 (2010) 264–273
www.onlinepcd.com

Left Ventricular Noncompaction

Radha J. Sarma[a,*], Amar Chana[b], Uri Elkayam[c]

[a]*ABIM, Internal Medicine and Cardiovascular Diseases, University of Southern California, Keck School of Medicine, Division of Cardiovascular Medicine, Los Angeles County + USC Medical Center, Los Angeles, CA 90033, USA*
[b]*Cardiovascular Medicine, University of Southern California, Keck School of Medicine, Los Angeles County + USC Medical Center, Los Angeles, CA 90033, USA*
[c]*University of Southern California, Keck School of Medicine, Division of Cardiovascular Medicine, Los Angeles County + USC Medical Center, Los Angeles, CA 90033, USA*

Abstract According to the World Health Organization classification of cardiomyopathies, left ventricular noncompaction is still an unclassified cardiomyopathy. In 2006, the American Heart Association classified this entity as a primary cardiomyopathy of genetic origin. In 2008, the European Society of Cardiology updated the classification scheme similar to the World Health Organization classification. At present, there is no consensus on the diagnostic criteria, and diagnosis is based on the morphologic features identified by cardiac imaging studies or at autopsy. Due to lack of standardization of the diagnostic criteria and little awareness of this condition among clinicians, the true prevalence of this disease is not clear. There is no specific therapy for this condition. However, it seems prognosis is much better than initially reported. The current status of diagnosis, prognosis, and management of isolated noncompaction in adults is discussed in this review. (Prog Cardiovasc Dis 2010;52:264-273)

Keywords: Noncompaction; Hypertrabeculation; Cardiomyopathy; Echocardiography; Pregnancy

Left ventricular noncompaction (LVNC) is a congenital cardiomyopathy characterized by a distinctive spongy appearance of the myocardium, due to increased trabeculation and deep intertrabecular recesses that communicate with the left ventricular cavity. After the first case of isolated LVNC was reported by Engberding and Bender[1] 25 years ago, much has been published about this entity. The first case series with echocardiographic quantitative criteria was reported by Chin et al[2] in 1990, followed by the first 10-year observational study by Ritter et al[3] in 1996. In 2006, LVNC was classified as a primary cardiomyopathy of genetic origin by the American Heart Association (AHA).[4] This review will focus on isolated LVNC in the adult population.

Epidemiology

The true prevalence of LVNC remains unclear at this time and varies considerably depending on the patient population sampled.[5,6] One study[7] in which 14 years of echocardiograms was reviewed, 34 patients with LVNC were identified and the prevalence of LVNC was found to be 0.014%. In another study conducted for 4.5 years[8] in which 57 cases of LVNC were identified using echocardiographic criteria, the prevalence was found to be 0.14%. Several other studies[3,5,9,10] have determined the prevalence to be between 0.05% and 0.24%. The age at presentation is extremely variable. There have been at least 2 cases diagnosed in utero,[11,12] and the oldest patient diagnosed with LVNC was 94 years old at presentation.[13] In an extensive review of case reports published including 223 patients,[5] the age at presentation spanned the spectrum and showed no predilection for a specific age. What has become clear in almost all studies is that LVNC seems to affect more males than females. In a few large series,[2,3,6,7] 56% to 82% of cases

Statement of Conflict of Interest: see page 271.

* Address reprint requests to Radha J. Sarma, MBBS, 1200 North State Street, Unit 1, Room 7431, Los Angeles County + USC Medical Center, Los Angeles, CA 90033.
E-mail address: sarma@usc.edu (R.J. Sarma).

0033-0620/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.pcad.2009.11.001

Abbreviations and Acronyms

ACC = American College of Cardiology

AF = atrial fibrillation

AHA = American Heart Association

C = compact

CMR = cardiac magnetic resonance

CRT = cardiac resynchronization therapy

CT = computed tomography

ICD = implantable cardioverter-defibrillator

LV = left ventricular

LVNC = left ventricular noncompaction

NC = noncompacted

NYHA = New York Heart Association

were male. Because there is a lack of widespread knowledge of LVNC among clinical echocardiographers, Left ventricular noncompaction may often go undiagnosed or misdiagnosed as another type of cardiomyopathy, most often hypertrophic or dilated cardiomyopathy. Even among those familiar with LVNC, the diagnosis can be difficult if the images are suboptimal. As patients typically undergo echocardiography for abnormal signs and symptoms, there is inherent selection bias that can artificially alter the prevalence of the disease. Also, because larger series are often conducted at tertiary care facilities, referral bias can also complicate the picture.

Genetics

Elucidating a genetic basis for the phenotypic expression of LVNC has been difficult because both familial and sporadic forms have been described. It seems that the pediatric presentation may have a distinct genetic basis as compared with the adult presentation. Different genes found to be associated with LVNC are (1) taffazin, (2) β-dystrobrevin (DTNA), (3) Cypher/ZASP (LDB3), (4) lamin A/C (LMNA), (5) SCN5A, (6) MYH7, and (8) MYBPC3.[14] There is also significant overlap in the phenotypes of the genetically mediated cardiomyopathies. Thus, LVNC can occur with dilated or hypertrophic cardiomyopathy.[15] Although further research is needed to elucidate the genetic basis of LVNC, at this time, it seems clear that there is considerable genetic heterogeneity involved.[14,16] In 3 of the largest series of patients, the rate of familial involvement was 18%, 25%, and 33%.[7,8,16] Although genetic testing is not routinely recommended at this time, the Heart Failure Society of America practice guidelines[17] recommend clinical screening of all first-degree relatives of affected patients for LVNC. Genetic testing is to be considered for affected patients with a firm diagnosis of LVNC to help with family screening.[17]

Embryology, anatomic pathology, and histology

During the early development of the myocardium before the formation of coronary arteries, the myocardium is a loose meshwork of trabeculations and deep recesses. Between the fifth and eighth week in the normal heart, the myocardium is compacted and the epicardial coronary arteries are formed.[18] The left ventricular myocardium is more compact than the right ventricular myocardium, which is more trabeculated even

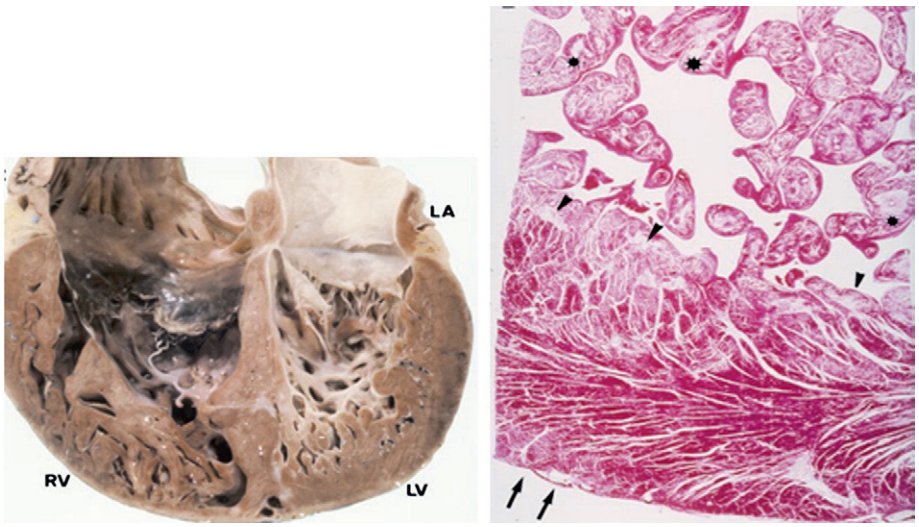

Fig 1. Left: transsectional view from the anterior on the dorsal half of the heart of a 21-year-old man. There are both numerous trabeculations and deep recesses. Note the marked fibroelastosis of the LV. Right: transmural, histologic section (hematoxylin and eosin stain). There are both an epicardial (compacted) layer (arrows) and an endocardial (noncompacted) layer. Note the necrosis within the trabeculations (asterisks) as well as in the subendocardial area but not in the epicardial zone (arrowheads). *Abbreviations*: LA indicates left atrium; RV, right ventricle. Reproduced with permission from Elsevier, JACC 36, No. 2, 2000.

in the adult life. It is commonly believed that LVNC is due to an arrest of this normal "compaction,"[2,19,20] a theory supported by Freedom et al,[18] who have shown stark similarities between the developing heart and hearts affected by LVNC. In contrast, Bleyl et al[21] described 3 cases in which intrauterine echocardiography did not show noncompaction in the infants who were later diagnosed to have LVNC. In addition, several other investigators have reported cases of so-called acquired LVNC,[19,22,23] All these reports call into question the assumption that LVNC is due to an arrest in normal myocardial development.[10,21,24] Boyd et al[25] examined 474 normal hearts at autopsy and found 68% of them to have up to 3 trabeculations in the left ventricle (LV). The trabeculated endocardial layer of normal hearts is never thicker than the compact myocardium. In LVNC, the trabeculations are excessive in number and the trabeculated endocardial layer is at least 2 times thicker than the compacted layer[2,5,7,26] (Fig 1). The trabeculations are usually muscle bundles covered by the same endocardium that lines the left ventricular cavity. Those trabeculations communicate with the ventricular cavity but not with the epicardial coronary arteries. They are most frequently near the apex and gradually decrease up to the papillary muscles, which are not well formed.[27] Trabeculations are rare in the basal segments of the ventricle. Histological examination again shows the multiple trabeculations with deep intertrabecular recesses and the thin compact epicardial layer separated by a thin fibrous band of tissue[26-28] (Fig 1).

Clinical presentation: signs and symptoms

Patients may present at any age from infancy to older than 94 years.[13] Males seem to be more commonly affected than do females. Symptomatic presentation of patients with isolated LVNC varies widely with some patients remaining asymptomatic for many years, whereas others develop symptoms very early in childhood.[6,29,30] Asymptomatic individuals may be diagnosed with LVNC either during family screening or after an incidental diagnostic test such as an echocardiogram.[31,32] One group of investigators[5,33,34] reported associated neuromuscular disorders and facial dysmorphism in more than 50% of patients with LVNC, whereas others did not find such association.[19,35] Symptoms are mainly due to left ventricular systolic dysfunction, arrhythmias, and thromboembolic complications. In most patients with left ventricular systolic dysfunction, dyspnea seems to be the most common presenting symptom. Other major symptoms include chest pain, palpitations, syncope, cerebrovascular accidents, and other systemic or pulmonary embolic complications. Sudden death is not uncommon in this group because of malignant ventricular arrhythmias. The frequency of these symptoms is variable with wide ranges in the published literature.

Electrocardiogram

Electrocardiogram abnormalities are common in LVNC and include mostly ST-T wave changes, left ventricular hypertrophy,[36,37] left bundle branch block (21%-44%),[3,7,8,38-40] complete atrioventricular block,[41-43] atrial fibrillation (AF; 7%-26%),[7,8,36,38,39] ventricular ectopic beats, ventricular tachycardia (4.2%-30%),[44-47] or ventricular fibrillation. Case reports of giant P waves[48] and persistent atrial standstill with junctional rhythm[49] have been published. Wolff Parkinson White pattern is more common in children and infrequent in adults.[19] Serial Holter monitoring of 238 patients every 6 months for 4 years detected 9 patients with AF[50] and 11 patients with ventricular tachycardia.[46]

Diagnosis

The diagnosis of LVNC is mostly based on the morphologic features of the LV.[2,5,7,51,52] Echocardiography has been the routine initial noninvasive diagnostic test to detect LVNC and is still the diagnostic test of choice.[26,53,54] When the transthoracic echocardiogram is not satisfactory, contrast echocardiography,[55,56] transesophageal echocardiography,[57] and real time 3-dimensional echocardiography[58-60] are also useful in diagnosing LVNC. With the advancement of echocardiographic technology, image quality has significantly improved the resolution of the finer details of the trabeculations, with results that seem very close to what was reported in pathologic studies.[54] Cardiac magnetic resonance (CMR)

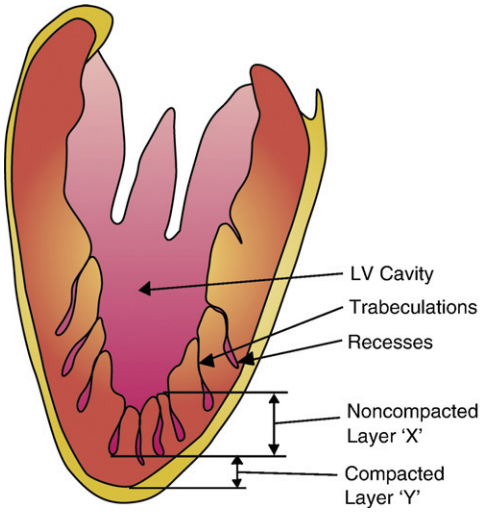

Fig 2. Artist's rendering of LVNC.

imaging[61-63] has also been validated in small number of patients and at times may be complimentary or even superior[64] to echocardiography in establishing the diagnosis. Computed tomography (CT) has been found to be useful in a limited number of cases.[65-67] Among invasive tests, contrast left ventriculography,[68] video angioscopy,[69] and endoscopy[70] have been used to establish the diagnosis. Finally, a diagnosis of LVNC may be made or confirmed from an explanted heart, or at autopsy.[26,27,71] Unless the physicians are aware of this particular morphologic pattern, they may misdiagnose the condition as dilated or hypertrophic cardiomyopathy.

Echocardiography

Typically, the echocardiogram shows a 2-layered appearance of the myocardium (an outer thin compact layer and a noncompact trabeculated thick endocardial layer), with deep intertrabecular spaces mostly near the left ventricular apex below the papillary muscle level. A schematic of this is shown in Fig 2. Systolic and diastolic function abnormalities may be seen frequently in the symptomatic patients. At the present time, there is no consensus on the echocardiographic criteria for the diagnosis of LVNC. The 3 most widely used diagnostic criteria are (1) the ratio of compact layer to total thickness of the LV less than 0.5, measured at end diastole from the parasternal short axis view or the apical views (Chin et al[2]); (2) a 2-layer structure of the LV, ratio of noncompacted (NC) to compact (C) layer of more than 2 in the parasternal short axis view, at end systole; absence of other coexisting cardiac structural abnormalities plus numerous excessively prominent trabeculations and deep intertrabecular spaces; recesses perfused by intraventricular blood as seen on the color Doppler imaging (Fig 3; Jenni et al[26]); (3) more than 3 trabeculations protruding from the left ventricular free wall apically to the papillary muscles seen on 1 imaging plane; intertrabecular spaces perfused from the left ventricular cavity shown by the color Doppler (Stollberger et al[10]). Although the criteria of Stollberger et al[10] are more qualitative without reference to the cardiac cycle, the other 2 from other studies[2,26] are more quantitative but differ as to when the measurements are made, at end systole[26] or end diastole.[2] Kohli et al[52] applied the 3 echo criteria described above to 199 patients referred to their heart failure clinic, and 47 of those patients satisfied at least 1 of the criteria for LVNC; 78.7% of patients fulfilled the criteria suggested by Chin et al,[2] 63.8% by Jenni et al,[26], and 53.2% by Stollberger et al.[10] Only 29.8% of patients fulfilled all 3 criteria. A high proportion of the healthy black control subjects also satisfied the criteria for LVNC (4/30 blacks versus 1/30 nonblacks). The authors are concerned that the echocardiographic criteria may be too sensitive and result in overdiagnosis of LVNC.[52] An additional difficulty in making a definitive diagnosis is the morphologic changes in the same patient over time.[22] Finsterer and Stollberger[72] proposed to combine and categorize the criteria by Jenni and Stollberger to diagnose LVNC as (1) possible, (2) probable, or (3) definite, based on the number of criteria present. Another classification scheme ranging from none, mild moderate, or severe LVNC, based on the NC/C ratio ranging from 0 to more than 2, and the area of noncompaction ranging from 0 to more than 5 cm^2 has recently been proposed by Belanger et al.[73]

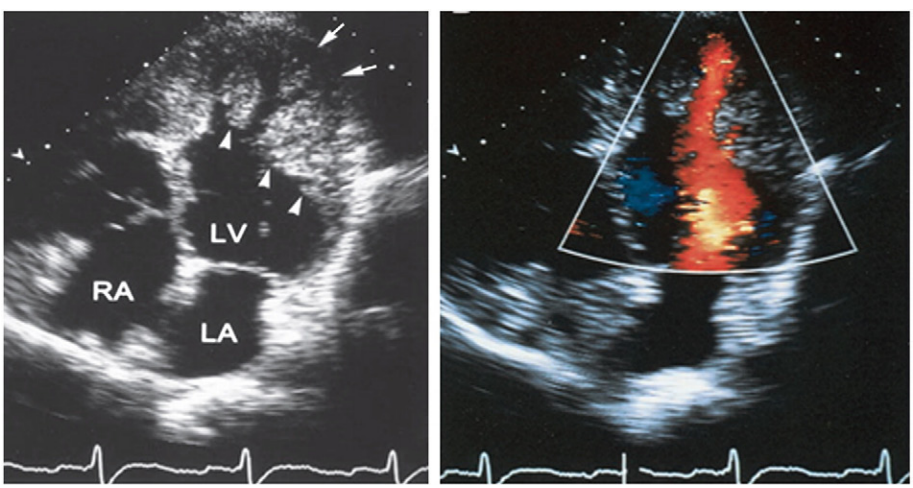

Fig 3. Left: Apical 4 chamber view of a 2-dimensional echocardiogram of a patient with LVNC. There is a thin epicardial layer (thin arrows) and an extremely thickened endocardial layer with prominent trabeculations and deep recesses (arrowheads). Right: apical 4-chamber view (end-diastolic still frame) of the same patient. There is blood flow from the ventricular cavity into the deep recesses visualized on color Doppler imaging. Reproduced with permission from Elsevier, JACC 36, No. 2, 2000).

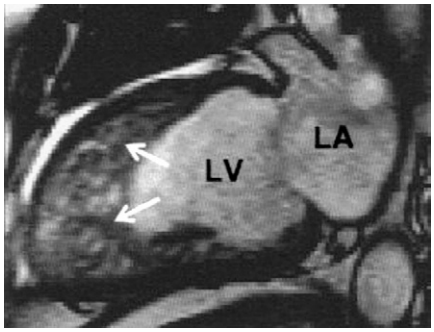

Fig 4. Cardiac magnetic resonance image of the LV showing prominent muscular trabeculations (white arrows) with deep intertrabecular recesses. *Abbreviations:* LA indicates left atrium. Reproduced with permission from the Oxford Press, European Journal of Cardiology, doi: 10.1093/eurheart/ehm625.

CMR and cardiac CT imaging

Petersen et al[61] used CMR to study 7 patients with clinically documented LVNC and compared the results with healthy volunteers, athletes, and patients with hypertrophic cardiomyopathy, dilated cardiomyopathy and aortic stenosis, in order to establish specific diagnostic criteria for pathologic noncompaction. They found a ratio between the trabecular and compact layers greater than 2.3, measured at end diastole, to be accurate in diagnosing LVNC. In addition, the end-diastolic NC/C ratio was on average at least 60% greater in the LVNC patients compared with the other groups. Video image of a CMR study is available online (Video 1, Fig 4). There are few case reports where CMR established the diagnosis of LVNC when echocardiogram did not correctly identify the condition,[64,74] or the diagnosis was incidental when the study was evaluating other indications. In addition to its diagnostic value, CMR is also useful in detecting delayed hyperenhancement, which correlates with the degree of subendocardial fibrosis.[63,75] The usefulness of CT in detecting LVNC has been reported in a few cases.[65,66] Additional information on the coronary arteries is of added value when the CT angiography is performed.

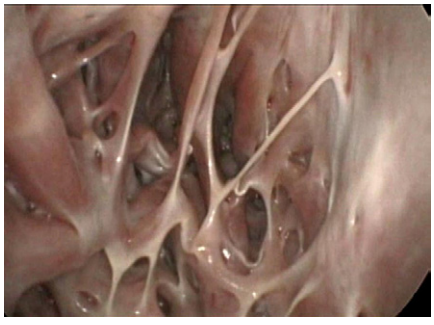

Fig 5. Video angioscopy of the LV showing the spongy myocardium. Reproduced with permission from the Oxford Press, European Journal of Cardiology, doi:10.1093/eurheart/ehm625.

Invasive diagnostic tests

Contrast left ventriculography shows typical deep intertrabecular recesses and spongy pattern of the cavity.[68] Video angioscopy[69] (Video 2, Fig 5) and intraoperative endoscopy[70] of the LV were also reported to clearly identify the deep trabeculations and recesses, which communicate with the left ventricular cavity.

Management of isolated LVNC

Asymptomatic subjects with LVNC diagnosed by family screening or have the diagnosis made incidentally after an echocardiogram[31] or other diagnostic tests and who have normal left ventricular systolic function do not need treatment but need to be followed. This is supported by the experience of 238 asymptomatic patients with LVNC followed for 6 years by Fazio et al[76] and Corrado et al[77] in the Italian Registry; none of them developed any symptoms of heart failure. However, all symptomatic patients should be followed closely. Although genetic testing is not recommended at this time because of the uncertainty of the genetic tests available, the Heart Failure Society of America recommends screening first-degree relatives with echocardiography and obtaining family history up to 3 or more generations.[17] Repeat clinical screening also was recommended every 3 years. These recommendations are similar to those reported by Robin et al.[78]

Heart failure

Incidence of New York Heart Association (NYHA) class I/II heart failure in 65% and class III/IV in 35% has been reported by Oechslin et al[7] in their 34 patients. Lofiego et al[38] reported heart failure in 83% (40 of 48) and NYHA class III/IV heart failure in 44% (21 of 48) of their patients. Higher incidence of heart failure has been reported in adults compared with pediatric population.[19] Incidental and familial cases without symptoms have a lower incidence of heart failure, 2% compared with 61% of symptomatic patients with LVNC.[79] Conventional therapy per the American College of Cardiology (ACC)/AHA guidelines[80] is recommended for patients with LVNC and heart failure. β-Blockers,[81] angiotensin-converting enzyme inhibitors, and diuretics are the main stay of therapy in symptomatic patients with LV systolic dysfunction. Digitalis, aldosterone inhibitors, and vasodilators are also used as needed. When heart failure progresses despite maximum medical therapy, device-based therapy has been recommended.[82] Cardiac resynchronization therapy (CRT) with or without an implantable cardioverter defibrillator (ICD) is a class I recommendation for those patients with symptomatic heart failure, NYHA functional class III, or

ambulatory class IV while on optimal medical therapy, left ventricular ejection fraction less than 35% and QRS duration more than 0.12 seconds. Stollberger et al[83] reported improvement of functional capacity in all the 8 patients who received CRT and improved systolic function in half of the patients at a mean follow-up of 39 months (range, 4-68 months). Another group from Japan[84] reported their experience with 4 cases of LVNC with refractory heart failure who had CRT-D or CRT-P followed for 28 ± 23 months. They found improvement in cardiothoracic ratio, B-type natriuretic peptide level, LV systolic dimension, and ejection fraction. They did not notice any defibrillator shocks in the patients with CRT-D. Cardiac resynchronization therapy therefore seems to be beneficial in patients with LVNC and should be considered in appropriate patients. Stollberger et al[85] reported a decrease in the trabeculations with improvement in left ventricular systolic function after biventricular pacing, on a follow-up echocardiogram. Improvement in heart failure after medical therapy was also associated with improved left ventricular function and decrease in the degree of noncompaction 6 months after the initial CMR.[86] If heart failure is refractory to intensive medical management, surgery should be considered. There have been several case reports of successful heart transplantation in patients with LVNC[3,7,38,87-90] and a favorable outcome at 2 to 2.5 years.[89,90] There is 1 case report of removal of left ventricular thrombi, mitral, and tricuspid annuloplasty along with left ventricular restoration surgery[91] with good results. Surgery for valve replacement and coronary artery disease should be considered based on the ACC/AHA guidelines. One case of aorto-left ventricular tunnel was repaired using the Amplatzer occlusion device.[92]

Supraventricular arrhythmias

Atrial fibrillation is a common arrhythmia in patients with LVNC, with a reported incidence between 7%[39] and 26%.[7] Kobza et al[47] reported supraventricular arrhythmias in 8 of their 12 patients during interrogation of the ICDs. There is no specific treatment for patients with LVNC, and reported drug therapy included digoxin, β-blockers, calcium channel blockers, and amiodarone. Radiofrequency ablation has been successful in a case with atrioventricular nodal reentry tachycardia.[93] The ACC/AHA/European Society of Cardiology (ESC) guidelines for the management of patients with AF[94] are useful in the management patients with LVNC and AF. Other supraventricular arrhythmias may also be treated using standard recommended therapy.

Ventricular arrhythmias

Incidence of ventricular arrhythmias in patients with LVNC has been reported to be as high as 62%[2] to as low as 6%.[38] Patients with sustained ventricular tachycardia or ventricular fibrillation had ICD implantation. Radiofrequency ablation was reported to be useful in few cases.[95-97] Kobza et al[47] reported their experience with 12 patients

Table 1
Pregnancy in patients with LVNC

Author	Age (y)	Presentation	Delivery	Comments
Williams[102]	28	3rd pregnancy; 22 wk with heart failure	Cesarean section at 36 wk; baby was healthy	Echo showed LVNC and low EF; 10 d postpartum had VT and later got an ICD. Previous 2 pregnancies were uneventful.
Kitao et al[103]	Not given	1st pregnancy. Heart failure and fetal hydrops	Emergency cesarean section	Echo showed LVNC and low EF; baby died 2 d later and autopsy showed LVNC.
Uesugi et al[104]	Not given	1st pregnancy at 24 wk in heart failure. 2nd pregnancy 2 y later	Cesarean section using propofol and fentanyl; cesarean section under spinal anesthesia	Patient with known LVNC. Both deliveries were uneventful.
Munehisa et al[105]	24	1st pregnancy at 5 wk; 2nd pregnancy monitored from the start	Miscarriage; cesarean section at 32 wk	Heart failure at age 4 mo. Echo at 1st pregnancy showed LVNC; BNP elevated during pregnancy. Family screening of patient's mother and baby also showed LVNC on echo.
Patel[106]	26	1st pregnancy preeclampsia; 2nd pregnancy 31 wk	Labor induced at 35 wk; labor induced at 37 wk	Tracheoesophageal fistula repair at age 9; repeated pneumonias; echo at 2nd pregnancy showed LVNC and EF <20%; RF ablation of atrial flutter and ventricular tachycardia performed 2 mo postpartum
Patel[106]	14	1st pregnancy; presented at 36 wk in pulmonary edema	Emergency cesarean section	Complicated course due to sickle cell trait and anemia, streptococcal positive blood cultures, gonorrhea; echo LVNC and EF 17%
Kobza et al[47]	Not given	No details	Cesarean section; baby was healthy	Patient with LVNC and had an ICD implanted 33 mo before the cesarean section; no arrhythmias on Holter during pregnancy

Abbreviations: BNP indicates B type natriuretic peptide; EF, left ventricular ejection fraction; RF, radiofrequency; VT, ventricular tachycardia.

with ICDs followed for 3 years; appropriate shocks were detected in 42% of the patients; 1 patient needed heart transplant 4 months post-ICD; 1 female patient had a successful pregnancy and delivered a healthy baby by caesarian section, 33 months after the implantation of an ICD. There are many case reports on ICD implants in patients with LVNC for ventricular arrhythmias both for primary and secondary prevention of sudden death with favorable results. Patients with LVNC should be closely followed for ventricular arrhythmias. According to the Device Based Therapy guidelines,[82] implantation of ICD for the prevention of sudden death in patients with LVNC is a class IIb recommendation. Medical therapy of ventricular arrhythmias in LVNC is the same as for other patients with ventricular arrhythmias.[98]

Treatment of heart block

Complete heart block has been reported in several patients with LVNC.[41-43] Pacemaker therapy using the current ACC/AHA/Heart Rhythm Society (HRS) guidelines[82] seems appropriate for these patients. A case of persistent atrial standstill with no P waves on electrocardiogram, and normal ventricular rate has been reported in 1 patient with LVNC[49] who did not need any therapy. Follow-up was uneventful at 1 year.

Thromboembolic complications

Systemic thromboembolic complications are the third major complication in LVNC. In the presence of AF and left ventricular systolic dysfunction, the thromboembolic risk is high.[99] Systemic embolic events including cerebrovascular accidents, transient ischemic attacks, embolism to coronary, and superior mesenteric arteries have been reported.[2,3,7,8,38,99,100] Although left ventricular thrombus formation in noncompaction is rare according to the review of 22 articles by Stollberger et al,[99] reported incidence of thromboembolic complications ranges from 5% to 38%.[2,3,7,8,38,99,100] Routine anticoagulation with warfarin has therefore been recommended by few, whereas others reported using anticoagulation therapy in high-risk individuals with LVNC.[99,101]

Pregnancy and LVNC

Pregnancy and child birth usually can be managed successfully in patients with LVNC as in other cardiac conditions if the diagnosis is made early in the pregnancy and appropriate interventions are carried out. There are few case reports of pregnancy in patients with LVNC[102-107] (Table 1). Because some of the babies may also have LVNC, it is important to obtain echocardiograms.

Prognosis

As expected, the prognosis of asymptomatic individuals with LVNC seems to be much better than those with symptoms.[77] Left ventricular ejection fraction les than 31% has been reported to have a 71% sensitivity and 90% specificity to predict major adverse events; left atrial dilatation more than 40 mm is also associated with poor prognosis.[77] Another group reported 22% mortality during a 51-month follow-up; advanced age, associated neuromuscular disorders, heart failure with dilated LV, and decreased ejection fraction were all associated with higher mortality.[34] Atrial fibrillation with or without neuromuscular disease was associated with poor prognosis.[36] It should be noted that prognosis seems to be more favorable in the recent compared with the early reports. This may be related to (1) aggressive medical management of patients with heart failure, arrhythmias, and thromboembolic events; (2) better and more easily available diagnostic testing resulting in a broader spectrum of patients, which includes asymptomatic individuals with the morphologic diagnosis of LVNC; and (3) the patient groups in the later reports include both symptomatic and asymptomatic individuals with much better prognosis than in the earlier reports, which included mostly symptomatic patients with some degree of complications.

Future goals to further understand LVNC

High priority should be given to establishing standard nomenclature and diagnostic criteria for future research.[52,108,109] Genetic testing of the most clinically affected individuals, echocardiographic, or CMR screening of all first-degree relatives and obtaining family history for at least 3 generations need to be implemented in clinical practice to further understand the influence of genetic mechanisms in this disorder. The yield of systematic family screening is variable.[7,8,16] Murphy et al[39] identified 8 affected relatives from 32 patients. Fazio et al[79] identified 48 affected relatives from 31 patients. Serial follow-up studies of affected individuals might help elucidate the changing morphology noted after medial therapy or biventricular pacing. The association of neuromuscular diseases and LVNC also needs further research to identify the mechanisms involved in such association. Finally, the clinicians, imaging specialists, geneticists, and pathologists all need to contribute scientific knowledge to define this elusive entity called "ventricular noncompaction."[108-112]

Acknowledgments

The authors are grateful to Shubhodeep Das for his artistic rendering of the LVNC and to Bhargav Dronamraju and Anita Peddada for making the video clips and still

images for this manuscript. They also appreciate the contribution of the very unique video-angioscopic images by Dr Steffen Schoen and the generous permission by Oxford University Press, the publishers of the European Heart Journal.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pcad.2009.11.001.

References

1. Engberding R, Bender F: Echocardiographic detection of persistent myocardial sinusoids. Z Kardiol 1984;73:786-788.
2. Chin TK, Perloff JK, Williams RG, et al: Isolated noncompaction of left ventricular myocardium. A study of eight cases. Circulation 1990;82:507-513.
3. Ritter M, Oechslin E, Sutsch G, et al: Isolated noncompaction of the myocardium in adults. Mayo Clin Proc 1997;72:26-31.
4. Maron BJ, Towbin JA, Thiene G, et al: Contemporary definition and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 2006;113:1807-1816.
5. Stollberger C, Finsterer J: Left ventricular hypertrabeculation/noncompaction. J Am Soc Echocardiogr 2004;17:91-100.
6. Ichida F, Hamamichi Y, Miyawaki T, et al: Clinical features of isolated noncompaction of the ventricular myocardium: long-term clinical course, hemodynamic properties, and genetic background. J Am Coll Cardiol 1999;34:233-240.
7. Oechslin E, Attenhofer Jost C, Rojas J, et al: Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. J Am Coll Cardiol 2000;36:493-500.
8. Aras D, Tufekcioglu O, Erfun K, et al: Clinical features of isolated ventricular noncompaction in adults long-term clinical course, echocardiographic properties, and predictors of left ventricular failure. J Card Fail 2006;12:726-733.
9. Stollberger C, Finsterer J, Blazek G: Isolated left ventricular abnormal trabeculation is a cardiac manifestation of neuromuscular disorders. Cardiology 2000;94:72-76.
10. Stollberger C, Finsterer J, Blazek G: Left ventricular hypertrabeculation/noncompaction and association with additional cardiac abnormalities and neuromuscular disorders. Am J Cardiol 2002;90:899-902.
11. McCaffrey F: Around Pediheart: noncompaction of the left ventricle. Pediatr Cardiol 2001;22:399.
12. Winer N, Lefevre M, Nomballais MF, et al: Persisting spongy myocardium: a case indicating the difficulty of antenatal diagnosis. Fetal Diagn Ther 1998;13:227-232.
13. Sato Y, Matsumoto N, Matsuo S, et al: Isolated noncompaction of the ventricular myocardium in a 94-year-old patient: depiction at echocardiography and magnetic resonance imaging. Int J Cardiol 2007;119:e32-e34.
14. Zaragoza M, Arbustini E, Narula J: Noncompaction of the left ventricle: primary cardiolyopathy with an elusive genetic etiology. Curr Opin Pediatr 2007;19:619-627.
15. Biagini E, Ragni L, Ferlito M, et al: Different types of cardiomyopathy associated with isolated ventricular noncompaction. Am J Cardiol 2006;98:821-824.
16. Xing Y, Ichida F, Matsuoka T, et al: Genetic analysis in patients with left ventricular noncompaction and evidence for genetic heterogeneity. Mol Genet Metab 2006;88:71-77.
17. Hershberger R, Lindenfeld J, Mestroni L, et al: Genetic evaluation of cardiomyopathy—a Heart Failure Society of America Practice Guideline. J Card Fail 2009;15:83-97.
18. Freedom R, Yoo S, Perrin D, et al: The morphological spectrum of ventricular noncompaction. Cardiol Young 2005;15:345-364.
19. Ichida F: Left Ventricular Noncompaction. Circ J 2009;73:19-26.
20. Dusek J, Ostadal B, Duskova M: Postnatal persistence of spongy myocardium with embryonic blood supply. Arch Pathol 1975;99:312-317.
21. Bleyl SB, Mumford BR, Brown-Harrison MC, et al: Xq28-linked noncompaction of the ventricular myocardium: prenatal diagnosis and pathologic analysis of affected individuals. Am J Med Genet 1997;72:257-265.
22. Hofer M, Stollberger C, Finsterer J: Acquired noncompaction associated with myopathy. Int J Cardiol 2007;121:296-297.
23. Markovic N, Dimkovic N, Damjanovic T, et al: Isolated ventricular noncompaction in patients with chronic renal failure. Clin Nephrol 2008;70:72-76.
24. Weiford B, Subbarao V, Mulhern K: Noncompaction of the ventricular myocardium. Circulation 2004;109:2965-2971.
25. Boyd MT, Seward JB, Tajik AJ, et al: Frequency and location of prominent left ventricular trabeculations at autopsy in 474 normal human hearts: implications for evaluation of mural thrombi by two-dimensional echocardiography. J Am Coll Cardiol 1987;9:323-326.
26. Jenni R, Oechslin E, Schneider J, et al: Echocardiographic and pathoanatomical characteristics of isolated left ventricular noncompaction: a step towards classification as a distinct cardiomyopathy. Heart 2001;86:666-671.
27. Burke A, Mont E, Kutys R, et al: Left ventricular noncompaction: a pathological study of 14 cases. Hum Pathol 2005;36:403-411.
28. Finsterer J, Stollberger C, Feichtinger H: Histological appearance of left ventricular hypertrabeculation/noncompaction. Cardiology 2002;98:162-164.
29. Pignatelli RH, McMahon CJ, Dreyer WJ, et al: Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. Circulation 2003;108:2672-2678.
30. Jenni R, Oechlin E, van der Loo B: Isolated ventricular noncompaction of the myocardium in adults. Heart 2007;93:11-15.
31. Kim H, Chang S, Kim Y, et al: Fireworks in the left ventricle: doppler manifestation of left ventricular noncompaction. J Am Coll Cardiol 2009;53:2009.
32. Koh YY, Seo YU, Woo JJ, et al: Familial isolated noncompaction of the ventricular myocardium in asymptomatic phase. Yonsei Med J 2004;45:931-935.
33. Finsterer J, Stöllberger C, Blazek G: Neuromuscular implications in left ventricular hypertrabeculation/noncompaction. Int J Cardiol 2006;110:288-300.
34. Stöllberger C, Winkler-Dworak M, Blazek G, et al: Prognosis of left ventricular hypertrabeculation/noncompaction is dependent on

cardiac and neuromuscular comorbidity. Int J Cardiol 2007;121: 189-193.
35. Fazio G, Novo G, Visconti C, et al: Neuromuscular disorders and non compaction: how much is the strength of the association and how can it be suspected? Int J Cardiol 2009;136:215-216.
36. Stöllberger C, Blazek G, Winkler-Dworak M, et al: Atrial fibrillation in left ventricular noncompaction with and without neuromuscular disorders is associated with a poor prognosis. Int J Cardiol 2009;133:41-45.
37. Stöllberger C, Winkler-Dworak M, Blazek G, et al: Association of electrocardiographic abnormalities with cardiac findings and neuromuscular disorders in left ventricular hypertrabeculation/ noncompaction. Cardiology 2007;107:374-379.
38. Lofiego C, Biagini E, Pasquale F, et al: Wide spectrum of presentation and variable outcomes of isolated left ventricular non-compaction. Heart 2007;93:65-71.
39. Murphy RT, Thaman R, Gimeno Blanes J, et al: Natural history and familial characteristics of isolated left ventricular non-compaction. Eur Heart J 2005;24:187-192.
40. Stollberger C, Blazek G, Winkler-Dworak M, et al: Cardiac and neuromuscular implications of left bundle branch block in left ventricular hypertrabeculation/noncompaction. Can J Cardiol 2009; 25:e82-85.
41. Taniguchi M, Hioka T, Maekawa K, et al: Adult case of isolated noncompaction discovered by complete atrioventricular block. Circ J 2004;68:873-875.
42. Sajeev CG, Francis J, Shankar V, et al: Young male with isolated noncompaction of the ventricular myocardium presenting with atrial fibrillation and complete heart block. Int J Cardiol 2006;107: 142-143.
43. Yildiz A, Ozeke O, Akyol S, et al: Biventricular noncompaction presenting with complete atrioventricular block. Int J Cardiol 2009; 132:e34-e36.
44. Duru F, Candinas R: Noncompaction of ventricular myocardium and arrhythmias. J Cardiovasc Electrophysiol 2000;11:493-494.
45. Maile S, Kunz M, Oechslin E, et al: Intractable ventricular tachycardia and bridging to heart transplantation with a non-pulsatile flow assist device in a patient with isolated left ventricular non-compaction. J Heart Lung Transplant 2004;23:147-149.
46. Fazio G, Corrado G, Zachara E, et al: Ventricular tachycardia in non-compaction of left ventricle: Is this a frequent complication? PACE 2007;30:544-546.
47. Kobza R, Jenni R, Erne P, et al: Implantable cardioverter-defibrillators in patients with left ventricular noncompaction. PACE 2008;31:461-467.
48. Zhou Y, Zhang P, Zhou Q, et al: Giant P waves and focal atrial tachycardia in a patient with ventricular noncompaction. Int J Cardiol 2008;123:210-212.
49. El Menyar AA, Gendi SM: Persistent atrial standstill in non-compaction cardiomyopathy. Cardiology 2006;27:364-366.
50. Fazio G, Corrado G, Pizzuto C, et al: Supraventricular arrhythmias in noncompaction of left ventricle: is this a frequent complication? Int J Cardiol 2008;127:255-256.
51. Ramaraj R, Sorrell VL, Marcus F, et al: Recently defined cardiomyopathies: a clinician's update. Am J Med 2008;121:674-681.
52. Kohli S, Pantazis A, Shah J, et al: Diagnosis of left-ventricular non-compaction in patients with left-ventricular systolic dysfunction: time for a reappraisal of diagnostic criteria? Eur Heart J 2008;29: 89-95.
53. Frischknecht B, Attenhofer Jost C, Oechslin E, et al: Validation of noncompaction criteria in dilated cardiomyopathy, and valvular and hypertensive heart disease. J Am Soc Echocardiogr 2005;18: 865-872.
54. Tamborini G, Pepi M, Celeste F, et al: Incidence and characteristics of left ventricular false tendons and trabeculations in the normal and pathologic heart by second harmonic echocardiography. J Am Soc Echocardiogr 2004;17:367-374.
55. De Groot-de Laat L, Krenning B, ten Cate F, et al: Usefulness of contrast echocardiography for diagnosis of left ventricular non-compaction. Am J Cardiol 2005;95:1131-1134.
56. Lowery M, Martel J, Zambrano J, et al: Noncompaction of the ventricular myocardium: the use of contrast-enhanced echocardiography in diagnosis. J Am Soc Echocardiogr 2003;16:94-96.
57. Maltagliati A, Pepi M: Isolated noncompaction of the myocardium: multiplane transesophageal echocardiography; diagnosis in an adult. J Am Soc Echocardiogr 2000;13:1047-1049.
58. Rajdev S, Singh A, Nanda NC, et al: Comparison of two- and three-dimensional transthoracic echocardiography in the assessment of trabeculations and trabecular mass in left ventricular noncompaction. Echocardiography 2007;24:760-767.
59. Yelamanchili P, Nanda NC, Patel V, et al: Live/real time three-dimensional echocardiographic demonstration of left ventricular noncompaction and thrombi. Echocardiography 2006;23: 704-706.
60. Porciani MC, Rao CM, Perini AP, et al: Real-time 3-dimensional transthoracic echocardiography improves the diagnosis of isolated ventricular noncompaction. J Ultrasound Med 2007;26:551-553.
61. Petersen SE, Selvanayagam JB, Wiesmann F, et al: Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. J Am Coll Cardiol 2005;46:101-105.
62. Stollberger C, Kopsa W, Tscherney R, et al: Diagnosing left ventricular noncompaction by echocardiography and cardiac magnetic resonance imaging and its dependency on neuromuscular disorders. Clin Cardiol 2008;31:383-387.
63. Dodd J, Holmvang G, Hoffmann U, et al: Quantification of left ventricular noncompaction and trabecular delayed hyperenhancement with cardiac MRI: correlation with clinical severity. Am J Roentgenol 2007;189:974-980.
64. McCrohon J, Richmond D, Pennell D, et al: Isolated noncompaction of the myocardium: a rarity or missed diagnosis? Circulation 2002;106:e22-e23.
65. Conces Jr DJ, Ryan T, Tarver RD: Noncompaction of ventricular myocardium: CT appearance. Am J Roentgenol 1991;156: 717-718.
66. Hamamichi Y, Ichida F, Hashimoto I, et al: Isolated noncompaction of the ventricular myocardium: ultra fast computed tomography and magnetic resonance imaging. Int J Card Imaging 2001;17: 305-314.
67. Bladt O, Vanhoenacker P, Bevernage C, et al: Isolated noncompaction of ventricular myocardium. Diagnosis with multidetector computed tomography. JBR–BTR 2008;91:153-154.
68. Engberding R, Bender F: Identification of a rare congenital anomaly of the myocardium by two-dimensional echocardiography: persistence of isolated myocardial sinusoids. Am J Cardiol 1984;53: 1733-1734.
69. Schoen SP, Strasser RH, Kappert U: Non-compaction cardiomyopathy with low-gradient aortic valve stenosis. Eur Heart J doi: 10.1093/eurheartj/ehm625.
70. Ohki S, Moriyama Y, Jun Mohara J, et al: Aortic valve replacement for aortic regurgitation in a patient with left ventricular noncompaction. Ann Thorac Surg 2009;87:290-292.
71. Kaneda T, Shimizu M, Ino H, et al: Adult patient with isolated noncompaction of ventricular myocardium. Circulation 2005;112: e96-e97.
72. Finsterer J, Stollberger C: Letter to the Editor: Definite, probable, or possible left ventricular hypertrabeculation/noncompaction. Int J Cardiol 2008;123:175-176.
73. Belanger AR, Miller MA, Donthireddi UR, et al: New classification scheme of left ventricular noncompaction and correlation with ventricular performance. Am J Cardiol 2008;102:92-96.

74. Perez-David E, Garcia-Fernandez MA, Gómez-Anta I: Isolated noncompaction of the ventricular myocardium: infrequent because of missed diagnosis? J Am Soc Echocardiogr 2007;20:439.e1-439.e4.
75. Fazio G, Visconti C, D'Angelo L, et al: Delayed MRI hyperenhancement in noncompaction: sign of fibrosis correlated with clinical severity. AJR Am J Roentgenol 2008;190:273.
76. Fazio G, D'angelo L, Visconti C, et al: Isolated left ventricular noncompaction: a larger part of submerged iceberg with criteria for diagnosis to the limits of standard. Int J Cardiol 2008, doi:10.1016/j.ijcard.
77. Corrado Gm, Fazio G, Zachara E, et al: Natural history of isolated noncompaction of the ventricular myocardium in adults. Data from the Societa Italiana di Ecografia Cardiovascolare (SIEC) Registry. Circulation 2008;118:S948.
78. Robin N, Tabereaux P, Benza R, et al: Genetic testing in cardiovascular disease. J Am Coll Cardiol 2007;50:727-737.
79. Fazio G, Sutera L, Corrado G, et al: The chronic heart failure is not so frequent in non-compaction. Eur Heart J 2007;28:1269.
80. Jessup M, Abraham WT, Casey DE, et al: 2009 Focused Update ACCF/AHA guidelines for the diagnosis and management of heart failure in adults. J Am Coll Cardiol 2009;54:1343-1382.
81. Takano N, Komuro I: Beta-blockers have beneficial effects even on unclassified cardiomyopathy such as isolated ventricular noncompaction. Int Med 2002;41:601-602.
82. Epstein A, DiMarco J, Ellenbogen K, et al: ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. J Am Coll Cardiol 2008;51:1-62.
83. Stöllberger C, Blazek G, Bucher E, et al: Cardiac resynchronization therapy in left ventricular hypertrabeculation/non-compaction and myopathy. Europace 2008;10:59-62.
84. Oginosawa Y, Nogami A, Soejima K, et al: Effect of cardiac resynchronization therapy in isolated ventricular noncompaction in adults: follow-up of four cases. J Cardiovasc Electrophysiol 2008;19:935-938.
85. Stollberger C, Keller H, Finsterer J: Disappearance of left ventricular hypertrabeculation/noncompaction after biventricular pacing in a patient with polyneuropathy. J Card Fail 2007;13:211-214.
86. Eurlings LW, Pinto YM, Dennert RM, et al: Reversible isolated left ventricular non-compaction? Int J Cardiol 2009;136:e35-e36.
87. Conraads V, Paelinck B, Vorlat A, et al: Isolated non-compaction of the left ventricle: a rare indication for transplantation. J Heart Lung Transplant 2001;20:904-907.
88. Kovacevic-Preradovic T, Jenni R, Oechslin E, et al: Isolated left ventricular noncompaction as a cause for heart failure and heart transplantation: a single center experience. Cardiology 2009;112:158-164.
89. Stamou S, Lefrak E, Athari F, et al: Heart transplantation in a patient with isolated noncompaction of the left ventricular myocardium. Ann Thorac Surg 2004;77:1806.
90. Tigen K, Karaahmet T, Kahveci G, et al: Left ventricular noncompaction: case of a heart transplant. Eur J Echocardiogr 2008;9:126-129.
91. Shimamoto T, Marui A, Yamanaka K, et al: Left ventricular restoration surgery for isolated left ventricular noncompaction: report of the first successful case. J Thorac Cardiovasc Surg 2007;134:246-247.
92. Vida VL, Bottio T, Stellin G, et al: An unusual case of aorto-left ventricular tunnel. Cardiol Young 2004;24:203-205.
93. Enriquez SG, Entem FR, Cobo M, et al: Uncommon etiology of syncope in a patient with isolated ventricular noncompaction. PACE 2007;30:577-579.
94. Fuster V, Ryden LE, Cannom DS, et al: ACC/AHA/ESC practice guidelines. JACC 2006;48:e149-246.
95. Fichet J, Legras A, Bernard A, et al: Aborted sudden cardiac death revealing isolated noncompaction of the left ventricle in a patient with Wolff-Parkinson-White syndrome. Pacing Clin Electrophysiol 2007;30:444.
96. Derval N, Jais P, O'Neill M, et al: Apparent idiopathic ventricular tachycardia associated with isolated ventricular noncompaction. Heart Rhythm 2009;6:385-388.
97. Lim HE, Pak HN, Shim WJ, et al: Epicardial ablation of ventricular tachycardia associated with isolated ventricular noncompaction. PACE 2006;29:797-799.
98. Zipes D, Camm JA, Borggrefe M, et al: ACC/AHA/ESC practice guidelines. J Am Coll Cardiol 2006;48:e247-e346.
99. Stöllberger C, Finsterer J: Thrombi in left ventricular hypertrabeculation/noncompaction: review of the literature. Acta Cardiol 2004;59:341-344.
100. Pitta S, Thatai D, Afonzo L: Thromboembolic complications of left ventricular noncompaction: case report and brief review of the literature. J Clin Ultrasound 2007;35:465-468.
101. Fazio G, Corrado G, Zachara E, et al: Anticoagulant drugs in noncompaction: a mandatory therapy? J Cardiovasc Med 2008;9:1095-1097.
102. Williams RI, Masani ND, Buchalter MB, et al: Abnormal myocardial strain rate in noncompaction of the left ventricle. J Am Soc Echocardiogr 2003;16:293-296.
103. Kitao K, Ohara N, Funakoshi T, et al: Noncompaction of the left ventricular myocardium diagnosed in pregnant woman and neonate. J Perinat Med 2004;32:527-531.
104. Uesugi T, Nishiyama J, Kimura Y, et al: Anesthetic management for cesarean section in a patient with left ventricular noncompaction. Jpn J Anesth 2005;54:522-524.
105. Munehisa Y, Watanabe H, Kosaka T, et al: Successful outcome in a pregnant women with isolated noncompaction of the left ventricular myocardium. Int Med 2007;46:285-289.
106. Patel C, Shirali G, Pereira N. Left ventricular noncompaction mimicking peripartum cardiomyopathy. J Am Soc Echocardiogr 2007;20:1009,e9-e12.
107. Rehfeldt K, Pulido J, Mauermann W, et al: Left ventricular hypertrabeculation/noncompaction in a patient with peripartum cardiomyopathy. Int J Cardiol 2008;2008:025, doi:10.1016/j.ijcard.
108. Lurie P: The perspective of ventricular noncompaction as seen by a nonagenarian. Cardiol Young 2008;18:243-249.
109. Anderson RH: Ventricular noncompaction—a frequently ignored finding. Eur Heart J 2008;29:10-11.
110. Stollberger C, Finsterer J: Pitfalls in the diagnosis of left ventricular hypertrabeculation/noncompaction. Postgrad Med J 2006;82:670-683.
111. Nair SB, Khattar RS: Isolated left ventricular non-compaction: an emerging cause of heart failure in adults. Postgrad Med J 2009;85:202-207.
112. Engberding R, Yelbuz T, Breithardt G: Isolated noncompaction of the left ventricular myocardium. A review of the literature two decades after the initial case description. Clin Res Cardiol 2007;96:1-8.