

CLINICAL CASE REPORTS

Medicina (Kaunas) 2010;46(3):193-9

Heart transplantation in an adult patient with isolated noncompaction of the left ventricular myocardium

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Key words: *isolated noncompaction of the left ventricular myocardium; echocardiography; computed tomography; cardiovascular magnetic resonance; heart transplantation.*

Summary. *Isolated noncompaction of the ventricular myocardium is defined as a rare cardiomyopathy caused by intrauterine arrest of compaction of the myocardial fibers and meshwork, an important process in myocardial development, in absence of any coexisting congenital heart lesions. A lot of controversies exist about diagnostic criteria, nomenclature, origin, pathogenesis, and prognosis of this disease. Here, we describe an adult patient with isolated left ventricular noncompaction who presented with worsening congestive heart failure and was successfully treated with heart transplantation.*

Case report

A 35-year-old white male was referred to the Cardiac Intensive Care Unit of Vilnius University Hospital Santariškių Klinikos because of fever, dyspnea, and cough. The patient had a history of undefined asymptomatic heart disease from the childhood (pathological heart murmur was heard from the age of 7 years). At the age of 17 years, diagnosis of hypertrophic cardiomyopathy was established based on echocardiographic findings. The patient had no symptoms even performing moderate-to-severe physical activity until age of 35 years, when after severe physical activity, he experienced fever, cough, dyspnea, and abdominal pain. There was no family history of cardiomyopathy, although first-degree relatives had not been screened.

On admission during physical examination, the patient was slightly pallid with a regular heart rate of 32–36 beats per minute (on subsequent days after admission, patient's heart rate increased up to 100 beats per minute) and blood pressure of 105/65 mm Hg. Lung auscultation revealed wheezes in both the lungs. Abdominal palpation showed slight distention and tenderness to palpation in the epigastric, left and right hypochondriac regions; the liver was 3–4 cm below the right costal margin.

The laboratory findings were as follows (normal values in brackets): elevated Westergren erythrocyte sedimentation rate (ESR) and leukocyte count to 62 mm/h (2–10 mm/h) and $13.3 \times 10^9/L$ ($<10 \times 10^9/L$),

respectively; elevated cardiospecific markers troponin I to 11.68 $\mu\text{g/L}$ ($<0.5 \mu\text{g/L}$), creatine kinase MB fraction to 13.5 $\mu\text{g/L}$ ($\leq 5 \mu\text{g/L}$), elevated fibrinogen 5.19 g/L (2–4 g/L); C-reactive protein and D-dimers were elevated to 57.5 mg/L ($\leq 5 \text{ mg/L}$) and 3580 $\mu\text{g/L}$ ($<250 \mu\text{g/L}$), respectively. The elevation of liver enzymes – glutamate oxaloacetate transaminase (GOT), 1036 U/L ($\leq 37 \text{ U/L}$); glutamic-pyruvic transaminase (GPT) 1138 U/L, ($\leq 40 \text{ U/L}$) – and urea (10.55 mmol/L [2.5–7.5 mmol/L]) was observed on admission. No serological markers of viral hepatitis were detected.

The electrocardiogram (ECG) showed sinus rhythm, 32 beats per minute, first-degree AV block, hypertrophy of both ventricles, and features of myocardial scar in inferior leads.

Transthoracic echocardiography (TTE) demonstrated marked thickening and heavy trabeculation of the left ventricle apex, inferior, septal, anterior, and lateral walls. Thrombi in the projection of deep intertrabecular recesses in the apical region of the left ventricle were seen on TTE (Figs. 1 and 2). Color Doppler displayed flow within the deep intertrabecular recesses. The left ventricle was slightly dilated, and marked dilatation of both atria was observed with a restrictive pattern of left ventricular filling. There was hypokinesis of the left ventricle apex, septal and anterior walls with reduction of global left ventricular ejection fraction (LV EF about 30%). The right ventricle appeared to be more heav-

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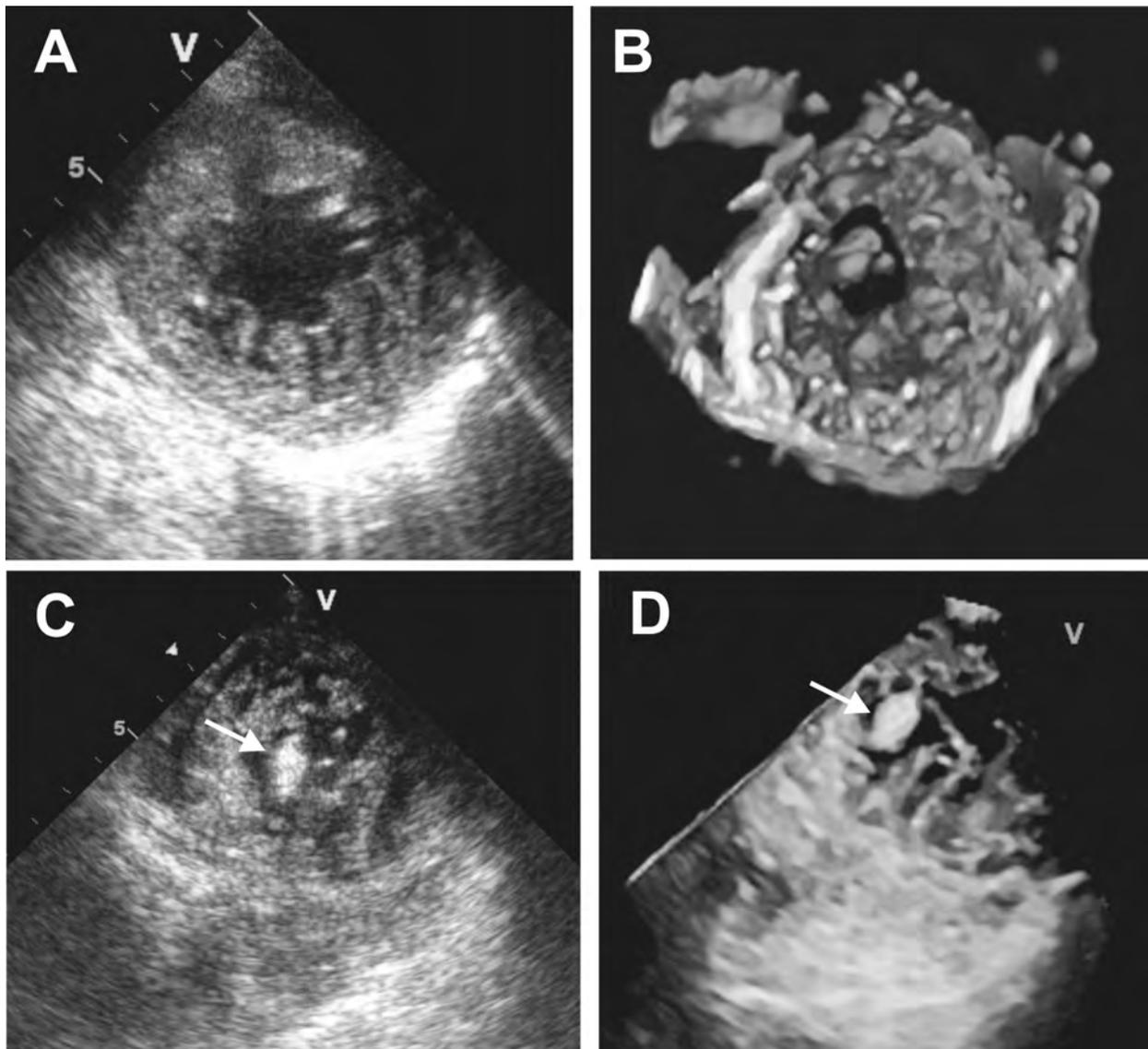


Fig. 1. Echocardiographic two-dimensional (left) and three-dimensional (right) short axis views of the left ventricle at the levels of papillary muscles (top) and apex (bottom) show prominent trabeculation with deep intertrabecular recesses and thrombus (arrow) in the apical region of the left ventricle

ily trabeculated than usual. Mild relative mitral and tricuspid regurgitation jets were seen. No additional abnormalities were present. Based on above-mentioned findings, isolated ventricular noncompaction (IVNC) was suspected.

For clarification of diagnosis, cardiovascular magnetic resonance (CMR) was performed. CMR demonstrated prominent, numerous trabeculations in the apical region and midventricular segments of the left ventricle with deep intertrabecular recesses communicating with the left ventricle cavity. The end-diastolic ratio of noncompacted to compacted myocardium was >2.3 , consistent with diagnosis of left ventricular noncompaction according to Petersen et al. (1) (Fig. 3). CMR examination showed a totally reduced LV EF of about 30% and traces of fluid in

both the pleural cavities and in the pericardium. Using segmented inversion-recovery turboFLASH sequence 15 min after contrast administration, a hyperintense focus 1.8×1.9 cm in size was observed in the projection of the midventricular segment of the inferoseptal wall, consistent with the region of myocardial fibrosis or necrosis. The right ventricle appeared to be more trabeculated than usual; however, we did not attempt to diagnose involvement of the right ventricle, as the exact differentiation between normal variants of the usually highly trabeculated right ventricle and pathological forms may be difficult. CMR images were not informative about the presence of thrombi in the left ventricle because of artifacts due to cardiac arrhythmia.

Abdominal sonography revealed hepatomegaly

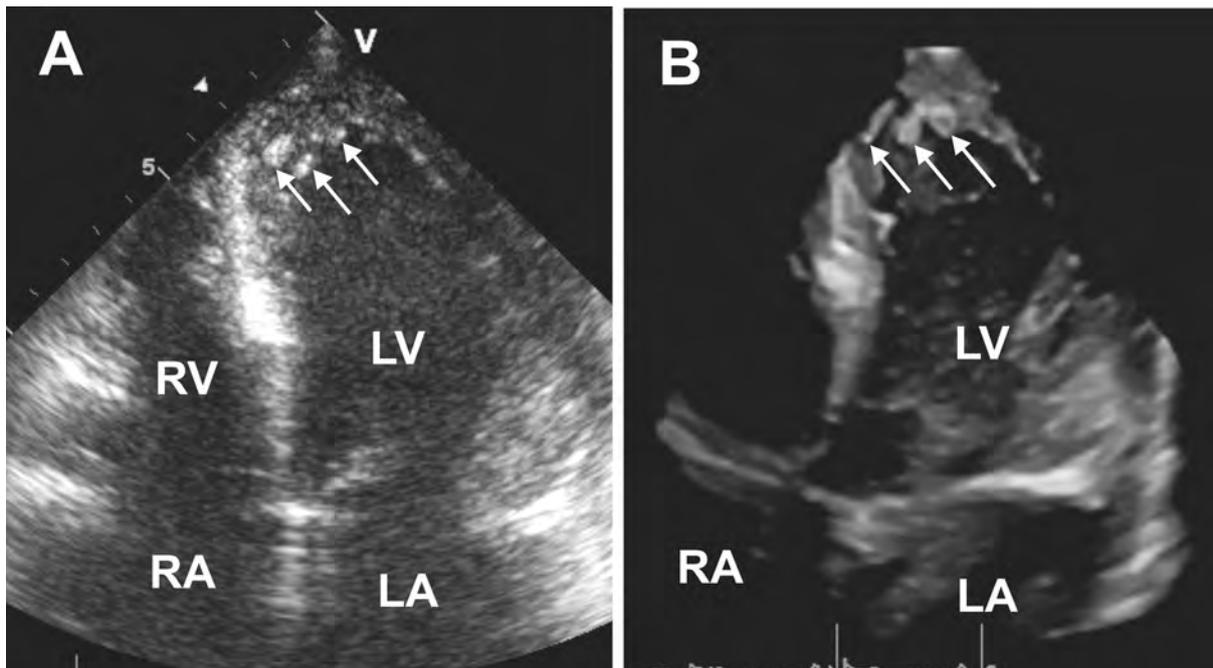


Fig. 2. Echocardiographic two-dimensional (A) and three-dimensional (B) four-chamber views. Three intertrabecular thrombi (arrows) are seen in the apex of the left ventricle.

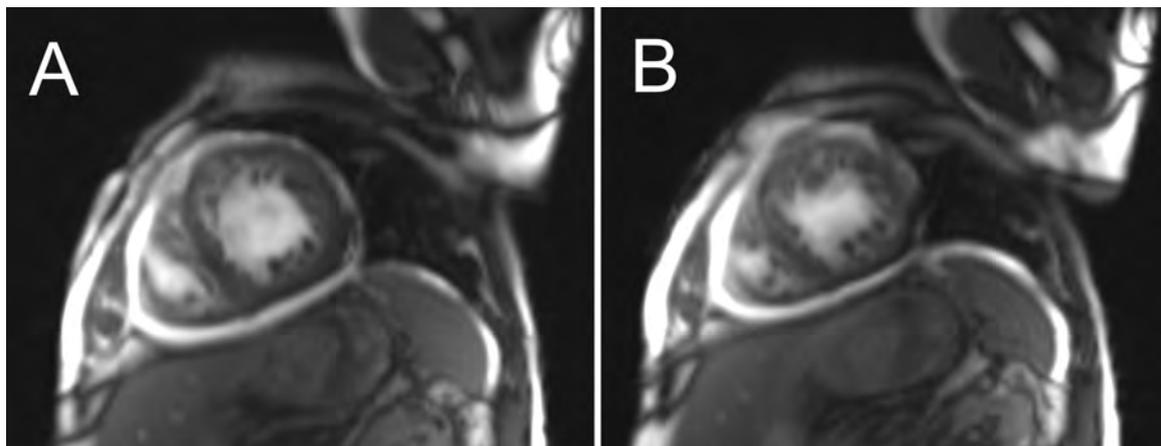


Fig. 3. Electrocardiographically gated cardiovascular magnetic resonance images. A, TrueFisp short axis image in end-diastole at the midventricular level shows excessive trabecularization of anterior, lateral, and inferior left ventricular walls; B, TrueFisp end-diastolic short axis image more apical to A revealing the end-diastolic ratio of noncompacted to compacted myocardium of 2.4.

with signs of mild venous stasis and focal changes in the spleen. Contrast-enhanced chest and abdominal computed tomography (CT) was performed to refine focal pulmonary changes seen on chest x-ray and focal changes in the spleen. Abdominal CT confirmed multiple hypointense splenic foci typical of spleen infarctions. Left ventricular noncompaction and apical thrombi reported on echocardiography were clearly seen on chest CT (Fig. 4).

The findings from coronary angiography and neurological examination were normal.

The diagnosis of isolated left ventricular noncompaction with possible embolization of ventricular thrombi, causing splenic and myocardial infarctions, was established based on clinical, laboratory, and radiological findings.

Our patient was treated conservatively with anticoagulants, antibiotics, antifungal agents, beta-blockers, diuretics, and angiotensin-converting enzyme inhibitors. During treatment, an improvement in symptoms and exercise tolerance, reduction of left lung infiltration were noted, and the patient was



Fig. 4. Nongated contrast-enhanced chest computed tomography images

A, reformatted short axis image at the midventricular level shows hypertrabecularization of anterior, lateral, and inferior left ventricular wall; B, abnormal left ventricular apex and anterolateral wall depicted in reformatted four-chamber view; C and D images confirm thrombi in the apical region of the left ventricle seen on echocardiography (arrowheads).

referred to ambulatory treatment.

On subsequent outpatient follow-up visits, the patient complained of frequent palpitations, increasing dyspnea, and reduced exercise tolerance despite adequate treatment. On follow-up ECG, multiple episodes of paroxysmal self-limiting atrial fibrillation and couplets of ventricular premature beats were registered. During ambulatory treatment despite adequate anticoagulation, the patient experienced cerebral infarction with left hemiparesis, which regressed partially.

Four months after establishment of diagnosis, the

patient was admitted to the Heart Surgery Center of Vilnius University Hospital Santariškių Klinikos for the assessment of indications for heart transplantation because of refractory congestive heart failure and cerebral embolization despite adequate anticoagulation.

On admission during physical examination, the patient was slightly cyanotic, subicteric with irregular heart rate of 90 beats per minute, blood pressure of 120/70 mm Hg. The liver was 4 cm below the right costal margin.

The ECG showed atrial fibrillation, 100 beats per minute, couplets of ventricular premature beats. TTE and cardiac CMR were repeated for the assessment of disease progression. TTE displayed negative echocardiographic dynamics. The left ventricle remained only slightly dilated, LV EF reduced from 30% to 25%, multiple thrombi were seen in both the ventricles, dilation of both the atria progressively increased, signs of pulmonary hypertension were observed. CMR scan revealed multiple thrombi not only within deep intertrabecular recesses of both the ventricles but also in the left appendage and in the right pulmonary artery. Reduction in systolic function of both the ventricles was pronounced (LV EF of 14% and right ventricle EF of 16%) with an increased amount of fluid in the pericardial and pleural cavities. Using segmented inversion-recovery turboFLASH sequence 15 min after contrast administration, an enlarged hyperintense focus not only in the projection of the midventricular segment of the inferoseptal wall but also extending to the left ventricle apical region was observed.

Based on clinical findings and results of investigations, the patient was placed on emergency waiting list for the heart transplantation. Orthotopic heart transplantation was performed without significant complications. Macroscopic examination of explanted native heart (Fig. 5) revealed dilated heart with

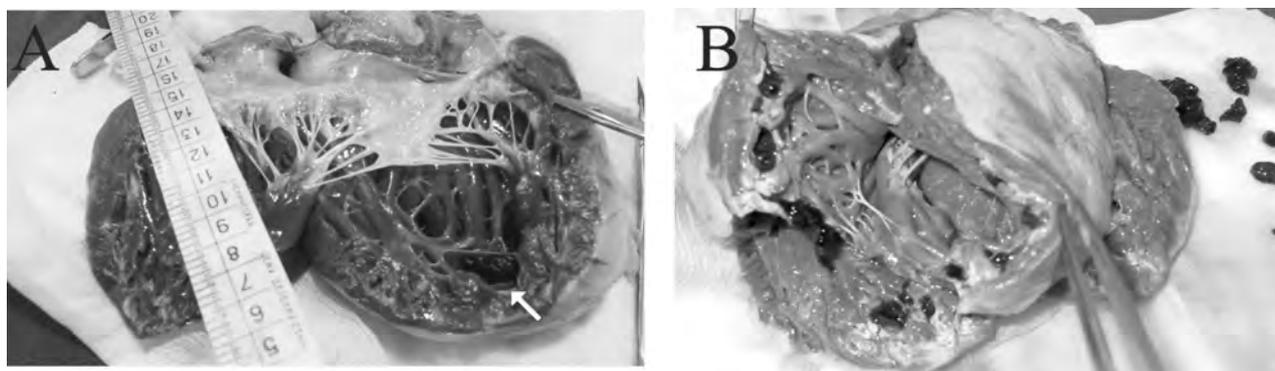


Fig. 5. Macroscopic specimen of native heart

A, prominent trabeculations and intertrabecular recesses at the left ventricular walls, thickened noncompacted myocardial layer as compared to compacted myocardial layer, thrombus (arrow) in the left ventricle; B, multiple thrombi in heart chambers.

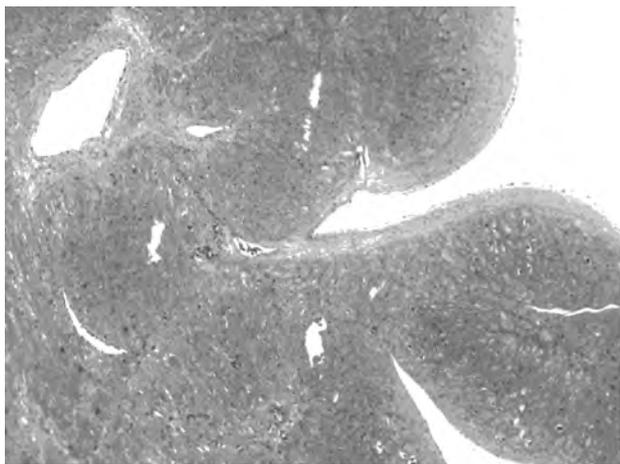


Fig. 6. Transmural, histological section of the left ventricle. Note trabeculations with deep intertrabecular recesses (hematoxylin-eosin, $\times 20$).

prominent trabeculations and invaginations at the left ventricular apex, anterior, inferior, and lateral walls with multiple thrombi. The layer of noncompaction was markedly thicker when compared with the layer of compacted myocardium in the above-mentioned left ventricle areas. The coronary arteries were normal.

Histological examination of the explanted heart showed prominent trabeculations of the left ventricle, left ventricle endocardial thickening and fibrosis, prominent hypertrophy of cardiomyocytes, with some areas of interstitial and focal fibrotic changes, discordance of myocardial fibers, and thrombi in all cardiac chambers (Fig. 6).

The patient was discharged from the hospital with signs of minimal heart transplant rejection reaction on heart biopsy and without any clinical symptoms and remained well and fully active for the subsequent 1.5 years.

Discussion

IVNC of the ventricular myocardium is defined as a rare cardiomyopathy caused by intrauterine arrest of compaction of the myocardial fibers and meshwork, an important process in myocardial development (2). IVNC is characterized by the presence of deep intertrabecular recesses in hypertrophied and often hypokinetic segments of the myocardium of the left or both ventricles. By definition, IVNC occurs in the absence of other coexisting cardiac abnormalities (3). In IVNC, the deep intertrabecular recesses communicate with the cavity of the left ventricle but not with the coronary circulation, whereas in noncompaction associated with other congenital heart disease (non-isolated noncompaction), the intertrabecular recesses communicate both with the left ventricular cavity and the coronary circulation (4).

The major clinical manifestations are impaired left ventricular systolic and diastolic function, systemic embolism, ventricular tachyarrhythmias, conduction disorders, and neurological abnormalities (5, 6). Systolic dysfunction is most probably the result of relative ischemia of the myocardium due to mismatch of myocardial oxygen supply and demand (5). Mechanisms implicated in the diastolic dysfunction include a combination of abnormal ventricular relaxation and restriction to ventricular filling secondary to the prominence of intracavitary trabeculations (5). The age at onset of heart failure is variable. It ranges from infancy to old age, possibly because of variable degree of myocardial trabeculations and the effects of chronic myocardial ischemia. Various patterns of arrhythmias, ranging from atrial fibrillation to sustained ventricular tachycardia, can be observed. When the series of adult patients is compared with the pediatric series (7), the most important differences are the lack of facial dysmorphism and Wolff-Parkinson-White syndrome in the adult population. This may be due to a different genetic background but with the same morphological appearance of the cardiac anomaly.

Recent epidemiological studies or single-center experience showed that IVNC was responsible for 9.2–9.5% of cardiomyopathies diagnosed in children (6, 8). In the largest series of adult patients with IVNC (4), the prevalence was 0.014% in patients referred to the echocardiography laboratory. The true prevalence of IVNC in adults remains unclear.

IVNC is a genetically heterogeneous disorder. Neonatal IVNC can be a disease caused by mutations in the G 4.5 gene located on the X chromosome, associated with Barth syndrome (9), other X-linked infantile cardiomyopathies, and X-linked endocardial fibroelastosis. Adult forms of IVNC are genetically distinct from X-linked infantile cases and suggest to be transmitted by an autosomal dominant trait (10). Because of generally poor prognosis and because of the familial association of IVNC, first-degree relatives should be screened by echocardiography.

Prominent left ventricular trabeculation can be found in healthy hearts as well as in hypertrophic cardiomyopathy and in LVH secondary to dilated, valvular, or hypertensive cardiomyopathy. Thus, the differentiation between variants and IVNC may often be challenging (3). IVNC should be differentiated from normal heart with prominent left ventricular trabeculations (the normal variants have up to 3 trabeculations) (11), apical hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, endocardial fibroelastosis, cardiac metastases, left ventricular thrombus (12).

Echocardiography is considered the reference standard for the diagnosis of IVNC. Diagnostic echocardiographic criteria for isolated noncompaction of the myocardium (13) are listed below:

1. Absence of coexisting cardiac abnormalities (other than 2–4) by definition.
2. Typical two-layered structure of the myocardium with a thin, compacted outer (epicardial) band and a much thicker, noncompacted inner (endocardial) layer consisting of trabecular meshwork with deep endocardial spaces (the maximum end-systolic ratio of the noncompacted endocardial layer to the compacted myocardium of >2 is characteristic).
3. Predominant segmental location of the abnormality (that is, noncompacted myocardium is predominantly ($>80\%$) found in the apical and midventricular areas of both the inferior and the lateral wall.
4. Color Doppler echocardiographic evidence of deeply perfused intertrabecular recesses (in contrast to myocardial sinusoids, intertrabecular spaces do not communicate with the coronary circulation).

Transesophageal echocardiography and contrast echocardiography may be helpful when the quality of standard echocardiographic image is limited or the diagnosis is questionable.

Although ultrafast CT provides high-resolution imaging of noncompacted myocardium, CT, unlike CMR, has not been widely used in the diagnosis of IVNC and will perhaps not be used in the future. Clear diagnostic criteria for IVNC have not been established in CT (13).

Currently, several echocardiographic definitions of IVNC exist, and up to now, attempts were made to determine specific magnetic resonance criteria of IVNC. One study reported that the ratio of noncompacted to compacted myocardium of >2.3 in diastole in the 17-segment model accurately distinguishes pathological noncompaction from the degrees of noncompaction observed in healthy, dilated, and hypertrophied hearts (1). The CMR measurements are taken in diastole, perhaps because the presence of deep recesses filled with blood, and trabeculations of the myocardium are evident during diastole, whereas during systole, the recesses collapse and the myocardium appears to be compacted.

The pathological anatomical examination usually confirms the localization of the noncompacted my-

ocardium corresponding to the echocardiographic recordings. Histological examination confirms that the recesses are covered by ventricular endocardium in continuity with the left ventricular cavity (3). No specific histological finding has been described in IVNC, although increased subendocardial fibrosis and endocardial fibroelastosis were found in IVNC cases (13).

The prognosis of IVNC is quite poor. During the six-year follow-up of patients in the study by Ritter and colleagues (14), 8 of the 17 patients died and 2 underwent heart transplantation. In the larger series of patients (4), long-term follow-up (44 ± 39 months) showed that 35% of patients died, half of them because of sudden cardiac death, and 12% (four patients) had undergone heart transplantation. The high incidence of both thromboembolic events (24%) and ventricular tachycardia (41%) in that series underscores the poor clinical prognosis for patients with impaired left ventricular function.

Management of patients with IVNC includes an appropriate treatment for heart failure, management of arrhythmias and oral anticoagulation to prevent systemic emboli in patients with simultaneous atrial fibrillation or severe left ventricular dysfunction. Implantation of an internal cardioverter defibrillator system and early listing of symptomatic patients for heart transplantation have to be seriously considered. In particular, patients with a high-risk clinical constellation for nonsurvivors (higher left ventricular end-diastolic diameter at the time of initial presentation, New York Heart Association class III/IV, chronic atrial fibrillation, and bundle branch block) should be chosen for an early, more aggressive strategy. If standard drug treatment for heart failure is unsuccessful, emergency cardiac transplantation is ultimately the only therapeutic possibility. Due to thromboembolic events and prominent trabeculations of the left ventricle, using left ventricle assist devices as the bridge to transplantation could be dangerous in this group of patients. Until 2008, only 9 cases of IVNC leading to cardiac transplantation have been published to date (15).

In conclusion, the present case suggests that diagnosis of IVNC is often challenging and delayed. Multimodality imaging helps in most cases to establish proper diagnosis. Cardiac transplantation is the best solution for those patients who have refractory congestive heart failure due to IVNC.

Širdies transplantacija, atlikta suaugusiam pacientui, sergančiam izoliuotu kairiojo skilvelio miokardo nekompaktiškumu

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Raktažodžiai: izoliuotas kairiojo skilvelio miokardo nekompaktiškumas, echokardiografija, kompiuterinė tomografija, širdies ir kraujagyslių magnetinis rezonansas, širdies transplantacija.

Santrauka. Izoliuotas skilvelių miokardo nekompaktiškumas apibrėžiamas kaip reta kardiomiopatija, kurią sukelia svarbaus miokardo vystymosi proceso – intrauterinio miokardo skaidulų bei tinklo kompaktizacijos sutrikimas, nesant kitų, susijusių įgimtų širdies pažeidimų. Egzistuoja daug prieštarų nuomonių apie šios ligos diagnostikos kriterijus, nomenklatūrą, kilmę, patogenezę ir prognozę. Šiame straipsnyje mes aprašome suaugusį pacientą, sergantį izoliuotu kairiojo skilvelio nekompaktiškumu, kuris kreipėsi dėl progresuojančio stazinio širdies nepakankamumo ir kuriam sėkmingai atlikta širdies transplantacija.

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Received 26 January 2009, accepted 5 March 2010

Straipsnis gautas 2009 01 26, priimtas 2010 03 05