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Original Article

The variable clinical presentation of, and outcome for, noncompaction of the ventricular myocardium in infants and children, an under-diagnosed cardiomyopathy

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Abstract Noncompaction of the ventricular myocardium is increasingly recognized as an important cause of cardiomyopathy. Its echocardiographic definition, however, is not yet clearly refined, and differentiation from other conditions with hypertrabeculation can be difficult. We report a prospective short-term follow-up of 15 children with noncompaction, excluding those with associated complex congenital cardiac disease.

The clinical presentation and outcome were variable, with 2 patients being asymptomatic. For 5 patients, presentation was with cardiac failure due to depressed myocardial function. The function deteriorated in two, remained the same in two, and improved in the other patient. Cardiac failure due to mitral regurgitation was the mode of presentation in 2 patients with preserved myocardial function, one of whom needed replacement of the mitral valve. In 6 patients (40%), symptoms of cardiac failure were due to noncomplex congenital cardiac disease. All of them had ventricular septal defects. In addition, two had cleft mitral valves, and one had a large persistently patent arterial duct. The diagnosis of noncompaction was initially missed on more than one echocardiographic study in one-third of our patients. We conclude that noncompaction is under-diagnosed, and is not as rare as is thought. In children, it is often associated with other cardiac lesions that can cause cardiac failure in the presence of preserved myocardial function.

Keywords: Ventricular mass; congenital heart disease; echocardiography

INTEREST IN NONCOMPACTION OF THE VENTRICULAR myocardium has been enhanced recently by the increasing number of case reports to be found in the current literature.[1–3] Clinical presentation usually reflects systolic ventricular dysfunction, although many patients are discovered at routine echocardiographic examinations, and remain asymptomatic for variable periods of time.[4,5] Noncompaction may either be associated with complex congenital cardiac disease, or be present as an isolated abnormality. An association also with simpler congenital cardiac malformations has recently been described.[3] We report here a prospective short-term follow-up of 15 children in whom we discovered ventricular noncompaction. There was a wide spectrum of clinical presentation, and an incidence that suggests that this is an under-diagnosed cardiomyopathy. Although there is currently no consensus regarding the echocardiographic criterions for diagnosis of noncompaction, and it is often difficult to differentiate from primary or secondary ventricular hypertrabeculation, we have used the strict quantitative criterions proposed by Jenni et al.[6] as the basis for our study. We have opted to exclude patients with associated complex congenital cardiac malformations, as their hearts are grossly abnormal, and noncompaction of the ventricular myocardium is not the main pathology in such settings.

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Patients and methods

We included the patients seen with the diagnosis of noncompaction of the ventricular myocardium at a

tertiary referral centre, namely the King Abdulaziz Cardiac Centre, Riyadh, Saudi Arabia. Our index case was seen in February 2000. Between this date and October 2003, we encountered 15 additional patients, all of whom have been followed up prospectively. During this period, we performed a total of 7250 transthoracic echocardiograms. The patients were evaluated clinically and by echocardiography. All echocardiographic studies were done using a Hewlett Packard Sonos 5500 (Andover, MA, USA) machine. Follow-up clinical examination and echocardiograms were obtained at least twice, with a minimum interval of 3 months between examinations for all patients, except for one patient who died, and for our fifth patient. Ventricular dimensions and shortening fraction were measured at each study.

Diagnostic criterions for noncompaction of the ventricular myocardium

We diagnosed noncompaction according to the criterions suggested by Oechslin et al.,[7] and by Jenni et al.,[6] specifically

- the finding of multiple trabeculations and recesses on cross-sectional imaging, with the appearance of distinct compacted and noncompacted myocardial layers.
- low scale colour flow mapping delineating the continuity of intertrabecular recesses with the ventricular cavity.
- a ratio of 2:1 or more between the thicknesses of the noncompacted compared to the compacted layers at the end of systole as assessed using the parasternal short axis view (Fig. 1).

We did not, however, follow the suggestion of Jenni et al.[6] that there should be no associated cardiac defect. We did exclude, nonetheless, those patients with associated complex congenital cardiac malformations as discussed in our introduction.

Results

The ages of the children ranged from 1 day to 20 months, with a mean of 5.4 months. The ratio of males to females was 1:2.2. The duration of follow-up ranged from 0 to 24 months, with a mean of 8 months. The ratio of the noncompacted to the compacted layers of the ventricular myocardium ranged from 2:1, to 3.2:1, with a mean of 2.3:1. In all patients, the noncompaction was noticeable at the apex and along the lateral wall of the left ventricle at the site of papillary muscles. The clinical course of the patients is summarized in Figure 2, with the clinical and echocardiographic features detailed in the Table 1.

Mode of presentation

No symptoms had been described by 3 patients, in whom echocardiography was carried out for screening, in one because of a heart murmur, one for Down's syndrome, and one because of history of ventricular noncompaction in a sibling. Heart failure had been the presenting symptom in 12 patients (80%), due to depressed function in 5, associated ventricular septal defect in 6, and mitral regurgitation in 1.

In 5 patients (33%), the diagnosis had initially been missed on two or more echocardiographic examinations. We made the diagnosis while reviewing echocardiograms of patients with Down's syndrome for an unrelated study in 4 patients, and during routine review of a fifth patient.

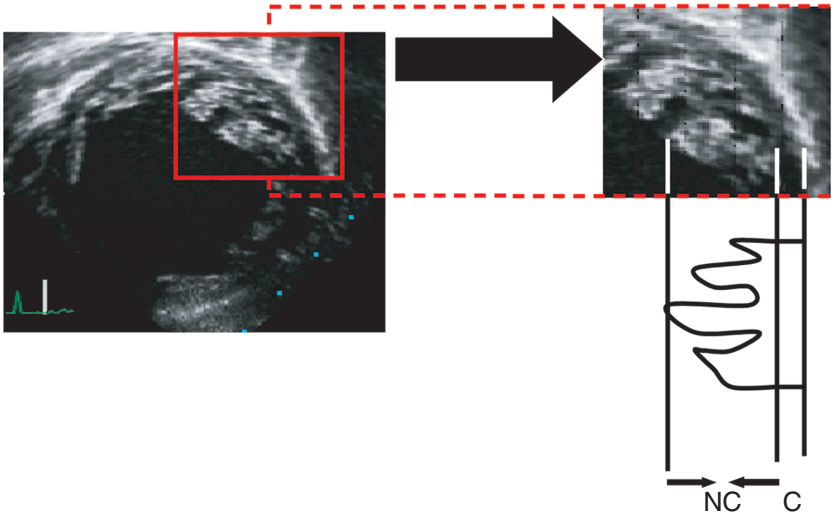

Figure 1.
Measurement of the ratio of the thickness of the noncompacted (NC) to compacted (C) layers of the ventricular myocardium as judged in the parasternal short axis view.

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Clinical course and echocardiographic features

Of the 5 patients with depressed myocardial function, one deteriorated over a few days and died, one showed slow deterioration of function, while in two, the function remained the same. In our second patient, there was an improvement of function, with fractional shortening increasing from 15% to 30%. Although the trabeculations were still seen, the ratio of the noncompacted to compacted layers decreased from 2.2:1 to 0.9:1 because of thickening and hypertrophy

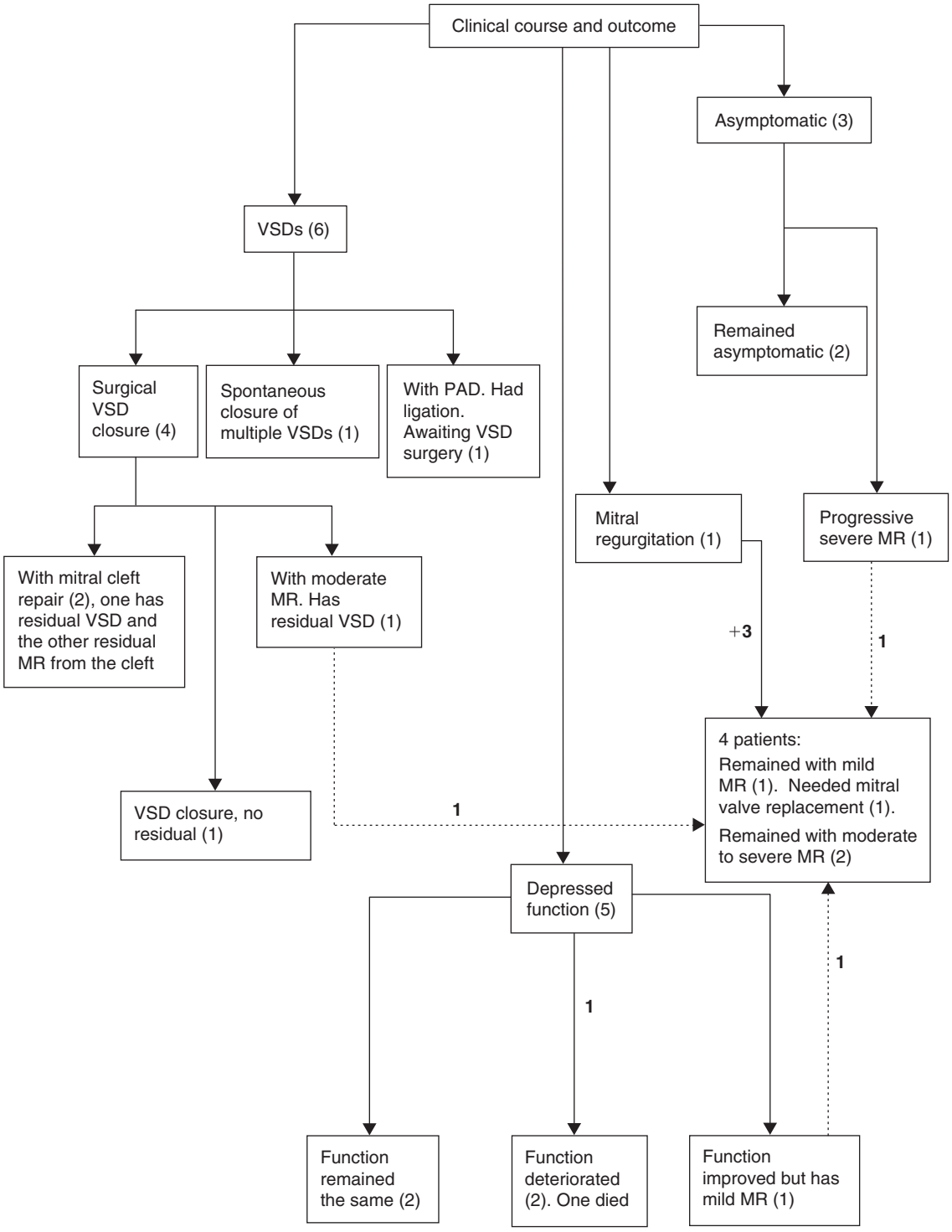

Figure 2.
Algorithm summarizing the clinical course of, and outcome for, the 15 patients with noncompaction. MR: mitral regurgitation; VSD: ventricular septal defect; PAD: persistent patency of the arterial duct.

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Table 1. Patients' clinical and echocardiographic features according to the mode of presentation.

Patient	Age at diagnosis	Sex	Clinical presentation and echocardiographic features	Noncompacted/ compacted ratio	Follow-up
(a) Heart failure due to depressed myocardial function					
1	1 day	Female	Abnormal ante-natal ultrasound, hydrops fetalis, severely depressed function. Fractional shortening 14%.	2.5:1	Died on day 6 with ventricular tachycardia.
2*	12 days	Female	Metabolic acidosis, heart failure, impaired function. Dilated ventricles. Fractional shortening 15%. Mild mitral regurgitation.	2.2:1 then 0.9:1	Followed for 12 months. Function *improved.* Fractional shortening 30%. Mild mitral regurgitation. Failure to thrive.
3	10 months	Female	Heart failure, depressed function. Fractional shortening 9%.	3.2:1	F/U for 12 months. Still with depressed function. Fractional shortening 8%. On anti-failure medications.
4	20 months	Male	Dandy Walker's syndrome with ventriculo-peritoneal shunt. Fractional shortening 20%.	2.4:1	Followed for 18 months. Myocardial function deteriorated. Fractional shortening decreased to 14%. On anti-failure medications.
5	6 months	Female	Heart failure and depressed function. Fractional shortening of 10%. Positive family history of a 5-month-old brother who died with cardiomyopathy.	2.5:1	Newly diagnosed
(b) Heart failure due to mitral regurgitation					
6*	2 months	Female	Initially asymptomatic then developed heart failure, failure to thrive. Moderate mitral regurgitation, normal ventricular function. Fractional shortening 36%.	2.4:1	Followed for 14 months. Severe mitral regurgitation. Fractional shortening 30%. Had mitral valve replacement with smooth post-operative course.
7	18 months	Male	Heart failure, moderate mitral regurgitation. Normal ventricular function. Fractional shortening 30%.	2.4:1	Followed for 8 months. Continued to have moderate mitral regurgitation and preserved function on anti-failure medications.
(c) Heart failure due to non-complex congenital heart disease					
8	5 months	Female	Heart failure due to multiple ventricular septal defects. Dilated left ventricle and atrium. Normal function. Fractional shortening 35%.	2.3:1	Followed for 24 months. Heart failure resolved with decrease in the size of ventricular septal defects. Heart dimensions normalized. Function remained normal.
9	6 months	Female	Down's syndrome. Large ventricular septal defect with heart failure. Normal function. Diagnosis missed on 4 echocardiographic studies.	2.3:1	Followed for 6 months, ventricular septal defect closed surgically with moderate size (6 mm) residual patch leak. Preserved function.
10	3 weeks	Female	Down's syndrome. Small ventricular septal defect with cleft mitral valve. Large patent arterial duct. Congestive heart failure. Diagnosis missed on 3 echocardiographic studies. Normal function.	2:1	Followed for 3 months. Duct ligated surgically. Heart failure improved Preserved function.
11	2 months	Female	Down's syndrome. Large ventricular septal defect with cleft mitral valve. Heart failure. Normal function. Diagnosis missed on 3 echocardiographic studies.	2.4:1	Followed for 6 months. Ventricular septal defect surgical closure with mitral valve repair. Residual moderate mitral cleft regurgitation. Preserved function.
12	4 months	Female	Large muscular ventricular septal defect with mitral regurgitation. Normal function. Fractional shortening 30%. Diagnosis missed on 3 echocardiographic studies.	3:1	Followed for 6 months. Ventricular septal defect closed surgically with moderate (4 mm) patch leak. Had postoperative ventricular fibrillation leading to hypoxic ischemic encephalopathy. Moderate mitral regurgitaiton. Normal function.

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Table 1. (Continued).

Patient	Age at diagnosis	Sex	Clinical presentation and echocardiographic features	Noncompacted/ compacted ratio	Follow-up
13	5 months	Male	Heart failure due to a large inlet ventricular septal defect. Normal function. Shortening fraction of 36%.	2.2:1	Followed for 6 months. Surgical closure of the ventricular septal defect with no complications or residual shunt. Normal function.
(d) Asymptomatic					
14	2 months	Male	Heart murmur due to patent arterial duct. A symptomatic. Normal function. Fractional shortening 35%.	2:1	Duct coiled at 10 months of age. Remained asymptomatic with normal function.
15	2 days	Male	Down's syndrome. Echocardiography was done for routine screening. A small muscular apical ventricular septal defect. Normal function, FS 38%. Diagnosis missed on 2 echocardiographic studies.	2:1	Followed for 6 months. Continued to be asymptomatic with normal function and a small ventricular septal defect.

*Twin sisters

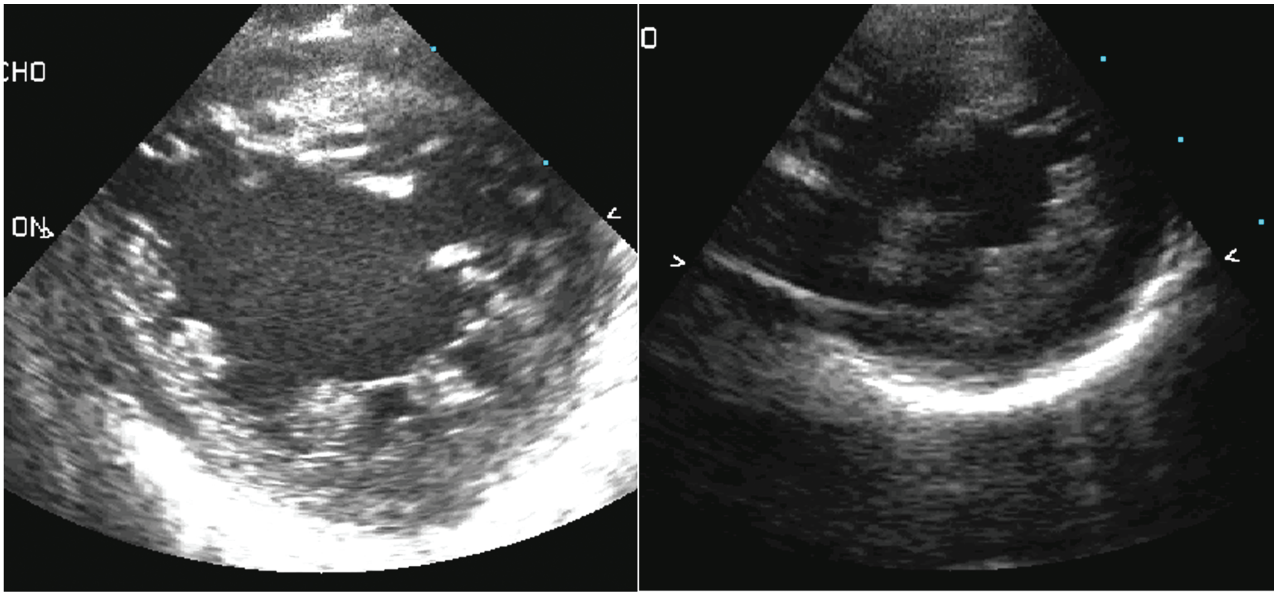

Figure 3.
The parasternal short axis view from our second patient (left) shows a dilated left ventricle with noncompaction. The parasternal short axis view from the same patient (right) taken 2 months later reveals resolution of the ventricular dilation and left ventricular hypertrophy. Noncompaction is still seen.

of the compacted layer (Fig. 3). In 4 patients, changes were seen in the structure of the mitral valve, with development of thickened leaflets with an abnormal pattern of coaptation and mitral regurgitation (Fig. 4). In our sixth and seventh patients, this mitral regurgitation was sufficiently severe to cause cardiac failure. In the sixth patient, a screening echocardiographic examination done at birth because of noncompaction diagnosed in the patient's twin sister showed extensive noncompaction of the ventricular myocardium (Fig. 5) with a normal mitral valve. She subsequently developed progressive severe mitral regurgitation, and needed replacement of the mitral valve at 14 months of age.

In 8 patients (53%), noncompaction of the ventricular myocardium was associated with congenital cardiac malformations we had deemed to be noncomplex, specifically one patient with multiple ventricular septal defects (Fig. 6), 4 patients with large ventricular septal defects, 3 perimembranous inlet and 1 muscular trabecular, one with a small perimembranous inlet ventricular septal defect and a large persistently

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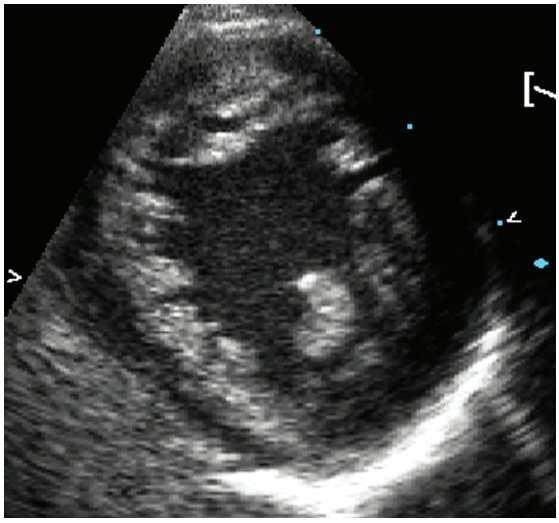

Figure 4.
The parasternal short axis view in our fifth patient showing noncompaction involving all segments.

patent arterial duct, one with a small muscular ventricular septal defect, and one with a small persistently patent arterial duct. In 5 patients, the ventricular septal defect was large enough to cause cardiac failure. On follow-up, the cardiac failure and dilation of the left-sided chambers improved with spontaneous closure of the defects in the patient with multiple ventricular septal defects.

Of the 4 patients who underwent surgical closure of ventricular septal defects, two had significant residual leaks of 4 and 6 mm across the patch, while a third patient in whom associated cleft of the mitral valve had been repaired developed severe regurgitation through the cleft post-operatively.

Discussion

In this study, we have used strict echocardiographic criterions[6,7] to make the diagnosis of ventricular noncompaction in a group of patients with heterogeneous

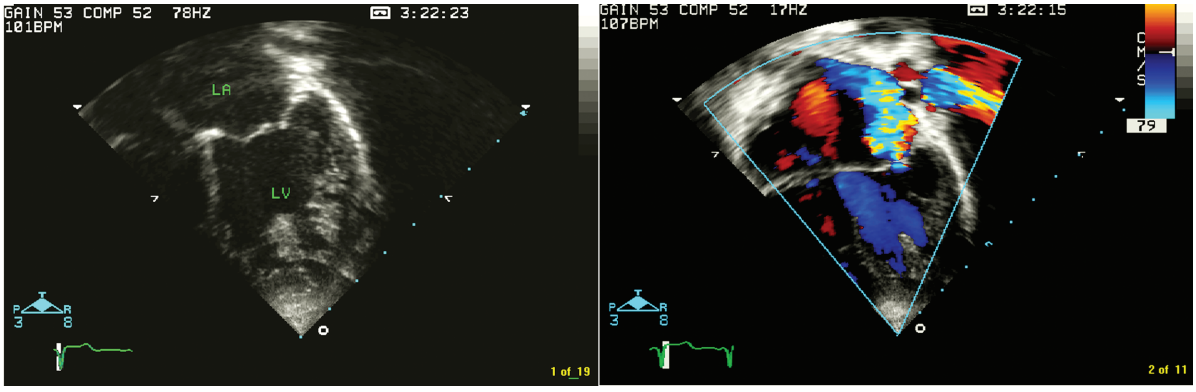

Figure 5.
The apical 4-chamber view of our sixth patient (left) shows noncompaction at the apex of the left ventricle. Note the abnormal coaptation of the mitral valve. The same view with colour flow mapping (right) reveals multiple recesses in the myocardium (arrows) and mild mitral regurgitation.

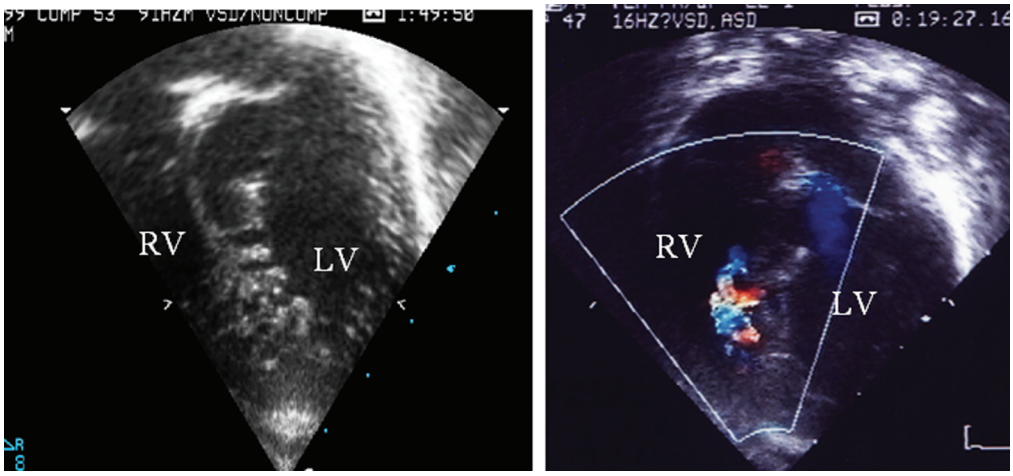

Figure 6.
The apical 4-chamber view of our seventh patient (left) shows noncompaction of the apex and septal surface of the left ventricle. The same view with colour flow mapping (right) shows multiple ventricular septal defects.

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clinical presentation. In making our echocardiographic diagnosis, we recognize that the anatomicopathological definition of the condition needs further refinement, and that such definitions, not only anatomic but also echocardiographic, remain contentious issue.[8,9] Based on our experience, we believe that the recognition of deep intertrabecular recesses in hearts with a noncompacted ventricular layer is a feature which can be helpful in making the differentiation from primary or secondary ventricular hypertrophy, but further anatomico-pathological evidence is required to determine whether this feature is truly of value in defining a specific phenotype.

The criterions proposed by Jenni et al.[6] use a strict measurement of the ratio of thicknesses of the noncompacted and compacted layers of the ventricular walls as well as taking account of intertrabecular recesses. Although these criterions would appear to provide reasonable echocardiographic definition for noncompaction, they have recognizable limitations. First, the site of maximum noncompaction in most series, as in ours, is at the level of papillary muscles, which may make measurement somewhat difficult. Second, the ratio of 2:1 proposed by Jenni et al.[6] is arbitrary, and as the presence of recesses depends on the volume of the ventricle, as noted by Stollberger et al.,[8] this ratio may differ if the ventricular dimensions themselves changed, as was the case in our second patient, where the ratio decreased from 2.2:1 to 0.9:1 on follow-up. Had this patient not been seen initially, then presumably, using the criterions of Jenni et al.,[6] we would not now be justified in making the diagnosis of noncompaction. Such difficulties are now compounded by the suggestion of Ricardo et al.,[10] who propose that a ratio of 1.4:1 be taken as indicative of noncompaction. The criterions of Jenni et al.[6] also require the exclusion of associated cardiac disease. Thus, they describe the disease as "isolated" noncompaction of the ventricular myocardium, possibly in an attempt to distinguish the entity from that associated with complex congenital cardiac malformations. We chose to exclude this latter group of patients from our series, but believe that the application of the echocardiographic criterions is feasible and of value in patients with simpler congenital cardiac anomalies. In this respect, our study shows that noncompaction of the ventricular myocardium can be associated with a variety of "simple" congenital cardiac malformations, as described by others,[3] and it is certainly the case that noncompaction can be found also in association with complex malformations. The criterions used in our study have previously been used mainly in adults, but again like others, we did not find particular difficulty in applying them to infants. In spite of their recognizable limitations, therefore, we think that the criterions suggested by Jenni et al.[6] remain of value in helping to clarify the nature and frequency of noncompaction. Congenital heart defects that cause ventricular dilation, such as ventricular septal defect, or persistent patency of the arterial duct, are not known to cause the trabeculations and recesses characteristic of noncompaction, and thus we believe that the recognition of those features should alert the observer to the diagnosis of this disease.

The association of noncompaction with ventricular septal defects in our series may well reflect a higher incidence of asymptomatic cases with noncompaction in the population than previously thought. The presence of a murmur, or cardiac failure, brings these patients to medical attention earlier. It is known that, in the chick, the muscular ventricular septum develops by coalescence of sheets of primitive myocardial trabeculations,[11] although there is no evidence that a similar mechanism is active in mammals.[12] Noncompaction of the septum, nonetheless, would explain our frequent finding of ventricular septal defects in the setting of failure of the normal compaction of the parietal ventricular walls. In this respect, although a "cause and effect" relation is not clear, it was recently found that all mouse embryos with a deficiency of a nuclear protein necessary for cardiac development called "jumonji" were found to have noncompaction of the ventricular myocardium along with ventricular septal defects, indicating a likely association.[13]

Only one-third of our patients presented with signs of cardiac failure due to depressed myocardial function. This rate is comparable to that seen in adults.[6] Although the majority continued to have depressed function, one patient showed an unexpected improvement of her ventricular dimensions and function with decrease of the observed ration between the noncompacted and compacted layers associated with thickening of the compacted layer, an observation also recently been reported by Ricardo et al.[10] The mechanism of mitral regurgitation in the four patients with preserved myocardial systolic function was unclear. The presence of a normal mitral valve at birth in our sixth patient excludes congenital mitral regurgitation as a cause. The mitral valve in all four patients showed significant echocardiographic abnormalities, and a characteristic abnormal pattern of coaptation. Some reports have documented that noncompaction of the ventricular myocardium is associated with significant myocardial ischaemia, as shown by positron emission tomography and magnetic resonance imaging.[14,15] The presence of thickening of the leaflets, nonetheless, militates against an ischaemic aetiology as the sole cause of mitral regurgitation in these patients.

The association of noncompaction of the ventricular myocardium with Dandy Walkers syndrome,

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comprising a cerebellar cyst with communicating hydrocephalus, and Down's syndrome, has not to our knowledge been reported in the literature. The clinical course of our second and sixth patients, both being twins, was strikingly different. Although both patients had an abnormal mitral valve, the second patient developed a transient depression of her function, with no progression of the mitral regurgitation, while her twin sister progressed to develop severe mitral regurgitation with preserved ventricular function.

The incidence of noncompaction of the ventricular myocardium was clearly higher in females, indicating that the genetic abnormality is likely to be different from the known Xq 28 deletion.[16] Of the 6 patients who had cardiac surgery, the twelfth patient suffered postoperative ventricular arrhythmias, which is a known complication of noncompaction of the ventricular myocardium. In the others, the postoperative course was uneventful, but 3 out of 4 patients who underwent closure of their ventricular septal defects ended with significant residual lesions. In two, there were significant residual leaks, and one had severe regurgitation across a repaired cleft in the mitral valve. This incidence of residual lesions is higher than observed in the patients who underwent similar repairs in our centre with no evidence of noncompaction of the ventricular myocardium.

The frequency of noncompaction as detected in our echocardiography laboratory, at 20 per 10,000 echocardiograms, excluding those with complex congenital cardiac malformations, is high. The reported frequency of detection from Switzerland in adults was 4.5 in 10,000, which was comparable to that reported in children from Turkey, namely 6 per 10,000. Although this might well be due to geographical and genetic variation, we believe that the rate of detection is improving with increasing awareness of this disease. Recent reports from Australia[17,18] support this belief, with the authors concluding that noncompaction of the ventricular myocardium is an important, and often under-diagnosed, cause of cardiomyopathy. In its isolated form, noncompaction accounted for almost one-tenth of cases of cardiomyopathy, and for children with congenital cardiac disease undergoing angiography, it was noted in 2% of cases. A report from the United States of America[10] also concluded that this disease is relatively common. In our experience, noncompaction of the ventricular myocardium in children is not usually isolated, but is rather associated with a variable range of abnormalities, which as shown by our experience, includes noncomplex congenital cardiac disease and mitral regurgitation. The clinical course can be variable, even within the same family. We conclude, therefore, that noncompaction of the ventricular myocardium is not as rare as previously thought, and the finding should always be carefully sought during echocardiographic examinations.

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