Isolated Noncompaction of Left Ventricular Myocardium
A Study of Eight Cases

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Isolated noncompaction of left ventricular myocardium is a rare disorder of endomyocardial morphogenesis characterized by numerous, excessively prominent ventricular trabeculations and deep intertrabecular recesses. This study comprised eight cases, including three at necropsy. Ages ranged from 11 months to 22.5 years, with follow-up as long as 5 years. Gross morphological severity ranged from moderately abnormal ventricular trabeculations to profoundly abnormal, loosely compacted trabeculations. Echocardiographic images were diagnostic and corresponded to the morphological appearances at necropsy. The depths of the intertrabecular recesses were assessed by a quantitative echocardiographic X-to-Y ratio and were significantly greater than in normal control subjects (p < 0.001). Clinical manifestations of the disorder included depressed left ventricular systolic function in five patients, ventricular arrhythmias in five, systemic embolization in three, distinctive facial dysmorphism in three, and familial recurrence in four patients. We conclude that isolated noncompaction of left ventricular myocardium is a rare if not unique disorder with characteristic morphological features that can be identified by two-dimensional echocardiography. The incidence of cardiovascular complications is high. The disorder may be associated with facial dysmorphism and familial recurrence. (Circulation 1990;82:507–513)

In the early embryo, the heart is a loose interwoven mesh of muscle fibers.1-3 The developing myocardium gradually condenses, and the large spaces within the trabecular meshwork flatten or disappear. Trabecular compaction is normally more complete in left ventricular than in right ventricular myocardium. Noncompaction of ventricular myocardium (sometimes referred to as “spongy myocardium”) is believed to represent an arrest in endomyocardial morphogenesis.4,5 The gross anatomical appearance is characterized by numerous, excessively prominent trabeculations and deep intertrabecular recesses. Rare in any case, noncompaction is almost invariably associated with other congenital cardiac malformations.4-5 Isolated noncompaction of left ventricular myocardium (INVM) (i.e., without associated anomalies) is rarer still.5-7 This report represents the largest study population to date.

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Methods
The study comprised eight patients referred to the UCLA Medical Center during a 5-year period ending in December 1988. The sex ratio was 1.7:1 (five males and three females). The mean age at presentation was 8.9 years (range, 11 months to 22.5 years). The data included a personal and family history, physical examination, 12-lead scalar electrocardiogram, chest roentgenogram, two-dimensional echocardiogram with Doppler interrogation, and necropsy studies in three patients (patients 1, 5, and 6; Table 1). Patients 4, 7, and 8 had 24-hour Holter monitoring, and patients 7 and 8 had intracardiac electrophysiological studies.

Two-dimensional echocardiograms were recorded in all patients with the ATL Ultramark 6 or 8 Advanced Technology Laboratories, Bothell, Wash. Diagnoses of INVM were based on the presence of numerous, excessively prominent trabeculations associated with deep intertrabecular recesses (Figures 1 and 2). Coexisting cardiac anomalies were meticulously excluded. Standard measurements of left ventricular end-diastolic dimensions (LVEDD), left ventricular free wall thickness at end diastole (LVWTd), and fractional shortening (FS) were normalized to body surface area. LVWTd was measured.
at the level of the mitral valve and at the level of the papillary muscles with the parasternal long-axis view. Measurements at the apex used the subxiphoid or apical four-chamber views.

To quantify the depth of penetration of the intertrabecular recesses with two-dimensional echocardiography, an X-to-Y ratio was developed (Figure 3). This ratio is the quotient of the distance between the epicardial surface and trough of a trabecular recess (represented by X) and the distance between the epicardial surface and peak of the trabeculation (represented by Y). The X-to-Y ratios at the levels of the mitral valve, papillary muscles, and apex in patients with INVM were compared with values from a control group of eight subjects with normal two-dimensional echocardiograms (sex ratio, 1.7:1; mean age, 5 years; range, 1.3-10.8 years). Two observers independently interpreted the echocardiograms in

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**FIGURE 1. Echocardiogram of patient 1.** Subxiphoid long-axis view shows numerous prominent left ventricular trabeculations, increased depth of intertrabecular recesses (arrows), and apical thickening. LA, left atrium; LV, left ventricle; s, superior; i, inferior; r, right; l, left.
FIGURE 2. Panel a: Photomicrograph of autopsy specimen from patient 1 showing numerous verrucous protrusions (upper black arrows), deep interventricular recesses (lower black arrows), and endocardial surface (upper white arrows). Panel b: Photograph of myocardium specimen from patient 6 showing thrombi (black arrows) in cross section within interventricular recesses at apex of left ventricle (LV). White arrows identify some excessively numerous, deep interventricular recesses penetrating the endocardial surface.
the patients and the controls. Results were evaluated for the degree of interobserver variation with the paired Student's t test. Significant differences in X-to-Y ratios between patients and controls were determined with the nonpaired Student's t test.

Necropsy studies were performed on the three patients who died. After formalin fixation, histological sections of ventricular myocardium and septum were stained with hematoxylin and eosin, Masson trichrome, and Van Gieson elastic stains.

Results

Clinical Information

Two patients were asymptomatic but were identified because of a sibling who had INVM (Table 1). Depressed left ventricular systolic function was clinically overt in five patients (63%). FS ranged from 10% to 33%. LVEDD (five patients) and LVWTd (six patients), adjusted for body surface area, were greater than the 95th percentile.

Five patients (63%) had ventricular arrhythmias ranging from isolated, unifocal premature ventricular beats not clearly outside normal range (patients 1 and 7) to ventricular tachycardia and fibrillation (patients 3–5). Patient 3 had supraventricular tachycardia with Wolff-Parkinson-White bypass tracts (documented at 2 months of age) and experienced four episodes of cardiac arrest ascribed to ventricular fibrillation (when 6–15 months old). Patient 4 exhibited runs of ventricular tachycardia; subsequent development of complete heart block required resuscitation and a right ventricular pacemaker. Patients 7 and 8 had resting heart rates of less than 40 beats/min. Patient 7's heart rate decreased to 20 beats/min during sleep. Premature ventricular beats occurred during subsequent exercise testing in this patient, but ventricular tachycardia was not inducible during intracardiac electrophysiologic study. Patient 5 had no history of ventricular arrhythmias but died in ventricular fibrillation after hospitalization for a cerebral embolus and depressed left ventricular function.

Systemic emboli were clinically overt in three patients (38%). In patients 1 and 5, the emboli were cerebral. Patient 6 had a saddle embolus to the bifurcation of the abdominal aorta. Left ventricular mural thrombi were identified on echocardiography in patient 5 and at necropsy in patient 6 (Figure 2b). Noncardiac malformations included a distinctive dysmorphic facial appearance characterized by prominent forehead, strabismus, low-set ears, and micrognathia (patients 1–3; Figure 4). The three patients with facial dysmorphism exhibited motor and speech defects; these defects had been present since birth in patients 1 and 2. In patient 3, these defects were attributed (perhaps incorrectly) to cerebral hypoxia after cardiac arrest.

Familial recurrence of INVM was present in two brothers (patients 7 and 8). There was also familial recurrence in two half-brothers (patients 1 and 2) born to the same mother.

Scalar electrocardiograms showed left- or right-axis deviation in two patients (patients 2 and 8), broad or peaked P waves in three (patients 2, 4, and 5), first-degree heart block in two (patients 1 and 2), and left ventricular conduction defects (intraventricular) in two (patients 4 and 5).

Chest roentgenograms were normal in the asymptomatic patients. There was cardiomegaly in patients 1 and 4–6, who had clinically overt depressed left
ventricular function. Pulmonary edema was evident in the roentgenograms of patients 5 and 6.

Two-dimensional echocardiograms disclosed numerous prominent trabeculations and deep intertrabecular recesses (Figure 1) in all eight patients. The trabeculations were least prominent and least numerous near the level of the mitral valve where the X-to-Y ratio was 0.92±0.07 (mean±SEM). The X-to-Y ratio decreased to 0.59±0.05 at the papillary muscle level and decreased further to 0.20±0.04 at the apex of the left ventricle (Figure 5a) where the depth of the intertrabecular recesses and the increased wall thickness were most prominent. The mean LVWTd was 8.6±1.6 mm at the level of the mitral valve, 13.3±1.2 mm at the papillary muscle level, and 22.9±1.2 mm at the apex (Figure 5b). The control echocardiograms did not disclose the progressive decrease in the X-to-Y ratio and the accompanying increase in LVWTd from mitral valve level to apex (Figure 5). There was a marked increase in apical wall thickness (Y) when normal control subjects were compared with patients (5.6 versus 22.9 mm, respectively), but epicardial surface to trough of trabeculation (X) was virtually the same (4.8 versus 4.7 mm, respectively). These observations encouraged our belief that the calculated abnormalities in X-to-Y ratios reflected the disease process—noncompaction—rather than a technical error in measurement because of proximity of the transducer to the heart in the apical view or a tangential beam in the subcostal view. The difference in X-to-Y ratio between patients and controls at the mitral valve level was not significant. At the levels of the papillary muscles and apex, the X-to-Y ratio was significantly smaller in the patients (p<0.001). Interobserver variation in measurements of the X-to-Y ratio was insignificant at the levels of the mitral valve and papillary muscles but were significant at the apex (p<0.001). Echocardiographic abnormalities of right ventricular myocardium were not detected.

At necropsy (three patients), the gross left ventricular endomyocardial morphology (Figure 2) corresponded to the two-dimensional echocardiographic patterns. Patient 6 had clot within the intertrabecular recesses of the left ventricular apex (Figure 2b). The deep intertrabecular recesses were successfully examined histologically in two patients. The recesses, including their troughs, were lined with endothelium that was continuous with ventricular endocardial endothelium (Figure 6), indicating that the recesses were not sinusoids. Zones of fibrous and elastic tissue were scattered on the endocardial surfaces, with extension into the intertrabecular recesses (Figure 2). Because areas of normal endomyocardium might be interspersed with noncompaction (patient 5), sections were taken with meticulous care to avoid missing the typical histology of noncompaction. In patient 1, the right ventricular trabeculations and intertrabecular recesses were relatively prominent, but no quantitative conclusions could be drawn.

Discussion

“Discrete muscle bundles, more than 2 mm in diameter, that stood out against the background of the left ventricular endocardium” have been reported in 68% of normal hearts but are virtually always three or less in number.8 In contrast, noncompaction of ventricular myocardium, exemplified by our cases, is characterized by numerous, prominent trabeculations and conspicuous intertrabecular recesses that penetrate deep into the left ventricular myocardium (Figures 1, 2, and 6). Left ventricular noncompaction—a rare if not unique disorder of endomyocardial morphogenesis—consists of trabeculations that are both increased in prominence and excessive in number. The echocardiographic pattern is diagnostic (Figure 1) and can be quantified with relative confidence by an X-to-Y ratio that decreases from the level of the papillary muscles to the apex (Figure 5a). Discrimination of the epicardial surface was difficult at the left ventricular apex due to proximity of the echocardiographic transducer to the heart. Accordingly, there was significant interobserver variation in the X-to-Y ratio at the apex in contrast to insignificant interobserver variation at the levels of the mitral valve and papillary muscles. However, variation in measurement at the apex in any given case was small (mean±SEM, 1.4±0.5 mm; range, 0–5 mm) compared with the
differences between patient and control groups (mean±SEM, 4.8±0.2 versus 4.7±1.0 mm for X and 5.6±0.2 versus 22.9±1.2 mm for Y).

Histological examination disclosed that the deep intertrabecular recesses were lined with endothelium that was continuous with the endocardial endothelium (Figure 6), indicating that the “spongy” appearance of noncompaction was due to the deep intertrabecular recesses per se and not to intramyocardial sinusoids. Accordingly, the term “persistent sinusoids” is not appropriate. The descriptive term “spongy myocardium” has the virtue of precedence, but we prefer “ventricular noncompaction” for two reasons. First, it underscores the hypothesis that the basic morphogenetic abnormality may be an arrest of the normal process of compaction of the loose interwoven mesh of myocardial fibers in the embryo. Second, some hearts with “spongy myocardium” have heavy trabeculations in the affected ventricle, but it does not follow that every heavily trabeculated ventricle has a “spongy myocardium.”

Relatively rare in any case, ventricular noncompaction has almost invariably been associated with other congenital cardiac malformations, including anomalous origin of the left coronary artery from the pulmonary trunk6 and obstruction to right or left ventricular outflow.9–11 Isolated left ventricular noncompaction is even more rare6–7; its natural history and clinical manifestations have therefore been ill defined. Our eight patients represent the largest study population to date and shed new light on the clinical and morphological spectrum of this disorder. Based on these observations, three major cardiac risks emerged: 1) depressed systolic function of the noncompacted left ventricle, 2) endocardial clot with systemic embolization, and 3) ventricular arrhythmias, sometimes fatal.

Depressed left ventricular function may be absent at the time of presentation (patients 2, 7, and 8) or may be clinically overt since infancy or childhood (patients 1 and 3–5) or since young adulthood (patient 6). The cause of depressed left ventricular function is not clear. The coronary arterial circulation is normal in hearts with isolated ventricular noncompaction (noncompacted left ventricle perfused by a morphological left coronary artery), so extramural myocardial blood supply is not likely to be at fault. However, intramural perfusion, particularly subendocardial, may be adversely affected by the prominent trabeculations and deep intertrabecular recesses. The increased fibrous and elastic tissue on the endocardium and within the intertrabecular recesses (Figure 2) may be due to subendocardial ischemia, perhaps in response to isometric contraction among the trabeculae and within the recesses. The prominent trabeculations of left ventricular noncompaction resemble right ventricular endomyocardial morphology. It may therefore be relevant that patients with univentricular hearts of the morphological right ventricular type have poorer ventricular function than those of the left ventricular type,12 despite similar extramural coronary circulations.

The endomyocardial morphology of left ventricular noncompaction lends itself to the development of mural thrombi within the deep intertrabecular recesses.
(Figure 2b). Three of our patients (1, 5, and 6) had overt systemic emboli from this source. In two patients (1 and 5), the emboli were cerebral. Accordingly, it is prudent to repeat the echocardiogram at periodic intervals, regardless of whether clot is initially identified. Anticoagulants are warranted when thrombi are seen on echocardiography.

Ventricular arrhythmias were documented in five of the eight patients and were the presenting complications in two. It is unclear why isolated left ventricular noncompaction is arrhythmogenic. Zones of thin ventricular wall in the troughs of the intertrabecular recesses are reminiscent of the morphology of the right ventricle in arrhythmogenic right ventricular dysplasia. An analogy to arrhythmogenic right ventricular dysplasia is attractive but conjectural. 13-15

Patients 1 and 2 and patients 7 and 8 are the first known examples of familial recurrence of isolated noncompaction of left ventricular myocardium. Because of potential familial recurrence, identification of an index case warrants echocardiographic assessment of first-degree relatives, particularly siblings; patients 2 and 7 were identified in this fashion. Patients 1–3 represent the first reported association between facial dysmorphism and INVM (Figure 4). These three dysmorphic patients also had developmental and mental defects. Patient 3's motor and cognitive abnormalities were attributed (perhaps incorrectly) to cerebral hypoxia induced by cardiac arrest.

Conclusions

Isolated noncompaction of left ventricular myocardium is a rare if not unique disorder that may manifest itself from infancy through young adulthood. Both sexes are affected. Distinct morphological features can be diagnosed on two-dimensional echocardiography; these features correspond to the gross endomyocardial morphology at necropsy. Isolated noncompaction of left ventricular myocardium is accompanied by three major cardiac risks: 1) depressed ventricular function, 2) endocardial clot with systemic embolization, and 3) ventricular arrhythmias, sometimes fatal. The disorder may be familial and may be associated with distinctive facial dysmorphism.

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References


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