Mortality and Sudden Death in Pediatric Left Ventricular Noncompaction in a Tertiary Referral Center

Samuel T. Brescia, MD; Joseph W. Rossano, MD; Ricardo Pignatelli, MD; John L. Jefferies, MD; Jack F. Price, MD; Jamie A. Decker, MD; Susan W. Denfield, MD; W. Jeffrey Dreyer, MD; O’Brian Smith, PhD; Jeffrey A. Towbin, MD; Jeffrey J. Kim, MD

Background—Left ventricular noncompaction is a cardiomyopathy characterized by excessive trabeculation of the left ventricle, progressive myocardial dysfunction, and early mortality. Left ventricular noncompaction has a heterogeneous clinical presentation that includes arrhythmia and sudden cardiac death.

Methods and Results—We retrospectively reviewed all children diagnosed with left ventricular noncompaction at Texas Children’s Hospital from January 1990 to January 2009. Patients with congenital cardiac lesions were excluded. Two hundred forty-two children were diagnosed with isolated left ventricular noncompaction over the study period. Thirty-one (12.8%) died, and 13 (5.4%) were received a transplant. One hundred fifty (62%) presented with or developed cardiac dysfunction. The presence of cardiac dysfunction was strongly associated with mortality (hazard ratio, 11; \( P < 0.001 \)). ECG abnormalities were present in 87%, with ventricular hypertrophy and repolarization abnormalities occurring most commonly. Repolarization abnormalities were associated with increased mortality (hazard ratio, 2.1; \( P = 0.02 \)). Eighty children (33.1%) had an arrhythmia, and those with arrhythmias had increased mortality (hazard ratio, 2.8; \( P = 0.002 \)). Forty-two (17.4%) had ventricular tachycardia, with 5 presenting with resuscitated sudden cardiac death. In total, there were 15 cases of sudden cardiac death in the cohort (6.2%). Nearly all patients with sudden death (14 of 15) had abnormal cardiac dimensions or cardiac dysfunction. No patient with normal cardiac dimensions and function without preceding arrhythmias died.

Conclusions—Left ventricular noncompaction has a high mortality rate and is strongly associated with arrhythmias in children. Preceding cardiac dysfunction or ventricular arrhythmias are associated with increased mortality. Children with normal cardiac dimensions and normal function are at low risk for sudden death. (Circulation. 2013;127:2202-2208.)

Key Words: arrhythmias, cardiac ■ cardiomyopathies ■ death, sudden ■ heart failure
the ventricular cavity, as demonstrated by color Doppler; and (3) a 2-layered structure of the endocardium with a noncompacted to compacted ratio >2.0. Patients were included in the cohort only if both echocardiogram reviewers agreed on the diagnosis. Patients with LVNC and associated congenital heart disease or known metabolic syndromes (nonisolated LVNC) were excluded. Only patients primarily followed up at Texas Children’s Hospital for LVNC were included; patients referred for isolated second opinions or only seen for single visits (without longitudinal follow-up) were excluded. The present study was approved by the Baylor College of Medicine Institutional Review Board, and individual consent was waived. Medical records were reviewed to document clinical presentation and course. Serial echocardiograms were analyzed for measures of systolic function (shortening fraction and ejection fraction), and cardiac dimensions were measured by M-mode echocardiography. Ejection fraction was calculated by the Simpson biplane method. Cardiac systolic dysfunction was defined as an ejection fraction <55% or, if unavailable, a shortening fraction less than −2 z scores for age. Patients were divided into 4 distinct phenotypes of LVNC: Dilated, hypertrophic, mixed, and normal dimensions. The dilated phenotype was assigned if the left ventricular end-diastolic dimension was >2 z scores for age. The hypertrophic phenotype was assigned if septal or posterior wall diastolic measurements were >2 z scores for age. Trabecular myocardium was not included in the measurement. Patients were classified as having the mixed phenotype if there was evidence of both left ventricular dilation and hypertrophy based on M-mode measurements. Patients were classified as having the normal-dimension phenotype if all cardiac dimensions were found to be within normal limits (within 2 z scores) for body surface area. Holter evaluations and 15-lead ECGs were reviewed by a blinded pediatric electrophysiologist (J.K.) and examined for abnormalities. ECG findings were defined as atrial tachycardia, atrial flutter, junctional tachycardia, or reentrant supraventricular tachycardia. ECG findings were also analyzed and compared with clinical outcomes. Univariate survival data were evaluated with Kaplan–Meier survival analysis with log-rank statistics. Time zero for survival analysis was at time of diagnosis/presentation (only factors present at the time of diagnosis were included). Cox proportional hazards regression analysis with covariates, including both continuous and categorical data, was used to fit the data. Statistical analysis was performed with SPSS statistical software, version 16.0 (SPSS Inc, Chicago, IL).

Results

Cohort Characteristics

Two hundred forty-two patients were diagnosed with isolated LVNC over the 18-year study period and were included in the present study. There were an additional 43 patients with prominent trabeculations and presumed LVNC who did not meet proposed diagnostic criteria based on echocardiographic review and thus were excluded from the study. The diagnosis of LVNC became more common over time, with 25 patients being diagnosed over the first 9 years of the study and 217 patients being diagnosed over the last 9 years; however, the frequency of diagnosis stabilized over time, with no significant change in the incidence of diagnosis over the last 8 years of the study (P=NS). One hundred forty-five patients (60%) were male and 97 (40%) were female. Ninety-nine patients (41%) were black, 80 (34%) were white, 52 (21%) were Hispanic, 6 (2%) were Asian, and 5 (2%) were other. The mean age at diagnosis was 7.2±6.9 years, although 95 patients (39%) were presented within the first year of life (infantile LVNC). Fifty-six patients (23%) had a family history of cardiomyopathy in 91 relatives, although only 14 (25%) of 56 had a family history of LVNC, with the remainder having a family history of dilated cardiomyopathy (n=27), hypertrophic cardiomyopathy (n=5), or a combination of cardiomyopathy types (n=10). One hundred eighty-six patients (77%) had de novo presentations. The median duration of follow-up was 4.0 years (range, 1.8–15.9 years). Demographic factors are summarized in Table 1.

Clinical Presentation

Sixty patients (25%) presented primarily with signs and symptoms of congestive heart failure. Forty-two patients (17%) presented with arrhythmias or suspected arrhythmias. Of these, 25 patients (10%) presented with documented arrhythmias, 5 presented with aborted sudden death, and an additional 12 were referred for evaluation of unexplained syncope. Twenty-two patients (9%) presented with a primary complaint of chest pain. Forty-five patients (19%) were referred for evaluation of murmurs or abnormal heart sounds, 24 (10%) were referred for abnormal baseline ECG findings, and 16 (7%) were referred because of cardiomegaly noted on chest radiograph. Thirty-three patients (14%) were found to have LVNC on screening echocardiography related to family history or as an incidental finding on echocardiography performed for other reasons (athletic screenings or for other indications). LVNC was primarily followed up at Texas Children’s Hospital for LVNC were included; patients referred for isolated second opinions or only seen for single visits (without longitudinal follow-up) were excluded. The present study was approved by the Baylor College of Medicine Institutional Review Board, and individual consent was waived. Medical records were reviewed to document clinical presentation and course. Serial echocardiograms were analyzed for measures of systolic function (shortening fraction and ejection fraction), and cardiac dimensions were measured by M-mode echocardiography. Ejection fraction was calculated by the Simpson biplane method. Cardiac systolic dysfunction was defined as an ejection fraction <55% or, if unavailable, a shortening fraction less than −2 z scores for age. Patients were divided into 4 distinct phenotypes of LVNC: Dilated, hypertrophic, mixed, and normal dimensions. The dilated phenotype was assigned if the left ventricular end-diastolic dimension was >2 z scores for age. The hypertrophic phenotype was assigned if septal or posterior wall diastolic measurements were >2 z scores for age. Trabecular myocardium was not included in the measurement. Patients were classified as having the mixed phenotype if there was evidence of both left ventricular dilation and hypertrophy based on M-mode measurements. Patients were classified as having the normal-dimension phenotype if all cardiac dimensions were found to be within normal limits (within 2 z scores) for body surface area. Holter evaluations and 15-lead ECGs were reviewed by a blinded pediatric electrophysiologist (J.K.) and examined for abnormalities. ECG findings were defined as atrial tachycardia, atrial flutter, junctional tachycardia, or reentrant supraventricular tachycardia. ECG findings were also analyzed and compared with clinical outcomes. Univariate survival data were evaluated with Kaplan–Meier survival analysis with log-rank statistics. Time zero for survival analysis was at time of diagnosis/presentation (only factors present at the time of diagnosis were included). Cox proportional hazards regression analysis with covariates, including both continuous and categorical data, was used to fit the data. Statistical analysis was performed with SPSS statistical software, version 16.0 (SPSS Inc, Chicago, IL).

Table 1. Demographics and Patient Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=242)</th>
<th>Death (n=31)</th>
<th>Transplant (n=13)</th>
<th>Sudden Death (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (iqr), mo</td>
<td>150 (185–170)</td>
<td>150 (115–170)</td>
<td>150 (120–170)</td>
<td>150 (115–170)</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>150 (50)</td>
<td>150 (50)</td>
<td>150 (50)</td>
<td>150 (50)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>90 (37)</td>
<td>90 (30)</td>
<td>90 (30)</td>
<td>90 (30)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (2)</td>
<td>5 (2)</td>
<td>5 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Myocardial phenotype, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated</td>
<td>150 (50)</td>
<td>150 (50)</td>
<td>150 (50)</td>
<td>150 (50)</td>
</tr>
<tr>
<td>Mixed</td>
<td>90 (37)</td>
<td>90 (30)</td>
<td>90 (30)</td>
<td>90 (30)</td>
</tr>
<tr>
<td>Hypertrophic</td>
<td>90 (37)</td>
<td>90 (30)</td>
<td>90 (30)</td>
<td>90 (30)</td>
</tr>
<tr>
<td>Normal dimensions</td>
<td>60 (25)</td>
<td>60 (20)</td>
<td>60 (20)</td>
<td>60 (20)</td>
</tr>
<tr>
<td>Cardiac dysfunction, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>150 (50)</td>
<td>150 (50)</td>
<td>150 (50)</td>
<td>150 (50)</td>
</tr>
<tr>
<td>VT/VF</td>
<td>42 (17)</td>
<td>42 (13)</td>
<td>42 (13)</td>
<td>42 (13)</td>
</tr>
</tbody>
</table>

Demographic factors and myocardial phenotype were as noted at presentation; cardiac dysfunction and arrhythmias were noted at any time during follow-up. IQR indicates interquartile range; VT, ventricular fibrillation; and VF, ventricular tachycardia.
Echocardiographic Findings

Two-dimensional echocardiography and standard M-mode measurements were reviewed for the entire cohort. Four distinct myocardial phenotypes were identified in patients with LVNC: Dilated, hypertrophic, mixed, and normal dimensions. Patients were classified on the basis of presenting echocardiograms as defined in Methods. Sixty-eight patients (28%) had a mixed phenotype with evidence of both dilation and hypertrophy. Sixty-six patients (27%) had the hypertrophic phenotype, and 46 patients (19%) had the dilated phenotype. Sixty-two patients (26%) had normal M-mode indices. Overall, ventricular systolic dysfunction was noted in 150 patients (62%) in the cohort (ejection fraction ranging between 8% and 51%). The majority of these (131 patients; 54%) had systolic dysfunction at presentation. An additional 19 patients (8%) developed systolic dysfunction during follow-up, an average of 47 months after presentation (range, 1–175 months). With regard to phenotype and the presence of dysfunction, 41 (89%) of 46 with dilated phenotype, 28 (42%) of 66 with hypertrophic phenotype, 59 (87%) of 68 with mixed phenotype, and 22 (35%) of 62 with normal dimensions were documented as having depressed systolic function.

ECG Findings

Two hundred ten patients (87%) were noted to have an abnormal ECG on presentation. Only 32 patients (13%) had normal ECGs. The most common ECG finding was voltage criteria for ventricular hypertrophy (predominantly left ventricular or biventricular hypertrophy), which was noted in 41% of patients. Some patients had extreme QRS voltage similar to that seen in Pompe disease; these were usually in infants or in the setting of ventricular preexcitation. Other common findings included isolated or diffuse T-wave inversion (39%), ST-segment abnormalities or strain (34%), atrial enlargement (19%), and left-axis deviation (9%). Twenty-two patients (9%) had a prolonged corrected QT interval (461–652 ms), and 20 patients (8%) had manifest preexcitation consistent with Wolff-Parkinson-White syndrome.

Arrhythmias

In total, 81 patients (33%) had a documented tachyarrhythmia. Forty-two patients (17%) had VT, 14 (6%) had atrial tachycardia, and an additional 19 (8%) had reentrant supraventricular tachycardia. Four patients had atrial flutter, 2 had accelerated junctional rhythm, and 1 had atrial fibrillation. Only 25 of these 81 patients had documented arrhythmias as a part of their presentation complex. The majority (56/81) developed arrhythmias during the course of their follow-up evaluation, an average of 27 months after presentation (range, 1–143 months).

Medical Therapy

Outpatients with cardiac dysfunction were typically treated with a combination of β-blockade and ACE inhibition. Of these patients, 61 (of 150; 41%) were noted to have some improvement in cardiac systolic function with medical therapy over follow-up. Per institutional practice, patients with normal cardiac dimensions and normal function were not placed on medical therapy and were not restricted in any way.

Thirty of the 42 patients with VT were initially treated with β-blockade alone, whereas 8 patients with associated severely depressed systolic function were treated with amiodarone as the initial primary therapy. Patients with recurrent VT while taking β-blockers were transitioned to more aggressive antiarrhythmic therapy, including amiodarone, sotalol, or mexiletine.

Invasive Therapy

Nineteen patients underwent invasive electrophysiological testing during follow-up. Six patients were found to have reentrant forms of supraventricular tachycardia, and 5 underwent successful radiofrequency ablation. One patient with a Wolff-Parkinson-White pattern on her surface ECG was found to be pseudopreexcited without intracardiac evidence of an accessory pathway. Eleven patients underwent programmed stimulation to evaluate for inducible ventricular arrhythmias. Four patients had inducible and sustained ventricular arrhythmias and subsequently underwent implantation with an implantable cardioverter-defibrillator. Two additional patients with monomorphic VT underwent successful mapping and ablation of a ventricular focus, neither of whom have had recurrent VT to date. In total, 11 patients underwent implantation with an implantable cardioverter-defibrillator. Two of these patients subsequently received transplants, and there has been 1 appropriate discharge for ventricular fibrillation over a mean follow-up of 4.8±3.4 years. One additional patient had an implantable cardioverter-defibrillator malfunction, refused a revision procedure, and subsequently died suddenly.

Figure 1. Clinical presentation and symptoms. Chart demonstrates distribution of primary clinical symptoms at initial presentation and primary reasons for referral. CHF indicates congestive heart failure; and CXR, chest X-ray.
Mortality
During the study period, 31 patients (12.8%) died and 13 (5.4%) underwent cardiac transplantation, thereby resulting in an 18% incidence of death or transplantation in the total cohort. Of the 44 patients who died or received transplants, 24 (55%) presented in the first year of life. Of the 95 patients who presented in the first year of life, 20 died and 4 required transplantation. The incidence of death or transplantation in infantile LVNC was thus 25%. By Cox proportional hazards regression with demographic factors as covariates, presentation within the first year of life was associated with increased mortality (hazard ratio [HR], 2.1; 95% confidence interval [CI], 1.0–3.9; \( P = 0.02 \); Table 2).

Ventricular systolic dysfunction developed in 150 patients (62%). The presence of cardiac systolic dysfunction was significantly associated with death or transplantation (HR, 11; 95% CI, 2.6–45; \( P < 0.001 \)), based on Cox proportional hazards regression with myocardial phenotype, arrhythmias, and parameters of function as covariates (Table 2). The cumulative 5-year survival from death or transplantation for patients with systolic dysfunction was 60% versus 98% for those with normal cardiac function (Figure 2). The patients’ identified phenotype also bore a direct relationship to the risk of death or transplantation based on log-rank statistics (\( P = 0.01 \)), with actuarial 5-year survival rates of 63% for the dilated phenotype, 64% for the mixed phenotype, 86% for the hypertrophic phenotype, and 98% for the normal-dimension phenotype (Figure 3). Patients with a normal-dimension phenotype had a significantly decreased risk of mortality (HR, 0.44; 95% CI, 0.32–0.60; \( P = 0.01 \)).

ECG abnormalities and arrhythmias were also strongly associated with outcomes. T-wave inversion (HR, 2.1; 95% CI, 1.1–4.2; \( P = 0.02 \)) and ST-segment abnormalities (HR, 4.0; 95% CI, 1.0–19.9; \( P = 0.05 \)) were independently associated with death or transplantation (Table 2) based on Cox proportional hazards regression with ECG findings, arrhythmias, and parameters of function as covariates. Interestingly, of the 32 patients with normal ECGs, none died during the study period. The presence of arrhythmias increased the risk of death or transplantation in this model (HR, 2.8; 95% CI, 1.4–5.6; \( P = 0.002 \)), with 30% of these patients dying or receiving a transplant during the study period. Of the 42 children who had documented VT, 18 (43%) died or received a transplant during follow-up, which represents a 4-fold increase (95% CI, 2.1–9.0; \( P < 0.001 \)) in this group (Table 2). Seven of these children died suddenly. Seven children presented with depressed systolic function and VT within the first year of life. Five of these children had calcificentric ventricular arrhythmias and died during follow-up, which represents a 12-fold increase (95% CI, 2.4–69.2) in the hazard for children presenting with cardiac dysfunction and VT before the age of 1 year compared with the hazard for children presenting later in life (\( P = 0.002 \)).

Sudden Death
In total, 15 patients (6.2%) experienced sudden cardiac death during the study period. Abnormal M-mode measurements with left ventricular dilatation, hypertrophy, or a combination of both were identified in 14 of 15 patients before their event. Preceding systolic dysfunction was identified in 13 of 15 patients with an average shortening fraction of 15.3%±8.1%. Nine of 15 patients also had a documented arrhythmia before cardiac arrest, with 8 patients having preexisting VT. The hazard of sudden death increased significantly in patients with a preceding arrhythmia (HR, 7.6; 95% CI, 1.5–37.8; \( P = 0.01 \)) based on Cox proportional hazards regression with ECG abnormalities and arrhythmias as covariates. Both patients who experienced sudden cardiac death who did not have associated cardiac dysfunction had preceding arrhythmias, with documented VT in 1 patient and Wolff-Parkinson-White syndrome and suspected atrial fibrillation in the other. No patient with normal cardiac dimensions and function without preceding arrhythmias died suddenly.

Discussion
In recent years, LVNC has become increasingly recognized as a discrete form of cardiomyopathy with a distinct underlying cause and prognosis.15 In the developing embryo, the myocardium begins as a loose interwoven mesh of muscle fibers and gradually condenses from epicardium to endocardium, which generally results in compaction of the endocardial surface between the fifth and eighth weeks of fetal life. This process of trabecular compaction typically progresses from the base of the heart toward the apex and is usually more complete in the left ventricle than in the right ventricle. Arrest in normal endomyocardial morphogenesis is thought to result in LVNC.5,14 Although initially thought to be a rare disorder, it has become clear that it is much more prevalent than previously recognized.9,12 Indeed, in the present study cohort, the diagnosis of LVNC increased over time, with the preponderance of cases being diagnosed over the past 10 years. This is likely attributable to an increased index of suspicion at our institution coupled with the enhanced quality of echocardiographic images in the current era. Our suspicion is that this pattern of increased recognition is likely mimicked globally, although it may have stabilized in recent years.

Table 2. Risk Factors for Death or Transplantation

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac dysfunction</td>
<td>11.1</td>
<td>2.6–45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T-wave inversion</td>
<td>2.1</td>
<td>1.1–4.2</td>
<td>0.02</td>
</tr>
<tr>
<td>ST-segment abnormalities or strain</td>
<td>4.0</td>
<td>1.0–19.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Any arrhythmias</td>
<td>2.8</td>
<td>1.4–5.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>4.0</td>
<td>2.1–9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presentation &lt;1 y with ventricular arrhythmias</td>
<td>12.0</td>
<td>2.4–68.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The table demonstrates the significant risk factors for death or cardiac transplantation during follow-up. Separate Cox proportional hazards models were used for demographic factors and other risk factors. \( P < 0.05 \) was considered significant. Only factors found to be statistically significant are displayed.
The present study is the largest report on the natural history of children with LVNC to date and highlights mortality profiles and the incidence of arrhythmias and sudden cardiac death in this patient population. Previous reports on pediatric LVNC have suggested mortality rates of 15% to 20% in short-term follow-up (2–3 years).\(^9,15\) Although those reports included patients with associated congenital heart lesions, the present study cohort had similar findings, with an overall mortality rate of 12.8% and a rate of death or transplantation of 18.2%. The present series suggests, as one might expect, that patients with myocardial dysfunction or preceding arrhythmias have a worse prognosis than those with isolated hypertrabeculation. Although this is not unique to LVNC compared with other forms of cardiomyopathy, it does confirm presumptions. Conversely, the cohort of patients with a diagnosis of LVNC and no signs of functional cardiomyopathy (no myocardial dysfunction, cardiac dilation, or arrhythmias) are distinctive in that they have some phenotypic manifestation of disease (hypertrabeculation) without existing functional abnormalities. Other forms of cardiomyopathy do not typically have a comparative population. In the present study, this group of patients appeared to do particularly well, and further long-term evaluation of this cohort is prudent.

Similar to previous studies, mortality in children presenting in the first year of life was significantly higher at 30.4%. The reason for higher mortality in infantile LVNC is not entirely clear, although they are more likely to present with symptomatic heart failure or arrhythmias, and this may underscore a more malignant genotype or more global, systemic disease. Although infants with known mitochondrial disease or metabolic syndromes were excluded, it is likely that some of these children escaped diagnosis and harbored the known higher mortality profiles associated with these syndromes. In the present study cohort, presentation in the first year of life with ventricular systolic dysfunction and...
associated ventricular arrhythmias predicted a particularly poor prognosis, with a 12-fold increase in the hazard of dying. Previous studies have described a heterogeneous phenotypic presentation of LVNC. In concordance, we identified 4 phenotypic subtypes of isolated LVNC in children (dilated, hypertrophic, mixed, and normal dimensions). There was a clear discrepancy in prognosis among these groups, with those expressing a dilated or mixed phenotype being the most likely to experience death or transplantation. More importantly, children with normal cardiac dimensions (no evidence of hypertrophy or dilation) did well, with very low mortality. Specific genetic mutations are possibly responsible for the phenotypic variability; ongoing studies hope to elucidate the cause of this heterogeneity. In addition, consideration should be given to the possibility that our current diagnostic standards for LVNC may be imprecise. Continued follow-up and additional study are necessary to further fine-tune diagnostic standards. The inclusion of more advanced imaging modalities and genetic testing may be warranted.

ECG abnormalities should also be considered as an adjunctive diagnostic feature of LVNC. In the present study cohort, ECG abnormalities were present in 87% of patients and were prevalent in both symptomatic and asymptomatic children. In 5% of cases, an abnormal ECG led to the diagnosis of LVNC by prompting additional evaluation. Characteristic ECG abnormalities included ventricular hypertrophy and repolarization abnormalities such as T-wave inversion and ST-segment changes. Similar repolarization abnormalities have been reported previously in children. In the present study cohort, T-wave inversion and ST-segment abnormalities were independently associated with cardiac death, whereas normal ECGs were associated with decreased mortality. We recommend obtaining ECGs in all patients referred for evaluation of possible LVNC and yearly in patients followed up with a diagnosis of LVNC, because they appear to harbor diagnostic and prognostic potential. Although early reports suggested that ventricular arrhythmias were uncommon in adults with LVNC, a recent review found the incidence to be as high as 33%. In pediatric patients, ventricular arrhythmias are indeed a relatively common complication of LVNC, affecting 17% of the children in the present study cohort. Additionally, ventricular arrhythmias continue to be a major cause of mortality, with the onset of VT being an indicator of poor prognosis. In the present study population, the presence of any arrhythmia was associated with an increased risk of death or transplantation; however, further stratification and survival analysis revealed that the predominant contributing rhythm abnormality was indeed ventricular arrhythmias. Infants with VT in association with depressed ventricular function appear to do particularly poorly, with the majority (71%) dying in the first year of life. This population warrants close observation and early consideration for transplantation.

It is unclear why the noncompacted myocardium is arrhythmogenic. With regard to Wolff-Parkinson-White syndrome and reentrant supraventricular tachycardia, it is hypothesized that primitive atrioventricular connections persist because of a generalized arrest in cardiac development. This developmental arrest in the ventricle may also result in increased dispersion of repolarization, as is often seen in immature myocardium, and may predispose to ventricular arrhythmias. Additionally, 2 separate studies have implicated progressive myocardial ischemia as a potential source for arrhythmogenesis. Myocardial perfusion scans of patients with LVNC demonstrate evidence of microcirculatory dysfunction, and pathological specimens demonstrate fibroelastosis of affected myocardium. In the present study cohort, ECG findings consistent with ischemia or strain were associated with increased mortality, which may support this hypothesis. Lastly, it has recently been recognized that certain genetic mutations can predispose individuals to both heart failure and arrhythmias by their resultant functional effects on both sarcomeric structure and ion channels. This may play a role in inherited forms of LVNC. Xq28 chromosomal abnormalities identified in separate families with LVNC have been localized to the G4.5 or tafazzin gene. This region has already been implicated in other cardiomyopathies that are associated with significant arrhythmias, including Barth syndrome, myotubular myopathy, and Emery-Dreifuss muscular dystrophy.

There are limited data about the clinical management of children with LVNC and arrhythmias, particularly regarding activity restrictions. Our practice has been to restrict activity for any patient with abnormal cardiac dimensions, cardiac dysfunction, or arrhythmias. We do not restrict patients with normal cardiac dimensions and function without evidence of arrhythmias from activity. To date, no patient with normal cardiac dimensions and function without preceding arrhythmias has died suddenly, and our data suggest that their risk of sudden death is low. We do recommend, however, continued follow-up, including yearly echocardiograms and Holter evaluations, to monitor for the development of occult abnormalities.

Study Limitations
The present study was a single-center retrospective evaluation from a large tertiary referral center and has limitations intrinsic to such an analysis. Although only patients primarily followed up at Texas Children’s Hospital for LVNC were included, it is possible that some patients presented with a presumptive diagnosis of LVNC before initial evaluation at our institution. As such, the use of time of diagnosis for survival analysis may harbor subtle inaccuracies. Findings in the present cohort may not be universally applicable to all populations. Also, although not insignificant, there were relatively few sudden death events, which limits the statistical power to analyze associated risk factors. Follow-up was also limited to 4 years to date. Lastly, because of the retrospective nature of echocardiographic review, diastolic parameters of cardiac function and a more detailed assessment of systolic function could not be analyzed extensively.

Conclusions
Although heterogeneous in its presentation and course, LVNC has a relatively high incidence of cardiac death and is strongly associated with life-threatening arrhythmias in children, particularly in those presenting with LVNC in the first year of life. ECG abnormalities are prominent and may harbor diagnostic and prognostic potential. Preceding cardiac dysfunction or ventricular arrhythmias have a robust
association with increased mortality and an increased risk of sudden cardiac death. As such, children with LVNC should have lifelong monitoring for the development of ventricular dysfunction or arrhythmias. Children with normal cardiac dimensions and normal function without preceding arrhythmias are likely at low risk for sudden death.

Disclosures

None.

References


CLINICAL PERSPECTIVE

Left ventricular noncompaction is a cardiomyopathy characterized by excessive trabeculation of the left ventricle, progressive myocardial dysfunction, and early mortality. There remains great interest in characterizing the natural history of this disease to help guide counseling and management of what is known to be a heterogeneous patient population. Current understanding of the natural history of left ventricular noncompaction is restricted to several case series and small studies. Although arrhythmias and sudden death have been reported, our understanding of mortality profiles in left ventricular noncompaction remains limited. This retrospective review of all children diagnosed with isolated left ventricular noncompaction at a single tertiary referral center provides the largest analysis to date, examining the mortality profiles and the incidence of arrhythmias and sudden death in this patient population.
Mortality and Sudden Death in Pediatric Left Ventricular Noncompaction in a Tertiary Referral Center

Circulation. 2013;127:2202-2208; originally published online April 30, 2013;
doi: 10.1161/CIRCULATIONAHA.113.002511
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/127/22/2202

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/