ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Natural History of Dilated Cardiomyopathy in Children

Ilaria Puggia, MD; Marco Merlo, MD; Giulia Barbati, PhD; Teisha J. Rowland, PhD; Davide Stolfo, MD; Marta Gigli, MD; Federica Ramani, PhD; Andrea Di Lenarda, MD; Luisa Mestroni, MD, FACC, FESC; Gianfranco Sinagra, MD, FESC

***Background*—**The long-term progression of idiopathic dilated cardiomyopathy (DCM) in pediatric patients compared with adult patients has not been previously characterized. In this study, we compared outcome and long-term progression of pediatric and adult DCM populations.

***Methods and Results*—**Between 1988 and 2014, 927 DCM patients were consecutively enrolled. The pediatric population (aged <18 years at enrollment) included 47 participants (5.1%). At presentation, the pediatric population compared with adult patients had a significantly increased occurrence of familial forms (P=0.03), shorter duration of heart failure (P=0.04), lower systolic blood pressure (P=0.01), decreased presence of left bundle-branch block (P=0.001), and increased left ventricular ejection fraction (P=0.03). Despite these baseline differences, long-term longitudinal trends of New York Heart Association class III to IV, left ventricular dimensions, left ventricular ejection fraction, and restrictive filling pattern were similar between the 2 populations. Regarding survival analysis, because of the size difference between the 2 populations, we compared the pediatric population with a sample of adult patients randomly matched using the above-mentioned baseline differences in a 3:1 ratio (141 adult versus 47 pediatric patients). During a median follow-up of 110 months, survival free from heart transplantation was significantly lower among pediatric patients compared with adults (P<0.001). Furthermore, pediatric age (ie, <18 years) was found to be associated with an increasing risk of both death from pump failure and life-threatening arrhythmias.

***Conclusions*—**Despite the pediatric DCM population having higher baseline left ventricular ejection fraction and similar long-term echocardiographic progression compared with the adult DCM population, the pediatric DCM patients had worse cardiovascular prognosis. **(*J Am Heart Assoc*. 2016;5:e003450 doi: 10.1161/JAHA.116.003450)**

Key Words: cardiomyopathy • death • dilated • echocardiography • heart failure • pediatrics • sudden

Idiopathic dilated cardiomyopathy (DCM) is a heart muscle disorder characterized by systolic dysfunction and dilation of the left or both ventricles in the absence of any other possible cause.[1] DCM can develop in people of any age or ethnicity, although it is more common in male than female persons (occurring at a ratio of ≈3:1 in male to female persons) and typically manifests in the third to fourth decades of life.[2,3] DCM is the predominant cause of cardiomyopathy in both adult and pediatric populations.[3,4] In adults, DCM has an estimated prevalence of 1:2500.[3] In contrast, annual incidence in pediatric populations has been reported to be much lower: ≈1:170 000 in the United States[5] and 1:140 000 in Australia.[6]

Although pediatric DCM has a lower annual incidence than adult DCM, the outcome for pediatric DCM patients is particularly severe.[7–9] DCM is the most frequent cause of heart transplantation (HTx) in pediatric patients.[10] Data from international pediatric DCM registries indicate that the rates of death or HTx over 1- and 5-year periods were 31% and 46%, respectively.[4] Conversely, recent data showed that the HTx-free survival rate in adult DCM patients receiving optimal treatment is >85% at 8 years.[2]

Comparative studies between pediatric and adult DCM populations are currently lacking in the literature. This is clinically relevant. In fact, because of the difficulty of performing controlled clinical trials with pediatric populations, the number of such trials has been limited.[10] Consequently, the treatment strategies used for pediatric DCM patients have

From the Cardiovascular Department, Azienda Ospedaliero-Universitaria "Ospedali Riuniti" of Trieste, Trieste, Italy (I.P., M.M., G.B., D.S., M.G., F.R., G.S.); Cardiovascular Center, Azienda per i Servizi Sanitari N°1, Trieste, Italy (G.B., A.D.L.); Cardiovascular Institute and Adult Medical Genetics Program, University of Colorado Denver Anschutz Medical Campus, Aurora, CO (T.J.R., L.M.).

Correspondence to: Marco Merlo, MD, Cardiovascular Department, Azienda Ospedaliero-Universitaria "Ospedali Riuniti" of Trieste, Trieste, Italy. Ospedale di Cattinara- Polo Cardiologico- Via Valdoni 7, 34149 Trieste, Italy. E-mail: marco.merlo79@gmail.com

Received February 29, 2016; accepted May 24, 2016.

been extrapolated primarily from data based on clinical trials using adult DCM patients. By better characterizing the baseline and long-term progression and outcome of pediatric DCM patients in comparison to adult DCM patients, for which ample data have already been collected, it is thought that improved treatment strategies could be developed for pediatric patients.

The aim of this study was to provide insights into the long-term characterization and outcome of DCM in a pediatric population compared with an adult one to ultimately improve the clinical management of DCM in children.

Methods

Study Population

We analyzed data from all DCM patients that had consecutively enrolled in the Trieste Heart Muscle Disease Registry in Italy between 1988 and 2014, according to the protocol approved by the institutional review board of the Trieste Hospital administration and the local ethics committee. Informed consent was obtained from all participants. The investigation was in line with the principles outlined in the Declaration of Helsinki.[11]

The diagnosis of DCM was assigned according to the current guidelines.[1,12,13] We excluded patients with a secondary cause of myocardial damage, including coronary artery disease (investigated with coronary angiography/computed tomography), hypertensive disorder, valvular disease, biopsy-proven active myocarditis, associated congenital heart disease, history of chemotherapy or pharmacologic cardiotoxicity, pulmonary parenchymal or vascular disease, immunological disease, and mitochondrial disease (studied by complete neurological examination, plasma lactate and amino acids, urine amino and organic acids, and pyruvate and acylcarnitine profiles, if indicated).[2] Neuromuscular disease was investigated with a laboratory test (ie, creatine kinase) and electromyography and, for final diagnosis, by skeletal muscle biopsy if clinically indicated. In the absence of family history of DCM and in the presence of severe recent-onset heart failure (HF), all pediatric patients underwent endomyocardial biopsy and, from 2010, cardiac magnetic resonance to exclude active myocarditis. At enrollment, all patients underwent an initial screening that included a detailed clinical and family history interview, a complete clinical examination, an electrocardiogram, 24-hour Holter monitoring, and a comprehensive echocardiographic evaluation. Conventional 2-dimensional echocardiographic M-mode pulsed Doppler and tissue Doppler imaging were all performed according to international guidelines.[14,15] After enrollment, if not contraindicated, all patients received standard medical therapy with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers titrated to the highest tolerated dose. Clinical and instrumental data were recorded at enrollment and then after ≈6 months (range 3–8 months), 12 months (range 9–18 months), and 24 months (range 19–36 months) in follow-up evaluations. At >24 months after enrollment, patients were recorded at least once every 2 years. Patients who were aged ≤18 years at enrollment were considered part of the pediatric population.[6,16] To improve the accuracy of our comparisons between 2 differently sized populations, prognostic assessment statistics compared the pediatric population with a sample of adult controls randomly matched in a 1:3 ratio (47 pediatric patients to 141 adult patients). This was adjusted for the most relevant baseline differences between the 2 groups, as explained in the "Statistical Analysis" section.

Clinical Outcomes

Three outcome measurements were primarily investigated: (1) death or HTx, (2) sudden cardiac death or malignant ventricular arrhythmia (MVA), and (3) death caused by pump failure or HTx. Data were collected over follow-up periods of 1, 6, and 9 years. All patients with refractory HF requiring inotropic treatment and/or mechanical support or with life-threatening arrhythmias unresponsive to medical therapy and/or catheter ablation and who did not have contraindications were listed for urgent HTx.[2]

Sudden death was defined as immediate death occurring within 1 hour after the onset of symptoms or during sleep in stable patients with New York Heart Association (NYHA) class I to III disease. MVAs were defined as ventricular fibrillation/flutter or sustained ventricular tachycardia (>30-second duration of >200 beats per minute or hemodynamically significant), as recorded by an implantable cardioverter-defibrillator or external defibrillation. Other investigated outcomes included cardiovascular death, noncardiac death, and death from unknown causes.

The Trieste Heart Muscle Disease Registry

The Trieste Heart Muscle Disease Registry is a local relational database, active since 1978, that systematically collects the data of patients affected by DCM and other cardiomyopathies consecutively evaluated in the cardiovascular department of the Azienda Ospedaliero-Universitaria "Ospedali Riuniti" of Trieste. Used as a client interface, the system has all of the characteristics of a rapid application development client/server system. Data registration is composed of a table series corresponding to the clinical (history, family study, clinical examination) and instrumental evaluation (laboratory examinations; electrocardiography; Holter monitoring; echocardiography; and, when indicated, cardiac catheterization and

endomyocardial biopsy) and pharmacological therapy at baseline and at scheduled follow-up evaluations. A section dedicated to fatal and nonfatal events and their causes is also present.

Statistical Analysis

Categorical data are reported as counts and percentages. Continuous variables are presented as means and standard deviations or medians and interquartile ranges, as appropriate. For descriptive comparisons, clinical and instrumental characteristics at baseline were compared between groups of patients. This was achieved by 1-way ANOVA for continuous variables or the nonparametric median test, as necessary; for categorical variables, the chi-square or Fisher exact test was used, as appropriate. To assess the longitudinal changes in the investigated parameters, 2 analyses were performed. First, simple tests for repeated consecutive measures were calculated separately for each group (the McNemar test for binary parameters and the paired *t* test for continuous parameters). Second, linear mixed-effects models with time and group as the covariates (in which time is the follow-up visit and group was defined as either pediatric or adult) were used to investigate whether a different behavior was present between the groups over time (by means of the interaction term time×group evaluated in the models). For the binary parameters, generalized linear mixed models were applied.[17] Because of the size difference between the pediatric and adult groups, we compared the survival of the pediatric patients with that of a sample of adult patients randomly matched in a 1:3 ratio to increase the efficacy of the survival comparison. The matching procedure accounted for the variables that were significantly different at baseline between the 2 populations and that had known possible relevance for the outcome in DCM patients. Event-free survival curves for the 3 primarily investigated outcomes (described in the "Clinical Outcomes" section) were estimated and plotted using the Kaplan–Meier method. The differences between the groups were assessed using the log-rank test. Last, univariate and multivariate Cox regression models were estimated in the target population (pediatric patients). The limited sample size and number of events in this group were taken into account using a backward-conditional stepwise procedure to select the subset of the most powerful independent predictors. Only univariable hazard ratios were estimated for the secondary end points (sudden cardiac death or malignant ventricular arrhythmia and death from pump failure or HTx). Statistical analyses were conducted using the IBM SPSS Statistics version 19 (IBM Corp) and R software version 3.0.2 (R Foundation for Statistical Computing) with the "matching" and "rgenoud" libraries.

Results

Clinical and Echocardiographic Characterization

Of the entire population of 927 DCM patients enrolled between 1988 and 2014, 47 (5.1%) were pediatric. The median follow-up time after the first clinical evaluation was 110 months (interquartile range 54–185 months). Table 1 shows the clinical data of the pediatric population at baseline compared with the adult group.[18] A family history of DCM was

Table 1. Clinical Data at Baseline for Pediatric and Adult DCM Patients

Characteristic	Adult Population (n=880; 94.9%)	Pediatric Population (n=47; 5.1%)	*P* Value
Male sex (%)	79.5	69.6	0.180
Age, y	47±13	15±3	<0.001
BSA, m^2	1.88±0.23	1.69±0.44	<0.001
Family history of DCM	17.5	34.8	0.03
Family history of SD	9.1	13.6	0.289
SBP, mm Hg	124.6±17.4	116.2±20.2	0.01
DBP, mm Hg	80.5±29.8	71.5±10.4	0.04
Diabetes mellitus type 1 (%)	0.5	0	0.7
Diabetes mellitus type 2 (%)	8.1	0	0.07
Smoking (%)	30.1	8.3	0.005
NYHA III–IV (%)	23.4	19.1	0.5
HF duration, mo, median (IQR)	0 (0–6)	1 (0–7)	0.04
LBBB (%)	31.9	4.4	<0.001
LVEDD,* mm/m^2	35.8± 15.9	39.3 ± 13.3	0.9
LVESD,* mm/m^2	29.6±12.5	31.9±12.7	0.1
LVEDV, mL/m^2	96.6±37.5	102.7±44.9	0.4
LVESV, mL/m^2	67.9±34.3	69.1±39.8	0.3
LVEF (%)	32.3±10.9	36.0±13.2	0.03
Moderate to severe MR (%)	33.5	25.5	0.3
Beta blockers (%)	83.3	76.7	0.26
ACEIs (%)	86.1	83.7	0.66
Digoxin (%)	54.7	55.8	0.89
Diuretics (%)	64.2	48.8	0.04

ACEI indicates angiotensin-converting enzyme inhibitor; BSA, body surface area; DCM, dilated cardiomyopathy; DBP, diastolic blood pressure; HF, heart failure; IQR, interquartile range; LBBB, left bundle-branch block; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MR mitral regurgitation; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, sudden death.
*The pediatric left ventricular diameters are represented also as *z* scores[18]: LVEDD, $z=-1.87$; LVESD, $z=0.66$.

significantly more common among the pediatric population (34.8% versus 17.5%; $P<0.03$). The pediatric patients presented with significantly lower systolic arterial blood pressure (116±20 versus 125±17 mm Hg; $P<0.01$), a lower presence of left bundle-branch block (4.4% versus 31.9%; $P<0.001$), and a higher occurrence of left ventricular ejection fraction (LVEF; 36±13 versus 32±11; $P<0.03$). Pediatric patients were also characterized by a shorter duration of HF symptoms (median 0 months [interquartile range, 1st–3rd quartiles: 0–6 months] versus 1 month [interquartile range, 1st–3rd quartiles: 0–7 months]; $P<0.04$). Both groups received optimized treatments for HF without age-related differences. Despite different features at baseline, no significant differences were observed between the pediatric and adult populations regarding the long-term longitudinal trends in NYHA functional classes III–IV, left ventricular end-diastolic diameter and volume, LVEF, and restrictive filling pattern. An initial improvement under treatment, midterm stabilization, and then a subsequent trend to progressive worsening of these parameters were observed in the long term in both the adult and pediatric populations (Figure 1). The matched sample was built by adjusting for differences in familiar forms, duration of HF, systolic blood pressure, left bundle-branch block, and LVEF; moreover, we checked for others parameters that were different in the original sample and found nonsignificant differences (diastolic blood pressure in the matched sample was 74±12 mm Hg in the adult population versus 72±11 mm Hg in the pediatric patients, $P=0.09$; diabetes mellitus 6% versus 0%, $P=0.11$; smokers 26% versus 10%, $P=0.05$; and diuretics 49% versus 46%, $P=0.967$).

Long-Term Outcomes

Table 2 shows the incidence of major events in the pediatric population and the entire adult DCM population. The incidence of death or HTx was significantly higher for the pediatric patients compared with the adults (43.5% [5 events per 100 patients per year] versus 25.8% [3.4 events per 100 patients per year]; $P<0.018$). The worst outcomes for the pediatric patients were death caused by HF or HTx (21% [2.5 events per 100 patients per year] in pediatric patients versus 7% [0.8 event per 100 patients per year] in adults, $P<0.001$) and sudden death or MVA (21% [2.5 events per 100 patients per year] versus 14% [1.7 events per 100 patients per year], respectively; $P<0.001$).

Figure 2A shows that long-term survival free from death or HTx was significantly lower among the 47 pediatric DCM patients compared with the matched sample of 141 adults ($P<0.001$). Notably, a significant survival difference can be seen as early as 12 months after enrollment (survival rates at 1 year: 82% versus 98% in pediatric versus adult populations, respectively; $P<0.001$). At follow-up time points of 6 and

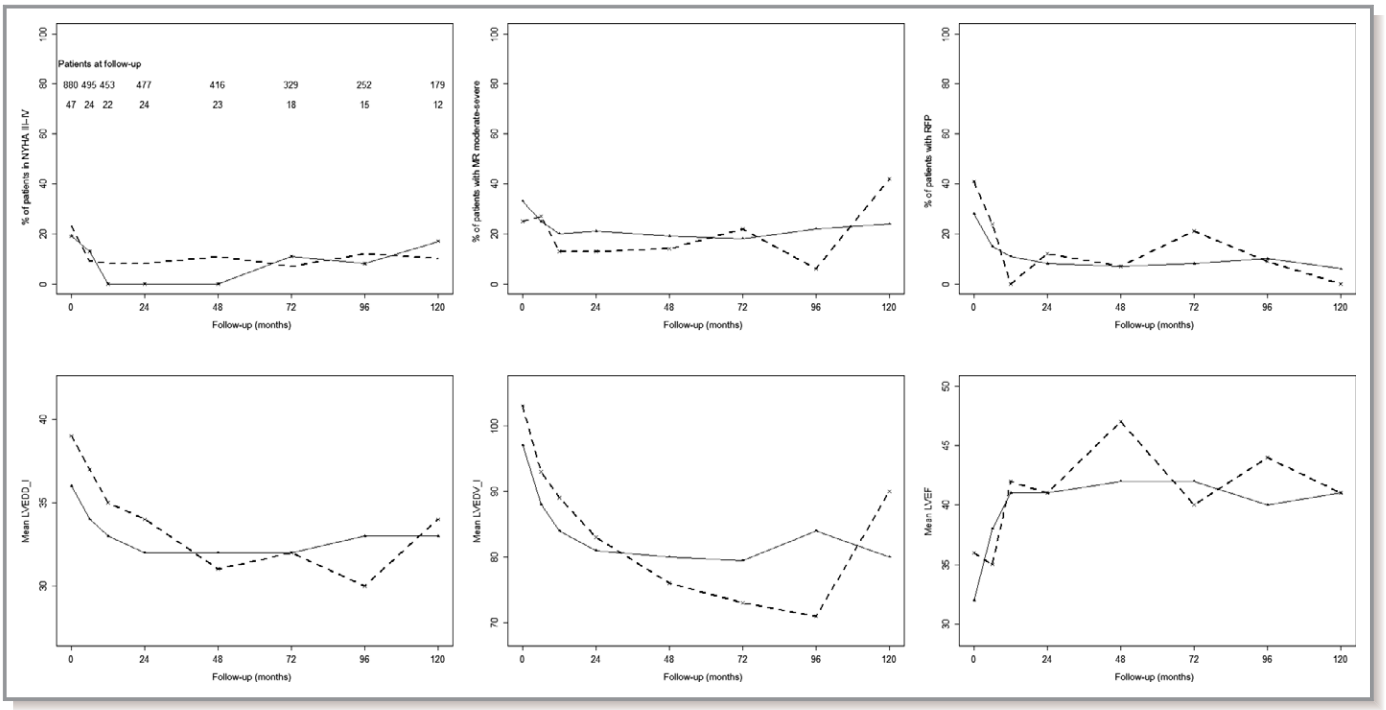

Figure 1. Long-term longitudinal trends of clinical and echocardiographic parameters (NYHA classes III–IV class, LVEDD_I, LVEDV-I, LVEF, RFP) in pediatric (solid line) and adult (dotted line) populations. LVEDD_I indicates indexed left ventricular end-diastolic diameter; LVEDV_I, indexed left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart association; RFP, restrictive filling pattern.

Table 2. Incidence of Major Cardiovascular Outcomes in Pediatric and Adult Patients With Idiopathic Dilated Cardiomyopathy

Outcome, n (%); incidence (events/ 100 patients/year)	Adult Population (n=880; 94.9%)	Pediatric Population (n=47; 5.1%)	*P* Value
Death or HTx	253 (25.8); 3.4	20 (42.5); 5.0	0.018
Death for refractory HF or HTx	63 (7); 0.8	10 (21); 2.5	<0.001
SD or MVA	126 (14); 1.7	10 (21); 2.5	<0.001
ICD implantation	155 (17.6); 2.3	10 (21); 2.5	0.556
Death from unknown cause	64 (7); 0.8	1 (2); 0.2	0.178

HF indicates heart failure; HTx, heart transplant; ICD, implantable cardioverter-defibrillator; MVA, major ventricular arrhythmias; SD, sudden death.

9 years, the survival rates were 71% versus 89%, respectively, in the pediatric patients and 68% versus 89%, respectively, in the adult patients ($P<0.0001$). Similar results were obtained when examining survival rates free from the combined end points of sudden death or MVA and death from pump failure or HTx ($P<0.001$ for both) (Figure 2B and 2C). Figure 3 shows the effect of the age at enrollment on patient outcome, with pediatric age (ie, <18 years) associated with a significantly decreased mortality rate and increased occurrence of HTx.

Finally, we performed a univariate and subsequent multivariate Cox analysis among the pediatric population to identify possible prognostic indicators. We found that lower LVEF and NYHA functional class III–IV at baseline were the most powerful independent predictors of the occurrence of death or HTx. Conversely, the use of beta blockers was found to be a protective factor (Table 3). The pediatric patients received beta blocker treatment throughout the enrollment period (ie, beta blocker therapy before versus after the year 2000: 76% versus 84%, $P=0.421$). The univariate analyses for sudden death or MVA and for pump-failure death or HTx are reported in Tables 4 and 5. Of note, a positive family history for DCM emerged as the only significant predictor (hazard ratio 3.79, 95% CI 1.224–14.7; $P=0.045$) for arrhythmic events in the pediatric population (Table 5).

Discussion

Main Findings

This study compared the characterizations, long-term progression, and outcomes of adult and pediatric DCM patients. Most studies of pediatric DCM populations have been based on registries drawn from the United States or Australia, and recent data on European populations, provided in this study, have been less represented. Furthermore, in the current literature, comparative studies of adult and pediatric DCM patients are lacking. This issue is relevant because the management of pediatric DCM is based largely on long-term data derived from adult cohorts.

In this study, we reported a large and well-selected idiopathic DCM cohort in which pediatric cases are rare, representing only 5% of the whole population; however, clinical cardiologists have to pay particular attention to pediatric DCM. In fact, in our pediatric population, we saw that the disease was less severe at baseline compared with adults, as suggested by the lower percentage of left bundle-branch block, the higher occurrence of LVEF, and the shorter

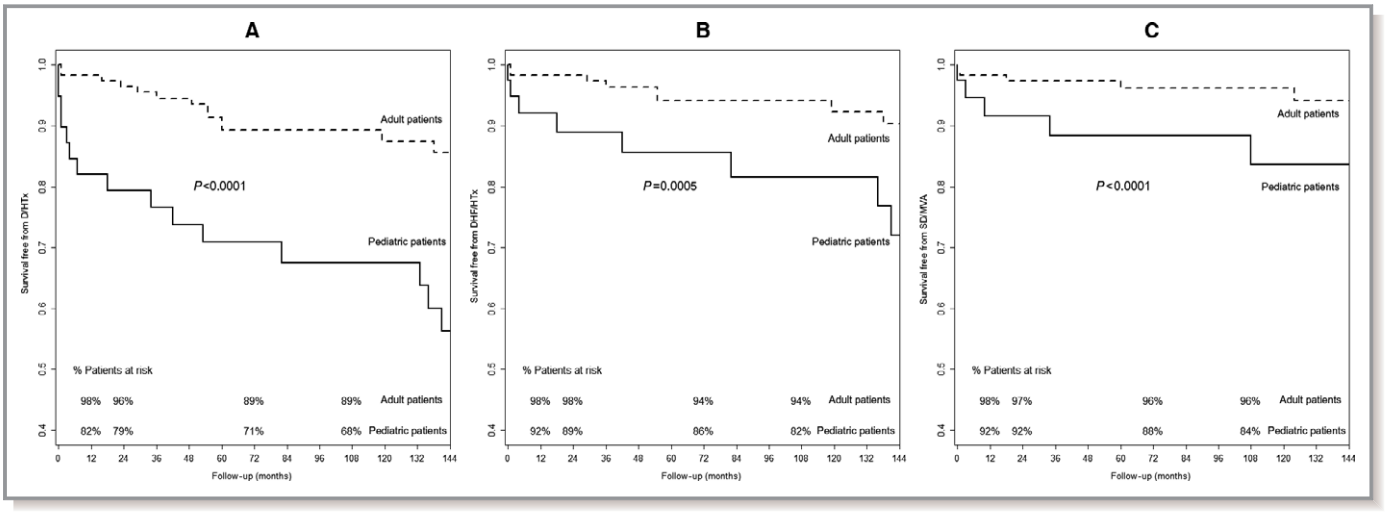

Figure 2. Rates of long-term survival free from D/HTx (A), DHF/HTx (B), and from SD/MVA (C) in 47 pediatric (solid line) vs 141 adult patients (dotted line) matched in a 1:3 ratio after adjustment for baseline differences between the 2 subgroups. D/HTx indicates death or heart transplantation; DHF/HTx, heart-failure death or heart transplantation; SD/MVA, sudden death or major ventricular arrhythmias.

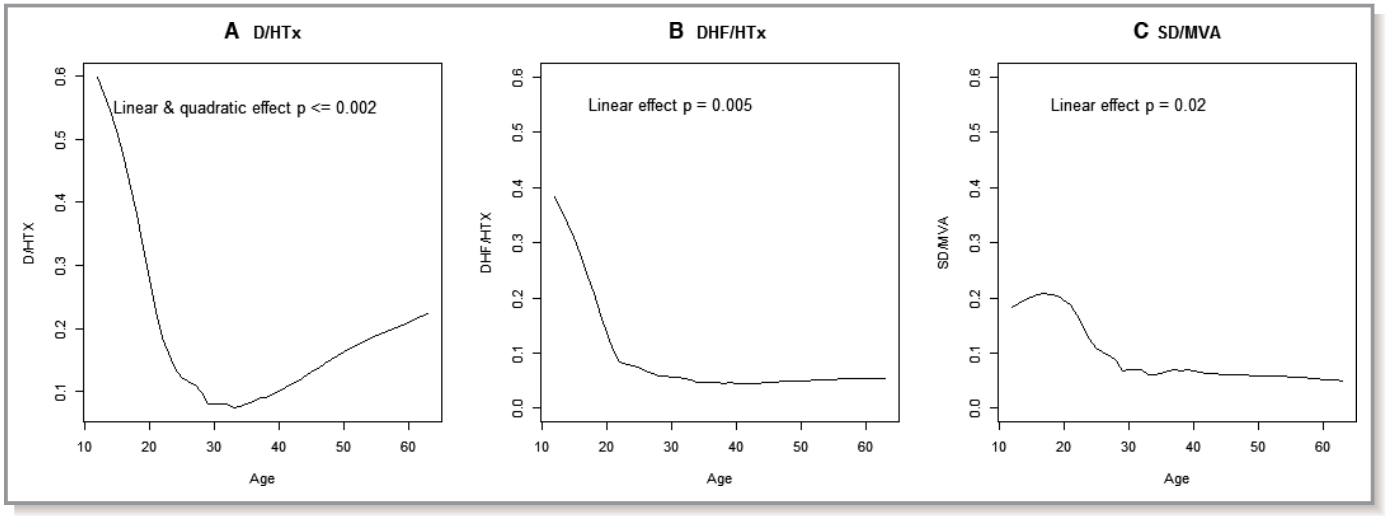

Figure 3. Effect of age on outcome measurements. Pediatric age (ie, <18 years) was associated with increasing risk of all major events: D/HTx (A), DHF/HTx (B), SD/MVA (C). D/HTx indicates death or heart transplantation; DHF/HTx, heart-failure death or heart transplantation; SD/MVA, sudden death or major ventricular arrhythmias.

duration of HF symptoms. This could be due to having an earlier diagnosis, which may be partially explained by a systematic and detailed collection of familial history of the probands and thus the earlier screening of relatives.

Despite these differences at baseline, both populations share similar long-term clinical and echocardiographic progression. This may suggest a quicker progression of DCM in younger patients. As seen previously, our pediatric population had a significantly poorer long-term outcome compared with adults. All analyzed combined end points (ie, death/HTx, death from HF/HTx, and sudden death/MVA) had higher incidence in the pediatric population, even after adjustment for baseline differences between groups. The long-term incidence of death/HTx in the pediatric population reached 5 events per 100 patients per year, which is markedly higher than 3.4 events per 100 patients per year in the adult population. These event rates are similar to those reported in the United States and Australia.[5,6] Furthermore, the survival rate curves of both populations start to diverge early after the first evaluation and progressively increase the survival gap in the long term. This was particularly evident considering the combined end point of death/HTx (82% versus 98% in children versus adults at 1-year follow-up). These issues highlight the aggressiveness of DCM in pediatric cases. Finally, the onset of disease at an age <18 years clearly emerged as a risk factor for all combined end points (Figure 3). This underscores the relevant role of pediatric age for short- and long-term management of DCM.

These results apparently contrast with the known beneficial effects on the prognosis from familial screening. The latter usually allows earlier diagnosis, often at a less severe stage of the disease, and subsequent benign outcome.[19] One could argue that familial screening is useful for more accurately managing the disease with tighter and more aggressive follow-up when DCM is discovered at a pediatric age. In adults, familial screening allows diagnosis at an earlier stage of the disease, with a consequently better long-term outcome.

The Arrhythmic Burden

Notably, in our study, the poorer prognosis in pediatric cases resulted not only from the progression of HF and HTx but also from arrhythmic events (Figures 2C and 3C). In the current literature, much more attention has been paid to HF than to arrhythmias in pediatric DCM patients. Nevertheless, an important arrhythmic profile in the pediatric patients compared with the adults clearly emerged in this study. This topic highlights a challenging issue in the management of DCM: whether to implant an implantable cardioverter-defibrillator for primary prevention in children. The current HF pediatric guidelines[10] recommend this procedure for pediatric DCM patients with unexplained syncope and at least moderate left ventricular dysfunction (class of recommendation IIa, level of evidence C) or with LVEF <35% and NYHA class II–III (class of recommendation IIb, level of evidence C). They also recommend this procedure for adolescent patients with a familial cardiomyopathy associated with sudden death or for younger patients, considering the risk–benefit ratio and technical issues (class of recommendation IIa, level of evidence C). The low level of evidence for the guidelines suggests the ethical and technical difficulty of this decision and the necessity of risk stratification models. Some models have been proposed previously to identify implantable cardioverter-defibrillator candidates among children. In particular, a left ventricle thinning and dilation ratio, diagnosis before age 13 to

Table 3. Univariate and Multivariate Analysis in the Pediatric DCM Population: Predictors of Death or Heart Transplantation

		95% CI				95% CI		
	HR	Lower	Upper	*P* Value	HR	Lower	Upper	*P* Value
Sex	1.262	0.416	3.829	0.681	—	—	—	—
BSA (for 1-U increase)	0.405	0.131	1.251	0.116	—	—	—	—
Family history of DCM	0.798	0.33	1.930	0.616	—	—	—	—
Family history of SD	1.102	0.249	4.887	0.898	—	—	—	—
NYHA III to IV	2901	1.110	7.612	0.031	3.827	1.194	12.27	0.024
SBP (for 1-mm Hg increase)	0.974	0.944	1.005	0.097	—	—	—	—
DBP, mm Hg	0.957	0.913	1.002	0.061	—	—	—	—
LBBB (%)	4.079	0.890	18.685	0.070	—	—	—	—
LVEDD (for 1-mm/m^2 increase)	1.029	1.006	1.052	0.012	—	—	—	—
LVESD (for 1-mm/m^2 increase)	1.039	1.013	1.067	0.003	—	—	—	—
LVEDV (for 1-mL/m^2 increase)	1.019	1.010	1.029	<0.001	—	—	—	—
LVESV (for 1-mL/m^2 increase)	1.023	1.011	1.035	<0.001	—	—	—	—
LVEF (for 1-U increase)	0.960	0.924	0.988	0.039	0.939	0.895	0.986	0.012
Moderate to severe MR	2.582	1.051	6.345	0.039	—	—	—	—
RFP	2725	0.092	6.800	0.032	—	—	—	—
ACEIs	0.208	0.028	1.564	0.127	—	—	—	—
Antiarrhythmics	0.894	0.364	2.199	0.808	—	—	—	—
Beta blockers	0.380	0.148	0.973	0.044	0.082	0.021	0.323	0.000
Enrollment period (before 2000)	3.335	0.411	27.028	0.259	—	—	—	—

Em dash indicates no data. ACEI indicates angiotensin-converting enzyme inhibitor; BSA, body surface area; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; HR, hazard ratio; LBBB, left bundle-branch block; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MR mitral regurgitation; NYHA, New York heart Association; RFP, restrictive filling pattern (left ventricle); SBP, systolic blood pressure; SD, sudden death.

14 years, and use of antiarrhythmic therapy within 1 month of diagnosis emerged as predictors of sudden cardiac death[20]; however, no univocal statement currently exists on this topic in the literature. The identification of predictors of sudden death and MVA in pediatric DCM patients was beyond the scope of our study because of the limited number of events. Interestingly, at univariate analysis, family history positive for DCM emerged as the only significant predictor of arrhythmic events in the pediatric population. This could suggest that some clusters of gene mutations have an important role in inducing specific arrhythmic phenotypes. Future studies are needed for the investigation of such a hypothesis.

DCM at Pediatric Age: A Distinct Disease

The reasons for the relatively poor outcome in pediatric DCM patients remain largely unknown. Most cases are idiopathic, followed by familial forms[3]; therefore, pediatric forms may be caused by particularly aggressive genetic mutations leading to rapidly progressive disease. Accordingly, our study showed twice the prevalence of familial forms of DCM in the pediatric population compared with the adult patients (34.8% versus 17.5%), encouraging genetic screening in these patients and their relatives. In some cases, a positive result may influence clinical management, as in the presence of lamin A/C (*LMNA*) mutations.[21,22] In other cases, the discovery of a mutation has no impact on the clinical management of the disease because, currently, wide genotype–phenotype correlation data are still lacking. Furthermore, it is known that active myocarditis in children is more aggressive than in adults, probably caused by a predominant immune response.[23] Consequently, postinflammatory DCM in children is also likely to be more severe, and more aggressive follow-up and therapeutic strategies are advised.

Finally, the resulting independent prognostic factors that emerged from our multivariate analysis (tolerance of beta blocker therapy, LVEF, NYHA class) confirm previous studies[24,25] and reflect the same features that are included in adult DCM prognostic models.[2] The protective role that emerged for beta blockers could confirm their benefit in pediatric as well as adult DCM patients. Nevertheless, because of the observational nature of the present study, it is possible that beta

Table 4. Univariate Analysis in the Pediatric DCM Population: Predictors of Death from Heart Failure or Heart Transplantation

	HR	95% CI		*P* Value
		Lower	Upper	
Sex	1.548	0.192	12.509	0.682
BSA (for 1-U increase)	0.193	0.053	0.703	0.013
Family history of DCM	1.011	0.284	3.595	0.987
Family history of SD	1.137	0.135	9.587	0.906
NYHA III–IV	6573	1.882	22.963	0.003
SBP (for 1-mm Hg increase)	0.914	0.867	0.964	0.001
DBP, mm Hg	0.955	0.893	1.020	0.172
LBBB (%)	5.204	0.578	46.856	0.141
LVEDD (for 1-mm/m^2 increase)	1.041	1.013	1.069	0.003
LVESD (for 1-mm/m^2 increase)	1.054	1.020	1.089	0.002
LVEDV (for 1-mL/m^2 increase)	1.021	1.008	1.035	0.002
LVESV (for 1-mL/m^2 increase)	1.027	1.010	1.044	0.002
LVEF (for 1-U increase)	0.944	0.893	0.999	0.046
Moderate to severe MR	5.849	1.637	20.906	0.007
RFP	4.412	1.137	17.118	0.032
ACEIs	26.093	0.013	52.214	0.400
Antiarrhythmics	0.699	0.179	2.725	0.605
Beta blockers	0.773	0.159	3.757	0.749

ACEI indicates angiotensin-converting enzyme inhibitor; BSA, body surface area; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; HR, hazard ratio; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MR mitral regurgitation; NYHA, New York heart Association; RFP, restrictive filling pattern (left ventricle); SBP, systolic blood pressure; SD, sudden death.

Table 5. Univariate in the Pediatric DCM Population: Predictors of Major Ventricular Arrhythmias or Sudden Death

	HR	95% CI		*P* Value
		Lower	Upper	
Sex	0.852	0.180	4.039	0.840
BSA (for 1-U increase)	3.578	0.226	56.574	0.365
Family history of DCM	3.794	1.224	14.744	0.045
Family history of SD	3.051	0.556	16.760	0.199
NYHA III–IV	0.678	0.085	5.395	0.714
SBP (for 1-mm Hg increase)	0.987	0.945	1.031	0.549
DBP, mm Hg	0.957	0.894	1.024	0.204
LBBB (%)	0.046	0.001	49.29	0.744
LVEDD (for 1-mm/m^2 increase)	0.994	0.934	1.059	0.858
LVESD (for 1-mm/m^2 increase)	1.010	0.957	1.065	0.728
LVEDV (for 1-mL/m^2 increase)	1.016	0.999	1.032	0.059
LVESV (for 1-mL/m^2 increase)	1.018	0.999	1.036	0.063
LVEF (for 1-U increase)	0.956	0.907	1.008	0.096
Moderate to severe MR	0.508	0.064	4.041	0.522
RFP	1.457	0.408	5.196	0.562
ACEIs	2.472	0.266	17.396	0.472
Antiarrhythmics	3.650	0.938	14.209	0.062
Beta blockers	0.711	0.147	3.443	0.671

ACEI indicates angiotensin-converting enzyme inhibitor; BSA, body surface area; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; HR, hazard ratio; LBBB, left bundle-branch block; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MR mitral regurgitation; NYHA, New York heart Association; RFP, restrictive filling pattern (left ventricle); SBP, systolic blood pressure; SD, sudden death.

blocker intolerance was a surrogate for advanced disease state, and a large-scale randomized trial is needed to definitively assess the benefit of beta blockers in a pediatric DCM population. Beta blockers are currently more widely used in children than in previous decades. Only 5% of the pediatric patients enrolled in the American Pediatric Cardiomyopathy Registry received beta blockers in the 1990s compared with 18% after 2000.[26] An increasing burden of studies about the pathophysiological differences of pediatric and adult HF mechanisms characterizes the current literature.[27–29] This contributes to our understanding of the different age-related responses to therapy. Performing clinical trials in children with DCM is very difficult, but it appears to be the only way to identify the most useful treatments to improve outcome.

Our population has some analogies with large-scale observational studies in the pediatric DCM population[5,6,16]; however, some notable differences have to be highlighted. The mean age of our pediatric cohort was 15 years, which is older than most other studies on DCM in children. Moreover, there were higher proportions of familial and male cases. These differences should be explained by the fact that ours is a cardiomyopathy referral center that is mostly used to evaluate patients that are affected by idiopathic DCM, without known causes and with an important genetic–familial or postmyocarditis background and rarely associated with congenital syndromes or neuromuscular diseases. In this sense, the comparison with the adult population was not previously reported and appears to be particularly relevant to the clinical management of such patients. Another relevant discrepancy concerns the prognostic longitudinal trends that are shown in the present study. In our population, there appears to be a continued risk of death or transplant after 1 year of follow-up after enrollment; that characteristic is different from other pediatric DCM international registries.[5,6,16] It is particularly interesting and is probably related to the above-mentioned characteristics of idiopathic DCM enrolled in the present registry. These characteristics revealed a particularly aggressive nature of the disease in the short and long terms in children more than in adults.

Limitations

Our study has some limitations. First, selection biases relate to its retrospective and registry-based nature. Moreover, the rarity of this disease among the pediatric population in general influenced the size of the samples studied. To overcome this issue, a "case-control–like" strategy was achieved by means of a random matching procedure. Another limitation concerns the availability of long-term follow-up data, which were not complete for all patients because of the event rates and censoring mechanism. Consequently, the long-term trends of the main clinical and echocardiographic features shown in Figure 1 should be interpreted with caution and confirmed by future studies that go on for a longer time. In our opinion, however, the comparison with the adult population (affected by the same limit) is reliable. For most of the patients, the genetic data and cardiac magnetic resonance information were lacking, thus we could not include these data in our analyses. Because of the limited number of events, uni- and multivariable analyses were presented mainly for exploratory purposes and should be confirmed in larger series. Future focused studies are warranted to assess the possible prognostic role of these tools in pediatric populations compared with adults. Finally, we included HTx in the composite end point even though it is not a fatal event. In our opinion, it remains a major event in the natural history of DCM that has the same impact of death in the prognostic evaluation of the disease, especially considering that only urgent HTx examples were included.

Conclusions

The data of this Italian registry suggest that pediatric DCM patients are rare but have a worse outcome than adult patients. This is despite similar treatments, a less advanced stage of the disease at baseline in children, and similar clinical and echocardiographic long-term progression. These findings were further confirmed after adjusting for other covariates that were significantly different from adults at the time of the onset of the disease. Finally, pediatric age emerged as an important prognostic predictor of both death from HF and life-threatening ventricular arrhythmias.

Disclosures

None.

References

1. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Function. *Circulation*. 2006;113:1807–1816.
2. Merlo M, Pivetta A, Pinamonti B, Stolfo D, Zecchin M, Barbati G, Di Lenarda A, Sinagra G. Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: changing mortality over the last 30 years. *Eur J Heart Fail*. 2014;16:317–324.
3. Jefferies JL, Towbin JA. Dilated cardiomyopathy. *Lancet*. 2010;375:752–762.
4. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, Messere J, Cox GF, Lurie PR, Hsu D, Canter C, Wilkinson JD, Lipshultz SE. Incidence, causes, and outcomes of dilated cardiomyopathy in children. *JAMA*. 2006;296:1867–1876.
5. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, Lurie PR, McCoy KL, McDonald MA, Messere JE, Colan SD. The incidence of pediatric cardiomyopathy in two regions of the United States. *N Engl J Med*. 2003;348:1647–1655.
6. Nugent AW, Daubeney PEF, Chondros P, Carlin JB, Cheung M, Wilkinson LC, Davis AM, Kahler SG, Chow CW, Wilkinson JL, Weintraub RG. The epidemiology of childhood cardiomyopathy in Australia. *N Engl J Med*. 2003;348:1639–1646.
7. Wilkinson JD, Landy DC, Colan SD, Jeffrey A, Sleeper LA, Orav EJ, Cox GF, Canter E, Hsu DT, Webber SA, Lipshultz SE. The pediatric cardiomyopathy registry and heart failure: key results from the first 15 years. *Hear Fail Clin*. 2011;6:401–413.
8. Daubeney PEF, Nugent AW, Chondros P, Carlin JB, Colan SD, Cheung M, Davis AM, Chow CW, Weintraub RG. Clinical features and outcomes of childhood dilated cardiomyopathy: results from a national population-based study. *Circulation*. 2006;114:2671–2678.
9. Everitt MD, Sleeper LA, Lu M, Canter CE, Pahl E, Wilkinson JD, Addonizio LJ, Towbin JA, Rossano J, Singh RK, Lamour J, Webber SA, Colan SD, Margossian R, Kantor PF, Jefferies JL, Lipshultz SE. Recovery of echocardiographic function in children with idiopathic dilated cardiomyopathy. *J Am Coll Cardiol*. 2014;63:1405–1413.
10. Kirk R, Dipchand AI, Rosenthal DN, Addonizio L, Burch M, Chrisant M, Dubin A, Everitt M, Gajarski R, Mertens L, Miyamoto S, Morales D, Pahl E, Shaddy R, Towbin JA, Weintraub R. The International Society of Heart and Lung Transplantation guidelines for the management of pediatric heart failure: executive summary. *J Heart Lung Transplant*. 2014;33:888–909.
11. World Medical Association, Human Experimentation. Code of ethics of the World Medical Association. Declaration of Helsinki. *Br Med J*. 1964;2:177.
12. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kuhl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2007;29:270–276.
13. Rapezzi C, Arbustini E, Caforio AL, Charron P, Gimeno-Blanes J, Heliö T, Linhart A, Mogensen J, Pinto Y, Ristic A, Seggewiss H, Sinagra G, Tavazzi L, Elliott PM. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013;34:1448–1458.
14. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.
15. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009;10:165–193.
16. Grenier MA, Osganian SK, Cox GF, Towbin JA, Colan SD, Lurie PR, Sleeper LA, Orav EJ, Lipshultz SE. Design and implementation of the North American Pediatric Cardiomyopathy Registry. *Am Heart J*. 2000;139:S86–S95.
17. McCulloch CE, Searle SR, Neuhaus JMN. *Generalized, Linear, and Mixed Models*. 2nd edition Wiley Series in Probability and Statistics, 2008.
18. Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. *J Am Soc Echocardiogr*. 2008;21:922–934.
19. Moretti M, Merlo M, Barbati G, Di Lenarda A, Brun F, Pinamonti B, Gregori D, Mestroni L, Sinagra G. Prognostic impact of familial screening in dilated cardiomyopathy. *Eur J Heart Fail*. 2010;12:922–927.
20. Pahl E, Sleeper LA, Canter CE, Hsu DT, Lu M, Webber SA, Colan SD, Kantor PF, Everitt MD, Towbin JA, Jefferies JL, Kaufman BD, Wilkinson JD, Lipshultz SE.

Incidence of and risk factors for sudden cardiac death in children with dilated cardiomyopathy: a report from the Pediatric Cardiomyopathy Registry. *J Am Coll Cardiol*. 2012;59:607–615.

21. Taylor MR, Fain PR, Sinagra G, Robinson ML, Robertson AD, Carniel E, Di Lenarda A, Bohlmeyer TJ, Ferguson DA, Brodsky GL, Boucek MM, Lascor J, Moss AC, Li Wai-Lun P, Stetler GL, Muntoni F, Bristow MR, Mestroni L. Natural history of dilated cardiomyopathy due to lamin A/C gene mutations. *J Am Coll Cardiol*. 2003;41:771–780.
22. Van Rijsingen IAW, Arbustini E, Elliott PM, Mogensen J, Hermans-Van Ast JF, Van Der Kooi AJ, Van Tintelen JP, Van Den Berg MP, Pilotto A, Pasotti M, Jenkins S, Rowland C, Aslam U, Wilde AAM, Perrot A, Pankuweit S, Zwinderman AH, Charron P, Pinto YM. Risk factors for malignant ventricular arrhythmias in lamin A/C mutation carriers: a European cohort study. *J Am Coll Cardiol*. 2012;59:493–500.
23. Anzini M, Merlo M, Sabbadini G, Barbati G, Finocchiaro G, Salvi A, Perkan A, Di Lenarda A, Bussani R, Bartunek J. Long-term evolution and prognostic stratification of biopsy-proven active myocarditis. *Circulation*. 2013;128:2384–2394.
24. Molina KM, Shrader P, Colan SD, Mital S, Margossian R, Sleeper LA, Shirali G, Barker P, Canter CE, Altmann K, Radojewski E, Tierney ESS, Rychik J, Tani LY. Predictors of disease progression in pediatric dilated cardiomyopathy. *Circ Hear Fail*. 2013;6:1214–1222.
25. Alexander PMA, Daubeney PEF, Nugent AW, Lee KJ, Turner C, Colan SD, Robertson T, Davis AM, Ramsay J, Justo R, Sholler GF, King I, Weintraub RG. Long-term outcomes of dilated cardiomyopathy diagnosed during childhood: results from a national population-based study of childhood cardiomyopathy. *Circulation*. 2013;128:2039–2046.
26. Harmon WG, Sleeper LA, Cuniberti L, Messere J, Colan SD, Orav EJ, Towbin JA, Wilkinson JD. Treating children with idiopathic dilated cardiomyopathy (from the Pediatric Cardiomyopathy Registry). *Am J Cardiol*. 2010;104:281–286.
27. Nakano SJ, Miyamoto SD, Movsesian M, Nelson P, Stauffer BL, Sucharov CC. Age-related differences in phosphodiesterase activity and effects of chronic phosphodiesterase inhibition in idiopathic dilated cardiomyopathy. *Circ Heart Fail*. 2015;8:57–63.
28. Miyamoto SD, Stauffer BL, Nakano S, Sobus R, Nunley K, Nelson P, Sucharov CC. Beta-adrenergic adaptation in paediatric idiopathic dilated cardiomyopathy. *Eur Heart J*. 2014;35:33–41.
29. Miyamoto SD, Karimpour-Fard A, Peterson V, Auerbach SR, Stenmark KR, Stauffer BL, Sucharov CC. Circulating microRNA as a biomarker for recovery in pediatric dilated cardiomyopathy. *J Heart Lung Transplant*. 2015;34:724–733.

Natural History of Dilated Cardiomyopathy in Children

Ilaria Puggia, Marco Merlo, Giulia Barbati, Teisha J. Rowland, Davide Stolfo, Marta Gigli, Federica Ramani, Andrea Di Lenarda, Luisa Mestroni and Gianfranco Sinagra

J Am Heart Assoc. 2016;5:e003450; originally published June 30, 2016;
doi: 10.1161/JAHA.116.003450
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980