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ORIGINAL RESEARCH

Elevated Heart Rate and Survival in Children With Dilated Cardiomyopathy: A Multicenter Study From the Pediatric Cardiomyopathy Registry

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BACKGROUND: In adults with heart failure, elevated heart rate is associated with lower survival. We determined whether an elevated heart rate was associated with an increased risk of death or heart transplant in children with dilated cardiomyopathy.

METHODS AND RESULTS: The study is an analysis of the Pediatric Cardiomyopathy Registry and includes baseline data, annual follow-up, and censoring events (transplant or death) in 557 children (51% male, median age 1.8 years) with dilated cardiomyopathy diagnosed between 1994 and 2011. An elevated heart rate was defined as 2 or more SDs above the mean heart rate of children, adjusted for age. The primary outcomes were heart transplant and death. Heart rate was elevated in 192 children (34%), who were older (median age, 2.3 versus 0.9 years; $P<0.001$), more likely to have heart failure symptoms (83% versus 67%; $P<0.001$), had worse ventricular function (median fractional shortening z score, –9.7 versus –9.1; $P=0.02$), and were more often receiving anticongestive therapies (96% versus 86%; $P<0.001$) than were children with a normal heart rate. Controlling for age, ventricular function, and cardiac medications, an elevated heart rate was independently associated with death (adjusted hazard ratio [HR] 2.6; $P<0.001$) and with death or transplant (adjusted HR 1.5; $P=0.01$).

CONCLUSIONS: In children with dilated cardiomyopathy, elevated heart rate was associated with an increased risk of death and cardiac transplant. Further study is warranted into the association of elevated heart rate and disease severity in children with dilated cardiomyopathy and as a potential target of therapy.

Key Words: dilated cardiomyopathy ■ heart rate ■ pediatric

Dilated cardiomyopathy (DCM) is a common cause of heart failure (HF) in children.[1,2] Although outcomes of children with DCM have improved over the past 2 decades,[3] these children remain at high risk of death, and many will require advanced HF therapies, including mechanical circulatory support and heart transplantation.[4–6] Managing children with DCM is challenged by the relatively few risk factors known to be associated with long-term outcomes and by the unclear efficacy of medical therapies in this population.[2,7–10] Moreover, the factors associated with long-term outcomes, including age at diagnosis, severity of disease at diagnosis, and underlying cause of DCM, are generally not modifiable or targets of therapy.[2,7,8,10]

Elevated resting heart rate (HR) is associated with increased mortality in adults, with or without heart disease.[11] In adults with HF, reducing HR with beta-blocking agents, ivabradine, or both is associated with improved outcomes.[12–18] However, there are no data

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CLINICAL PERSPECTIVE

What Is New?

- In a large, multicenter study of pediatric patients with dilated cardiomyopathy, elevated heart rate at the time of diagnosis was associated with a greater risk of death or heart transplant.
- This finding was independent of age, cardiac medications, and ventricular function.

What Are the Clinical Implications?

- Heart rate may be an important marker for predicting outcomes in pediatric patients with dilated cardiomyopathy and is a potential target for therapy.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
DCM	dilated cardiomyopathy
EF	ejection fraction
FS	fractional shortening
HF	heart failure
HR	heart rate
LV	left ventricular
PCMR	Pediatric Cardiomyopathy Registry

describing whether this association between elevated HR and long-term outcomes is important in children. Therefore, we tested the hypothesis that elevated HR at diagnosis is associated with worse outcomes in children with DCM. The primary outcomes were transplant free and overall survival.

METHODS

The PCMR (Pediatric Cardiomyopathy Registry) is a National Heart, Lung, and Blood Institute-sponsored registry of children with cardiomyopathy referred from 98 pediatric centers in North America. The PCMR was established to describe the clinical course and epidemiologic features of the pediatric cardiomyopathies. Details of the registry have been described previously.[2,3,19] All participating centers obtained institutional review board approval for the study. Subjects enrolled with informed consent from 2005 onward and with waiver of consent from 1994 to 2004. The registry was analyzed for children enrolled with the diagnosis of DCM between 1994 to 2011. Anonymized data and materials have been made publicly available by the PCMR and can be accessed at https://dev.childrenscardiomyopathy.org/Pediatric-Cardiomyopathy-Registry-71-315.

Disease Classification

As with previous studies from the PCMR, DCM was defined as left ventricular (LV) dilation with decreased LV systolic function.[2,3,7] Left ventricular dilation was defined as an LV end-diastolic dimension more than 2 SDs above the mean normal value for body surface area (ie, a *z* score >+2), and LV systolic dysfunction was defined as an ejection fraction or fractional shortening more than 2 SDs below the mean value for healthy children, adjusted normal value for age (ie, a *z* score of <2).[2,3,7] Children with a diagnosis of myocarditis, neuromuscular disease, mixed cardiomyopathy, or malformation syndromes were excluded because the natural history of these diseases differs from that of idiopathic DCM and DCM from other causes.[2,10,20] Heart rates were recorded at diagnosis. Elevated HR was defined as 2 SDs above the mean HR for healthy children, adjusted for age. No serial assessment of HR during the course of therapy was made in this analysis.

Data Collection

Baseline demographic information, vital signs, symptoms status, and clinical data on the type of cardiomyopathy were collected at enrollment. Additional data, including echocardiographic measurements, the presence of HF, and medications, were collected at enrollment and at annual follow-up exams. Censoring events (death or transplant) were recorded at the time of the event.[3,7]

Statistical Methods

The statistical analyses were performed by the Data Coordinating Center at the New England Research Institute, Watertown, Massachusetts. Data are reported as medians and interquartile ranges or as percentages, as appropriate. Baseline data were compared with Mann–Whitney *U* tests for continuous variables and chi-square tests for categorical variables.

Time-dependent analyses for transplant-free survival and for overall survival were also performed to assess differences between children with and without elevated HRs. Kaplan–Meier curves were constructed, and log-rank statistics were used to assess differences in overall survival, transplant-free survival, and survival at specific time points 1 year, 2 years, and 5 years after enrollment. In order to assess for selection bias or selective survival bias among children included in the analyses, we used survival analysis to compare events (death or heart transplant) between the children with and without HR data.

Table 1. Demographic Characteristics, Echocardiographic Characteristics, and Medication Use at Time of Cardiomyopathy Diagnosis

Parameter	Overall (N=557)	Elevated HR (N=192)	Normal HR (N=365)	*P* Value
Age at diagnosis, y				<0.001
Mean (SD)	4.8 (5.8)	6.0 (6.0)	4.2 (5.6)	
Median (25th%, 75th%)	1.3 (0.3, 9.8)	2.3 (0.6, 11.6)	0.9 (0.2, 8.4)	
Age <1 y at diagnosis, N (%)	250 (44.9)	58 (30.2)	192 (52.6)	<0.001
Male, N (%)	282 (50.6)	94 (49.0)	188 (51.5)	0.568
Race/Ethnicity, N (%)				0.078
White	294 (54.1)	88 (47.1)	206 (57.9)	
Black	125 (23.0)	53 (28.3)	72 (20.2)	
Hispanic/Latino	80 (14.7)	31 (16.6)	49 (13.8)	
Other*	44 (8.1)	15 (8.0)	29 (8.1)	
Weight *z* score (age adjusted)				0.215
N	357	117	240	
Mean (SD)	−0.3 (1.5)	−0.2 (1.5)	−0.4 (1.5)	
Median (25th%, 75th%)	−0.4 (−1.4, 0.5)	−0.3 (−1.3, 0.8)	−0.5 (−1.4, 0.4)	
Congestive heart failure, N (%)	402 (72.3)	160 (83.3)	242 (66.5)	<0.001
Family history of sudden death, N (%)	44 (13.4)	13 (11.5)	31 (14.4)	0.462
Hospitalization, N (%)	211 (37.9)	79 (41.1)	132 (36.2)	0.249
At least one cardiac (heart failure related) hospitalization	178 (32.0)	68 (35.4)	110 (30.1)	
No HF-related hospitalizations, but at least 1 cardiac (non-HF related) hospitalization	18 (3.2)	5 (2.6)	13 (3.6)	0.540
No cardiac hospitalizations, but at least 1 noncardiac hospitalization	15 (2.7)	6 (3.1)	9 (2.5)	
Medication use at enrollment, N (%)				
Anti-congestive therapy	487 (89.2)	180 (95.7)	307 (85.8)	<0.001
Antiarrhythmic	130 (24.1)	58 (30.9)	72 (20.5)	0.008
ACE inhibitor	391 (72.8)	138 (73.4)	253 (72.5)	0.821
CA++ channel antagonist	5 (0.9)	2 (1.1)	3 (0.9)	0.812
Beta blocker	81 (15.1)	32 (17.0)	49 (14.0)	0.350
Heart rate, bpm				<0.001
N	557	192	365	
Mean (SD)	128.1 (33.0)	150.6 (25.6)	116.2 (30.2)	
Median (25th%, 75th%)	129 (108, 150)	149 (131, 168)	119 (95, 140)	
Heart rate *z* score				<0.001
N	557	192	365	
Mean (SD)	1.4 (1.4)	2.8 (0.7)	0.6 (1.1)	
Median (25th%, 75th%)	1.5 (0.5, 2.3)	2.6 (2.3, 3.1)	0.9 (0.1, 1.4)	
LVFS *z* score				0.023
N	451	145	306	
Mean (SD)	−8.6 (3.9)	−9.2 (3.8)	−8.3 (3.9)	
Median (25th%, 75th%)	−9.3 (−11.4, −6.8)	−9.7 (−11.5, −7.5)	−9.1 (−11.3, −6.2)	
LV end-diastolic dimension *z* score				0.001
N	438	143	295	
Mean (SD)	4.5 (2.9)	5.1 (2.4)	4.2 (3.1)	
Median (25th%, 75th%)	4.8 (2.5, 6.4)	5.4 (3.3, 6.8)	4.3 (2.2, 6.1)	
LV end-systolic dimension *z* score				0.002
N	382	118	264	

(*Continued*)

Table 1. Continued

Parameter	Overall (N=557)	Elevated HR (N=192)	Normal HR (N=365)	*P* Value
Mean (SD)	6.2 (3.0)	6.8 (3.1)	5.9 (3.0)	
Median (25th%, 75th%)	6.7 (4.3, 8.3)	7.4 (5.0, 8.8)	6.3 (3.9, 8.1)	
LV ejection fraction *z* score				0.024
N	180	59	121	
Mean (SD)	−6.2 (2.5)	−6.8 (2.4)	−5.9 (2.5)	
Median (25th%, 75th%)	−6.5 (−8.2, −4.8)	−7.2 (−8.5, −5.4)	−6.1 (−8.0, −4.2)	
LV posterior wall thickness *z* score				0.102
N	346	105	241	
Mean (SD)	−0.6 (2.2)	−0.2 (2.4)	−0.7 (2.2)	
Median (25th%, 75th%)	−0.7 (−1.9, 0.7)	−0.4 (−1.7, 1.0)	−0.8 (−2.0, 0.6)	
LV thickness to dimension ratio *z* score				0.117
N	364	114	250	
Mean (SD)	−1.3 (3.5)	−1.5 (2.6)	−1.2 (3.8)	
Median (25th%, 75th%)	−1.8 (−2.9, −0.3)	−2.0 (−3.1, −0.7)	−1.7 (−2.8, −0.2)	

ACE indicates angiotensin-converting enzyme; bpm, beats per minute; HF, heart failure; HR, heart rate; LV, left ventricular; LVFS, left ventricular fractional shortening.

*Other category includes American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, More than One Race, Other, and Unknown.

Nonparametric competing risk analyses were also performed to estimate the cumulative probability of death, transplant, and survival without heart transplantation. Factors associated with the probability of death, transplant, and the composite outcome of death or transplant were identified with Cox regression models. Unadjusted regression models were first fit with HR status (elevated versus normal) as the only predictor, then adjusted models were fitted step by step by adding covariates significant in the unadjusted analyses at the *P*=0.05 level. Finally, backwards variable selection was used to create the final model. An interaction term for HR and age at diagnosis was added to the models to assess whether the effect of HR was homogenous across subgroups on the outcomes of death, heart transplantation, and the composite end point of death or transplantation.

Patients were divided into 2 groups based on their age at DCM diagnosis. Subgroup 1 includes infants (age <1 year) and subgroup 2 includes patients 1 year of age or older. There were 250 subjects under 1 year of age (58 with an elevated HR and 192 with a normal HR) and 307 subjects 1 year of age or older (134 with an elevated HR and 173 with a normal HR). The interaction between HR and these age subgroups was not significant at the *P*=0.05 level for any of the 3 outcomes (*P* values for the interaction >0.5). As such, additional analyses on these subgroups are not reported.

RESULTS

During the study period, 2145 children with DCM were enrolled in the PCMR. Of these, 468 were excluded for having a diagnosis of myocarditis, neuromuscular disease, or a malformation syndrome; 160 were excluded for having a mixed cardiomyopathy phenotype; and 960 were excluded for not having HR data available at study entry. The remaining 557 children comprised the cohort for this study.

The median (Q1, Q3) HR was 149 (131, 168) among the 192 (34.5%) children with an elevated HR (median HR *z* score=2.6; 2.3, 3.1) and 119 (95, 140) among the 365 children with a normal HR (median HR *z* score=0.9; 0.1, 1.4). The groups were similar with respect to race and ethnicity, sex, weight, family history of sudden death, and hospitalization at study entry. However, children with an elevated HR were significantly more likely to be older, have congestive HF, be treated with anticongestive therapy, and be treated with an antiarrhythmic medication (Table 1). Children with an elevated HR were more likely to have lower LV fractional shortening (LVFS) *z* scores, lower LV ejection fraction z-scores, and greater systolic and diastolic LV end-diastolic dimension *z* scores (Table 1).

Median follow-up between cardiomyopathy diagnosis and death, heart transplantation, or last contact was 0.8 years for children with an elevated HR and 2.3 years for the children with a normal HR (*P*<0.001). This difference is partially explained by the increased number of deaths and heart transplants at 1, 2, and 5 years after the diagnosis of DCM among children with an elevated HR (Figure 1). Time to death, heart transplantation, and the composite end point of death or transplantation are all shorter for patients with an elevated HR, compared with those with a normal HR. Of the 192 children with an elevated HR, 38 (19.8%)

died without heart transplant, whereas among the 365 children with a normal HR, 39 (10.7%) died without heart transplant (log-rank test, $P<0.001$). Of the 192 children with an elevated HR and 365 children with a normal HR, 59 (30.7%) and 88 (24.1%), respectively, underwent heart transplantation (log-rank test, $P<0.001$). Children without HR data (n=960) had a greater risk of death or heart transplant in the first year after diagnosis than did those with HR data (log-rank test, $P=0.02$; Figure 2).

Outcomes

Cox regression models were used to identify factors associated with the probability of death, transplant, and the composite outcome of death or transplant

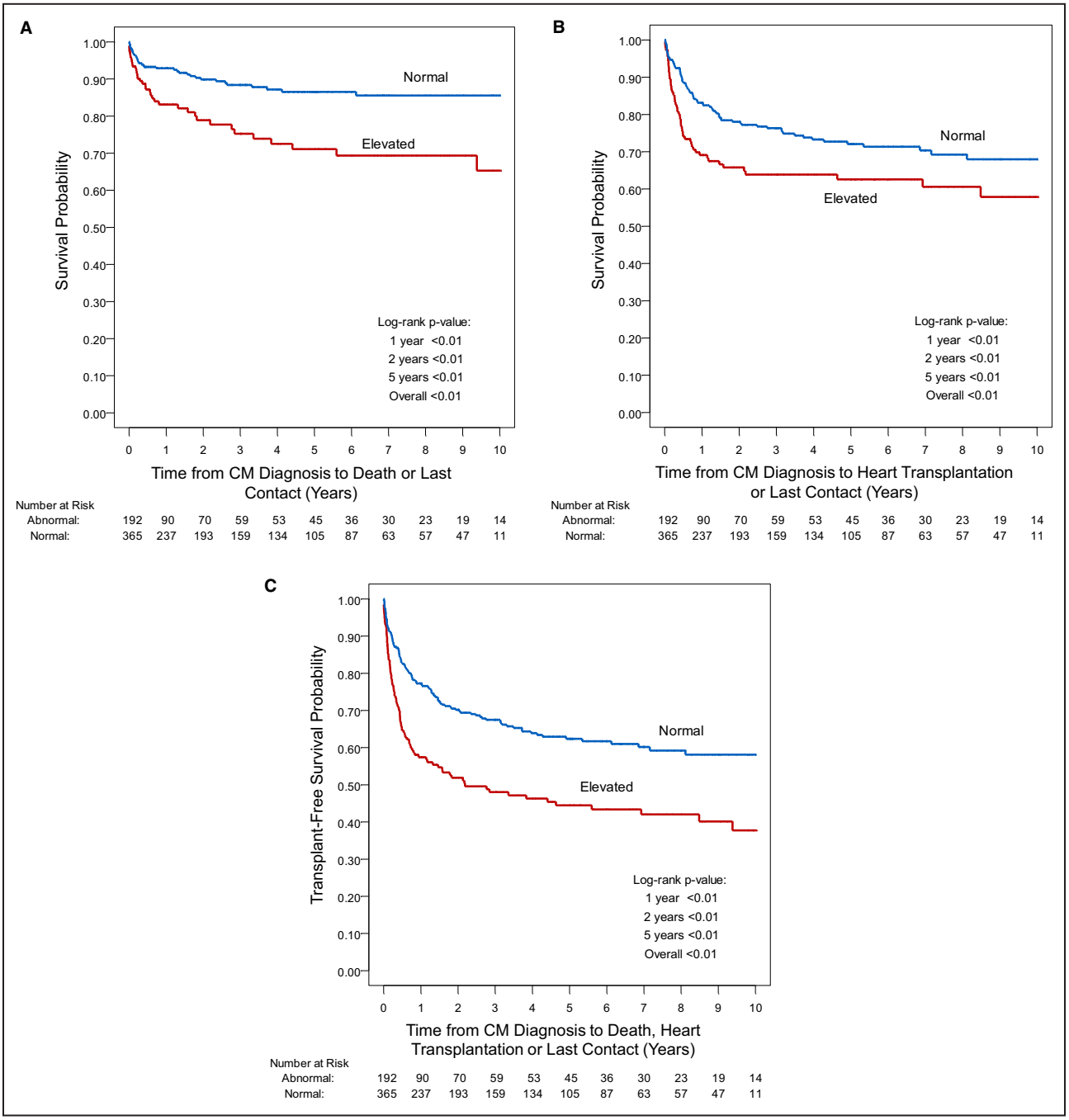

Figure 1. Kaplan–Meier plot of time to (A) death, (B) heart transplant, and (C) death or heart transplant.
Time to death, time to heart transplantation, and time to the composite end point of death or transplantation are all shorter for patients with an elevated heart rate, compared with those with a normal heart rate. Log-rank testing *P* values for the probabilities of freedom from all 3 outcomes at 1, 2, and 5 years after diagnosis of cardiomyopathy are <0.01. CM indicates cardiomyopathy.

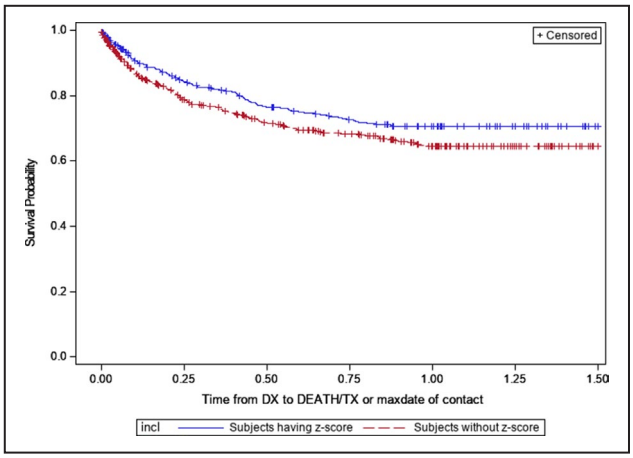

Figure 2. Product-limit survival estimates for patients with and without baseline heart rate data.
Among the 1517 patients with dilated cardiomyopathy, 557 had heart rate *z* score at baseline and were included in the analysis. Among them, 151 (27.1%) had death or heart transplant in the first year. The subjects with baseline heart rate data had a lower risk of death or transplant in the first year than those without baseline heart rate data (log rank test *P*=0.018). DX indicates diagnosis; maxdate, date of last contact; and TX, transplant.

overall and within 5 years of diagnosis (Tables 2 and 3, and Tables S1 and S2).

Death

In the unadjusted and in all adjusted Cox regression analyses, an elevated HR was associated with an increased risk of death. This association was not attenuated when adjusting for multiple factors. an elevated HR was associated with an increased risk of death. After adjusting for LVFS *z* score and use of angiotensin-converting enzyme (ACE) inhibitor, an elevated HR was independently associated with an increased risk of death (hazard ratio [HR] 2.60; 95% CI, 1.55–4.36 in the final model). In the final model (Model 6; R^2=0.08, Harrell's C-statistic 0.72; 95% CI, 0.66–0.79), LVFS *z* score and ACE inhibitors were associated with a decreased risk of death (Table 2).

Transplant

In the unadjusted Cox regression, and when adjusting for age, an elevated HR was associated with an increased risk of heart transplantation (HR, 1.47; 95% CI, 1.06–2.06; *P*=0.02; Model 2; R^2=0.04, Harrell's C-statistic 0.61; 95% CI, 0.56–0.66; Table 2). However, when further adjusting for the presence of congestive HF at diagnosis, LVFS *z* score, and/or medication use, the risk of transplant did not significantly differ between the 2 groups (Models 3–6). In the final model (Model 6), age and the presence of congestive HF at time of cardiomyopathy diagnosis were associated with an increased risk of transplantation (Table S1).

Death or Transplant

For the composite outcome of death or heart transplantation, an elevated HR remained a significant predictor of outcome in the unadjusted and all adjusted Cox regressions (Model 6: HR, 1.50; 95% CI, 1.10–2.06; *P*=0.01) (Table 2). In the final model (Model 6), age at diagnosis and the presence of congestive HF at the time of cardiomyopathy diagnosis were associated with an increased risk of death or transplantation. LVFS *z* score and use of ACE inhibitors were associated with a decreased risk of death or heart transplantation (Table S1). When the same procedures were used to fit the models but shortened the follow-up time to 5 years (Table 3) the results remained largely the same for all 3 outcomes.

Competing risk analysis was used to compare the risk of 3 mutually exclusive outcomes of death, heart transplantation, and survival without transplant over time following diagnosis (Table 4, Figure 3). The cumulative incidence of death was 26% in the elevated HR group and 12% in the normal HR group (*P*=0.002). The

Table 2. Hazard Ratio of Elevated Heart Rate Versus Normal Heart Rate in Time to Death or Transplant

Outcome	Model 1 (N=557)	Model 2 (N=557)	Model 3 (N=556)	Model 4 (N=451)	Model 5 (N=436)	Model 6 (N=451/451/451)
Death	2.27 (1.45–3.56) <0.001	2.28 (1.45–3.58) <0.001	2.01 (1.27–3.19) 0.003	2.26 (1.35–3.79) 0.002	2.32 (1.33–4.04) 0.003	2.60 (1.55–4.36) <0.001
Transplant	1.60 (1.15–2.22) 0.006	1.47 (1.06–2.06) 0.023	1.19 (0.84–1.68) 0.323	1.20 (0.82–1.77) 0.353	1.10 (0.73–1.63) 0.656	1.20 (0.82–1.77) 0.353
Death or transplant	1.81 (1.39–2.35) <0.001	1.71 (1.31–2.24) <0.001	1.44 (1.09–1.89) 0.01	1.50 (1.10–2.05) 0.001	1.41 (1.02–1.95) 0.035	1.50 (1.10–2.06) 0.012

Data presented are hazard ratios (95% CIs) and *P* values. Covariates were included based on statistical (bivariate association with heart rate group *P*<0.05) or clinical significance. Model 1 is univariate Cox regression model with heart rate (HR) variable (elevated HR vs normal HR) only. Model 2 adjusts for age at diagnosis. Model 3 further adjusts for congestive heart failure (Yes/No) in addition to covariates in Model 2. Model 4 further adjusts for left ventricular fractional shortening (LVFS) *z* score in addition to covariates included in Model 3. Model 5 further adjusts for medication (including anticongestive therapy, antiarrhythmic, angiotensin-converting enzyme [ACE] inhibitor, and beta blocker) in addition to covariates included in Model 4. Model 6 is based on backwards model selection; all covariates deemed statistically or clinically significant were included in the initial model. The final model for death outcome adjusts for LVFS *z* score and ACE inhibitor use; the final model for heart transplant outcome adjusts for LVFS *z* score, age at diagnosis, and congestive heart failure; the final model for death or heart transplant outcomes adjusts for LVFS *z* score, age at diagnosis, congestive heart failure, and ACE inhibitor use.

Table 3. Hazard Ratio of Elevated Heart Rate vs Normal Heart Rate for Time to Death or Transplant Within 5 Years of Diagnosis

Outcome	Model 1 (N=557)	Model 2 (N=557)	Model 3 (N=556)	Model 4 (N=451)	Model 5 (N=436)	Model 6 (N=451/451/451)
Death	2.29 (1.44–3.64) <0.001	2.33 (1.46–3.71) <0.001	2.07 (1.29–3.34) 0.002	2.35 (1.38–4.02) 0.002	2.37 (1.33–4.22) 0.004	2.57 (1.50–4.40) 0.001
Transplant	1.65 (1.17–2.32) 0.004	1.53 (1.08–2.16) 0.016	1.21 (0.85–1.74) 0.286	1.30 (0.87–1.94) 0.201	1.18 (0.78–1.77) 0.436	1.30 (0.87–1.94) 0.201
Death or transplant	1.85 (1.41–2.44) <0.001	1.77 (1.34–2.33) <0.001	1.47 (1.11–1.96) 0.008	1.60 (1.16–2.20) 0.004	1.49 (1.07–2.08) 0.018	1.60 (1.15–2.21) 0.005

Data presented are hazard ratios (95% CIs) and *P* values. Covariates were included based on statistical (bivariate association with heart rate group $P<0.05$) or clinical significance. Model 1 is univariate Cox regression model with heart rate (HR) variable (elevated HR vs normal HR) only. Model 2 adjusts for age at diagnosis. Model 3 further adjusts for congestive heart failure (Yes/No) in addition to covariates in Model 2. Model 4 further adjusts for left ventricular fractional shortening (LVFS) *z* score in addition to covariates included in Model 3. Model 5 further adjusts for medication (including anticongestive therapy, antiarrhythmic, angiotensin-converting enzyme [ACE] inhibitor, and beta blocker) in addition to covariates included in Model 4. Model 6 is based on backwards model selection; all covariates deemed statistically or clinically significant were included in the initial model. The final model for death outcome adjusts for LVFS *z* score and ACE inhibitor use; the final model for heart transplant outcome adjusts for LVFS *z* score, age at diagnosis, and congestive heart failure; the final model for death or heart transplant outcomes adjusts for LVFS *z* score, age at diagnosis, congestive heart failure, and ACE inhibitor use.

cumulative incidence of heart transplantation was 36% for the elevated HR group and 29% for the normal HR Group ($P=0.04$).

Regression analysis using competing risks showed results similar to those from the Cox regressions (Tables 5 and 6). Children with an elevated HR had an increased risk of death relative to those with a normal HR in both the unadjusted competing-risk regression model and a model that adjusted for LVFS *z* score and use of angiotensin-converting enzyme inhibitors. An elevated HR was also associated with an increased risk of transplantation in the unadjusted competing-risk regression model but not after adjusting for age, presence of congestive HF, and LVFS *z* score at diagnosis. In an analysis restricted to the 5 years after diagnosis as the follow-up time (Figure 3, Tables 5 and 6), the association between an elevated HR and risk of death and the risk of heart transplantation remained unchanged, as observed previously.

DISCUSSION

We found that children with DCM and an elevated HR at diagnosis are at a greater risk of major adverse events. In our study, an elevated HR was associated with an increased risk of death and with the combined outcome of death or heart transplantation. These associations were independent of age, ventricular function, the presence of HF, and medication use.

These findings are consistent with what is known about the impact of elevated heart rate on outcomes among adults with HF. The CIBIS II (Cardiac Insufficiency Bisoprolol Study II) randomly assigned more than 2500 adults with HF to bisoprolol or placebo and followed them for a mean of 1.3 years.[21] In a subsequent analysis of the trial data, the baseline HR and HR reduction were independently associated with improved survival. A subsequent meta-analysis of 9 studies of beta blockers for treating chronic HF including a pooled sample of nearly 20 000 adults found a significant relationship between both the change in HR and final HR achieved and death.[14] An additional meta-analysis of beta blocker trials (23 trials; 19 202 patients) found that the magnitude of HR reduction was associated with survival, whereas the dose of beta blocker was not.[16] These findings suggest that reducing HR may be a key target of therapy.

More evidence that heart rate may be a modifiable risk factor in HF outcomes independent of beta

Table 4. Unadjusted Cumulative Incidence Rates of Events Among Children With DCM by Heart Rate Status With Death and Transplant as Competing Risks

Time, y	Elevated Heart Rate			Normal Heart Rate		
	Death	Transplant	Neither	Death	Transplant	Neither
0.5	0.12	0.24	0.65	0.06	0.11	0.83
1	0.15	0.28	0.57	0.07	0.16	0.77
2	0.17	0.31	0.52	0.09	0.21	0.70
5	0.22	0.33	0.44	0.12	0.26	0.62
10	0.26	0.36	0.38	0.12	0.29	0.58

DCM indicates dilated cardiomyopathy.

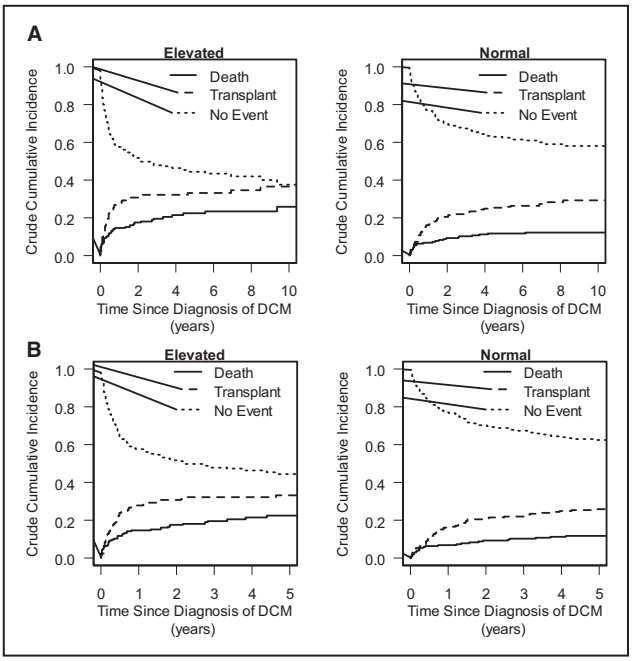

Figure 3. Unadjusted cumulative incidence of death, heart transplantation, or neither among 557 children with dilated cardiomyopathy within (A) 10 years of diagnosis and (B) 5 years of diagnosis.
DCM indicates dilated cardiomyopathy.

blocker dosing has come from the SHIFT (Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine) trial. The study randomized 6558 adults with HF and a resting HR of >70 bpm to either ivabradine or placebo. Importantly, 90% of these patients were taking beta blockers and either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker (93%) at study enrollment.[17] In this trial, mean HR fell by 15.4 bpm in patients taking ivabradine. This reduction was accompanied by a significant decrease in the primary end points of cardiovascular death or hospital admission for worsening HF and a decrease in multiple secondary end points, including all-cause hospital admission, hospital admission for worsening HF, and any hospital admission for a cardiovascular cause.[17] This has resulted in ivabradine being given a Class II indication in combination with ACE inhibitor and beta blocker therapy in Europe, although not in the United States.

Heart rate has not previously been considered a risk factor for poor outcomes in children with DCM. Established risk factors include patient age, cause of cardiomyopathy, LV size, and reduced LV systolic function.[2,7,8,22] Although these factors are important epidemiological findings and provide useful prognostic information, they are for the most part not modifiable and, with rare exception, do not represent targets of therapies. Therefore, HR is an intriguing physiologic "biomarker" in this population with the potential to provide useful prognostic information and conceivably to help guide therapy.

Heart rate has also not typically been a target of therapy in children, and indeed, data on the usefulness of HR-reducing therapies in children with DCM are limited. In a randomized, double-blind, placebo-controlled trial of 116 children with DCM and stable HF, mean resting HR was reduced and LV ejection fraction improved in children randomly assigned to receive ivabradine over 12 months.[23] However, this study was not powered to detect a difference in mortality or freedom from heart transplantation.

If an elevated baseline HR is associated with increased risk of mortality and decreased freedom from death or heart transplantation, as we have observed, and if therapies that decrease HR can improve echocardiographic indices of ventricular function, will ivabradine or other HR-lowering therapies improve survival in children with HF due to DCM and other causes? This critically important question is still unanswered.[24] There are no validated surrogate end points for mortality in these children, and history is filled with examples of harm to patients given therapies approved based on a surrogate end point.[25–30] Ideally, a larger trial with appropriate power to detect clinically meaningful end points should be performed in this population.

Table 5. Competing Risk Analysis of Time to Death or Transplant

	Hazard Ratio (95% CI), *P* Value			
	Death		Transplant	
Risk Factor	Unadjusted Analysis	Adjusted Analysis	Unadjusted Analysis	Adjusted Analysis
Heart rate (elevated vs normal)	2.00 (1.28–3.11) 0.002	2.23 (1.34–3.72) 0.002	1.43 (1.03–1.99) 0.035	1.03 (0.69–1.55) 0.874
Age at diagnosis, y				1.09 (1.05–1.12) <0.001
Congestive heart failure (yes vs no)				2.11 (1.21–3.69) 0.009
LVFS *z* score		0.88 (0.81–0.95) <0.001		0.89 (0.83–0.96) 0.002
ACE inhibitor (use vs no use)		0.38 (0.22–0.65) <0.001		

ACE indicates angiotensin-converting enzyme inhibitor; and LVFS, left ventricular fractional shortening.

Table 6. Competing Risk Analysis of Time to Death or Transplant Within 5 Years of Diagnosis

Risk Factor	Hazard Ratio (95% CI), *P* Value			
	Death		Transplant	
	Unadjusted Analysis	Adjusted Analysis	Unadjusted Analysis	Adjusted Analysis
Heart rate (elevated vs normal)	2.03 (1.28–3.22) 0.003	2.26 (1.32–3.86) 0.003	1.50 (1.06–2.12) 0.025	1.12 (0.74–1.70) 0.58
Age at diagnosis, y				1.09 (1.05–1.13) <0.001
Congestive heart failure (yes vs no)				2.33 (1.27–4.30) 0.007
LVFS *z* score		0.87 (0.79–0.94) <0.001		0.88 (0.82–0.96) 0.002
ACE inhibitor (use vs no use)		0.38 (0.22–0.66) <0.001		

ACE indicates angiotensin-converting enzyme inhibitor; and LVFS, left ventricular fractional shortening.

Limitations of the Study

Our study has several limitations. Almost 45% of the children with DCM in the PCMR did not have HR data available at study entry. Children without HR data were at a greater risk of death or transplant than were children with HR data. This may introduce bias into the study and the findings among the children with HR data may not be generalizable to the entire cohort in the PCMR or to the general population of children with DCM. Many children were not treated with beta blockers in this cohort, and therefore generalizability to a population on maximal medical therapy is uncertain. In addition, although the PCMR's data collection procedures are based on trained evaluator chart review and allow statistical control for important clinical variables, it is possible that unmeasured factors could have affected our findings. The number of children with serial data was also limited, precluding any analysis of the effect of changing HR over time, and therefore our findings are limited to the impact of HR at initial assessment. This would be an important topic for further study and allow for assessments of the changes in HR over time. It is interesting to note that elevated HR was not associated with transplant. As listing decisions for transplant vary among centers, there is some subjectivity in this endpoint.

CONCLUSIONS

In this observational study, HR was significantly elevated in one third of the children with DCM at the time of enrollment in the PCMR. Elevated HR was associated with a greater risk of death, and of death or heart transplantation. These findings suggest that HR may be a modifiable risk factor for poor outcomes in these children and that reducing HR may be a key target of therapy. Further study is warranted to assess efficacy of targeted therapy as a means of controlling elevated HR and the impact of such an approach on survival in pediatric patients with DCM.

ARTICLE INFORMATION

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Disclosures

Rossano is a consultant for Amgen, Novartis, Bayer, and Abiomed and reports travel support from Abbott. Kantor is a consultant for Novartis. Shaddy is a consultant for Amgen and Novartis. Jefferies is a consultant for Norvartis, Abbott, Protalix, Sanofi Genzyme, and Battelle and reports grant support from Medtronic. Wirtz is an employee of Amgen. Depre is a former employee of Amgen. Lipshultz reports investigator-initiated grant support from Amgen. The remaining authors have no disclosures to report.

Supplementary Materials

Tables S1–S2

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Supplemental Material

Table S1. Multivariate Cox Regression Modeling of Time to Death or Transplant.

Outcome	Covariates*	Model 1 (N=557)	Model 2 (N=557)	Model 3 (N=556)	Model 4 (N=451)	Model 5 (N=436)	Model 6[l] (N=451/451/451)
Death	Heart Rate (abnormal vs normal)	2.27 (1.45-3.56) <0.001	2.28 (1.45-3.58) <0.001	2.01 (1.27-3.19) 0.003	2.26 (1.35-3.79) 0.002	2.32 (1.33-4.04) 0.003	2.60 (1.55-4.36) <0.001
	Age at Diagnosis (years)		1.00 (0.96-1.04) 0.939	1.01 (0.97-1.05) 0.724	1.00 (0.95-1.06) 0.945	1.01 (0.96-1.07) 0.702	
	Congestive Heart Failure (yes vs no)			2.29 (1.22-4.30) 0.01	1.77 (0.87-3.61) 0.116	1.54 (0.72-3.29) 0.271	
	LVFS z-score				0.92 (0.83-1.01) 0.079	0.87 (0.78-0.97) 0.016	0.85 (0.78-0.93) <0.001
	Anticongestive therapy (use vs no use)					1.18 (0.38-3.71) 0.774	

Outcome	Covariates*	Model 1 (N=557)	Model 2 (N=557)	Model 3 (N=556)	Model 4 (N=451)	Model 5 (N=436)	Model 6[†] (N=451/451/451)
	Antiarrhythmic (use vs no use)					1.29 (0.73-2.27) 0.382	
	ACE Inhibitor (use vs no use)					0.33 (0.19-0.56) <0.001	0.33 (0.20-0.56) <0.001
	Beta Blocker (use vs no use)					0.74 (0.34-1.58) 0.4310	
Transplant	Heart Rate (abnormal vs normal)	1.60 (1.15-2.22) 0.006	1.47 (1.06-2.06) 0.023	1.19 (0.84-1.68) 0.323	1.20 (0.82-1.77) 0.353	1.10 (0.73-1.63) 0.656	1.20 (0.82-1.77) 0.353
	Age at Diagnosis (years)		1.05 (1.03-1.08) <0.001	1.07 (1.04-1.10) <0.001	1.09 (1.05-1.13) <0.001	1.10 (1.06-1.14) <0.001	1.09 (1.05-1.13) <0.001

Outcome	Covariates*	Model 1 (N=557)	Model 2 (N=557)	Model 3 (N=556)	Model 4 (N=451)	Model 5 (N=436)	Model 6[†] (N=451/451/451)
	Congestive Heart Failure (yes vs no)			3.02 (1.89-4.82) <0.001	2.21 (1.28-3.82) 0.004	2.12 (1.19-3.79) 0.011	2.21 (1.28-3.82) 0.0044
	LVFS z-score				0.88 (0.82-0.95) 0.001	0.88 (0.81-0.95) 0.001	0.88 (0.82-0.95) 0.001
	Anticongestive therapy (use vs no use)					4.15 (0.96-17.99) 0.057	
	Antiarrhythmic (use vs no use)					0.95 (0.62-1.46) 0.822	
	ACE Inhibitor (use vs no use)					0.83 (0.53-1.32) 0.441	
	Beta Blocker (use vs no use)					0.83 (0.50-1.36) 0.454	

Outcome	Covariates*	Model 1 (N=557)	Model 2 (N=557)	Model 3 (N=556)	Model 4 (N=451)	Model 5 (N=436)	Model 6[†] (N=451/451/451)
Death or Transplant	Heart Rate (abnormal vs normal)	1.81 (1.39-2.35) <0.001	1.71 (1.31-2.24) <0.001	1.44 (1.09-1.89) 0.01	1.50 (1.10-2.05) 0.001	1.41 (1.02-1.95) 0.035	1.50 (1.10-2.06) 0.012
	Age at Diagnosis (years)		1.04 (1.01-1.06) 0.001	1.05 (1.03-1.07) <0.001	1.06 (1.03-1.09) <0.001	1.07 (1.04-1.10) <0.001	1.07 (1.04-1.10) <0.001
	Congestive Heart Failure (yes vs no)			2.74 (1.88-3.98) <0.001	2.03 (1.31-3.12) 0.001	1.92 (1.21-3.04) 0.006	2.18 (1.39-3.43) 0.001
	LVFS z-score				0.89 (0.84-0.95) <0.001	0.87 (0.82-0.93) <0.001	0.87 (0.82-0.93) <0.001
	Anticongestive therapy (use vs no use)					2.19 (0.90-5.30) 0.083	

Outcome	Covariates*	Model 1 (N=557)	Model 2 (N=557)	Model 3 (N=556)	Model 4 (N=451)	Model 5 (N=436)	Model 6[l] (N=451/451/451)
	Antiarrhythmic (use vs no use)					1.08 (0.77-1.51) 0.676	
	ACE Inhibitor (use vs no use)					0.59 (0.42-0.82) 0.002	0.61 (0.44-0.86) 0.005
	Beta Blocker (use vs no use)					0.80 (0.53-1.22) 0.305	

Table S2. Multivariate Cox Regression Modeling of Time to Death or Transplant within 5 Years of Diagnosis.

Outcome	Covariates*	Model 1 (N=557)	Model 2 (N=557)	Model 3 (N=556)	Model 4 (N=451)	Model 5 (N=436)	Model 6[l] (N=451/451/451)
Death	Heart Rate (Abnormal vs normal)	2.29 (1.44-3.64) <0.001	2.33 (1.46-3.71) <0.001	2.07 (1.29-3.34) 0.002	2.35 (1.38-4.02) 0.002	2.37 (1.33-4.22) 0.004	2.57 (1.50-4.40) 0.001
	Age at Diagnosis (years)		0.99 (0.95-1.03) 0.601	1.00 (0.96-1.04) 0.900	0.99 (0.93-1.04) 0.627	1.00 (0.94-1.06) 0.912	
	Congestive Heart Failure (Yes vs no)			2.29 (1.19-4.41) 0.013	1.77 (0.84-3.71) 0.132	1.56 (0.70-3.46) 0.279	
	LVFS z-score				0.92 (0.83-1.02) 0.097	0.88 (0.78-0.98) 0.022	0.85 (0.77-0.93) <0.001
	Anticongestive therapy (use vs no use)					0.99 (0.31-3.12) 0.988	
	Antiarrhythmic					1.41 (0.78-2.53) 0.254	

	(use vs no use)						
	ACE Inhibitor (use vs no use)					0.33 (0.19-0.57) <0.001	0.34 (0.20-0.58) <0.001
	Beta Blocker (use vs no use)					0.67 (0.30-1.52) 0.340	
Transplant	Heart Rate (Abnormal vs normal)	1.65 (1.17-2.32) 0.004	1.53 (1.08-2.16) 0.016	1.21 (0.85-1.74) 0.286	1.30 (0.87-1.94) 0.201	1.18 (0.78-1.77) 0.436	1.30 (0.87-1.94) 0.201
	Age at Diagnosis (years)		1.05 (1.03-1.08) <0.001	1.07 (1.04-1.10) <0.001	1.09 (1.05-1.12) <0.001	1.09 (1.06-1.13) <0.001	1.09 (1.05-1.12) <0.001
	Congestive Heart Failure (Yes vs no)			3.49 (2.10-5.82) <0.001	2.46 (1.37-4.41) 0.003	2.25 (1.23-4.12) 0.008	2.46 (1.37-4.41) 0.003
	LVFS z-score				0.88 (0.81-0.95) 0.0009	0.88 (0.81-0.95) 0.003	0.88 (0.81-0.95) 0.001
	Anticongestive therapy (use vs no use)					7.53 (1.00-56.85) 0.050	

	Antiarrhythmic (use vs no use)					0.94 (0.60-1.47) 0.796	
	ACE Inhibitor (use vs no use)					0.80 (0.50-1.28) 0.354	
	Beta Blocker (use vs no use)					0.80 (0.48-1.33) 0.390	
Death or Transplant	Heart Rate (Abnormal vs normal)	1.85 (1.41-2.44) <0.001	1.77 (1.34-2.33) <0.001	1.47 (1.11-1.96) 0.008	1.60 (1.16-2.20) 0.004	1.49 (1.07-2.08) 0.018	1.60 (1.15-2.21) 0.005
	Age at Diagnosis (years)		1.03 (1.01-1.06) 0.006	1.04 (1.02-1.07) <0.001	1.05 (1.02-1.09) <0.001	1.06 (1.03-1.10) <0.001	1.06 (1.03-1.09) <0.001
	Congestive Heart Failure (Yes vs no)			3.00 (2.01-4.48) <0.001	2.17 (1.37-3.43) <0.001	2.01 (1.24-3.27) 0.005	2.29 (1.43-3.69) <0.001
	LVFS z-score				0.89 (0.84-0.95) <0.001	0.87 (0.82-0.93) <0.001	0.87 (0.82-0.93) <0.001

	Anticongestive therapy (use vs no use)					2.31 (0.89-6.02) 0.087	
	Antiarrhythmic (use vs no use)					1.10 (0.78-1.57) 0.587	
	ACE Inhibitor (use vs no use)					0.58 (0.41-0.82) 0.002	0.61 (0.43-0.86) 0.005
	Beta Blocker (use vs no use)					0.77 (0.50-1.18) 0.229	

Data presented are hazard ratios (95% confidence intervals) and *P*-values. * Covariates were included based on statistical (bivariate association with heart rate group $P < 0.05$) or clinical significance. † Backwards model selection; all covariates deemed statistically or clinically significant were included in the initial model.