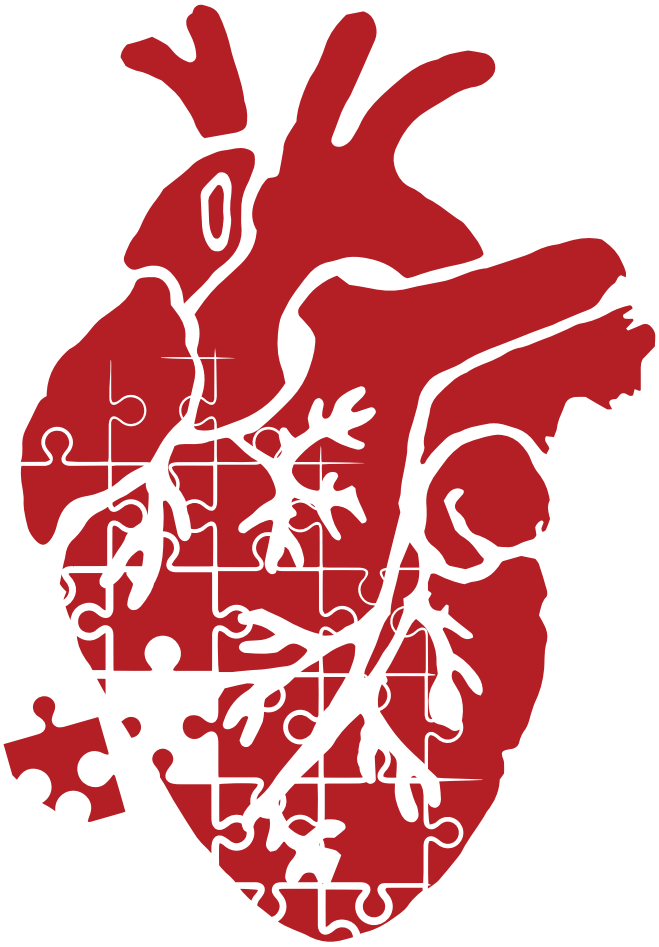
Dilated Cardiomyopathy in Children

UNRAVELING THE DETERMINANTS
OF DISEASE PROGRESSION



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Unraveling the determinants of disease progression

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Dilated Cardiomyopathy in Children

Unraveling the determinants of disease progression

Gedilateerde cardiomyopathie bij kinderen

Ontrafelen van determinanten van ziekte progressie

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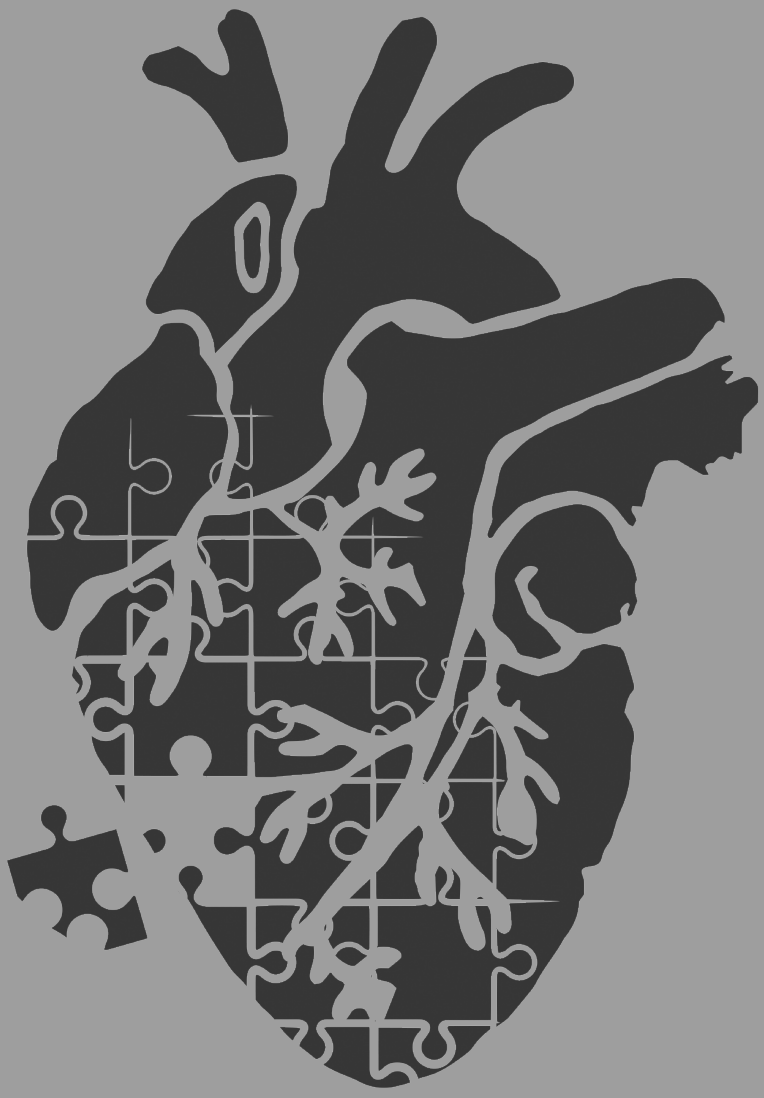
PART 1

Introduction



Chapter 1

General introduction

DILATED CARDIOMYOPATHY

Most common heart disease in children is congenital heart disease, with an incidence of 8 per 1,000 live births.[1] Much less prevalent is cardiomyopathy, with an incidence which is approximately 700 times lower (1.13 per 100.000 children) than congenital heart disease.[2] Cardiomyopathy is classified by the World Health Organization as dilated, hypertrophic, restrictive and arrhythmogenic right ventricular dysplasia cardiomyopathy.[3]

Dilated cardiomyopathy (DCM) is the most common form in children, characterized by systolic dysfunction and left ventricular dilation. Two large cohort studies in the United States (PCMR – Pediatric Cardiomyopathy Registry) and Australia (NACCS – National Australian Childhood Cardiomyopathy Study) have shown incidence rates varying from 0.58-0.73 per 100,000 children per year.[2, 4] The annual incidence was higher in boys than in girls (0.67 vs 0.48 per 100,000 children) and much higher in children aged <1 year compared to those between 1-18 years (4.58 vs 0.34 per 100,000 children).[2] If we apply these numbers to the Dutch pediatric population, we expect approximately 21 new DCM cases per year, of whom approximately half are <1 year of age at diagnosis (population numbers used from Statistics Netherlands, den Haag/Heerlen). Clinical symptoms at diagnosis vary between patients and ranges from no symptoms (10-30%) to (severe) congestive heart failure in the majority of children (70-90%).[5-7] Presenting symptoms vary between ages; young children mostly present with symptoms as feeding difficulties, failure to thrive and dyspnea, while older children commonly present with fatigue, exercise intolerance and weight loss.[5]

Etiology

The underlying etiology of DCM varies widely. Cohort studies have reported causes as myocarditis (14-22%), arrhythmias (7%), anthracycline toxicity (5%), metabolic (4-7%) and neuromuscular disorders (2-9%), and familial disease with or without proven genetic mutations (5-15%). Nevertheless, in the majority of the cases (50-66%) the cause remains unknown and DCM is called “idiopathic”.[6-8]

The diagnostic work-up is a complex process. If a child presents with DCM, the detection of arrhythmias, a history of anthracycline therapy or underlying neuromuscular or metabolic disorders may be relatively easy. In contrast, myocarditis and genetic mutations are much more difficult to detect. In adults with idiopathic DCM, pedigree analysis and examination of asymptomatic family members revealed suspected and confirmed familial DCM in one-third of the cases.[9, 10] Furthermore, in 20% of the idiopathic cases sequelae of an earlier myocarditis may have caused DCM.[11]

In case of a newly diagnosed DCM it is recommended to perform an endomyocardial biopsy (EMB).[12] An EMB fulfilling the Dallas criteria is the gold standard to diagnose myocarditis.[13] However, the risk of complications in children is high, and probably the main

reason to omit an EMB.[14] In clinical studies biopsy rates vary between 0-38%,[6, 8, 15] and the diagnosis of myocarditis is often a "clinical diagnosis", rather than confirmed by the gold standard. In the absence of an EMB, it is unclear what criteria need to be fulfilled to diagnose myocarditis, and several classification systems have been suggested.[16, 17]

Prognosis

DCM in children may have a poor prognosis. One-year survival has been reported at 87% and 5-year survival at 77%.[7] Although these numbers have improved after the introduction of pediatric heart transplantations, the number of patients that survived without transplantation is still poor; 1-year transplant-free survival has been reported between 66-74%, and 5-year transplant-free survival between 54-65%.[7, 8, 18] On the other hand, around one-third of the patients recover.[19]

For optimal individual treatment, it is the challenge to identify patients at high risk for death, and to list them early enough for heart transplantation. Therefore, risk factors need to be defined, which identify patients at high risk for disease progression and death, at time of diagnosis and during follow-up. Until now, several studies have reported risk factors present at diagnosis, including older age (> 5-6 year), congestive heart failure, lower fractional shortening (FS), and idiopathic and familial origin.[7, 8, 18] However, many of these markers at diagnosis do not take the response to medical therapy as well as the influence of the natural course of the disease on outcome into account. The individual alterations within risk markers may contain valuable prognostic information. Until now, markers which predict disease progression during follow-up are largely unknown.

In adults with heart failure several markers, that are potentially interesting to study in children, have been shown to be predictive for poor outcome. We focused on N-terminal pro-B-type natriuretic peptide (NT-proBNP), left ventricular strain assessed by echocardiography, the presence of central sleep apnea, 6-minute walk test results, quality of life reports and a heart failure severity score.

NT-proBNP

NT-proBNP is a cardiac neurohormone that is released in response to stretch of cardiac myocytes, i.e. in case of increased cardiac pressure and volume overload.[20] In adults with chronic heart failure, it has been shown that both a single concentration of NT-proBNP, as well as the change of NT-proBNP over time were independent predictors for mortality.[21, 22] Pediatric studies showed that NT-proBNP had a good correlation with the clinical severity of heart failure and with echocardiographic measures of LV dysfunction.[23, 24] Some studies have defined cut-off levels to predict outcome in selected groups of children with DCM.[25] However, the role of NT-proBNP at diagnosis and during subsequent follow-up as predictor for hard endpoints has not been established in pediatric DCM.

Left ventricular strain

Two-dimensional echocardiography is used to diagnose DCM. During follow-up, functional echocardiographic parameters such as left ventricular FS and ejection fraction (EF) are frequently measured. In cohort studies, a lower FS at diagnosis has been related to a higher risk of death and heart transplantation.[7, 18] Moreover, a lack of improvement of FS during follow-up has been associated with a higher risk of death and transplantation.[18] McMahon et al. studied a cross-sectional cohort of 54 children with DCM and found that lower EF was associated with a higher risk of death and heart transplantation.[26]

In the past two decades, speckle tracking echocardiography (STE) has been developed. Using STE, global left ventricular function can be quantified in a multidirectional way, specifically longitudinal, circumferential and radial movements can be evaluated. Moreover, STE can be used to study regional wall motion, and thus the presence of dyssynchrony can be assessed.[27] To predict prognosis in adults with heart failure, strain assessed by STE had additional value to EF.[28, 29] Furthermore, for adults not improving after optimal medical therapy, cardiac resynchronization therapy (CRT) has been effective and recommended.[30, 31] Nevertheless, accurate patient selection for CRT is essential, since a significant proportion remain non-responder and in a subset CRT may even be harmful.[32] Recently, a qualitative analysis of strain patterns showed a high sensitivity to predict CRT response, in a selective population of heart failure patients with left bundle branch block and QRS-duration >130 ms.[33, 34]

In children with DCM, STE has been reported in three small studies, with limited results.[35-37] The studies suggest that radial strain is reduced in DCM patients,[36] and that dyssynchrony may be present in the pediatric DCM population, using intraventricular time differences and strain pattern analysis.[35, 37] However, the reproducibility of radial strain and intraventricular time differences is rather poor,[38, 39] and none of the studies correlated STE with clinical outcome.

Central sleep apnea

Sleep apnea is defined as a drop in airflow of ≥ 90% during sleep.[40] Central sleep apnea (CSA) is characterized by the absence of inspiratory effort. CSA is highly prevalent in adults with heart failure.[41-43] The pathophysiology is multifactorial. First, increased venous return during supine position and increased capillary wedge pressure lead to a slightly increased respiration rate during sleep.[44] As a consequence, pCO_2 does not increase at the onset of sleep (which happens in the normal situation). This may easily result in a drop of the pCO_2 below the apneic threshold resulting in an apnea. Furthermore, the sensitivity to CO_2 is increased in patients with heart failure.[45] This leads to a hyperventilatory response after an apnea, inducing a vicious cycle of subsequent apneas. Cheyne-Stokes breathing is a form of central sleep apnea, with at least 3 central apnea cycles, in a crescendo-decrescendo

pattern.[40] In adults with heart failure, the presence of Cheyne-Stokes breathing has been associated with a higher risk of death and heart transplantation.[46]

In children with DCM, CSA and its relation to outcome have not been described. Anecdotal occurrence of CSA has been observed in children with severe heart failure admitted to the intensive care unit of our center (unpublished data). However, structural assessment of the prevalence and its implications has not been done.

6-minute walk test

Cardiopulmonary exercise testing (CPET), measuring peak oxygen consumption, has been shown a valuable predictor for outcome in adults with chronic heart failure.[47] Also in children with DCM, Giardini et al. showed comparable results.[48] However, CPET has several limitations. It is time consuming, requires sophisticated equipment and specially trained staff and can only be performed in children aged > 8-9 years old. Another exercise test is the 6-minute walk test. The 6-minute walk test is cheap, easy to perform, and can be used from the age of 6 years onwards. In adults with heart failure, it has been shown that the distance walked in 6 minutes was predictive for mortality and morbidity.[49, 50] Furthermore, in children with pulmonary hypertension, the 6-minute walk test has been used to grade disease severity and to measure treatment effect.[51, 52] So far, the 6-minute walk test has not been systematically used in children with DCM, and its predictive power has not been investigated yet.

Health-related quality of life

Health-related quality of life (HRQoL) can be defined as 'the impact of a medical condition and/or its treatment, upon the physical, social and emotional aspects of a patient's well-being that are relevant and important to the individual'.[53, 54] Nowadays, HRQoL is also being used as outcome marker for disease. Especially in case of chronic disease, when cure is impossible, it is important to determine that a treatment really improves the patient's quality of life. In adults with heart failure, HRQoL has been extensively investigated and it has been shown that HRQoL was significantly reduced compared to healthy age-matched controls, but also to other chronically ill patients.[55-57] Moreover, reduced HRQoL has been associated with increased mortality and hospitalization.[58, 59]

In children with DCM, HRQoL is unknown. An explorative study in the pediatric cardiology outpatient department investigated parent-reported HRQoL of all visiting patients for various diseases, including a small subgroup of 17 cardiomyopathy patients. Their results on the Child Health Questionnaire Parent-Form 50 were worse than all other illnesses on the subscales: Physical Functioning, General health perceptions, and Parental impact – emotional. This suggests that HRQoL may be severely impaired in children with DCM. Furthermore, using parent-reported HRQoL questionnaires enables a detailed and

structural assessment of the physical and psychosocial functioning of a child. Since parents 'know their child best', we speculated that the results of these reports may add predictive value to a physician's assessment of heart failure severity, using a validated heart failure severity score.

New York University Pediatric Heart Failure Index

The New York University Pediatric Heart Failure Index (NYU PHFI) is a standardized heart failure severity score specially designed for children.[60] In adults, the New York Heart Association (NYHA) Classification has been commonly used, which measures functional capacity.[61] However, since adults and (young) children differ in functional ability and heart failure symptoms, the NYHA is inappropriate for children. The NYU PHFI is a score that ranges from 0-30 points and includes symptoms, physical signs and medical treatment. A higher score, represents more severe heart failure. The predictive value of this score on outcome in children with DCM has not been investigated.

AIMS OF THIS THESIS

The aims of this thesis are:

- To evaluate the epidemiological aspects of pediatric DCM in The Netherlands.
- To determine risk factors at diagnosis and during follow-up for outcome of DCM.

Design of the CArdiomyopathy Registry Study (CARS)

To determine risk factors that predict outcome at DCM diagnosis or during follow-up, we started a multicenter, prospective, observational study "CARS". This study was conducted at 7 pediatric cardiology departments in the Netherlands (Academic Medical Center, Erasmus Medical Center, Free University Medical Center, University Medical Center Groningen, Leiden University Medical Center, Radboud University Medical Center and University Medical Center Utrecht).

Study population

Children (0-18 year) with a prior or new DCM diagnosis were included in CARS. DCM was defined as the presence of two out of three of the following criteria: 1. Symptomatic heart failure; 2. Severely impaired function (FS ≤ 25%); 3. Left ventricular dilation (left ventricular end-diastolic dimension z-score > +2). DCM could be secondary to several etiologies, though patients with a history of structural heart defects were excluded. Patients were followed-up for at least one year, with a maximum of three years.

Endpoints

We defined several outcomes. Firstly, a combined primary outcome of death or heart transplantation. Analyzing the NT-proBNP results, the start of mechanical circulatory support was also used as a primary endpoint, because the unloading of the heart influenced the NT-proBNP results. Secondly, recovery was also studied as outcome and defined as FS > 25% and left ventricular end-diastolic dimension z-score < +2 at the first of two consecutive time points. The remainder, third group, had ongoing disease.

Measurements

Potential risk factors were measured from diagnosis onwards, or from inclusion in the study, with an interval of 3-6 months. These measurements included: heart failure severity score (New York University Pediatric Heart Failure Index), electrocardiogram, echocardiography, nutritional status, growth, six-minute walk test (> 6 years), blood sample, HRQoL questionnaires. All patients were asked to undergo a single polysomnography at home.

OUTLINE OF THIS THESIS

PART II focusses on the incidence, causes and outcome of pediatric DCM in the Netherlands. In **chapter 2** we studied all patients that were diagnosed with DCM from 2005 until 2011 (the start of the prospective study CARS). We defined the incidence of DCM in the Netherlands, and performed a risk factor analysis for the endpoint of death or heart transplantation. In **chapter 3** we evaluated the diagnostic work-up of DCM and specifically, we focused on the difficulty of diagnosing myocarditis.

PART III focusses on risk factors that predict outcome of DCM using the results from the prospective multicenter observational study CARS. In **chapter 4** the predictive power of single and serial NT-proBNP measurements was investigated on the outcome of cardiac death. In **chapter 5, 6 and 7** we report on results of a cross-sectional analysis. In **chapter 5 and 6** we investigated if the presence of central sleep apnea and reduced left ventricular strain were predictive for death and heart transplantation. Furthermore, we studied the presence of different strain patterns to assess dyssynchrony. In **chapter 7** the predictive value of 6-minute walk test results were studied. In **chapter 8** longitudinal results were analyzed to investigate the predictive power of quality of life measurements and the New York University Pediatric Heart Failure Index on outcome.

PART IV summarizes the results of these studies. In **chapter 9** we discuss our findings in a broader perspective and speculate on future research topics. In **chapter 10** our findings, as described in this thesis, are summarized in English and in Dutch.

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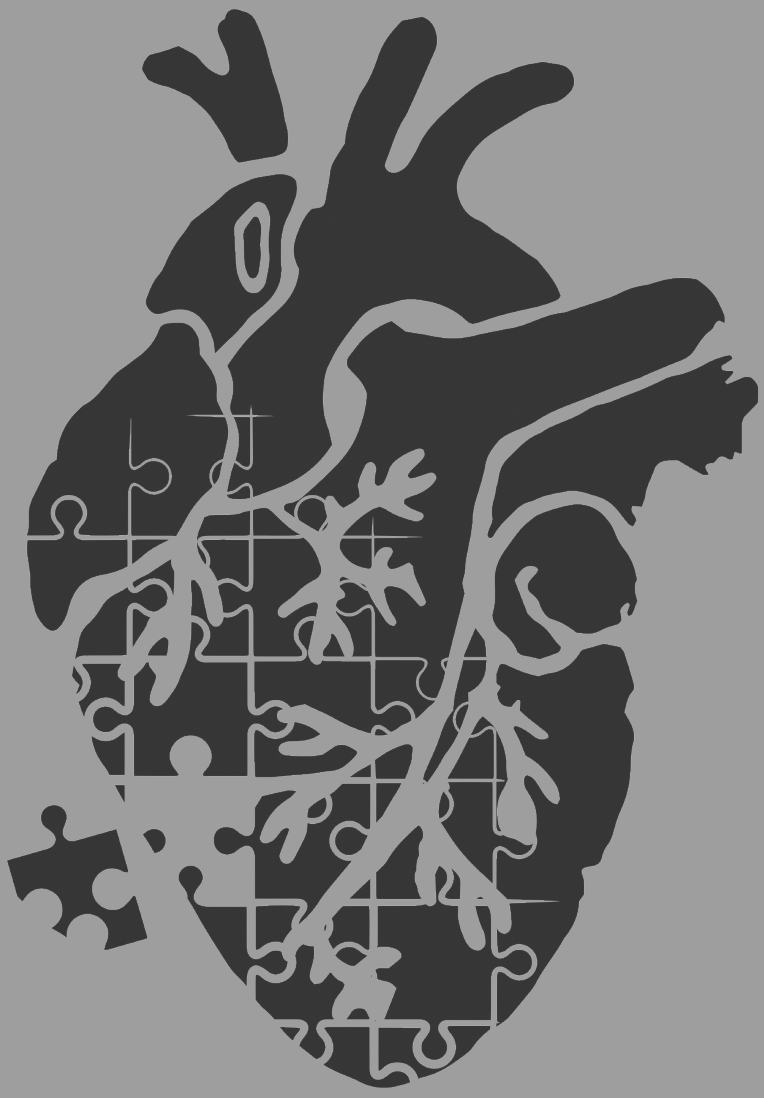
PART 2

Epidemiological aspects



Chapter 2

Management of children with dilated cardiomyopathy in The Netherlands: Implications of a low early transplantation rate

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ABSTRACT

Background

The policy for listing and transplant children with dilated cardiomyopathy (DCM) in the Netherlands has been conservative because of low donor availability. The effects of this policy on outcome are reported.

Methods

This was a multicenter, nationwide study performed in 148 children with DCM. The primary outcome was death or heart transplant.

Results

Overall, 43 patients (29%) died or were transplanted. Within 1 year of diagnosis, 21 patients died, and only 4 underwent transplantation (3 on mechanical circulatory support). The 1-year survival was 85% (95% CI 79-91), and 5-year survival was 84% (95% CI 78-90). Transplantation-free survival at 1 year was 82% (95% CI 75-88), and at 5 years was 72% (95% CI 64-80). Within 1 year of diagnosis, with death as main endpoint (21 of 25, 84%), ICU admission (HR 2.6, p = 0.05) and mechanical circulatory support (HR 3.2, p = 0.03) were risk factors (multivariable Cox analysis); inotropic support was longer in patients reaching an endpoint. At > 1 year after diagnosis, with transplantation as main endpoint (15 of 18, 83%), age > 6 years (HR 6.1, p = 0.02) was a risk factor. There were 56 (38%) children who recovered, 50% within 1 year of diagnosis. Recovery was associated with younger age, was similar in patients with myocarditis (43%) and idiopathic disease (41%); and was similar in patients initially admitted to the ICU, admitted to the ward, or treated as outpatients.

Conclusions

The transplantation rate in our cohort in the first year was low, with 1- and 5-year survival rates similar to other cohorts. Our results suggest that a conservative approach to list children for transplantation early after presentation may be justifiable, except for patients with prolonged ICU or mechanical circulatory support.

INTRODUCTION

In children, dilated cardiomyopathy (DCM) is a severe disorder with a poor prognosis.[1] In pediatric studies, transplantation rate in the first year after presentation has been relatively high.[1-3] During a first ICU hospitalization, 24% of the children with DCM died or underwent heart transplantation.[4] This emphasizes that a decision about transplantation is made early after first admission for a considerable subgroup of children.

Several studies identified risk factors for the combined endpoint of death or transplantation. These include etiology of DCM, and age, congestive heart failure, need for inotropic support and fractional shortening (FS) at diagnosis.[1, 3, 5-8] An analysis of the Pediatric Cardiomyopathy Registry (PCMR) showed that the median time between presentation with DCM and listing for transplantation was only 1.4 months. Because most children underwent transplantation, these risk factors may reflect the risk of being selected for transplantation, rather than the risk of dying.[5]

In the Netherlands, children with heart failure have been systematically evaluated for heart transplantation since 1998. However, donor hearts have been scarce and a conservative approach has been used to list children for transplantation early after presentation, resulting in only a few heart transplantations being performed.[9] We investigated whether this approach affected the prognosis of these children.

METHODS

The study was approved by the medical ethical committee of the Erasmus MC, Rotterdam, the Netherlands (MEC2013-239). We reviewed patient and echocardiography databases of all 8 pediatric cardiology centers in the Netherlands. Patients (< 18 years old at diagnosis) were eligible if they had presented with DCM between January 1, 2005 and December 31, 2010 in a participating center. They were included if they presented with at least 2 of 3 of the following criteria: 1. symptomatic heart failure; 2. severely impaired function (FS ≤ 25%); and 3. left ventricular dilation (LV end-diastolic dimension [LVEDD] > +2 z-score).

DCM could be secondary to myocarditis, familial or genetic disease, anthracycline toxicity, arrhythmias or heart block, neuromuscular or metabolic disease, or otherwise be labeled as idiopathic. Children with structural heart defects or Duchenne muscular dystrophy were excluded.

We defined 3 possible outcomes. The first group reached the combined primary endpoint of death or heart transplantation during the study period. The second group had ongoing disease and was still meeting the inclusion criteria at the end of the study. The third group recovered before the end of the study. Recovery was defined as FS > 25% and LVEDD < +2

z-score at the first of two consecutive time points. The database was closed on December 31, 2013 and follow-up ended either when the patient reached a primary endpoint or at the last available hospital visit.

The first available patient characteristics and clinical parameters, never recorded more than 2 weeks after diagnosis, were recorded and studied as potential risk factors for outcome. These included growth, echocardiography measurements, duration of hospital stay, and need for inotropic support and mechanical circulatory support (MCS). Growth parameters were transformed into standard deviation scores (SDS) according to Dutch references. [10] Malnutrition was defined as weight-for-height below -2 SDS for children aged > 1 year or weight-for-age below -2 SDS for children aged > 28 days and < 1 year and/or height-for-age below -2 SDS for children aged > 28 days. LV dimensions were measured in the parasternal long-axis view. End-diastolic and end-systolic diameters were transformed into z-scores using BSA.[11]

Statistical analysis

Continuous variables are reported as mean (±SD) if normally distributed or otherwise as median with interquartile range (IQR). To calculate incidence rates, population numbers (children 0 to < 18 years) from Statistics Netherlands were used. The Poisson distribution was used to estimate 95% confidence intervals (CIs).

Survival was estimated with the Kaplan-Meier method and 95% CIs were calculated using Greenwood's formula. The outcomes of death and transplantation were also analyzed by competitive risk analysis. Univariable and multivariable Cox regression were used to find risk factors for the risk of death or transplantation within 1 year or more than 1 year after diagnosis. All significant ($p < 0.05$) risk factors in univariable analysis were used in the multivariable Cox model. Patients who recovered and those who did not were compared using univariable Cox regression analysis. Unpaired and paired Student's t-tests were used to compare the baseline and follow-up measurements in patients with ongoing disease and in patients who recovered. Testing was performed two-sided and statistical significance was defined as $p < 0.05$. All analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY).

RESULTS

Baseline characteristics

We included 148 patients, 47% were boys (Table 1). Most patients were hospitalized at presentation; 41% were in the intensive care unit (ICU) receiving inotropic support, 37% were in the pediatric ward. There were 12 (8%) patients who needed MCS during first hospitalization. Of patients, 22% were initially treated as outpatients; they had mild symptoms or surveillance echocardiography performed because of an underlying condition associated with DCM.

Table 1: Baseline characteristics

	Study group n=148	
Male, n (%)	70	(47)
Age at diagnosis, yr	2.2	(0.3-9.6)
<1 year, n (%)	59	(40)
1-6 years, n (%)	42	(28)
6-<18 years, n (%)	47	(32)
Etiology of DCM, n (%)		
Idiopathic	73	(49)
Myocarditis	23	(16)
Other*	52	(35)
Presentation, n (%)		
ICU receiving inotropic support	61	(41)
Pediatric ward	54	(37)
Outpatient clinic	33	(22)
Duration of first hospital stay, d, n=115	21	(13-40)
MCS during first hospitalization, n (%)	12	(8)
Follow-up time, months	19.7	(5.3-38.6)
Annual incidence / 100,000, average (95% CI)	0.69	(0.58-0.81)

* Category 'other' includes 21 patients (14%) with genetic/familial disease, 9 patients (6%) with anthracycline use in clinical history, 11 patients (7%) with heart block or arrhythmias, 2 patients (1%) with neuromuscular disease, 6 patients (4%) with metabolic disease, 1 patient with Alström syndrome, 1 patient with scleroderma and 1 patients with neonatal ischemic infarction.
Categorical variables are displayed as number (%), continuous variables are displayed as median (IQR). DCM indicates dilated cardiomyopathy; ICU, intensive care unit; MCS, mechanical circulatory support, and 95% CI, 95% confidence interval.

Echocardiography at baseline was available in almost all patients (146 of 148, Table 2). Two patients were diagnosed abroad resulting in missing baseline echocardiography data. In 2 patients a floppy ventricular septum made accurate measurement of FS impossible. The mean FS was 14%, the mean left ventricular end-systolic dimension (LVESD) z-score was +9.3 and the mean LVEDD z-score was +5.4. Malnutrition (acute and/or chronic) was found in 23% of the patients at diagnosis.

Table 2: Growth and echocardiographic parameters at diagnosis

	Study group n=148	
NYHA class	3	(2-4)
NYHA I-II, n (%)	62	(42)
NYHA III-IV, n (%)	85	(58)
WFH (SDS) (age > 1 year)	- 0.8	(± 1.3)
WFA (SDS) (age 28 days to 1 year)	- 1.1	(± 1.2)
HFA (SDS)	- 0.5	(± 1.5)
Boston Z-score LVEDD	+ 5.4	(± 3.4)
Boston Z-score LVESD	+ 9.3	(± 4.6)
Shortening fraction, %	14.0	(± 6.5)

Categorical variables are displayed as number (%), continuous variables are displayed as mean ±SD, or as median (IQR) where appropriate.
NYHA indicates New York Heart Association; WFH, weight-for-height; WFA, weight-for-age; HFA, height-for-age; SDS, standard deviation score; LVEDD, left ventricular end-diastolic dimension; and LVESD, left ventricular end-systolic dimension.

Survival and transplant-free survival rates

The combined endpoint of death or transplantation was reached in 29% of the patients (n = 43); 24 patients died and 19 patients underwent transplantation. Of patients who died, 6 were listed for transplantation or were mechanically supported as a bridge to transplantation. Recovery occurred in 38% of the patients (n = 56), and 33% (n = 49) had ongoing disease. The overall cohort median follow-up was 40 months (IQR 14-71), and for patients who survived 51 months (IQR 25-77). Almost all patients who died did so within the first year of presentation (21 of 24), resulting in an overall 1-year survival of 85% (95% CI 79-91), 2- and 5-year survival of 84% (95% CI 78-90). The transplantation rate in the first year was only 3%, the 1-year transplant-free survival (82%, 95% CI 75-88) was close to the overall 1-year survival. More transplantations were performed after the first year of presentation, with a 2-year transplant-free survival of 76% (95% CI 68-83), and a 5-year transplant-free survival of 72% (95% CI 64-80, Figure 1). The median time from presentation to death was 1.7 months (IQR 0.6-6.9 months); to listing for heart transplantation was 17.9 months (IQR 3.3-39.3 months); and to transplantation was 26 months (IQR 19.7-67.6 months).

Death or heart transplantation within 1 year of diagnosis

Within the first year of diagnosis, 21 patients (84%) died and 4 (16%) were transplanted, 3 of whom were on MCS. Median time to death was 1.2 months (IQR 0.6-6.0 months), to listing for transplantation 2.0 months (IQR 0.3-4.3 months) and to transplantation 4.4 months (IQR 2.4-9.7 months).

Of the patients who died, 5 were mechanically supported. Of the remaining 16 patients, 3 patients died directly after presentation in the hospital, 4 patients had a contra-indication for transplantation, 4 patients died at neonatal age, 1 patient died suddenly without previous arrhythmias, and 4 patients were not referred for transplantation.

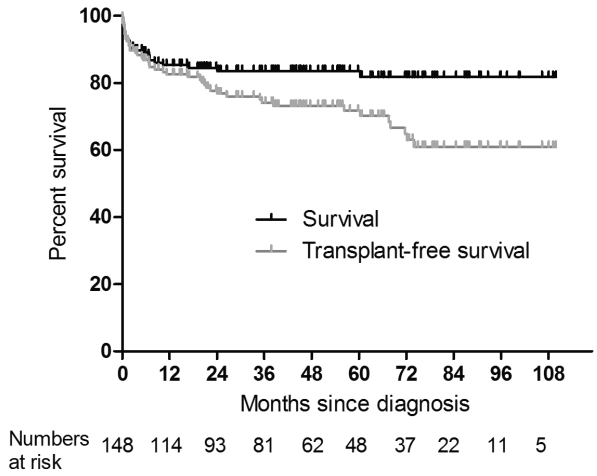

Figure 1A: Kaplan Meier plot showing the survival and transplant-free survival since diagnosis of 148 children with DCM.

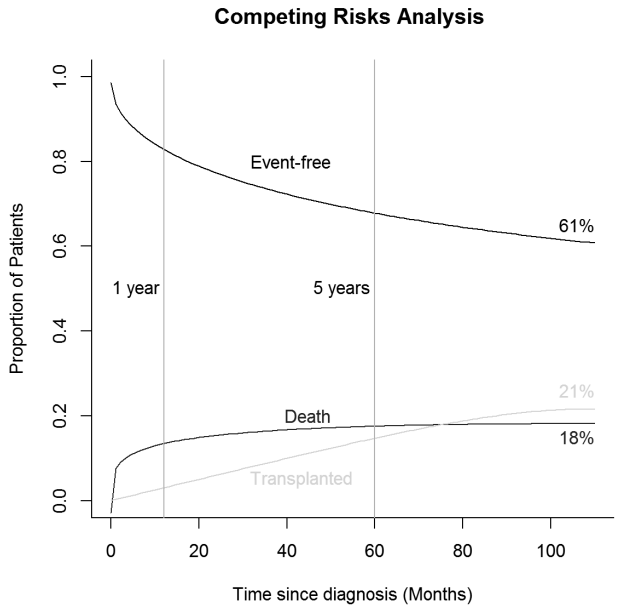

Figure 1B: Competitive risk analysis for children reaching the endpoint death or transplantation.

Death or heart transplantation more than 1 year after diagnosis

More than 1 year after presentation, 3 patients (17%) died and 15 patients (83%) were transplanted. Median time between diagnosis and listing was 24 months (IQR 16-56 months) and between diagnosis and transplantation 35 months (IQR 21-68 months).

Risk factors for combined endpoint within 1 year of diagnosis

Univariable analysis showed that admission to the ICU requiring inotropic support had a higher risk of death or transplantation within 1 year of diagnosis than admission to the ward (hazard ratio [HR] 2.4, p = 0.05) or presentation as outpatient (HR 11.5, p = 0.02, Table 3). Lower FS at presentation was associated with poor outcome within 1 year; each percentage decrease in FS resulted in a 1.1 times higher risk of death or transplantation within 1 year of diagnosis (HR 0.92, p = 0.02). Patients who needed MCS during first hospitalization had a 5.2 times higher risk of death or heart transplantation (p < 0.001). Multivariable analysis showed that admission to the ICU and MCS were independent risk factors for death or transplantation within 1 year (HR 2.6, p = 0.05 and HR 3.2, p = 0.03, respectively). Inotropic support was longer in children who reached an endpoint (median 19 days, IQR 11-30) than in children who did not (median 7 days, IQR 4-21 days, p < 0.05).

Table 3: Univariable and multivariable analysis comparing children who died or were transplanted within 1 year (n=25) with those who survived without transplantation (n=123)

	Univariable analysis			**Multivariable analysis ***		
	Hazard ratio	**95 % CI**	**p-value**	**Hazard ratio**	**95 % CI**	**p-value**
Age in subgroups, 1 - <6 years, versus						
<1 year	3.4	0.96-11.8	0.06			
6 - <18 years	2.7	0.74-10.1	0.1			
Etiology - other, versus						
Idiopathic	1.3	0.53-3.0	0.6			
Myocarditis	0.92	0.25-3.5	0.9			
Presentation, ICU receiving inotropic support, versus				2.6	1.0- 6.4	0.05
Pediatric ward	0.42	0.17-1.0	0.05			
Outpatient clinic	0.09	0.01-0.69	0.02			
MCS during first hospitalization	5.2	2.2-12.6	<0.001	3.2	1.1-9.02	0.03
WFH (SDS)	0.83	0.66-1.04	0.1			
HFA (SDS)	0.82	0.60-1.10	0.2			
Boston Z-score LVEDD	1.03	0.91-1.15	0.7			
Boston Z-score LVESD	1.05	0.96-1.14	0.3			
Fractional shortening, %	0.92	0.87-0.99	0.02	0.98	0.9-1.1	0.5

* multivariable Cox regression model with ICU requiring inotropic support present or absent, MCS during first hospitalization present or absent and fractional shortening.
ICU indicates intensive care unit; WFH, weight-for-height; SDS, standard deviation score; HFA, height-for-age; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; and MCS, mechanical circulatory support.

Risk factors for combined endpoint more than 1 year after diagnosis

Univariable analysis showed that only age > 6 years was a risk factor (HR 6.1, p = 0.02) for reaching an endpoint more than 1 year after diagnosis.

Ongoing disease and recovery

By the end of the study, 49 patients had ongoing disease. LVEDD and LVESD z-scores and LV function improved during follow-up. Recovery occurred in 56 patients, of whom 50% recovered within 1 year of diagnosis (Table 4). Mean weight-for-height and height-for-age at presentation were below the mean of the Dutch norm population. By the end of the study, weight-for-height was at normal level while height-for-age decreased in patients with ongoing disease. At diagnosis, echocardiographic and growth parameters were not different between patients who recovered and patients who had ongoing disease.

A higher probability of recovery was found in patients 1 to 6 years old (29 of 42, 69%, HR 2.4, $p = 0.03$) compared to patients ≥ 6 years old at diagnosis (8 of 47, 17%), but not to children < 1 year old (19 of 59, 32%). The probability of recovery was higher in patients with myocarditis (10 of 23, 43%; $p = 0.04$), compared to those with 'other' etiology (16 of 52, 31%), but not to those with idiopathic disease (30 of 73, 41%). The probability of recovery did not differ between patients who were admitted to the ICU (25 of 61, 41%), admitted to the pediatric ward (22 of 54, 41%) or treated as outpatients (9 of 33, 27%).

Table 4: Baseline and follow-up measurements of patients with ongoing disease (n=49) and patients who recovered by the end of the study (n=56)

	Ongoing disease, n=49			**Recovery, n=56**		
Median time until follow-up measurement, months (IQR)	55.1 (27.2-76.5)			12.1 (3.2-32.7)		
Medication, n (%)						
ACEi	47 (96)			40 (71)		
B-blockers	33 (67)			20 (36)		
Diuretics	24 (49)			20 (36)		
Digoxin	12 (25)			9 (16)		
	At presentation	**End of study**	***p*-value ***	**At presentation**	**End of study**	***p*-value ***
WFH (SDS)	-1.0 ±1.4	0 ±1.3	<0.001	-0.9 ±1.6	-0.1 ±1.2	<0.001
HFA (SDS)	-0.4 ±1.5	-1.2 ±1.3	<0.001	-0.3 ±1.4	-0.7 ±1.2	NS
Boston Z-score LVEDD	5.2 ±3.2	3.5 ±2.0	0.001	5.4 ±3.5	0.9 ±0.8	<0.001
Boston Z-score LVESD	8.6 ±4.7	5.1 ±3.1	<0.001	9.3 ±4.6	1.2 ±1.3	<0.001
Fractional shortening, %	16.2 ±5.8	23.6 ±8.2	<0.001	14.4 ±6.4	33.5 ±5.2	<0.001

ACEi indicates angiotensin converting enzyme inhibitor; WFH, weight-for-height; SDS, standard deviation score; HFA, height-for-age; LVEDD, left ventricular end-diastolic dimension; and LVESD, left ventricular end-systolic dimension.
Categorical variables are displayed as number (%), continuous variables are displayed as mean ±SD, or as median (IQR) where appropriate.
* paired t-test comparing the measurement at presentation and the measurement at the end of the study.
No significant differences were found *at presentation* between patients with ongoing disease and those who recovered (unpaired t-test).

DISCUSSION

In this nationwide cohort of patients with DCM, we found dichotomous results for patients who died and patients who underwent transplantation. Almost all children reaching an endpoint in the first year after presentation died (21 of 25) early after presentation, whereas almost all children reaching an endpoint more than one year after presentation underwent transplantation (15 of 18). The risk factors that we identified for reaching an endpoint within 1 year of presentation were ICU admission requiring inotropic support and MCS. Older age was a risk factor for reaching an endpoint more than 1 year after presentation.

We report a higher 1-year transplant-free survival (82%) than has previously been reported (65-72%).[1, 3, 12, 13] Noteworthy, our 1-year (85%), 2-year and 5-year (84%) survivals are similar to survivals reported in other cohort studies, such as the PCMR (1-yr: 87%; 2-yr: 83%; 5-yr: 77%) and National Australian Childhood Cardiomyopathy Study (NACCS).[1, 2] Thus, the low transplantation rate in the first year (3%) as compared to other cohorts (PCMR 18%), did not lead to increased mortality.[5] The largest part of the mortality (88%) occurred within the first year of presentation and the median time to death was only 1.7 months. We suspect that mortality cannot be reduced by a more aggressive approach to selection for transplantation or improving drug therapy, because mortality occurred in children whom were bridged to transplantation on MCS (Berlin Heart Excor), or within 24 hours of presentation, or in patients with contraindications for transplantation, or in neonates in whom waitlist mortality is high and MCS has a poor outcome.[14, 15]

It is unclear why the 1-year transplantation-free survival in this study was higher as compared to other cohorts. It does not seem to be related to differences in demographics of our cohort as compared to other cohorts that have been previously reported;[2, 3, 5, 6] 40% of our patients were diagnosed at < 1 year of age, and 49% of the patients had idiopathic disease. Furthermore, 75% of the patients were hospitalized at presentation, of whom 40% in the ICU, LVEDD and LVESD z-scores were markedly increased and similar to, or somewhat larger, than those reported previously. The annual incidence of 0.69 per 100,000 children ≤17 years old in our study is close to earlier reported incidences (0.34/100,000 in Finland ≤ 20 years old for idiopathic etiology only, 0.57/100,000 in 2 regions in the US ≤ 17 years old and 0.76/100,000 in the United Kingdom < 16 years old).[1, 3, 12] However, differences in genetic composition and environmental exposures may exist among all these cohorts, which may explain some of the differences. Furthermore, slight differences in inclusion criteria exist between all these cohorts, which may affect the composition of subgroups and the severity of disease at presentation.

The low transplantation rate early after presentation in our cohort most likely reflects our reluctance to list children early for transplantation. Although we used generally accepted recommendations to guide our decision to pursue transplantation,[16] we generally limited it

to children with a class I indication. This is also reflected in the risk factors that we identified for reaching an endpoint in the first year: admission to the ICU requiring prolonged inotropic support and MCS. For children who underwent transplantation within 1 year of diagnosis, time to listing (median 2.0 months) was comparable to that in other cohorts (1.4 months).[5, 14]

After the first year, the number of transplantations was not higher than in other studies.[1, 2] For this subgroup the median time to listing was 2 years and to transplantation almost 3 years. The only risk factor that we identified was age > 6 years at presentation, which is compatible with previous studies.[1, 2, 12] We did not identify idiopathic disease as an independent risk factor, although this has been widely reported.[1-3] This may be explained by the way we analyzed our results: within 1 year and more than 1 year after presentation separately, leaving the number of events in each subgroup relatively low. Also, the way children presented was not identified as a risk factor anymore. This is compatible with PCMR data, which identified presentation with heart failure as a risk factor for adverse outcome within the first year of presentation, but not thereafter.[1] This suggests that the profile of patients requiring transplantation later on, mostly older children that initially may present with mild to moderate symptoms, differs considerably from children with a short-term grave prognosis.

One of the rationales behind our conservative approach to listing children early after presentation is to explore the potential benefit of oral heart failure medication. The long-term benefit of such a conservative approach may be quite acceptable, even though a subgroup of children still requires transplantation. Large trials in adult patients with heart failure have unequivocally demonstrated improvement of outcome with ACE-inhibitors and β-blockers [17, 18] which is associated with a decrease of LV volumes over time.[19, 20] In our subgroup with ongoing disease, the decrease in LVEDD and LVESD z-scores (Table 4) also suggests reverse ventricular remodeling. The long-term outcome in the NACCS supports this finding, showing that almost 70% of the survivors experienced reverse remodeling or normalization of the LV function. The decrease in LV dimensions in our survivors may be related to the large number receiving ACE-inhibitors (96%) and β-blockers (67%). However, it is uncertain whether reverse remodeling or recovery of heart function in the pediatric population is an effect of medication, or merely reflects the natural history of the disease. Kantor et al. suggested that introduction of ACE-inhibitors and β-blockers have not clearly improved the outcome of children with DCM over time.[21] Pediatric drug trials in children with DCM have been scarce, but have suggested a beneficial effect of ACE-inhibitors.[22] The randomized Pediatric Carvedilol Trial suggested a beneficial effect in children with LV morphology, but could not demonstrate overall efficacy in pediatric heart failure.[23] Results of our study and of other cohorts suggest that medical therapy cannot be explored in children presenting critically ill, who cannot be weaned from ICU support. However, we believe that

exploring the efficacy of heart failure therapy in all other children is a reasonable approach and may obviate or postpone the need for transplantation in many children.

We identified 'presentation in the ICU receiving inotropic support' and 'the need for MSC' as risk factors for adverse outcome within 1 year. However, 41% of the patients presenting in the ICU had recovered by the end of the study, indicating that a subgroup of these children may have a very good long-term outlook. We found a higher rate of recovery in young children (1-6 years) and similar rates of recovery for myocarditis and idiopathic disease (43 % and 41% respectively). Recovery of cardiac function was demonstrated within 1 year in 50% of the children; the number receiving heart failure therapy was relatively low (Table 4), suggesting that in a subgroup recovery may be related to the natural history of the disease. These results are compatible with the report from Everitt et al, who demonstrated a similar rate of recovery in children with idiopathic disease.[24] The long-term results from the NACCS demonstrate similarly favorable outcomes.[2] Regardless of what is driving recovery, our results suggest that, early after presentation, a conservative approach specifically in young children presenting with heart failure and requiring ICU admission, but not MCS, is justifiable.

Study limitations

This study was limited by its retrospective design and limited sample size. Although we may have missed patients with DCM, the close collaboration of all pediatric cardiology centers in the Netherlands, has resulted in a fairly complete overview of patients with DCM.

The limited sample size and the analysis in subgroups of patients reaching an endpoint within 1 year of and more than 1 year after diagnosis, limited the number of endpoints per stratum affecting the power of our analysis. Nevertheless, this approach to analysis allowed us to separate some risk factors at presentation, in the short-term and in the long-term.

Inclusion criteria for our study varied slightly with other cohorts, which affected the composition of the etiologic group "other". However, inclusion criteria varied among all cohorts to which we have been referring, and this did not seem to affect the similarities in demographics and outcomes among all these cohorts.

CONCLUSION

In this nationwide study among pediatric DCM patients, we showed that with a low transplantation rate in the first year, overall survival rates were similar to other cohorts. Mortality was mainly confined to the first year after presentation and mostly in children requiring ICU admission, with prolonged inotropic support or MCS. Transplantation rate after the first year was not increased as compared to other cohort studies, and was

associated with older age. Recovery rate was considerable, especially in young children with myocarditis, but also in patients with idiopathic disease. Our results suggest that a conservative approach to list children for transplantation early after presentation may be justifiable, except for children who require extensive ICU support or MCS.

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Chapter 3

Evaluation of the diagnostic work-up in children with myocarditis and idiopathic dilated cardiomyopathy

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ABSTRACT

Background

The underlying etiology of dilated cardiomyopathy (DCM) in children varies, 14-22% is secondary to myocarditis, and the majority remains idiopathic. Etiology has prognostic value, however 'a clinical diagnosis of myocarditis' has been frequently used because the gold standard (endomyocardial biopsy [EMB]) is often not performed. Therefore, a consistent diagnostic approach and interpretation is needed. In this multicenter study we evaluated the diagnostic approach and interpretation of the viral results in children with myocarditis and idiopathic DCM.

Methods and results

We included 150 children with DCM, of whom 103 were assigned the diagnosis myocarditis (n=21) or idiopathic DCM (n=82) by the attending physician. Viral tests were performed in 97/103 patients, in only 34% (n=35) some of the tests were positive. Of those patients, we evaluated the probability of the assigned diagnosis using the viral test results. We classified viral test results as reflecting definite or probable myocarditis in 14 children and possible or unlikely myocarditis in 21 children. Based on this classification 23% of patients were misclassified.

Conclusion

We found that in children with DCM the diagnostic approach varied and the interpretation was mainly based on viral results. Since a 'clinical diagnosis of myocarditis' has been frequently used in daily practice because of the lack of EMB results, a uniform protocol is needed. We propose to use viral test results in several steps (blood PCR, serology, PCR and/or cultures of the gastro-intestinal and respiratory tract and EMB results) to estimate the probability of myocarditis.

INTRODUCTION

Dilated cardiomyopathy (DCM) is a severe cardiac disorder. Although most children present with the same signs and symptoms of congestive heart failure, respiratory distress and failure to thrive, the underlying etiology of DCM is varying.[1-3] Large cohort studies have reported several etiologies such as myocarditis, genetic mutations, metabolic and neuromuscular disease. However, in 50-66% of the patients the cause is unknown and DCM is labeled idiopathic.[2-4]

Children with idiopathic DCM have a higher risk of death or heart transplantation than those with a known etiology.[3] In contrast, myocarditis seems to have a relatively favorable prognosis, while outcome after transplantation is less favorable than in subgroups with other etiologies.[5] Currently, a uniform approach to diagnostic work-up and interpretation of test results is not available. This may help to identify causes of the disease more reliably and may improve risk stratification in children presenting with DCM.

The diagnosis of myocarditis is difficult. Endomyocardial biopsy (EMB) has been considered the gold standard, but is infrequently performed in children.[2, 4, 6] Many studies reported that 'a clinical diagnosis of myocarditis' was accepted, but it is often unclear which tests were performed and how they were interpreted.[2-4, 7]

In this retrospective multicenter analysis we evaluated the diagnostic tests that were performed and the interpretation of these results in children who were assigned the diagnosis myocarditis or idiopathic DCM. We propose a diagnostic approach and interpretation of viral tests to assess the probability of myocarditis.

METHODS

All children (0-18 years) diagnosed with DCM in one of the seven participating centers, between January 1, 2005 and December 31, 2011, were included in this study. Patients were included if they presented with at least two out of three of the following criteria: 1. symptomatic heart failure; 2. severely impaired function (fractional shortening [FS] ≤ 25%); and/or 3. left ventricular dilation (left ventricular end-diastolic dimension [LVEDD] > +2 z-score for body surface area).[8] Children with a history of structural heart defects or other causes than myocarditis and idiopathic DCM were excluded for the analysis, i.e. arrhythmias associated with DCM, anthracycline use in medical history and metabolic, genetic or familial disease.

To assess if the assigned diagnosis myocarditis and idiopathic disease were according to current recommendations and if these diagnoses were consistent according to the available diagnostic test results, we registered the cause of DCM in the last available correspondence.

Secondly, we analyzed if patients had myocarditis according to the results of the EMB (gold standard). These results were scored as positive if either the histology met the Dallas criteria[9] or immunohistological analysis was positive for myocarditis. Thirdly, we registered the results of cardiovascular magnetic resonance (CMR) imaging. These images were reviewed according to the Lake Louise criteria to assess the probability of myocarditis.[10] Furthermore, we registered if patients presented with cardiovascular symptoms to categorize them according to the 3-tiered classification as proposed by Sagar et al. (Table 1).[11] In this classification positive EMB is defined as 'definite myocarditis'. 'Probable acute myocarditis' is defined if the patient has cardiovascular symptoms and if the ECG is suggestive for cardiac injury, or the echocardiogram or CMR shows abnormal cardiac function, or if biomarkers for cardiac injury are raised. If one of the abovementioned ECG, echocardiographic, CMR or laboratory findings are positive, but no cardiovascular symptoms are present, the patient is classified as 'possible subclinical acute myocarditis'.

Table 1: Three recommendations with which the assigned diagnosis was compared

Criteria	Description
Gold standard [9]	Endomyocardial biopsy performed and histological or immunohistological evidence of myocarditis
Lake Louise Criteria [10]	Cardiovascular magnetic resonance (CMR) imaging performed. If least 2 of the following criteria are present: (1) Regional or global myocardial signal intensity increase in T2-weighted images (2) Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium enhanced T1-weighted images (3) At least one focal lesion with nonischemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images
Sagar, et al. [11]	"Definite" – histological or immunohistological evidence of myocarditis "Probable acute" – clinical context of possible myocardial injury with cardiovascular symptoms and at least one of the following: 1. Biomarkers of cardiac injury raised; 2. ECG findings suggestive of cardiac injury; 3. Abnormal cardiac function on echocardiogram or cardiac MRI "Possible subclinical acute" – clinical context of possible myocardial injury without cardiovascular symptoms but with at least one of the following: 1. Biomarkers of cardiac injury raised; 2. ECG findings suggestive of cardiac injury; 3. Abnormal cardiac function on echocardiogram or cardiac MRI.

Finally, we registered all results of the viral tests that were performed within 2 weeks of presentation and used these to categorize all patients based on the available test results. We registered if viral cultures or PCR of feces, throat swab, cerebrospinal fluid (CSF) and blood were positive for viruses that have been associated with myocarditis (i.e. *enterovirus, adenovirus, parvovirus B19, human herpes virus type 6 [HHV6], human cytomegalovirus*

[CMV], Epstein-Barr virus [EBV], parechovirus, human parainfluenza virus).[12-15] Serology was defined as positive if IgM was detected for one of the abovementioned viruses.

To categorize all patients, "definite myocarditis" was defined as histological or immunohistological evidence of myocarditis. "Probable myocarditis" was defined as positive blood or CSF PCR or culture for enterovirus, adenovirus, parechovirus or human parainfluenza virus. "Possible myocarditis" was defined if one of the abovementioned viruses were detected in the respiratory or gastro-intestinal tract only (throat swab and/or feces), because mild (re)infections with these viruses are frequent and prolonged shedding from these tracts is common.[16] Serological evidence of recent infection with these viruses was also defined as "possible myocarditis". Patients with only a positive blood PCR or culture for *parvovirus B19, HHV6, CMV* or *EBV* were defined as "unlikely of having myocarditis", because positive blood PCR does not prove a primary infection with these viruses, but can indicate a reactivation or persistence of previous infection.[17-20] If a positive blood PCR was accompanied by serological proof of a recent primary infection (positive IgM) then it was classified as "probable myocarditis". Detection of the latter viruses in only the respiratory or gastro-intestinal tract was classified as "unlikely" (Table 2).

Table 2: Classification using viral test results

Classification	Criteria
Definite	Histological or immunohistological evidence of myocarditis
Probable	One of the following criteria - Blood plasma/serum or CSF PCR or culture positive for enterovirus, adenovirus, parechovirus or human parainfluenza virus - Blood plasma/serum PCR or culture positive for *parvovirus B19, HHV6, CMV* or *EBV* accompanied by serological proof of a primary infection (seroconversion and/or positive IgM)
Possible	One of the following criteria - Detection of enterovirus, adenovirus, parechovirus or human parainfluenza virus in the respiratory or gastro-intestinal tract only (throat swab and/or feces) - Seroconversion and/or positive IgM for enterovirus, adenovirus, parechovirus or human parainfluenza virus
Unlikely	One of the following criteria - If none of the performed viral tests show positive results - Blood plasma/serum PCR or culture positive for *parvovirus B19, HHV6, CMV* or *EBV*, without serological evidence of a recent primary infection (i.e. seroconversion and/or positive IgM) - Detection of *parvovirus B19, HHV6, CMV* or *EBV* in the respiratory or gastro-intestinal tract only (throat swab and/or feces)

Statistical analysis

Categorical variables were reported as number and percentages, and continuous variables as median with interquartile range (IQR). To compare the medians of two independent

groups the Mann Whitney-U tests was used. The Pearson chi-square was used to compare two independent categorical groups.

RESULTS

During the 7 years of the study, 150 patients were diagnosed with DCM. According to the last available correspondence, familial or genetic disease was diagnosed in 18 patients (12%), 10 patients (7%) had arrhythmias that were associated with DCM, 9 patients (6%) developed DCM after anthracycline treatment and 7 patients (5%) had DCM secondary to a metabolic disease. Two patients were diagnosed with Alström syndrome and one patient with Kawasaki disease. These patients were excluded from further analysis.

This resulted in 103 patients for further analysis, 21 (14%) of whom were labeled as having myocarditis and 82 (55%) as having idiopathic disease. Children with myocarditis were significantly younger at presentation (median age 0.04 years, IQR 0.03-1.0) than those with idiopathic disease (2.0 years, IQR 0.3-7.5, $p < 0.001$). 16/21 children with myocarditis (76%) were admitted to the intensive care unit (ICU); this was significantly more than children with idiopathic disease (34/82 [41%], $p < 0.05$).

Probability of myocarditis according to current recommendations

In the 103 patients who were labeled as myocarditis or idiopathic disease, we assessed the probability of myocarditis according to current recommendations (Table 1).

Firstly, the results of an EMB were used. An EMB was performed in only 14 patients (14%), 5/14 (36%) met the Dallas criteria and/or showed immunohistological evidence of myocarditis. The median time between EMB and presentation was 20 days (range 0-118 days).

Secondly, we analyzed the CMR imaging results according to the Lake Louise criteria.[10] CMR imaging had been performed in 11 patients (11%), within a median of 18 days of presentation (range 7-43 days). None of the CMRs showed myocarditis. However, contrast enhancement failed in 1 patient and was not performed in another, and in 5 patients early enhancement was not examined.

The three-tiered classification of Sagar et al. was used to assess the probability of myocarditis.[11] Five patients had “definite” myocarditis, because their EMB showed evidence of myocarditis. Eighty-eight (85%) were classified as “probable acute myocarditis” because they presented with symptomatic heart failure. Only 10 patients had “possible subclinical acute myocarditis”, as they did not present with cardiovascular symptoms.

Interpretation of the viral test results

The amount of tests and what tests had been performed varied per patient. In 94% (97/103) of the patients, one or more viral tests were performed. In the patients who were labeled as idiopathic disease, 76/82 had at least one viral test performed; 62 patients had no positive test result, 14 patients had one or more viral test positive. In total, we identified 35 patients with positive results of viral tests and/or with the diagnosis of myocarditis. Of these patients, 21 were labeled as myocarditis and 14 as having idiopathic disease. However, we found inconsistencies in the interpretation of the viral test results of the patients that were initially labeled as myocarditis and as idiopathic disease (Table 3 and 4). For example, case 11 in table 3 had positive feces and blood PCR for *parechovirus* and was labeled as myocarditis, whereas case 13 in table 4 had positive feces, throat swab and blood PCR for *parechovirus*, but was labeled as idiopathic disease.

Table 3: Viral test results of 21 cases that were assigned 'myocarditis'

	Viral PCR and/or cultures			Blood PCR	Serology	EMB histology	Classification based on viral results
Case	CSF	Feces	Throat swab				
1		-	-		-		Unlikely
2		-	-		-		Unlikely
3		+EV	-	-	-		Possible
4		+EV	-		-		Possible
5		+EV	-		-		Possible
6		-	+CMV		+PiV		Possible
7		+AV	+AV	-	-		Possible
8	+ EV	+EV					Probable
9		+EV	+EV	+EV	-		Probable
10	+ EV		-	+EV			Probable
11		+PEV	-	+PEV	-		Probable
12	+ EV	+EV	+EV	+EV	-		Probable
13	+ EV	+EV	-	+EV	-		Probable
14	+ EV	+EV	-	+EV	-		Probable
15	+ EV	+EV	-	+EV	-		Probable
16	+ EV	-	+EV	+EV	+EV		Probable
17		+PEV, AV	-	-	-	+	Definite
18		-	-	-	-	+	Definite
19		+EV		-	-	+	Definite
20		-	+EV	+EV	+EV	+	Definite
21		-	-	+ PVB19	-	+	Definite

+" indicates a positive test result, "-" indicates a negative test result; if the box is empty the test has not been performed. CSF indicates cerebrospinal fluid; PCR, polymerase chain reaction; AV, *adenovirus*; EV, *enterovirus*; PB19, *parvovirus B19*; PEV, *parechovirus* and PiV, *parainfluenzavirus*.

For these 35 patients we used viral test results to classify them as 'definite', 'probable', 'possible' or 'unlikely' to have myocarditis. All children had new onset heart failure, clinical symptoms of heart failure and reduced left ventricular function. Five patients had positive EMB results and were classified as 'definite myocarditis'. Ten were classified as 'probable myocarditis', because in 8 patients *enterovirus* (7x *coxsackievirus,* 1 unspecified) was found in CSF and/or blood PCR and in 2 patients *parechovirus* was detected with blood PCR. Nine of those 10 were initially labeled as myocarditis, 1 as idiopathic disease. Fourteen patients were classified as 'possible myocarditis', because virus was isolated from the respiratory or gastro-intestinal tract only (n=13) or accompanied by positive IgM (n=1). Of these 14 patients, 5 were initially labeled as myocarditis. Finally, 6 patients were classified as 'unlikely' since none of the viral tests were positive (n=2), or blood PCR was positive for viruses of which is known that genome can still be detected after the primary infection due to reactivation or persistence (n=4). The 2 cases without positive test results were initially labeled as myocarditis. In 8/20 patients that were classified as 'possible' or 'unlikely' no EMB and no PCR on blood or CSF was performed, thus these patients could not be classified as 'definite' or 'probable' (Table 3 and 4).

Table 4: Viral test results of 14 cases that were assigned 'idiopathic disease'

	Viral PCR and/or cultures			Blood PCR	Serology	Classification based on viral results
	CSF	Feces	Throat swab			
1				+EBV	-	Unlikely
2			+AV	-		Possible
3		+PEV		-	-	Possible
4		+PEV, AV	-		-	Possible
5			+EV	-	-	Possible
6		-	+HHV6	-	-	Unlikely
7		+EV	-	-	-	Possible
8		-	-	+PB19	-	Unlikely
9		+PEV	+PEV			Possible
10		-	-	+PB19	-	Unlikely
11		+PEV	-	+HHV6	-	Possible
12		+EV	+EV		+EV	Possible
13		+PEV, AV	+PEV, AV CMV	+PEV, PB19	-	Probable
14		+AV	+PB19, AV	+PB19	-	Possible

"+" indicates a positive test result, "-" indicates a negative test result; if the box is empty the test has not been performed.
CSF indicates cerebrospinal fluid; PCR, polymerase chain reaction; AV, *adenovirus*; EV, *enterovirus*; HHV6*, human herpes virus 6*; PB19, *parvovirus B19*; PEV, *parechovirus* and PiV, *parainfluenzavirus*.

In total, this resulted in 5 patients with 'definite myocarditis', 10 cases with 'probable myocarditis', 14 cases as 'possible myocarditis' and 6 as unlikely having myocarditis. In other

words, assuming that the classification of 'definite' and 'probable' myocarditis is compatible with having myocarditis, than 7% (1/15) of the patients were misclassified as idiopathic disease. Similarly, if the classification "possible" and "unlikely" myocarditis is compatible with not having myocarditis, than 35% (7/20) of patients were misclassified as having myocarditis. In total, 23% of the cases with positive viral test results (8/35) were misclassified. A decrease in the total number of patients with definite or probable myocarditis was seen after we used this classification (15/150 instead of 21/150).

DISCUSSION

We studied the diagnostic work-up in children presenting with DCM during 7 years in the Netherlands and focused on those children with myocarditis or idiopathic disease. The distribution of the causes of DCM in our study was comparable to those in other large cohorts.[2-4] In our cohort, 14% was labeled as myocarditis and 55% as idiopathic disease. However, we found that viral tests were not uniformly performed and the interpretation of the viral test results differed between these cases.

The diagnosis of myocarditis is complicated. An EMB that fulfills the Dallas criteria is still the gold standard to diagnose myocarditis.[9] However, the sensitivity is limited. A study among adults diagnosed with myocarditis on clinical criteria showed that only 38% of the biopsies were positive on histopathological Dallas criteria. Additional immunohistopathology resulted in 50% positive biopsies.[21] In a recent European recommendation it was advised that EMB tissue should be analyzed using histology, immunohistochemistry and viral PCR.[22] However, the use of PCR have led to an enormous increase in detection of viral genome in cardiac biopsies. In 2005 Kuhl et al. analyzed 172 biopsies of adults in which viral genome was detected at clinical presentation.[23] Histological analysis did not demonstrate active myocarditis in any of the samples and immunohistopathological analysis was positive in only 39%. Almost 60% of the patients had *parvovirus B19* and/or *HHV6* detected with PCR. After a median of 7 months *parvovirus B19* or *HHV6* could still be detected in 80% of the patients who was positive on the initial biopsy. Moreover, it has recently been shown that in 96% of the adults with serological evidence of past infection with *parvovirus B19* (IgG positive, IgM negative), this virus still was detectable in the EMB, even though these patients never had any signs or symptoms of cardiac disease or DCM. This suggests a lifelong asymptomatic persistence of *parvovirus B19* DNA in the myocardium after a primary infection.[24] Furthermore, *HHV6, CMV* and *EBV* DNA have been detected by PCR in cardiac tissue from patients without cardiac symptoms although to a much lower extent than *parvovirus B19.*[25, 26] In addition, DNA of these herpes viruses detected by PCR may be derived from latently infected mononuclear cells that are present in the EMB. Therefore, in this study we did not take the PCR analysis of the EMB for these viruses into account.

To reach a higher diagnostic accuracy than with EMB alone, it has been proposed to use CMR imaging.[10] Based on pooled data of control trials, it seemed that myocardial inflammation could be predicted or ruled out by CMR with a diagnostic accuracy of 68-78%. Although only based on expert consensus, CMR imaging seems promising as a diagnostic tool. The sensitivity of EMB can be increased if biopsies are taken from contrast-enhanced regions.[27]

The diagnosis of myocarditis in children may be even more complicated than in adults. Although, it is suggested to perform an EMB in case of unexplained cardiomyopathy,[28] the risk of complications may be the most important reason to omit EMB. Although a large series of biopsies in children showed a relatively low morbidity and mortality, these biopsies were generally performed for heart transplantation rejection surveillance.[29] Considering only biopsies for the evaluation of cardiomyopathies, a mortality rate around 1% and a morbidity rate of 11% was found. The risk of EMB was highest in young sick children with suspected myocarditis on inotropic support. Similarly, the children in our study with suspected myocarditis were young (median age 0.04 year) and critically ill (76% admitted to the ICU). Only 14% of the patients with idiopathic DCM or myocarditis underwent EMB. This number is comparable to other DCM cohorts, in which EMB has been performed in 0-38% of the cases.[2, 4, 6] In the remaining, the diagnosis of myocarditis is a "clinical diagnosis". In studies focusing on the etiology of DCM as prognostic factor, the rate of biopsy-proven myocarditis varied as much as from 0-100%.[2-4, 7]

During the 7 years of this study, CMR had not been routinely performed. It is suggested to perform the CMR study around the 7th day until 4 weeks after the onset of the disease.[10] Whereas the timing of CMR studies that have been performed in the current study was mostly within this range, the purpose of CMR was mostly not to diagnose myocarditis. Although, CMR seems useful to diagnose myocarditis in adults and older children,[10, 30] this may not be the case for infants and young children. Further development in CMR technology may be necessary to use this technique in young and critically ill children, because high heart rate and low muscle mass may impede accurate imaging.

Applying the three-tiered classification of Sagar et al.[11] to our data resulted in "probable acute myocarditis" in 85% of the cases. Thus, although we attempted to use current recommendations to classify myocarditis, these did not differentiate between cases. Therefore, we used the available viral test results to distinguish between probable, possible and unlikely of having myocarditis. Since enteroviruses (especially c*oxsackievirus*), parechoviruses and adenoviruses are known pathogens to cause myocarditis, an infection detected with blood PCR resulted in "probable myocarditis". Detection of these viruses in the respiratory and gastro-intestinal tract only resulted in "possible myocarditis", because prolonged shedding and mild gastro-intestinal and respiratory infections are common for these viruses. Even in non-epidemic periods, enteroviruses may be isolated from

the feces in more than 50% of the healthy day-nursery children.[31] We classified positive serology alone as "possible myocarditis", since the value of positive serology is still unclear. The correlation between positive serology and EMB has shown to be around 9%.[32] In our classification the detection of *parvovirus B19, HHV6, CMV* and *EBV* with positive blood PCR but with serological evidence of a past infection (i.e. IgG positive and IgM negative) resulted in "unlikely". *Parvovirus B19* can be detected in blood for a prolonged time after primary infection. Lindblom et al. detected *parvovirus B19* DNA in blood for over 1.5 years after primary infection in 5/5 immunocompetent patients showing that a positive *parvovirus B19* PCR in blood without evidence of a recent primary infection should be interpreted with caution in patients presenting with DCM or myocarditis.[20, 24] The same holds true for *HHV6, CMV* and *EBV* since these viruses remain latent in leukocytes and are able to reactivate throughout life.[18, 19] Only in very young children it should be taken into account that it may be the primary infection that is detected. Therefore, in the classification a positive PCR had to be accompanied by serological evidence of a primary infection to be classified as "probable". In addition, detection of *parvovirus B19, CMV, HHV6* and *EBV* by PCR in EMB should also be interpreted with caution, because these viruses, in particular *parvovirus B19*, can be detected in cardiac tissue long after primary infection in patients without cardiac symptoms.[24-26]

By applying the new classification to our data, the overall results changed marginally; 10% instead of 14% of the DCM population had probable or definite myocarditis. However, 33% of the children that were previously labeled as myocarditis were misclassified as well as 7% of the patients with idiopathic disease. This may affect risk stratification in which etiology has been used as a predictor for transplant-free survival.[2, 3, 7, 33] The distribution of causes in our data is comparable to other cohorts, but we showed inconsistencies in labeling patients as having myocarditis or idiopathic disease. Foerster et al. analyzed the outcome of children of clinically suspected myocarditis, 30% of which were biopsy proven.[7] They concluded that the outcome of the children with suspected myocarditis was substantially better than that of children with idiopathic DCM. Although their finding has been supported by the finding in an Australian cohort in which only biopsy proven myocarditis had been included,[2] the results of the present study showed the difficulty of the diagnosis of myocarditis in children with DCM.

To reach a consistent approach in diagnostic tests and interpretation of the results, we propose to perform blood plasma PCR in children with new onset heart failure. If viral genome is detected of *parvovirus B19, CMV, EBV or HHV6*, positive IgM titers should also be found to prove a primary infection. If blood PCR is negative, PCR on feces and throat swab can be performed, but will ultimately only result in "possible myocarditis". In children with neurological symptoms CSF examination may be necessary. EMB can be performed if it seems clinically relevant, however positive PCR for *parvovirus B19, CMV, EBV or HHV6*

should be interpreted with caution if these results are not accompanied by positive IgM titers.

The current study was limited by its retrospective nature. The inconsistency in diagnostic approach may be higher than in other, single-center reports, because the current study is multicenter. Since most large studies concerning this rare disease are multicenter, the current study may be a good reflection of daily clinical practice. The classification that we propose in this study can only be applied if there are viral test results available. Not all viral tests were performed in each patient, and this may have led to underdiagnoses. Unfortunately, this was the result of its retrospective nature, but again is a good reflection of daily clinical practice.

In summary, in this multicenter study, we analyzed the diagnostic approach to children with DCM with special emphasis on the diagnosis of myocarditis. We found that the diagnostic approach varied and the interpretation of the results was mainly based on viral test results. Since a 'clinical diagnosis of myocarditis' has been frequently used in daily practice, a uniform protocol and interpretation are needed. We propose to integrate viral test results in this interpretation.

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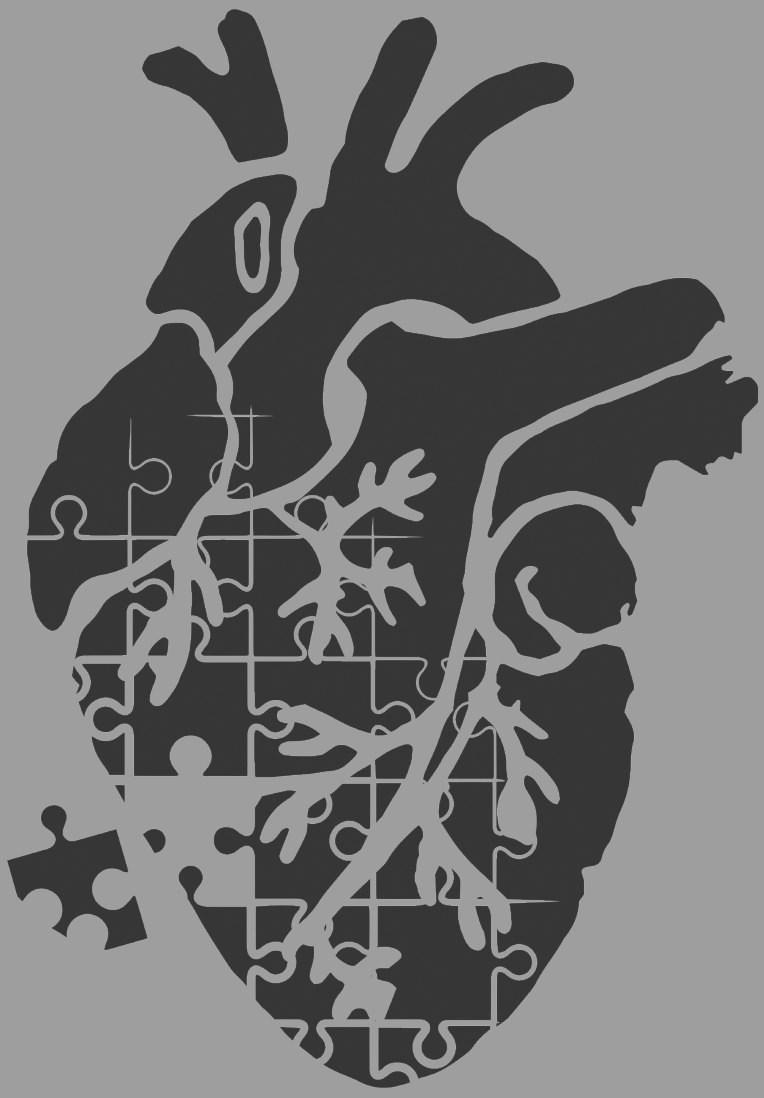
PART 3

Risk factors



Chapter 4

Serial N-terminal pro-B-type natriuretic peptide measurements predict cardiac death in acute and chronic pediatric dilated cardiomyopathy

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Submitted

ABSTRACT

Background

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is an important predictor of mortality and morbidity in adults with heart failure. In children with heart failure secondary to dilated cardiomyopathy (DCM) markers that reliably predict disease progression and outcome during follow-up are scarce.

Objectives

The aim of the study was to investigate whether serial NT-proBNP measurements were predictive for outcome in children with DCM.

Methods

Retrospective analysis of all available NT-proBNP measurements in children with DCM over a 7 year period. Two groups were defined, (1) children at DCM diagnosis with symptomatic heart failure (n=79), and (2) children who survived at least the first year after diagnosis (n=69). The endpoint was cardiac death (death, heart transplantation or mechanical circulatory support). Linear mixed effect models and cox regression were used.

Results

We included 115 patients (median age 2.2 years) with 2048 NT-proBNP measurements. Median follow-up was 30 months, 32% reached the endpoint of cardiac death. At diagnosis, median NT-proBNP was high and not predictive for outcome. At any time follow-up, a two-fold higher NT-proBNP resulted in a 2.9 times higher risk in the first year ($p<0.001$) and a 1.8 times higher risk thereafter ($p<0.001$). Furthermore, at any time, the slope of log10(NT-proBNP) was significantly predictive for the risk of an endpoint (0-30 days hazard ratio [HR]: 3.8, >30 days HR: 3.0; >1 year HR 6.8, all $p<0.05$). At 30 days after diagnosis, NT-proBNP ≥7990 pg/mL showed a 1- and 2-year event-free survival of 77% and 73%, and >1 year after diagnosis NT-proBNP ≥924 pg/mL showed a 2- and 4-year event-free survival of 68% and 64%, while values below both thresholds showed excellent event-free survival (95-100%).

Conclusion

NT-proBNP at any time during follow-up and its change over time, were significantly predictive for the risk of cardiac death in children with DCM.

INTRODUCTION

Dilated cardiomyopathy (DCM) in children causes heart failure and is characterized by a poor prognosis. Previous reports have shown that one year after diagnosis 18-31% of the patients have reached the endpoint of death or heart transplantation after a median time of 1-2 months.[1-3] Event rates decrease after the first year and 5 years after diagnosis transplant-free survival has been reported between 54-72%. In contrast to this poor prognosis, some children have stable disease and 22-38% of the patients recover.[1, 2, 4] There is a strong clinical need for predictors that identify children with a poor prognosis, both at diagnosis and during follow-up.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a biomarker that is predominantly released by myocytes in the ventricular walls in response to increased wall stress.[5] In adults with chronic heart failure, single NT-proBNP measurements have been shown to be an important predictor for short-term mortality.[6, 7] In addition, repeated NT-proBNP measurements have been proven a superior method for risk stratification.[8-10] More recently, NT-proBNP values have been used to guide pharmacological treatment regimens and have shown beneficial effects on outcome.[11] In children with heart failure, NT-proBNP has been associated with the clinical severity of heart failure and with echocardiographic measures of left ventricular (LV) dysfunction.[12-14] However, until now, no studies have been performed that investigated the predictive value of repeated NT-proBNP measurements on hard endpoints as death and heart transplantation in a relatively large pediatric DCM cohort. Therefore, the aim of this study was to investigate the predictive value of serial NT-proBNP measurements at diagnosis and during follow-up.

METHODS

All children (0-18 years) who fulfilled the criteria of DCM in a participating tertiary referral pediatric cardiology center between July 1, 2006 and October 1, 2013 were selected for this study. DCM was defined as the presence of two out of three of the following criteria: 1. symptomatic heart failure; 2. severely impaired systolic function (fractional shortening ≤ 25%); and 3. LV dilation (LV end-diastolic dimension > 2 z-score for body surface area).[15] DCM was idiopathic or secondary to other causes. Patients with structural heart or with neuromuscular diseases were excluded. All available NT-proBNP values were collected.

Besides NT-proBNP, additional information was obtained from medical charts, i.e. age, time since DCM diagnosis, presence of symptomatic heart failure at diagnosis. The estimated glomerular filtration rate (eGFR) was calculated using the modified Schwarz formula (children 1-17 years) or the MDRD formula (17 years).[16, 17] eGFR <90 mL/min per

1.73 m^2 was considered as renal dysfunction. No eGFR formula is available for children aged <1 year, thus we constructed the variable 'renal dysfunction present or absent' based on serum creatinine. Serum creatinine >2 SDS for age was considered as renal dysfunction.[18] Serum creatinine was preferably measured on the same day as NT-proBNP, yet the time difference was never more than one week.

Follow-up continued either until patients reached the primary endpoint, or the age of 18 years, or until the end of the study on October 1, 2013. The primary endpoint was cardiac death, defined as death, heart transplantation or need for mechanical circulatory support ([MCS], ventricular assist device or extracorporeal membrane oxygenation).

We analyzed the data in two groups; 1. NT-proBNP values from DCM diagnosis onwards in children presenting with symptomatic heart failure; and 2. NT-proBNP values of children who survived at least the first year after diagnosis and still met the criteria of DCM at 1 year. Children could be represented in both study groups.

Analyses in both groups were adjusted for renal function; in the first group, renal dysfunction was dichotomous, because this group comprised children <1 year of age, in the second group eGFR was used. The study was approved by the medical ethical committee of the Erasmus University Medical Center, Rotterdam, the Netherlands. Informed consent was waived.

Statistical analysis

For descriptive data analysis we used IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). Continuous data are reported as mean ± standard deviation if normally distributed or otherwise as median and interquartile range (IQR). Medians were compared using the Mann Whitney U test. Receiver operating characteristic curves were generated of available NT-proBNP values at 1 month and 1 year after diagnosis to determine the optimal threshold to identify the risk of an endpoint. Using these thresholds, endpoint-free survival was estimated with the Kaplan-Meier method and the log rank test was used to determine statistical significance between endpoint-free survival curves. For advanced statistical analysis of longitudinal and survival data we used the R environment for statistical computing and graphics (R version 3.0.2 [2013-09-25]). NT-proBNP was log-transformed in all analyses, because it was non-normally distributed. To assess changes in NT-proBNP levels over time, while accounting for the correlation between repeated follow-up measurements in each patient, a linear mixed-effects model analysis was used.[19, 20] To account for the medically expected differences in evolution of NT-proBNP,[2] we have included two separate slope parameters in the fixed- and random-effects parts of the model, one for the period from DCM diagnosis to 30 days, and one from 30 days to end of follow-up (segmented regression). Subsequently, a joint model was constructed to explore how serial NT-proBNP measurements were associated with the risk of an endpoint. Here, renal function was

included as covariate. Residual plots were used to validate the models' assumptions. The subject-specific regression coefficients from the mixed model that correspond to the slopes of the NT-proBNP profile for the two periods were incorporated in a Cox regression model in order to measure the strength of the association with the hazard of an endpoint; age was included as covariate. The significance level in all analyses was set to 5%.

RESULTS

Patient characteristics

We included 115 DCM patients at a median age of 2.2 years (IQR 0.3-11.6). In total, 2048 NT-proBNP values were analyzed. Of all patients, 79 were included at DCM diagnosis with symptomatic heart failure and were used in the first analysis. In these patients, 1260 NT-proBNP values were available, a median of 11 per patient (range 1-86). The first measurement was taken at day 1 (median, IQR 0-3 days). Patients were followed for a median time of 22 months. During follow-up, 26 patients (33%) reached the endpoint of cardiac death, at a median of 34 days. During the first 30 days after diagnosis, 7 patients died and 5 required MCS. From 30 days through 1 year, 4 patients died and 5 required MCS.

Table 1: Patients characteristics. Characteristics at first NT-proBNP measurement of all 115 patients, and divided in the two groups of analysis: patients who were included at DCM diagnosis (n=79), and of patients who survived at least the first year after diagnosis (n=68).

	All study patients at first measurement, n = 115		New DCM diagnosis, n = 79		Survived the first year after diagnosis, n = 68 *	
Age, years	2.2	(0.3-11.6)	0.8	(0.2-4.8)	4.5	(1.9-12.5)
Age at DCM diagnosis, years	1.3	(0.2-8.5)	0.8	(0.2-4.8)	1.9	(0.2-9.8)
Gender, male, n (%)	51	(44)	37	(47)	29	(43)
LVEDD, z-score	+5.9	(2.4-8.1)	+5.9	±3.6	+4.9	±3.4
Fractional shortening, %	13	(9-18)	12	±6	19	(13-28)
Primary endpoint, n (%)	37	(32)	26	(33)	16	(24)
Death	11		11		0	
Heart transplantation	12		4		12	
Mechanical circulatory support	14		11		4	
Follow-up, months	30	(10-65)	22	(3-46)	50	(24-72)

* 32 patients are also represented in the first group (new DCM diagnosis)
Continuous variables are represented as mean ±SD if normally distributed and as median (IQR) if non-normally distributed.
DCM indicates dilated cardiomyopathy; LVEDD, left ventricular end-diastolic dimension.

Of the 115 patients, 68 patients survived at least the first year after diagnosis and were used in the second analysis. Of them, 788 NT-proBNP values were analyzed, a median of 6 per patient (range 1-52). Median follow-up was 50 months. At first available NT-proBNP measurement, the median time since diagnosis was 1.4 years (IQR 1.2-2.7). Sixteen patients reached the endpoint, of whom 12 (75%) underwent transplantation. The median time from diagnosis to the endpoint was 3.1 years (IQR 1.9-6.0).

All patients in this study were on optimal pharmacological heart failure treatment. Early after diagnosis therapy varied widely. For patients who survived at least the first year of diagnosis, therapy included angiotensin-converting enzyme inhibitors (95%), beta-blockers (81%), loop diuretics (50%), spironolactone (66%), and digoxin (24%).

NT-proBNP values and survival

At diagnosis, NT-proBNP was not different between patients with and without subsequent cardiac death (median 33059 [IQR 11314-63420] vs 32292 [IQR 19738-56295] pg/mL, p=0.9). At 30 days after diagnosis, NT-proBNP was significantly higher in those with subsequent cardiac death than in those without (median 18707 pg/mL [IQR 4441-38102] vs 5744 pg/mL [IQR 2040-13220], p=0.018; Figure 1). The optimal threshold to predict cardiac death was 7990 pg/mL (sensitivity 75%, specificity 61%, area under the curve [AUC] 0.72, 95% CI 0.55-0.90, p=0.018). Survival analysis showed 1- and 2-year endpoint-free survival of 96% (95% CI 90-100) in those with NT-proBNP <7990 pg/mL, while the 1- and 2-year endpoint-free survival was 77% (95% CI 60-93) and 73% (95% CI 55-90) in patients with NT-proBNP ≥7990 pg/mL, p=0.046 (Figure 2a).

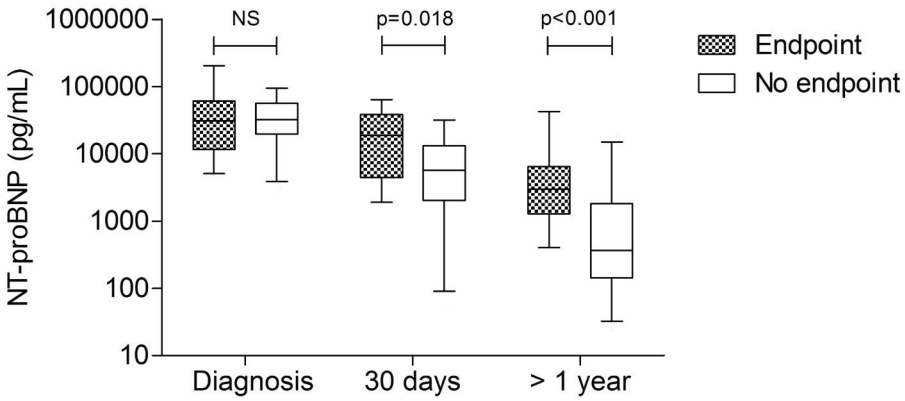

Figure 1: NT-proBNP (pg/mL) in patients with and without subsequent cardiac death. Box-plot showing the median NT-proBNP in children with dilated cardiomyopathy at diagnosis, 30 days and after 1 year, stratified by endpoint and no endpoint. NT-proBNP is displayed on the log scale, error bars indicate the 5th and 95th percentile. NT-proBNP indicates N-terminal pro-B-type natriuretic peptide.

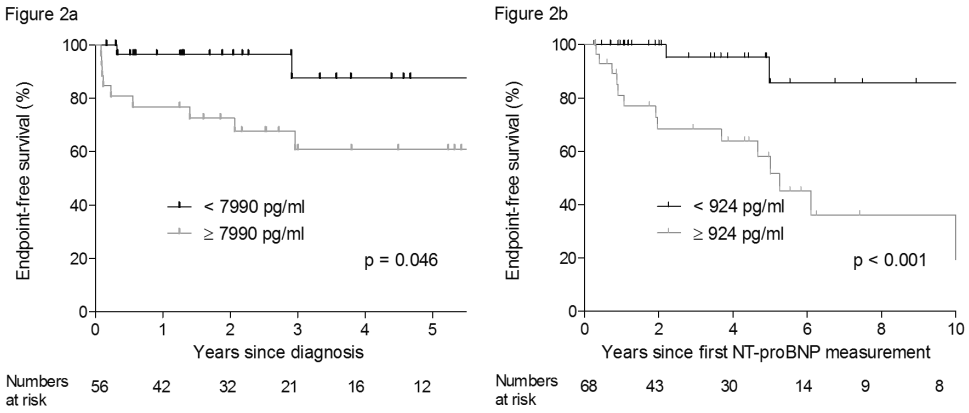

Figure 2: Endpoint-free survival in two groups using predefined cut-offs of NT-proBNP. Kaplan-Meier plots showing the estimates of freedom from an endpoint (death, heart transplantation or mechanical circulatory support) of children with dilated cardiomyopathy stratified by **PANEL A:** NT-proBNP value < 7990 pg/mL or ≥ 7990 pg/mL at 30 days after diagnosis. Log rank p=0.046. And **PANEL B:** NT-proBNP value < 924 pg/mL or ≥ 924 pg/mL in patients at least 1 year after diagnosis. Follow-up time since first NT-proBNP measurement. Log rank p<0.001. NT-proBNP indicates N-terminal pro-B-type natriuretic peptide.

In patients who survived at least the first year, the median NT-proBNP level was significantly higher in those with subsequent cardiac death, than in those without (2962 [IQR 1293-6453] vs 368 [IQR 143-1816] pg/mL, p<0.001), at a median time after diagnosis of 1.4 year (Figure 1). After 1 year of diagnosis, the optimal threshold to predict cardiac death was 924 pg/mL (sensitivity 88%, specificity 69%, AUC 0.83, 95% CI 0.73-0.93, p<0.001). The 2- and 4-year endpoint-free survival since the NT-proBNP measurement was respectively 100% and 95% (95% CI 86-100) for those with NT-proBNP <924 pg/mL, while this was 68% (95% CI 50-87) and 64% (95% CI 45-83) for those with NT-proBNP ≥924 pg/mL, p<0.001 (Figure 2b).

NT-proBNP values and the risk of an endpoint

A single NT-proBNP measurement at any time in the follow-up was significantly associated with the risk of cardiac death. Results for log10(NT-proBNP) are reported in Table 2. Transformed to the original scale this means that in patients with symptomatic heart failure, followed since diagnosis, a two-fold higher NT-proBNP (for example, comparing a patient with a value of 6000 pg/mL to a patient with a value of 3000 pg/mL) resulted in a 2.9 times higher risk of cardiac death (hazard ratio [HR] 2.9, 95% CI 2.1-3.5, p<0.001). For patients who survived more than one year, a two-fold higher level of NT-proBNP resulted in a 1.8 times higher risk (HR 1.8, 95% CI 1.4-2.4, p<0.001).

Table 2: Estimated hazard ratios and 95% confidence intervals.

Model	HR	95% CI	p-value
Newly diagnosed dilated cardiomyopathy			
Current NT-proBNP level			
Age	1.14	1.06; 1.22	0.002
Log10(NT-proBNP)	36.2	11.9; 63.4	<0.001
Change of NT-proBNP over time			
Age	1.08	0.98; 1.18	0.101
Log10(NT-proBNP): slope, 0-30 days, per year *	3.78	1.59; 9.19	0.001
Log10(NT-proBNP): slope, >30 days *	2.97	1.23; 7.46	0.011
Patients who survived at least the first year after diagnosis			
Current NT-proBNP level			
Age	0.96	0.87; 1.08	0.504
Log10(NT-proBNP)	7.24	3.26; 17.7	<0.001
Change of NT-proBNP over time			
Age	0.998	0.90; 1.10	0.957
Log10(NT-proBNP): slope *	6.83	1.76; 26.0	0.006

* Slope corresponds to a 10-fold increase in NT-proBNP over the time period of 1 year.
CI indicates confidence interval; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Longitudinal trajectory of NT-proBNP

At any time during follow-up, the change of log10(NT-proBNP) over time (slope) predicted the risk of cardiac death (Table 2). The average slopes of patients with and without an endpoint are displayed in Figure 3. The values of the mean slopes for the subsequent periods after diagnosis are described in Table 3.

In the first 30 days after diagnosis, a 10% increase of NT-proBNP over 1 week, gave a 18 times higher risk (HR 17.6, 95% CI 2.8-120.5 p=0.001); and a 10% decrease over 1 week gave a 24 times lower risk (HR 0.04, 95% CI 0.005-0.326 p=0.001). After 30 days of diagnosis, a 10% increase of NT-proBNP over 1 month resulted in a 1.7 times higher risk (HR 1.72, 95% CI 1.11-2.71, p=0.01) and a 10% decrease in a 1.8 times lower risk (HR 0.55, 95% CI 0.33-0.89). Similarly, in children who survived at least the first year after diagnosis, a two-fold increase in 3 months corresponded to a 10 times higher risk (HR 10, 95% CI 1.97-50.6), and a 50% decrease in 3 months corresponded to a 10 times lower risk of cardiac death (HR 0.10, 95% CI 0.020-0.508).

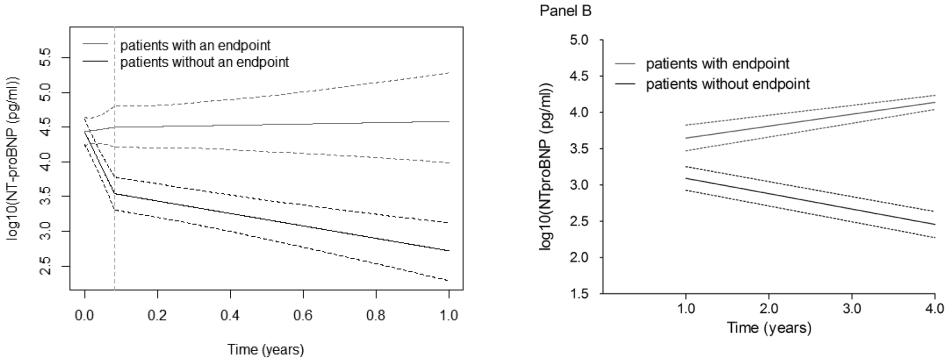

Figure 3: Average estimates of the longitudinal trajectory of log10(NT-proBNP). The average estimates of the longitudinal trajectory of log10(NT-proBNP) (pg/mL) of all patients with an endpoint (upper line) and those without (lower line) during the first year (Panel A) and in patients who survived the first year (Panel B). The dashed lines indicate the 95% confidence intervals. The vertical dashed line indicates the time point of 30 days after diagnosis. NT-proBNP indicates N-terminal pro-B-type natriuretic peptide.

Table 3: Mean slopes. Mean slopes for log10(NT-proBNP) in patients with and without an endpoint calculated in the predefined periods.

Time since diagnosis	Endpoint		No endpoint	
	Mean slope log10(NT-proBNP)	95% CI	Mean slope log10(NT-proBNP)	95% CI
0-30 days	+0.064 / 30 days	-0.014; 0.166	-0.887 / 30 days	-0.940; -0.833
> 30 days	+0.085 / 1 year	-0.227; 0.476	-0.823 / 1 year	-1.020; -0.662
> 1 year	+0.164 / 1 year	0.137; 0.189	-0.212 / 1 year	-0.207; -0.218

CI indicates confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide

DISCUSSION

This is the first study to show that serial NT-proBNP measurements during follow-up are predictive for the risk of cardiac death (death, heart transplantation and MCS) in a relatively large cohort of children with DCM. These results are important, because predictors for outcome during follow-up are scarce and will help to identify children at highest risk for cardiac death. Furthermore, parameters to guide medical treatment in these patients are urgently needed.

The present study demonstrates that in children with symptomatic heart failure, NT-proBNP at diagnosis was high and not predictive for outcome, while during follow-up NT-proBNP levels were higher in children with our predefined endpoint cardiac death. Based on our dataset, we defined two cut-off values to identify subgroups at a low and high risk. Those patients who were still alive at 30 days and had a level <7990 pg/mL had an excellent

1-year outcome, while in patients with a level >7990 pg/mL the 1-year event rate was 23%. Similarly, in patients who survived the first year after diagnosis, a value <924 pg/ml was associated with an excellent mid-term outcome, while in patients with a higher value the event rate was 32% in the next two years. Furthermore, according to the model, the actual level of NT-proBNP at any time after diagnosis, as well as the actual slope of log10(NT-proBNP), were predictive for the risk of cardiac death. In clinical practice, this means that high values and non-negative slopes are associated with a high risk. During follow-up, a lower NT-proBNP level was associated with a lower risk of cardiac death, and a (fast) decrease of NT-proBNP was associated with a lower risk, while NT-proBNP remained high or increased in those at high risk (Figure 3).

The predictive value of NT-proBNP in adults and children

In adults with heart failure, there is undisputed evidence that single and serial NT-proBNP measurements are independently predictive for the risk of mortality and hospital admissions.[7-11, 21-23] The risk increases with higher values and with larger absolute and percent increase of NT-proBNP over time. In the chronic heart failure population a value of 423 pg/mL has been suggested as 'well-controlled' and a value of >1000 pg/mL to identify a subgroup of patients at 'high risk'.[21, 24] Similarly, in children with heart failure it has been demonstrated that single BNP measurements were predictive for death, heart transplantation and hospitalization for worsening heart failure.[25-27] Previously, four pediatric studies have reported on serial NT-proBNP measurements.[12, 14, 28, 29] Two smaller studies focused on children who were admitted for acute decompensated heart failure and showed that NT-proBNP remained high in the first week in children who required MCS or were at risk for death or heart transplantation, while it decreased in others.[28, 29] The third study included 68 children at DCM diagnosis who survived at least 6 months.[14] At three months, children with a value ≥681 pg/mL were at high risk of the combined endpoint of severely impaired systolic function (FS <10%), death and heart transplantation. Finally, Rusconi et al. studied the relation of serial NT-proBNP measurements to clinical parameters during DCM follow-up.[12] An increase in NT-proBNP was associated with a decrease in LV ejection fraction and FS, an increase in LV end-diastolic and end-systolic dimensions and the odds of being in NYHA III-IV. They suggested a cut-off value of >1000 pg/mL to identify highly symptomatic children.

The results of the present study are in line with previous studies in children admitted with acute decompensated heart failure. We demonstrated that NT-proBNP that remains high or even increases early after diagnosis is an ominous sign, identifying a subgroup of children at high risk for early mortality or the need for MCS. After this early phase, our study demonstrates that NT-proBNP decreases less or increases in patients with adverse outcomes. The cut-off values that we provide are related to the endpoint of cardiac death and may

differ from those reported by other investigators using other endpoints. For example, Kim et al. found a much lower value to be predictive for a good prognosis than we report in the present study (<681 pg/mL at 3 months as compared to <7990 pg/mL at 1 month). However, they have used a different combined endpoint and have included only patients who survived at least 6 months after diagnosis. The results that we report in children >1 year after diagnosis are comparable to those in adults, with a median around 400 pg/mL in children without events and a threshold around 1000 pg/mL to identify patients at highest risk. Moreover, this was an almost similar cut-off as reported by Rusconi et al. (924 pg/mL vs 1000 pg/mL). In addition, we showed that in children this level was not only associated with the clinical severity of DCM, but was also predictive for hard endpoints such as death, heart transplantation and MCS.

Outcome in pediatric DCM

Outcome data are important to acknowledge interpreting the risks of an endpoint in children with DCM. Large registries have shown that the first year after diagnosis is most critical, since 18-31% of the patients die or undergo heart transplantation.[1-3, 32] Median time to death or listing for transplantation is short, around 1-2 months, underscoring the critical first 30 days after diagnosis. In the subsequent years, event-rates decline to 6-8%, and after 5 years an event-rate of about 1% has been reported. Our results indicate that a subgroup of patients with much higher event-rates can be identified using NT-proBNP.

NT-proBNP as surrogate marker

Children who survive the first year after DCM diagnosis represent a group with chronic heart failure and a relatively favorable prognosis. Angiotensin-converting enzyme inhibitors and beta-blockers have been widely used in these children,[2, 33] but studies demonstrating their efficacy have been hampered by the relatively low prevalence of meaningful endpoints and the absence of surrogate markers. For example, in the Pediatric Carvedilol Trial 18% of the children died or underwent heart transplantation, whereas in trials with adults mortality has been reported as high as 35-40%.[33, 34] Surrogate markers, like NT-proBNP, may serve as useful outcome markers for pharmacological studies and may help to improve heart failure treatment in children. For example, studies using NT-proBNP to tailor medical therapy in adults, have shown that higher dosages of heart failure medication could be reached, resulting in reduced mortality and hospitalization.[11, 35, 36] It has been suggested that in such studies a target level NT-proBNP should be set, rather than a percentage decrease of NT-proBNP.[23] To apply such strategies to children, our results suggest that future studies should target medical therapy to decrease NT-proBNP to at least 924 pg/mL or lower.

Study limitations

First, the retrospective design of the study resulted in a different number of NT-proBNP samples measured at different time points. However, this was accounted for using the longitudinal mixed model analysis. This analysis allows inclusion of different lengths of follow-up and the lack of follow-up measurements in patients with an endpoint. Secondly, due to relatively low endpoint numbers, we could not adjust for multiple covariates, such as LV dimensions and medication use, which may have had impact on NT-proBNP values and outcome. Thirdly, the median follow-up duration was only 2 years in patients followed from diagnosis onwards, and 4 years in patients with chronic DCM. Therefore, the results should be interpreted as being indicative of the predictive value of NT-proBNP on short to mid-term survival. Finally, clinicians treating the patients were not blinded to the NT-proBNP values. This may have caused minimal bias, but NT-proBNP values were not included in the treatment protocols during the study.

CONCLUSIONS

This is the first study demonstrating that NT-proBNP measurements at any time in the follow-up are significantly associated with the risk of death, heart transplantation and MCS in children with DCM. Taking the slope of NT-proBNP into consideration further enhances risk assessment. High values and non-negative slopes are associated with high risk of cardiac death. In clinical follow-up of children with DCM, the use of serial NT-proBNP measurements improves the identification of children at highest risk of cardiac death.

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Chapter 5

Prospective evaluation of sleep apnea as manifestation of heart failure in children

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ABSTRACT

Background

In adults with heart failure, central sleep apnea (CSA), often manifested as Cheyne-Stokes respiration, is common, and has been associated with adverse outcome. Heart failure in children is commonly caused by dilated cardiomyopathy (DCM). It is unknown whether children with heart failure secondary to DCM have CSA, and whether CSA is related to the severity of heart failure.

Methods and Results

In this prospective observational study, 37 patients (<18 year) with heart failure secondary to DCM were included. They underwent polysomnography, clinical and laboratory evaluation and echocardiographic assessment. After a median follow-up time of 2 years, eight patients underwent heart transplantation. CSA (apnea-hypopnea index [AHI] ≥1) was found in 19% of the patients. AHI ranged from 1.2 to 4.5/hour. The occurrence of CSA was not related to the severity of heart failure. Three older patients showed a breathing pattern mimicking Cheyne-Stokes respiration, two of whom required heart transplantation.

Conclusion

CSA was found in 19% of the children with heart failure secondary to DCM. No relation was found with the severity of heart failure. In a small subset of children with severe DCM, a pattern mimicking Cheyne-Stokes respiration was registered.

INTRODUCTION

In adults with heart failure, central sleep apnea (CSA) is highly prevalent.[1-4] Cheyne-Stokes respiration is a form of CSA and, in adults with heart failure, used as a synonym for CSA.[5] The occurrence of CSA in adults with heart failure is associated with the severity of heart failure and with higher mortality rates. [1, 2, 6, 7]

Dilated cardiomyopathy (DCM) in children is a severe cardiac disorder resulting in heart failure. To the best of our knowledge, so far, no study has been published that has investigated whether CSA occurs in children with heart failure. According to the prevalence in adults, we speculated that CSA occurs in children with heart failure and may also be related to the severity of heart failure. Therefore, we conducted a prospective study to determine the prevalence of CSA and its clinical relevance in children with heart failure secondary to DCM.

METHODS

Patient selection

Between October 2010 and October 2013, children (< 18 year) with DCM were asked to participate in a nationwide prospective follow-up study. DCM was defined as a left ventricle end-diastolic dimension (LVEDD) > 95th percentile for body surface area and a shortening fraction (SF) ≤ 25%. DCM was of idiopathic origin or secondary to other causes. Patients with DCM secondary to neuromuscular diseases were excluded, because sleep-disordered breathing can be present as result of muscular weakness.[8, 9]

As part of the follow-up study, an overnight polysomnography was planned. Furthermore, a detailed clinical evaluation, including echocardiography, NT-pro BNP measurement, and clinical assessment using the New York University Pediatric Heart Failure Index, [10] was performed within three months of the polysomnography. Medication use and demographic data (age, gender and duration of DCM) were recorded. Follow-up data were collected through January 2015. Primary endpoints were death and heart transplantation. The review board of all participating centers approved the protocol. All parents, and patients ≥ 12 year, gave their written informed consent.

Sleep study

Patients underwent overnight polysomnography either at home or in hospital. Measurements at home were done with the Embletta Portable Diagnostic System and analyzed using Somnologica for Embletta Software 3.3 ENU (Medcare Flage, Reykjavik, Iceland). Embletta is a multichannel test that continuously measures respiration by a pressure transducer attached to a nasal cannula (Salter labs, Arvin USA), breathing effort through respiratory

elastic belts at abdominal and chest level (X act), and oxygen saturation (SaO_2) and heart rate using an infant or pediatric oxygen sensor (OxiMax; Nellcor, Pleasanton, USA) on a fingertip. Caregivers were instructed to apply all sensors and to start the measurement at bedtime and to end the measurement the next morning. In hospital measurements were performed using BrainRT Shell+ (OSG BVBA, Rumst, Belgium) and analyzed using BrainRT Shell+ (version 1.0, Patch Pack 5, build 2570). Oronasal flow was measured with a thermal sensor. Breathing effort was measured through respiratory elastic belts at abdominal and chest level, heart rate using 3 electrocardiogram leads and SaO_2 using an infant or pediatric oxygen sensor on a fingertip (OxiMax; Nellcor, Pleasanton, USA) applied to a pulse oxymeter (Xpod, Nonin Medical). Recordings of both devices were analyzed using the same methods as described below.

Due to the absence of electroencephalography, arousals were not recorded and therefore not used in the criteria. In some patients one of the channels (SaO_2, nasal flow or impedance) showed a technical failure. Measurements were excluded if either the impedance or the SaO_2 was missing, because the purpose of the study was to detect central apneas. Mean pulse rate and mean respiratory rate were labeled as respectively tachycardia and tachypnea if they were > 90th percentile for age.[11]

Scoring respiratory events

One observer (SvdB), blinded to the clinical characteristics of the patients, scored the sleep studies. All respiratory events were scored according to the American Academy of Sleep Medicine (AASM) criteria.[12] An apnea was defined as a drop in peak signal excursions of ≥ 90%. Central apnea was scored if inspiratory effort was absent throughout the entire duration of the event and one of the following criteria were met: i) the event lasted ≥ 20 seconds; ii) the event lasted for at least 2 breaths and was accompanied by an oxygen desaturation of ≥ 3%. A central apnea following a sigh was scored only if it caused a desaturation ≥ 3%. Hypopnea was defined as a reduction of ≥ 30% of the pre-events baseline flow, lasted for at least 2 breaths and was accompanied by a desaturation of ≥ 3%.

We calculated the apnea-hypopnea index (AHI) as the number of central apneas and hypopneas per hour of sleep. An AHI of ≥ 1 was defined as abnormal.[13-17] Periodic breathing was scored if ≥ 3 episodes of central apnea lasted > 3 seconds separated by no more than 20 seconds of normal breathing.

Statistical analysis

All continuous variables are displayed as median (IQR), because of the low sample size in this study. Categorical variables are displayed as numbers and percentages. Difference between the median of two independent groups were assessed using the Mann-Whitney U test. Relationships between two non-normally distributed continuous variables were assessed using Spearman's correlation. Statistical significance was defined as $p < 0.05$.

RESULTS

Study group

During the 3 years of the follow-up study, 58 of 79 eligible patients were willing to undergo polysomnography. Of these 58, eight patients were not measured, because they died or received a heart transplantation shortly after inclusion and before the polysomnography was performed; and in 13 patients the measurement failed, due to a lack of patient cooperation. As a result, 37 measurements were available.

The median age of the patients was 11.1 years. The median time since diagnosis of DCM was 3.6 years (range 0-15.6 years). Almost all patients (97%) took angiotensin-converting enzyme inhibitors, 81% took β-blockers and 70% took diuretics as medical treatment for heart failure. The median LVEDD z-score was +4.7 and SF 19.4% (Table 1).

Table 1: Patient characteristics and clinical data within 3 months of the polysomnography

	All patients (n = 37)	**No endpoint (n = 29)**	**Heart transplantation (n = 8)**	**p-value**
Male, n (%)	19 (51)			
Age, yr	11.1 (3.3-15.5)	8.7 (2.5-15.5)	12.3 (6.2-15.2)	NS
Etiology of DCM, n (%)				
Idiopathic	26 (70)			
Myocarditis	3 (8)			
Other [a]	8 (22)			
Time since diagnosis of DCM, yr	3.6 (1.6-7.6)			
Medication use, n (%)				
Diuretics	26 (70)	18 (62)	8 (100)	0.04
ACEi	36 (97)	29 (100)	7 (88)	NS
ß-blockers	30 (81)	22 (76)	8 (100)	NS
NYU PHFI	8 (5-11)	8 (4-10)	13 (10-14)	0.004
NT-pro BNP (pmol/L)	132 (79-480)	96 (50-195)	502 (417-776)	0.001
LVEDD z-score	+4.7 (3.3-6.9)	+4.1 (3.1-6.1)	+6.3 (3.7-9.3)	NS
SF (%)	19.4 (13.6-26.1)	19.7 (15.8-26.6)	12.2 (5.9-19.6)	0.01

[a] Category 'other' includes four patients with familial or genetic disease, three patients with prior use of anthracycline and one patient with vasculitis.
Categorical variables are displayed as number (%), continuous variables are displayed as median (IQR). DCM, dilated cardiomyopathy; ACEi, angiotensin-converting enzyme inhibitor; NYU PHFI, New York University Pediatric Heart Failure Index, range 0-30; NT-pro BNP, N-terminal B-type natriuretic peptide; LVEDD, left ventricular end-diastolic dimension; SF, shortening fraction.

The 34 patients in whom polysomnography was not performed (n = 21 not willing to undergo polysomnography and n = 13 measurement failure) were significantly younger (median age 3.3 years; p = 0.007) than the study group. LV dilation and function was not significantly

different between groups (LVEDD z-score +5.8 [IQR 3.2-9.2], p = 0.3, and SF 16.8% [IQR 11.9-19.8], p = 0.08).

Sleep study

Thirty-three patients (89%) were measured at home with the ambulatory device, whereas four patients were measured in hospital. The median recording time was 513 minutes. Five recordings were shorter than 360 minutes (range 211-352). As we studied the prevalence of sleep-disordered breathing, we included these measurements in the analysis.

Of 37 patients, seven (19%) had AHI ≥ 1 (range 1.2-4.5). These children were significantly younger than children with AHI < 1 (median age 2.9 vs 12.3 year, p = 0.01). Three patients were younger than one year of age; all had an abnormal AHI (≥ 1) (Table 2).

Table 2: Polysomnography results

	All patients (n = 37)	**No endpoint (n = 29)**	**Heart transplantation (n = 8)**	**p-value**
Total registration time (min)	513 (481-576)			
Resting heart rate (bpm)	78 (62-97)			
Tachycardia, n (%)	2 (5)			
Respiratory rate (/min)	21 (18-24)			
Tachypnea, n (%)	9 (24)			
Mean O_2-saturation (%)	98 (97-98)			
Minimal O_2-saturation (%)	91 (88-94)			
Mean O_2-desaturation (%)	4.4 (3.9-5.2)			
AHI (/hr)	0.2 (0.05-0.55)	0.2 (0-0.5)	0.44 (0.13-1.01)	NS
0-1 /hr, number of patients (%)	30 (81)	24 (83)	6 (75)	NS
1-5 /hr, number of patients (%)	7 (19)	5 (17)	2 (25)	
≥5 /hr, number of patients (%)	0 (0)			

Categorical variables are displayed as number (%), continuous variables are displayed as median (IQR). AHI, apnea-hypopnea index; Tachycardia and tachypnea defined as > 90th percentile of the reference values [11]

In three patients clusters of apneas and hypopneas were noticed at the end of the night. The first patient (age 12 years) had a typical crescendo-decrescendo cyclic pattern in breathing amplitude with apneas and hypopneas with a maximal episode duration of 58 minutes (Figure 1). Only one apnea led to an oxygen desaturation, resulting in an AHI of only 0.1. The breathing pattern appeared as Cheyne-Stokes respiration and the duration of the episodes counted for 14.5% of the total registration time (Table 3). The second patient (age 16 years) had several apneas > 20 seconds with and without oxygen desaturations, reflected as an AHI of 2.6. The cyclic pattern appeared as both Cheyne-Stokes and as periodic breathing and accounted for 27% of the total registration time. The third patient (age 15 years) had

a mild cyclic breathing pattern without desaturations and a maximum duration of almost 17 minutes per episode (AHI 0). This breathing pattern appeared as periodic breathing and counted for 0.5% of the total registration time.

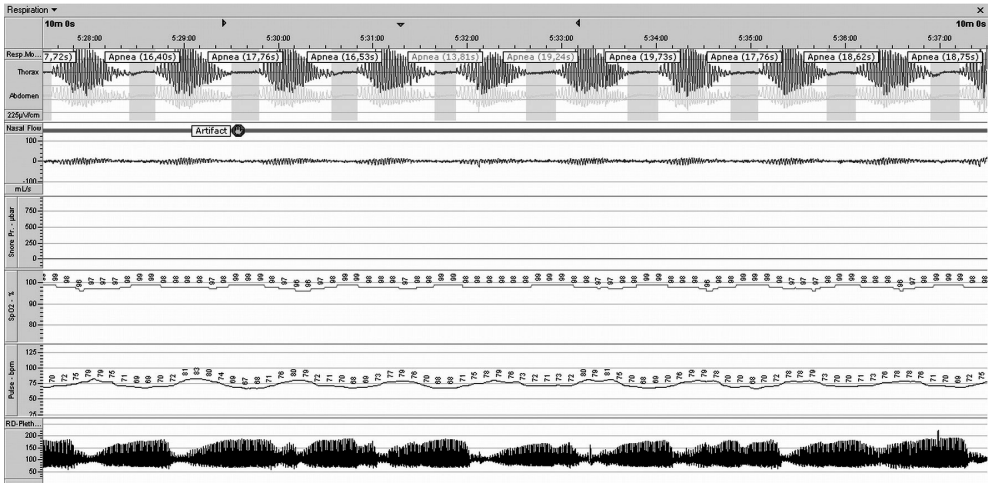

Figure 1: Recording of patient 1 (table 3) showing a crescendo-decrescendo cyclic pattern of the breathing amplitude with apneas

Table 3: Three patients with patterns of hypopneas and apneas

	Patient 1	**Patient 2**	**Patient 3**
Age, yr	12.0	15.9	15.4
Number of apneas	34	95	1
AHI (/hour of sleep)	0.1	2.6	0
Crescendo/decrescendo patterns			
Number	3	16	4
Minimal duration (mm:ss)	08:38	02:30	04:42
Maximal duration (mm:ss)	58:17	35:33	16:42
% of total sleep time	14.5	26.6	0.5

AHI, apnea-hypopnea index.

Heart failure severity and follow-up

During the measurement, tachycardia was present in two patients and tachypnea in nine patients. The AHI was not correlated with the severity of heart failure symptoms, expressed as NYU PHFI, and also not with the severity of LV dysfunction and dilation (SF and LVEDD z-score), and not with the time since DCM diagnosis. During follow-up (median 2.0 years, IQR 1.3-3.2) eight patients underwent heart transplantation, no deaths occurred. The patients who underwent heart transplantation had more heart failure symptoms and worse

LV function than those who survived without transplantation. AHI was not different between groups (Tables 1 and 2).

DISCUSSION

In this prospective observational study we assessed the prevalence of CSA in children with heart failure and DCM. In 19% of the children we detected CSA, defined as AHI > 1. We found no relation between the occurrence of CSA and the severity of heart failure in children. Three older patients showed episodes of a cyclic pattern of crescendo-decrescendo changes in breathing amplitude with apneas and hypopneas, according to pediatric criteria defined as periodic breathing and mimicking Cheyne-Stokes respiration.

The prevalence of CSA in children with heart failure was lower than in adults with heart failure. We found an increased number of central sleep apneas and hypopneas in seven children (19%), while reports in adults showed a prevalence of CSA around 35-40%.[1, 2, 4] CSA in children was defined as AHI ≥ 1 /hour, while in adults CSA is defined as mild if AHI ≥ 5, moderate if AHI 15-29 and severe if AHI ≥ 30.[18] Thus, as compared to adults with mean values reported around 30 /hour,[1, 2, 4] the severity of CSA in children seemed relatively mild. Since the prevalence of CSA was low, we were not able to relate CSA to outcome.

Cheyne-Stokes respiration is a typical breathing abnormality, which is seen in adults with heart failure, and associated with higher mortality rates.[19] In the current manual for scoring respiratory events in children, no rules for Cheyne-Stokes breathing are listed. However, scoring rules for periodic breathing are described for children and these mimic the rules for Cheyne-Stokes respiration.[12] Indeed, in 3 children a typical pattern of periodic breathing and Cheyne-Stokes respiration was detected. All were older children, respectively 12, 15 and 16 years old. The two patients with the most severe manifestation of Cheyne-Stokes respiration had both severe DCM: both underwent transplantation, respectively 14 and 22 months after the polysomnography; the third patient with mild periodic breathing is doing well on heart failure medication.

There may be several explanations why CSA in children with heart failure is less prevalent than in adults. One of the pathophysiological concepts of CSA is that the nocturnal fluid shift from legs to lungs stimulates pulmonary irritant chemoreceptors by pulmonary congestion, leading to hyperventilation and subsequently to a drop in PaCO2 below the apneic threshold. The amount of fluid that shifted from the legs was directly related to the amount of leg edema and sitting time, and inversely related to physical activity.[20] Leg edema has been associated with the presence of varicose veins and older age.[21] In contrast, fluid retention in children with heart failure is commonly associated with hepatomegaly, less often with ascites, but rarely with leg edema. These differences may be related to

lower hydrostatic venous pressure in the legs and with more physical activity in children as compared to adults. Thus the magnitude of the fluid shift may be smaller in children preventing the occurrence of CSA.

Another factor to take into consideration may be a difference in regulation of respiration in response to CO_2. One of the mechanisms that results in a drop in $PaCO_2$, leading to a central apnea, is hyperventilation initiated by an arousal.[22] Since the frequency of arousals increases with age,[23, 24] children may have a lower number of arousals and subsequently a lower prevalence of CSA. Furthermore, in adults with heart failure an increased sensitivity to CO_2 has been observed, and the sensitivity to CO_2 has been positively correlated to the AHI.[25] In children, it is unknown if such changes in the ventilatory response to CO_2 exist and contribute to the occurrence of CSA. Interestingly, Cheyne-Stokes breathing pattern in our study was observed in the oldest children with severe heart failure. One may speculate that it occurs in those with severe heart failure and most resembling adults.

In our study we reported the NYU PHFI to grade the severity of heart failure. We could not detect a correlation between NYU PHFI, LV function and dilation and the presence of CSA. The Cheyne-Stokes breathing pattern in two of eight children receiving a heart transplantation indicates that there might be a relation between the severity of heart failure and CSA, which needs further exploration.

This study has several limitations, which may have led to an underestimation or overestimation of the prevalence of CSA. Firstly, we recognize that we were unable to measure a substantial number of patients due to technical and practical problems. Although, we used ambulatory devices, several parents and children were not willing to undergo polysomnography. And probably, the use of ambulatory devices negatively influenced the success rate of the measurements. The children who were not measured were significantly younger, and their LV function was similar to children who were measured. Since the midterm prognosis of heart failure in young children is better than in older children,[26] and we found more severe breathing abnormalities in older children, this may lower the impact of missing these children in this study. Secondly, eight children could not undergo a polysomnography because they either died or underwent heart transplantation before they could be studied. As in adults the prevalence increases with decreasing LV function, CSA may have been missed because we could not study this severely ill subgroup. Thirdly, in our cohort, three of the seven patients with AHI > 1 were younger than 1 year of age. Especially in young infants, central sleep apneas may be the result of immature breathing, rather than the result of heart failure.[27] The young age of the patients may have overestimated the prevalence. Fourthly, we included five recordings shorter than 360 minutes. Regardless of total registration duration, every central apnea was important to acknowledge to calculate the prevalence. However, such short measurements without apneas did not guarantee that these patients were free from sleep apnea, and therefore may have led to an

underestimation of the prevalence. Finally, as already mentioned, electroencephalography was not recorded. Therefore, the total sleep time may have been overestimated, and central apneas and hypopneas associated with arousals, rather than with desaturations, were not scored. This may have led to an underestimation of the AHI.

In the present study, only a relatively small patient group remained for final analysis. In order to increase the number of eligible patients in future research, we suggest to use in-hospital measurements on all newly diagnosed patients, since almost 80% of the patients with DCM need hospital admission at diagnosis.[26] The use of in-hospital measurements may reduce the occurrence of technical failure. Furthermore, DCM symptoms may be worse during first admission, what may be therefore lead to a higher detection rate of CSA.

In conclusion, in this first prospective study to investigate the prevalence of central sleep apnea in children with moderate to severe heart failure, we found CSA in 19% of the patients. In a small subset of older children with signs of severe heart failure, a Cheyne-Stokes respiration pattern was noticed, similar to that has been observed in adults. For the whole study group, no relation was found with the severity of heart failure.

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Chapter 6

Longitudinal strain as risk factor for outcome in pediatric dilated cardiomyopathy

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ABSTRACT

Objectives

This study aimed to evaluate the predicting value of global peak strain and quantitative and qualitative dyssynchrony parameters as assessed by two-dimensional speckle-tracking echocardiography (STE) on outcome in children with dilated cardiomyopathy (DCM). Furthermore, the feasibility and reproducibility of these parameters were investigated.

Background

In previous studies in adults with heart failure, global strain has been a valuable predictor of clinical outcome and dyssynchrony parameters have been used to predict outcome and cardiac resynchronization therapy response.

Methods

This multicenter, prospective study included 75 children with DCM and 75 healthy age-matched controls. Using STE, global peak strain and quantitative (time to global peak strain and parameters describing intraventricular time differences) and qualitative dyssynchrony parameters (pattern analysis) of the apical 4-chamber, 3-chamber, 2-chamber view and the short axis of the left ventricle were assessed. Cox regression was used to identify risk factors for the primary endpoints of death and heart transplantation. Interobserver and intraobserver variability were described.

Results

During a median of 21 months follow-up, 10 patients (13%) reached an endpoint. Global peak strain was reduced in all views, compared to controls ($p<0.001$). Reduced global longitudinal peak strain of the 4-chamber was associated with the risk of death and heart transplantation (HR 0.81,$p=0.04$), while LVEF and FS were not. STE of the longitudinal 4-chamber view was feasible in 99% of the patients; intraobserver and interobserver variability were small. In contrast, quantitative dyssynchrony measures showed high variability. Pattern analysis showed mainly reduced strain, instead of dyssynchronous patterns.

Conclusions

In this study, reduced strain was associated with death and heart transplantation in children with DCM. Strain imaging was feasible and reproducible. In contrast, quantitative dyssynchrony parameters were not reproducible, precluding their use in children. Qualitative pattern analysis showed predominantly reduced strain, suggesting that in children with DCM dyssynchrony may be a minor problem.

INTRODUCTION

In children, dilated cardiomyopathy (DCM) is a severe cardiac disorder with a poor prognosis. The 1- and 5- year transplant-free survival is around 70% and 50%, respectively.[1] In children with DCM, follow-up of left ventricular (LV) function is predominantly performed by echocardiography. The most frequently used parameters are fractional shortening (FS) and left ventricular ejection fraction (LVEF), as assessed by two-dimensional echocardiography. However, the value of these parameters in predicting outcome during follow-up may be limited in children with DCM. Furthermore, when geometric assumptions do not apply or if increased dyssynchrony is present, these parameters are less reliable.[2] Speckle-tracking echocardiography (STE) can avoid these problems and has been shown to be a reliable measure of regional and global LV systolic function.[3, 4] Moreover, in adults with DCM it has been demonstrated that global longitudinal, circumferential and radial strain have additional value to LVEF in predicting the risk of all-cause mortality, heart transplantation and hospitalization due to acute decompensated heart failure.[5, 6] Furthermore, STE can be used to calculate parameters describing dyssynchrony. Its presence in adults, is related to adverse outcome and has been used to predict the effectiveness of cardiac resynchronization therapy (CRT).[7, 8] Considering the use of quantitative strain measures, it has been demonstrated that qualitative pattern analysis better predicts CRT response.[9, 10]

Until now, STE in children with DCM has only been reported in three small studies.[11-13] In these studies reproducibility was not sufficiently investigated and strain was not related to clinical outcome. Moreover, it has been shown that reproducibility of quantitative dyssynchrony parameters in healthy children is poor.[14] The present study had the following aims: (1) do STE derived parameters predict the risk of death and heart transplantation; (2) is obtaining these parameters feasible and are they reproducible; and (3) what is the presence and extent of dyssynchrony, by using qualitative pattern analyses.

METHODS

Patient selection

Children (<18 years) who fulfilled the criteria for DCM in one of the seven academic medical centers in the Netherlands were enrolled for this prospective study. DCM was defined as LV dilation (LV end-diastolic dimension [LVEDD]) ≥ +2 z-score for body surface area [15] and FS ≤ 25%. Children were excluded if they had repaired or unrepaired structural heart defects or if they were being paced. Follow-up data were collected through January 2015. Primary endpoints were death and heart transplantation. We selected age and sex-matched controls from an earlier described cohort of healthy children.[14] In patients and controls, STE was

performed according to the same protocol. The study was approved by the institutional review boards of all centers and patients and/or parents gave written informed consent.

Electrocardiogram

QRS duration was derived from an electrocardiogram made on the same day as the echocardiogram. QRS duration was calculated and labeled as above or below 98th percentile, according to reference values.[16]

Echocardiography

A complete two-dimensional echocardiographic study was performed in a uniform way using Vivid 7 or Vivid 9 ultrasound scanner (GE Vingmed Ultrasound AS, Horten, Norway). All children were at rest and in sinus rhythm during examination. All parameters were calculated using the mean of three consecutive cardiac cycles. M-mode of the parasternal long-axis was used to measure LVEDD and LV end-systolic dimension (LVESD) and subsequently, FS was calculated. LVEF was calculated from the apical 4-chamber and 2-chamber view using Simpson's biplane method.[2] End-systole was defined as the moment of aortic valve closure, measured in a Doppler flow image of the LV outflow tract. Two-dimensional grayscale images of the apical 4-chamber, 3-chamber, 2-chamber and parasternal short-axis view at the level of the papillary muscle were stored for offline speckle-tracking analysis using EchoPAC Software Version 12.0.1 (GE Vingmed Ultrasound AS).

Two-dimensional speckle-tracking strain imaging, quantitative analysis

Two-dimensional STE of the apical 4-chamber, 3-chamber, 2-chamber and parasternal short axis view were performed as previously described.[14] Peak strain was defined as the highest strain value at any time point in the cardiac cycle. For all six segments of the 4-chamber, 3-chamber and 2-chamber view peak longitudinal strain was registered. Likewise in the short-axis view, peak radial and circumferential strain was registered for each of the six segments. Time to peak strain was assessed for each segment using the beginning of the QRS complex as a reference point.

Individual peak strain values were combined in several models. For longitudinal strain these models included the 4-chamber (6 segments), the 4-chamber and 2-chamber (12 segments) and the 4-chamber, 3-chamber, and 2-chamber (18 segments) model. For radial and circumferential strain the models included the 6 segments of the short axis view. Global peak strain was calculated as the mean of the peak strain values of all segments in one model. Time to global peak strain was calculated as the mean of all time to peak strain values in one model.

Additionally, parameters describing intraventricular time differences were calculated, including the standard deviation of the time to peak strain of all segments in one model (e.g. SDt-6) and the difference in time to peak strain between two specified segments. For

longitudinal strain, the difference in time to peak strain between the basal septal and lateral segments was calculated (S-L delay). For circumferential and radial strain the difference in time to peak strain between the anteroseptal and posterior segment was calculated (AS-P delay).

Qualitative analysis: pattern recognition of strain curves of 4-chamber, 3-chamber, and 2-chamber

The strain curves of the apical 4-chamber, 3-chamber and 2-chamber views were analyzed using the qualitative methods as described by Carasso et al. and Risum et al.[9, 10] In short, the strain patterns of each segment of the 4-chamber and 2-chamber were scored as (1) normal, (2) mildly reduced shortening, (3) severely reduced shortening, (4) holosystolic stretching, (5) delayed systolic shortening, or (6) pseudodyssynchrony (Figure 1).[9]

Furthermore, the presence or absence of classical-pattern dyssynchrony (CPD) was scored in the 4-chamber, 3-chamber, and 2-chamber view. CPD was present if basal or midventricular segments showing early stretching and late shortening opposed by basal or midventricular segments showing early shortening and late lengthening.[10]

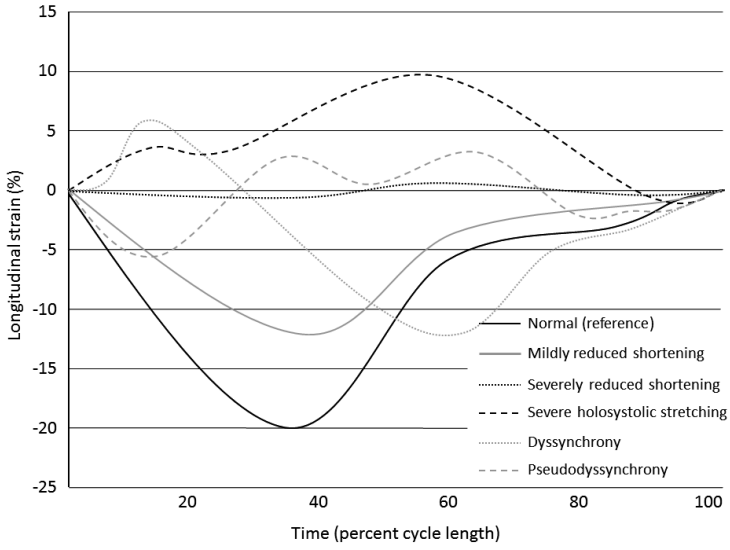

Figure 1: Mechanical patterns of DCM. Strain patterns according to the methods of Carasso et al., figure adapted from Carasso et al.[9] **Solid black** line represents 'normal' strain curve, shortening is initiated at the onset of QRS, reaches peak strain at aorta valve (AV) closure (≥17%), and stretches until next QRS. **Solid grey** line represents 'mildly reduced shortening', pattern as normal strain curve, with peak strain between -17% and -5%. **Speckled black** line represents 'severely reduced shortening', peak strain between -5% and +5%. **Dashed black** line represents 'holosystolic stretching', severe stretching throughout systole, shortening back starts after AV closure. **Speckled grey** line, 'delayed systolic shortening', stretching starts at the onset of QRS, subsequently shortening starts (during systole), and peak strain (≥5%) occurs after AV closure. **Dashed grey** line represents 'pseudodyssynchrony', shortening is initiated at the onset of QRS, but stops prematurely; the peak strain is very small.

Intraobserver and interobserver variability

Intraobserver and interobserver variability for quantitative analyses were assessed using 20 randomly selected patients. Using the same cardiac cycle, the first observer (SdB) traced the endocardial border again and registered strain parameters, after an interval >3 months. A second observer (AtH), who was blinded to the results of the first observer, traced the endocardial border and registered the strain parameters on the same image and cardiac cycle as the first observer did.

Statistical analysis

Continuous variables are reported as mean ±SD if normally distributed, or as median with interquartile range (IQR) if non-normally distributed. Differences in demographics and echocardiographic parameters between patients and controls were tested using independent sample t-test or Chi-square test if normally distributed, and using Mann Whitney U test if non-normally distributed. Two-proportion z-test was used to determine the difference in segment distribution. Univariable Cox regression was used to identify risk factors for death and heart transplantation. Intraobserver and interobserver variability were calculated using the intraclass correlation coefficient (ICC) and coefficient of variation (CV). All statistical analyses were performed using IBM SPSS Statistics 21; $p<0.05$ was considered as statistical significant.

RESULTS

Patient characteristics

We included 75 DCM patients and 75 healthy age and sex-matched controls. The mean age of all subjects was 7.5 years, range 0-17.9 years. All patients were treated with individually optimized medication. The mean LVEF and FS in patients were significantly lower than in controls (Table 1). Although the mean QRS duration in patients was within normal range, it was significantly longer than in controls. In patients, 25% had QRS duration >98th percentile for sex and age, compared to 2% in controls. Only 2 patients had QRS duration >120 milliseconds. During a median of 21 months (IQR 15.5-31.2 months) follow-up, 10 patients (13%) reached a primary endpoint; 8 underwent heart transplantation and 2 died.

Table 1: Baseline characteristics of the study and control population

	DCM n =75	Controls n =75	p-value
Male, n (%)	42 (56)	42 (56)	NS
Age (yr)	7.4 ± 6.4	7.6 ± 6.3	NS
Time since DCM diagnosis (yr), median (IQR)	1.0 (0.1 – 4.0)	-	-
Medication used, n (%)			
Diuretics	53 (71)	-	-
β-blockers	44 (59)	-	-
ACEi	64 (85)	-	-
NYU PHFI	8 ± 3	-	-
LVEDD z-score	+ 5.1 ± 3.0	- 0.1 ± 1.1	<0.001
LVESD z-score	+ 8.1 ± 4.1	- 0.2 ± 1.0	<0.001
Fractional shortening (%)	17.5 ± 6.5	37.0 ± 4.0	<0.001
LVEF (%)	32.7 ± 11.4	59.2 ± 4.2	<0.001
QRS duration (msec)	86 ± 18	79 ± 12	0.004
QTc (msec)	446 ± 35	409 ± 26	<0.001
Heart rate (bpm)	104 ± 34	104 ± 35	NS

All parameters are reported as mean ± SD, unless otherwise indicated.
ACEi indicates angiotensin-converting enzyme inhibitor; DCM, dilated cardiomyopathy; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; NYU PHFI, New York University Pediatric Heart Failure Index, range 0-30.

Global peak strain, time to global peak strain and intraventricular time differences

In patients, mean global peak strain of all models were significantly reduced compared to controls (Figure 2). No specified regions could be identified as more affected than others, since all segments were worse in patients than in controls ($p<0.001$). Time to global peak strain of the longitudinal models were significantly longer in DCM patients than in controls, whereas no significant differences were observed in time to global peak strain of the short-axis views (Table 2). The SD of the time to peak strain calculated in each model was considerably higher and the delay between two specified segments (S-L delay and AS-P delay) was significantly longer in patients as compared to controls.

Strain and the risk of death or heart transplantation

In univariable analysis, lower mean global peak strain of the 6-segment model was significantly associated with higher risk of poor outcome; each % decrease in mean global peak strain gave a 1.23 times higher risk of death or heart transplantation (hazard ratio 0.81 per % strain increase, 95%CI 0.66-0.99, $p=0.04$). LVEF, FS, LVEDD z-score and mean global radial and circumferential peak strain were not significantly associated with outcome (Table 3).

Table 2: Time to global peak strain and intraventricular time differences in patients (n=75) and controls (n=75)

	DCM n =75	Controls n =75	p-value
Time to global peak strain (msec)			
Longitudinal 6-segment model	366 ± 76	342 ± 56	0.03
Longitudinal 12-segment model	368 ± 72	338 ± 50	0.008
Longitudinal 18-segment model	364 ± 71	337 ± 49	0.03
Radial	344 ± 82	339 ± 56	NS
Circumferential	337 ± 78	322 ± 53	NS
Intraventricular time differences			
Longitudinal model (msec)			
S-L delay	65 (21-117)	19 (12-47)	<0.001
Longitudinal SDt-6	45 (37-79)	30 (24-37)	<0.001
Longitudinal SDt-12	46 (36-82)	31 (26-37)	<0.001
Longitudinal SDt-18	52 (34-83)	30 (24-36)	<0.001
Radial (msec)			
AS-P delay	34 (13-87)	24 (12-52)	0.033
SDt-6	34 (10-80)	16 (9-25)	<0.001
Circumferential (msec)			
AS-P delay	130 (72-234)	30 (12-65)	<0.001
SDt-6	106 (64-130)	27 (16-37)	<0.001

All parameters are expressed as mean ±SD or as median (IQR); AS-P indicates anteroseptal-posterior; SDt, standard deviation of time to peak strain; S-L, septal-lateral.

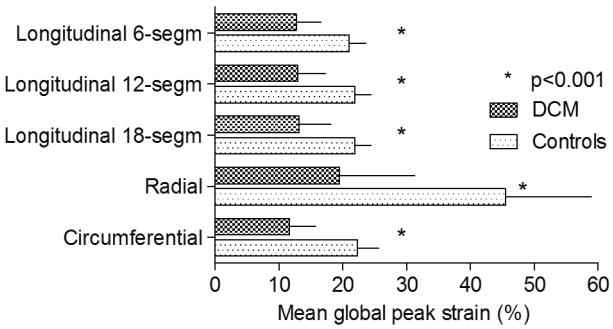

Figure 2: Showing mean global peak strain (%) +SD of the longitudinal 6-segment, 12-segment, 18-segment, radial and circumferential model in patients with dilated cardiomyopathy (DCM) and controls. * indicates p<0.001.

Table 3: Univariable analysis comparing children with an endpoint (n=10) with those without (n=65)

Univariable analysis	Hazard ratio	95% CI	p-value
Fractional shortening (%)	0.95	0.85-1.05	0.28
LVEF (%)	0.96	0.90-1.00	0.19
LVEDD z-score	1.12	0.94-1.34	0.22
Mean global peak strain 6-segment model (%)	0.81	0.66-0.99	0.04
Mean global peak strain 12-segment model (%)	0.89	0.75-1.05	0.17
Mean global peak strain 18-segment model (%)	0.93	0.76-1.14	0.50
Mean global circumferential peak strain (%)	0.83	0.68-1.01	0.07
Mean global radial peak strain (%)	0.94	0.88-1.00	0.07

Abbreviations as in table 1.

Qualitative analysis of longitudinal 4-chamber, 3-chamber, 2-chamber views

The distribution of patterns differed significantly between adults and children (Table 4). Remarkably, we identified 18% of the segments as a normal pattern, whereas in adults the presence of normal patterns was not described. In children, holosystolic stretching was rare and we found almost no pseudodyssynchrony. The presence of delayed systolic shortening did not differ between children and adults.

Table 4: Pattern distribution of the 4-chamber and 2-chamber view of the present study and of Carasso et al.

	Present study		Carasso et al. [9]		p-value
Total number of segments analyzed	800	(100)	902	(100)	
Normal	142	(18)	0	(0)	<0.001
Mildly to moderately reduced	344	(43)	282	(31)	<0.001
Severely reduced shortening	82	(10)	129	(14)	0.01
Severe holosystolic stretching	25	(3)	86	(10)	<0.001
Delayed systolic shortening	202	(25)	263	(29)	0.07
Pseudodyssynchrony	5	(1)	142	(16)	<0.001

Values are reported as number and percentage [n, (%)]

In patients with an endpoint we found more severely reduced patterns compared to those without an endpoint (19 vs 9%, p=0.001, Table 5). The presence of all other patterns was comparable.

Classical pattern dyssynchrony (CPD) was found in 5 patients (7%), 1 patient had CPD in the 4-chamber, 3 patients in the 3-chamber, and 1 patient in the 2-chamber view. In 2 of those, CPD manifested not as described by Risum et al, i.e. having early terminated septal or anteroseptal shortening and early stretch of the opposing wall, but those had early terminated shortening of a lateral wall segment and early stretch and late shortening in an opposing septal segment.

There was no relationship between the presence of CPD and the risk of death or heart transplantation; none of the patients with CPD had a primary endpoint. We found no relationship between CPD and QRS duration >98th percentile (p=0.8).

Table 5: Pattern distribution between patients with an endpoint (n=65) and those without (n=10)

	No endpoint n = 65		**Endpoint n = 10**		**p-value**
Total number of segments analyzed	690	(100)	110	(100)	
Normal	129	(19)	13	(12)	0.08
Mildly to moderately reduced	295	(43)	49	(45)	0.73
Severely reduced shortening	61	(9)	21	(19)	0.001
Severe holosystolic stretching	21	(3)	4	(4)	0.74
Delayed systolic shortening	180	(26)	22	(20)	0.17
Pseudodyssynchrony	4	(1)	1	(2)	0.68

Values are reported as number and percentage [n, (%)]

Feasibility

We aimed to analyze four views (apical 4-chamber, 3-chamber, 2-chamber and short-axis) in every patient and combined these views in several models. We successfully analyzed the 6-segment model in 99% of the patients, the 12-segment model in 85%, the 18-segment model in 64%, and the circumferential and radial model in 92% of the patients. In the controls, the 6-segment, 12-segment and 18-segment model were successful in respectively, 100%, 83% and 72% of the subjects.

The ICC of the interobserver variability of global peak strain of the 6-segment, 12-segment, 18-segment and circumferential view were good (0.88, 0.91, 0.89 and 0.89, respectively) the ICC for global radial peak strain was moderate (0.63). The interobserver and intraobserver variability of intraventricular time difference parameters were high; the ICCs varied from 0 to 0.82, while most parameters had an ICC <0.50. Only the ICC of the radial intraventricular time differences showed higher values, however, the CV was still 68-130% (Supplemental table 1).

DISCUSSION

This study demonstrated that global peak strain was reduced in children with DCM and that it was related to the risk of death and heart transplantation. Reproducibility of quantitative dyssynchrony parameters was very poor. Furthermore, qualitative dyssynchrony analysis showed predominantly reduced strain; dyssynchrony patterns in children were less common, in contrast to previously described findings in adults.

Global peak strain and the risk of an endpoint

We found that reduced LV global peak longitudinal strain was associated with a higher risk of death and heart transplantation. This is in accordance with studies in adults with chronic and acute heart failure, in which longitudinal and circumferential strain have been validated as independent predictors for death and heart transplantation.[5, 6]

In contrast to global strain, LVEF, FS and LVEDD were not related to death and heart transplantation in the present study. In other pediatric DCM cohorts, these parameters have been associated with the risk of an endpoint.[17-20] This difference may be explained by use of other endpoints and patient characteristics. McMahon et al. found that LVEF was predictive for the combined endpoint of death, heart transplantation and hospitalization, while we did not take hospitalization into account.[19] The studies that reported that LVEDD and FS were predictive for the same endpoint as we used, death and heart transplantation, measured these parameters at diagnosis, or when patients were hospitalized for symptomatic heart failure.[17, 18, 20] While in the present study, the majority of patients were at home with chronic heart failure, as reflected by a median time between echocardiography and DCM diagnosis of 1 year, and a mean symptom score of 8, on a range of 30.[21] This suggests that global longitudinal strain may be more sensitive than commonly used markers as LVEF and FS and may be useful as follow-up marker in children with stable heart failure.

Quantitative and qualitative measures of dyssynchrony

Dyssynchrony has been described in children with DCM in several small studies, mainly using Doppler Tissue imaging.[22-25] Only one small study used STE and analyzed quantitative dyssynchrony measures. They reported mechanical dyssynchrony in 76% of the children. In that study, they defined mechanical dyssynchrony according to the 96th percentile of the quantitative dyssynchrony results found in their control population. However, not all measures of dyssynchrony they used proved to be reproducible, i.e. moderate to poor reproducibility for SDt-12 and SL-delay, and good reproducibility for radial SDt-6 and AS-P delay.[12] Nonetheless, in the present study, we measured time to peak and intraventricular time differences in a large group of children and found poor reproducibility for all quantitative dyssynchrony parameters. Although, dyssynchrony may be present in children with DCM, the poor reproducibility of quantitative measures precludes its use for definition, risk stratification and patient follow-up.

In addition to quantitative dyssynchrony measures, we analyzed qualitative strain patterns according to earlier described methods.[9, 10] In adults, these methods have been very sensitive to distinguish between CRT responders and non-responders. In patients with QRS duration >130 msec the combination of (1) the absence of holosystolic stretching and (2) the presence of pseudodyssynchrony or delayed systolic shortening, was 100% sensitive and 94% specific for the response to CRT.[9] We showed that the distribution of these patterns

differed significantly between children and adults. In our group, holosystolic stretching and pseudodyssynchrony were both rare; only delayed systolic shortening was present in the same amount as in adults, suggesting that dyssynchrony in children is far less prevalent than in adults.

We analyzed the distribution of the patterns in relation to death and heart transplantation and found that only the presence of severely reduced strain patterns was associated with an endpoint. This is in agreement with our finding that reduced strain can be used as a predictor for death or heart transplantation. Furthermore, the presence of dyssynchronous patterns was not associated with an endpoint, suggesting that dyssynchrony may not play a critical role in children who are at risk of an endpoint.

In adults with left bundle branch block (LBBB), Risum et al. made a distinction between patients with a classical and heterogeneous dyssynchrony pattern and found classical pattern dyssynchrony (CPD) in 65% of the LBBB patients, and in almost all CRT responders.[10] Until now, one study has described CPD in 12% of the children with DCM. Additionally, these investigators described a case-report of an infant with critical heart failure, LBBB and CPD, who underwent successful CRT and showed full recovery after 2 years.[13] In the present study, the prevalence of CPD (7%) was much lower than in adults, but was comparable to the one reported in the pediatric study. Although, CRT might be effective in pediatric patients with strict criteria of LBBB and CPD, the prevalence of both conditions is very low in children with DCM.[12, 13, 22-24] Furthermore, it has been shown that the use of CRT in adults with QRS complexes <130 msec has no favorable effect on outcome and may even be harmful.[26] Therefore, we suspect that the role of CRT in children with DCM will be limited.

Reproducibility of global peak strain and intraventricular time differences

Present results illustrate that STE is feasible in children with DCM. Regarding reproducibility, ICC of global peak strain of the 6-segment, 12-segment, 18-segment and circumferential model were good. The reduced ICC of global peak radial strain is in accordance with earlier reports of healthy children[14] and DCM patients[11] and suggests limited value of global peak radial strain in the follow-up of children with DCM. Furthermore, the poor ICC of intraventricular time differences in the present study is in accordance with described poor reproducibility in healthy children.[14] This will hamper its use in clinical practice.

Feasibility

We performed echocardiography in seven different academic centers by different sonographers. To reduce variability we used a standardized protocol and performed the post-processing strain imaging analysis in one core laboratory. Despite the fact that different sonographers performed the echocardiographic studies, strain analysis of the longitudinal and short axis views could be performed in the majority of patients. These results imply

that in normal clinical practice, when different echocardiographic laboratories perform the studies, STE is feasible and reproducible in children with DCM.

Limitations

We were unable to analyze the 18-segment model in 36% of the patients. This is, however, comparable to healthy controls.[14] The absolute values, and also the interobserver and intraobserver variability results of the 6-segment, 12-segment, and 18-segment models were almost identical with the same distributions. Although the 18-segment model may be more precise than the 6-segment model, the 6-segment model could be performed in nearly all patients. Therefore we advocate using a 6-segment longitudinal strain model if not all echocardiographic views can be performed.

In this study, only univariable analysis could be performed. The value of global longitudinal strain of the 6-segment model in relation to other predictors for outcome in children with DCM should be further studied.

CONCLUSIONS

In children with DCM, global peak longitudinal strain of the LV was reduced and predicted the risk of death and heart transplantation. STE was feasible and interobserver and intraobserver variability were small, indicating that these parameters can be used in daily clinical practice. In contrast, quantitative dyssynchrony measures showed poor reproducibility making them useless as follow-up tool. Strain pattern analysis showed mainly reduced strain in children with adverse outcome, while dyssynchrony seemed not a major problem in these children.

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Supplemental table 1: Interobserver and intraobserver variability in a random sample of 20 DCM patients

	Interobserver			
Variable	ICC	Bias	Bland-Altman analysis 95% limits of agreement	CV
Global peak strain				
Longitudinal 6-segment model	0.88	-0.56	-4.6 to 3.5	15.8
Longitudinal 12-segment model	0.91	-0.75	-4.3 to 2.8	13.3
Longitudinal 18-segment model	0.89	-0.74	-4.5 to 3.1	14.4
Radial	0.63	0.65	-19.4 to 20.7	48.9
Circumferential	0.89	-0.76	-4.2 to 2.7	15.9
Time to global peak strain				
Longitudinal 6-segment model	0.72	11.6	-97.0 to 121.6	13.9
Longitudinal 12-segment model	0.76	15.9	-76.1 to 106.0	11.8
Longitudinal 18-segment model	0.63	17.9	-88.0 to 123.8	14.8
Radial	0.55	30.2	-141.4 to 201.9	24.1
Circumferential	0.64	14.9	-126.9 to 156.7	20.9
Intraventricular time differences				
Longitudinal model				
S-L delay	0.06	-34.9	-305.1 to 235.2	148.2
SDt-6	0.23	-5.0	-85.0 to 75.0	65.4
SDt-12	0.27	-5.4	-66.2 to 55.3	55.7
SDt-18	0.50	-11.7	-57.3 to 33.9	38.0
Radial				
AS-P delay	0.37	28.3	-172.3 to 228.8	130.2
SDt-6	0.64	2.6	-81.5 to 86.8	78.6
Circumferential				
AS-P delay	0.14	-9.9	-315.4 to 295.5	100.0
SDt-6	0.36	-6.2	-125.7 to 113.4	55.0

Bias represents mean difference between 2 measurements; 95% limits of agreement is calculated as ±1.96 SD of the mean difference; CV indicates coefficient of variation, calculated as [standard deviation of two measurements / mean of the two measurements] × 100%. ICC indicates intraclass correlation coefficient; SDt, standard deviation of time to peak strain; S-L, septal-lateral; AS-P, anteroseptal-posterior; of time to peak strain.

	Intraobserver			
Variable	ICC	Bias	Bland-Altman analysis 95% limits of agreement	CV
Global peak strain				
Longitudinal 6-segment model	0.89	-0.92	-4.0 to 2.2	14.0
Longitudinal 12-segment model	0.96	-0.47	-2.6 to 1.7	9.3
Longitudinal 18-segment model	0.97	-0.10	-2.0 to 1.8	8.3
Radial	0.70	-0.31	-19.5 to 18.9	54.6
Circumferential	0.94	-0.11	-2.7 to 2.5	12.2
Time to global peak strain				
Longitudinal 6-segment model	0.68	-29.0	-154.1 to 96.1	15.8
Longitudinal 12-segment model	0.79	-16.5	-111.5 to 78.6	12.0
Longitudinal 18-segment model	0.88	-16.0	-83.0 to 50.9	8.8
Radial	0.80	9.8	-108.5 to 128.1	16.1
Circumferential	0.86	-3.5	-89.6 to 82.7	12.8
Intraventricular time differences				
Longitudinal model				
S-L delay	-0.24	9.6	-354.1 to 373.3	177.5
SDt-6	0.46	21.1	-69.7 to 111.9	57.1
SDt-12	0.49	18.7	-53.2 to 90.7	50.6
SDt-18	0.53	5.0	-66.1 to 76.1	45.5
Radial				
AS-P delay	0.82	28.2	-127.2 to 183.6	78.1
SDt-6	0.73	18.8	-79.7 to 117.4	68.1
Circumferential				
AS-P delay	0.30	6.9	-248.6 to 262.5	81.1
SDt-6	0.63	1.4	-95.2 to 98.0	38.6

Abbreviations as in previous table.

RESEARCH LETTER

In adults with dilated cardiomyopathy (DCM) it has been demonstrated that global longitudinal, and circumferential strain have value in addition to left ventricular ejection fraction (LVEF) in predicting the risk of mortality, heart transplantation and hospitalization for worsening heart failure.[1] Measures that predict disease progression and outcome in children with DCM are needed. Therefore, we aimed to evaluate the predicting value of LV global peak strain in the outcome of children with DCM.

We prospectively included 75 children (< 18 year) with DCM (LV end-diastolic dimension [LVEDD] z-score ≥ 2 for body surface area and fractional shortening [FS] ≤ 25% on echocardiography) from 7 academic pediatric cardiology centers. Available data of 75 healthy age-matched controls were used.[2] A complete 2-dimensional echocardiographic study was performed in a standardized way; measurements (LV dimension, function and speckle-tracking echocardiography) were performed in a core echocardiography laboratory as previously described.[2] The mean age of all subjects was 7.5 ± 6.3 years. Patients were included at a median time of 1 year (IQR 0.1 - 4.0) after DCM diagnosis, the mean LVEF was 33 ± 11% and mean LVEDD z-score 5.1 ± 3.0. Mean LV global peak strain in all views was significantly reduced compared with that in control subjects (Figure 1). No specified regions could be identified as more affected than others because all segments were worse in patients than in control subjects ($p < 0.001$). The 6-segment model (longitudinal 4-chamber view) was feasible in 99% of the patients and the short-axis view in 92% of the patients. The 12-segment model (including the 4- and 2-chamber views) was feasible in 85% and the 18-segment model (including the 4-, 2- and 3-chamber views) in 64%. The mean global peak strain of the 6-, 12- and 18-segment models were comparable (13 ± 4%, 13 ± 4% and 13 ± 5%, respectively). Interobserver and intraobserver variability of longitudinal and circumferential strain were good (intraclass correlation coefficients 0.88 - 0.91) and of radial strain was moderate (0.63).

Median follow-up from echocardiography until an endpoint or censoring was 21 months (IQR 16 - 31), 10 patients (13%) reached a primary endpoint: 8 underwent heart transplantation and 2 died. Using univariable Cox regression analysis, we found that lower mean global longitudinal peak strain of the 4-chamber was significantly associated with higher risk of an endpoint; each percentage decrease in strain gave a 1.23 times higher risk of death or heart transplantation (hazard ratio [HR] 0.81 per percentage of increase in strain, $p = 0.04$). LVEF (HR 0.96, $p = 0.19$), FS (HR 0.95, $p = 0.28$), LVEDD z-score (HR 1.12, $p = 0.22$) and circumferential peak strain (HR 0.83, $p = 0.07$) were not significantly associated with outcome, nor were the 12-segment (HR 0.89, $p = 0.17$) and the 18-segment model (HR 0.93, $p = 0.50$) significantly predictive for outcome.

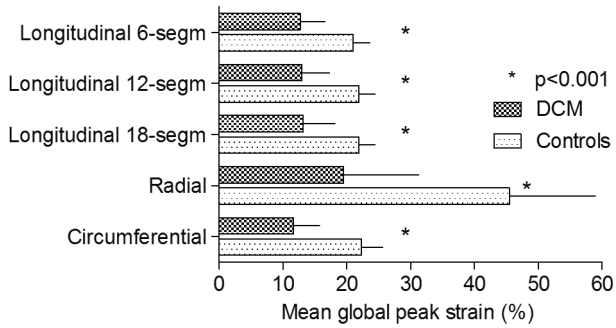

Figure 1: Strain was reduced in patients compared to controls. Mean global peak strain (%) in 75 children with dilated cardiomyopathy (DCM) and 75 healthy age-matched control subjects. The 6-segment model indicates a left ventricular 4-chamber view; the 12-segment model includes 4- and 2-chamber views; the 18-segment model includes 4-, 3- and 2-chamber views. Error bars indicate standard deviation.

This is the first study to report that, in pediatric DCM, LV global longitudinal strain was predictive of death and heart transplantation. In addition, circumferential strain tended to be significant and had good reproducibility, suggesting that it may be of interest for future studies. According to its feasibility and comparable strain results, in addition to its prognostic value, we advise to use the 6-segment model for longitudinal strain.

Our findings are in accordance to results from adults.[1] Until now, pediatric studies have mainly focused on measures at diagnosis, wherein FS and LVEDD at diagnosis were predictive for death and heart transplantation.[3] In the present study, patients had a median time of 1 year after diagnosis. Therefore, our results indicate that in the follow-up of pediatric DCM, LV global longitudinal peak strain may be used to predict outcome.

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Chapter 7

Six-minute walk test as predictor for outcome in children with dilated cardiomyopathy

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Submitted

ABSTRACT

Background

Cardiopulmonary exercise testing is an important tool to predict prognosis in children and adults with heart failure. A much less sophisticated exercise test is the six-minute walk test, which has been shown an independent predictor for morbidity and mortality in adults with heart failure. Therefore, we hypothesized that the six-minute walk test could be predictive for outcome in children with dilated cardiomyopathy.

Methods and Results

We prospectively included 49 children with dilated cardiomyopathy ≥6 years who performed a six-minute walk test. Median age was 11.9 years (interquartile range [IQR] 7.4-15.1), median time after diagnosis was 3.6 years (IQR 0.6-7.4). The 6-minute walk distance was transformed to a percentage of predicted, using age and gender specific norm values (6MWD%). For all patients, mean 6MWD% was 70 ±21%. Median follow-up was 33 months (IQR 14-50). Ten patients reached the combined endpoint of death and heart transplantation. Using univariable Cox regression, a higher 6MWD% resulted in a lower risk of death and transplantation (hazard ratio 0.95 per percentage increase, p=0.006). Patients with a 6MWD% <63% had a 2-year transplant-free survival of 73%, in contrast to 92% in patients with a 6MWD% ≥63% (p=0.003).

Conclusions

In children with dilated cardiomyopathy, the six-minute walk test is a simple and feasible tool to identify children with a higher risk of death and heart transplantation.

INTRODUCTION

Cardiopulmonary exercise testing (CPET) is an important tool which is used to predict prognosis in adults with heart failure.[1-3] Currently, heart transplantation is recommended in patients with a peak oxygen uptake (VO_2) <12-14 ml/kg/min, depending on whether patients tolerate beta-blockers or not. In women and in younger patients (<50 years), it has been suggested that those with a peak VO_2 <50% of predicted need to be considered for transplantation.[4] Similarly, for children a peak VO_2 <50% of predicted for age and sex has been accepted as a Class I indication for heart transplantation (level of evidence C).[5] More recently, Giardini et al. studied ambulatory children with dilated cardiomyopathy (DCM) and demonstrated that a peak VO_2 ≤62% of predicted was associated with a 10 times higher risk of death and urgent transplantation than a peak VO_2 >62%.[6] Although these results are of great importance for heart failure management in children, the use of CPET has major limitations. It is time-consuming, demanding for patients with severe heart failure and only applicable in children of at least 8-9 years old. Moreover, it requires sophisticated equipment and specially trained staff. A much less sophisticated exercise test is the six-minute walk test (6MWT). In adults with heart failure, this exercise test has been shown an independent predictor for morbidity and mortality.[7, 8] Furthermore, in children with pulmonary hypertension, the 6MWT has been used to indicate disease severity as predictor for death and transplantation and to measure treatment effects.[9, 10] Notably, an advantage of the 6MWT is that it can be performed starting from a younger age than CPET (6 years). In the present study we test the hypothesis that the 6MWT is predictive for the endpoint of death and heart transplantation in children with DCM.

METHODS

This prospective study was approved by the institutional review boards of all seven participating centers. All parents and patients ≥12 years gave their written informed consent.

Patients (≥6 years) diagnosed with DCM or followed up from 1st November 2010 until 1st July 2015 were asked to participate in this study. DCM was defined as the presence of impaired systolic function (fractional shortening [FS] ≤25%) and left ventricular (LV) dilation (LV end-diastolic dimension [LVEDD]> +2 z-score for body surface area). DCM could be idiopathic or secondary to other causes. Patients with structural heart defects or neuromuscular disease were excluded.

Six-minute walk test

At enrollment, all patients performed a six-minute walk test (6MWT) on an 8-meter track in a straight corridor. Patients were instructed to walk back and forth on a self-chosen walking speed; running was not allowed. The objective of the test was to walk as far as possible within 6 minutes. If needed, patients were allowed to slow down the pace or to stop, but were encouraged to resume walking as soon as they were able to. All patients got the same instructions and encouragement at regular intervals, according to the guideline of the American Thoracic Society.[11] During the test, the number of laps was counted. The lap that was partially completed at the end of the test was measured and added to the total distance. The distance walked during 6 minutes (6MWD) was compared with gender-specific norm values as reported by Geiger et al. using height and age in their regression equations.[12] A percentage of predicted (6MWD%) was calculated by dividing the patients' 6MWD by the patients' predicted 6MWD, and multiplying this by 100%. Transcutaneous oxygen saturation and heart rate were recorded before and immediately after the test. Using a maximum heart rate of 200 beats per minute (bpm) for all ages,[13] the heart rate immediately after the test was transformed to a percentage of the maximum.

At the same visit, patients' demographics were recorded. Height and weight were measured. A complete and standardized echocardiogram was performed and analyzed off-line by one investigator (SdB). M-mode of the parasternal long-axis was used to measure LVEDD and LV end-systolic dimension and subsequently, FS was calculated. LV ejection fraction was calculated using Simpson's biplane method. The treating physicians were blinded to the 6MWT results. The study endpoint was death or heart transplantation. Follow-up continued until September 15th, 2015.

Statistical analysis

Continuous variables are displayed as mean ± standard deviation (SD) if normally distributed, and as median with interquartile range (IQR) if non-normally distributed. Means across groups were compared using independent sample t-test. Transplant-free survival was estimated with the Kaplan-Meier method, and 95% confidence intervals (CI) were calculated using Greenwood's formula. The log rank test was used to determine statistical significance between two transplant-free survival curves. A receiver operating characteristic curve was generated using 6MWD% to define the optimal threshold to identify patients at highest risk for an endpoint. Univariable Cox regression analysis was used to test the predictive value of 6MWD% as a continuous and as a binominal variable based on the threshold. Other potential risk factors were also tested with univariable Cox regression. The number of variables allowed for multivariable analysis was set at the number of events divided by ten. All analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IMB Corp, Armonk, NY). Testing was performed two-sided and statistical significance was defined as $p<0.05$.

RESULTS

During the 4.5 years of the study, 64 patients were eligible, 56 (88%) gave written informed consent. Seven patients were too ill and reached the endpoint before they performed a 6MWT. In total, 49 patients performed a 6MWT, at a median age of 11.9 years. The median time since diagnosis was 3.6 years; 9 (18%) were included within 3 months of diagnosis, 35 (71%) more than 1 year after diagnosis. Patients were on optimal pharmacological therapy, 94% used angiotensin converting enzyme-inhibitors and 78% used beta-blockers (Table 1).

Table 1: Characteristics of children with dilated cardiomyopathy and 6-minute walk-test result

	n = 49
Gender, male, n (%)	26 (53)
Age, years	11.9 (7.4-15.1)
Time since DCM diagnosis, years	3.6 (0.6-7.4)
Cause of DCM, n (%)	
Idiopathic	24 (49)
Myocarditis	7 (14)
Other	18 (37)
Medication used, n (%)	
Beta-blocker	38 (78)
ACE-inhibitor	46 (94)
Spironolactone	27 (55)
Loop diuretics	28 (57)
Digoxin	8 (16)
LVEDD z-score	5.0 ± 3.2
Fractional shortening, %	18 ± 6
LV ejection fraction, %	33 ± 12
Endpoint, n (%)	10 (20)
Death	0
Heart transplantation	10 (100)
Follow-up since 6MWT, months	33 (14-50)
6MWD, meters	448 ± 144
6MWD%, %	70 ± 21

Continuous variables are represented as mean ±SD if normally distributed and as median (IQR) if non-normally distributed. 6MWD indicates 6-minute walk distance; 6MWD%, 6-minute walk distance as % of predicted; DCM, dilated cardiomyopathy; ACE, angiotensin converting enzyme; LVEDD, left ventricular end-diastolic dimension.

6-minute walk test results

Mean 6-minute walk distance as percentage of predicted (6MWD%) was 70 ±21%. Two patients (4%) stopped walking during the test. The distance that they covered was accepted as final result of the 6MWT. One patient, 6.8 years old, complained about chest pain and stopped walking at 3 minutes. The second patient, 6.0 years old, stopped several times,

because she felt too tired. She had severe heart failure and underwent a heart transplantation 4 months after the test. No other complications were registered during the tests. The heart rate before and immediately after the test are displayed in Table 2. Pre 6MWT, the mean heart rate in patients not taking beta-blockers was significantly higher (98 ±12 bpm) than in patients with beta-blocker therapy (85 ±15 bpm, p = 0.02). No differences in age were found between patients with and without beta-blocker therapy. Post 6MWT, the mean HR was 124 ±18 bpm, which was 62% of the maximum. Patients not taking beta-blockers had a mean heart rate of 66 ±8% of the maximum, while this was 61 ±9% in those using beta-blockers (p = 0.08).

Table 2: Heart rate and oxygen saturation pre and post six-minute walk test in 49 children with dilated cardiomyopathy

Age-range	n *	SaO_2		n *	Heart rate (bpm)		% of max
(years)		Pre 6MWT	Post 6MWT		Pre 6MWT	Post 6MWT	Post 6MWT
6 – 8	9	99 (98 , 100)	98 (95 , 98)	11	94 ±13	132 ±16	66 ± 8
8 – 12	10	99 (98 , 100)	98 (97 , 98)	11	88 ±13	125 ±20	63 ±10
12 – 15	12	98 (98 , 99)	97 (97 , 98)	12	85 ±15	121 ±16	61 ± 8
15 – 18	10	98 (97 , 99)	97 (96 , 98)	10	85 ±19	117 ±18	58 ± 9

* 8 cases were missing for SaO_2, 5 for heart rate;
6MWT indicates six-minute walk-test; bpm, beats per minute; SaO_2, percutaneous oxygen saturation

Outcome

During the study, 10 patients reached the endpoint of heart transplantation, none of the patients died. The median follow-up time was 33 months. This resulted in a 1-year transplant-free survival of 89% (95% CI 80-98) and 2-year transplant-free survival of 84% (95% CI 74-95). The median time from diagnosis to transplantation was 3.9 years (IQR 2.4-8.2). The 7 patients who were too ill to perform a 6 MWT before they reached an endpoint had a median time from diagnosis to the endpoint of 1.6 months (IQR 0.8-2.8). Of them, 3 died and 4 were transplanted (2 of whom were on mechanical circulatory support).

Risk factors for outcome

The 6MWD% was a significant predictor for the risk of death or transplantation (hazard ratio 0.95 per % of predicted, 95% CI 0.91-0.99, p=0.006). Thus, every % decrease in the 6MWD%, gave a 5% increase in the risk of death or transplantation. A 6MWD% <63% identified patients at highest risk for an endpoint (sensitivity 80% and specificity 69%, area under the curve 0.76, 95% CI 0.57-0.95, p=0.01). One-year transplant-free survival was 79% (95% CI 61-98) and 2-year transplant-free survival was 73% (95% CI 53-93), in contrast to patients with a 6MWD% ≥63% in whom 1-year transplant-free survival was 96% (95% CI 89-100) and 2-year transplant-free survival was 92% (95% CI 82-100, p=0.003, Figure 1). Univariable

analysis of other potential risk factors showed that higher LVEDD z-score and lower LV SF and EF were significantly predictive for the risk of death or transplantation (Table 3). The number of events did not allow multivariable analysis.

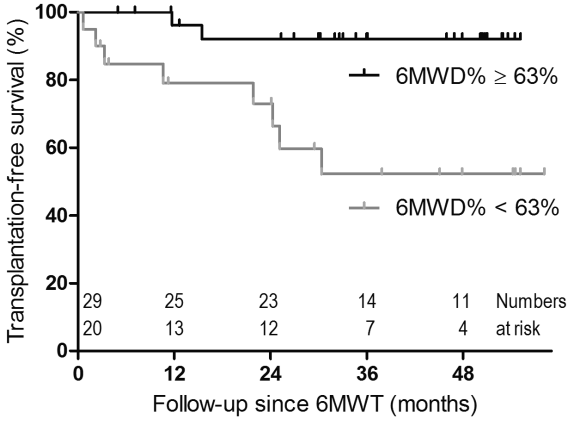

Figure 1: Transplant-free survival curves of DCM patients with a 6-minute walking distance ≥ 63% of predicted and of those < 63% of predicted.
6MWT indicates 6-minute walk test; 6MWD%, 6-minute walk distance as percentage of predicted.

Table 3: Univariable analysis of potential risk factors for death or heart transplantation in 49 children with dilated cardiomyopathy

Potential risk factors for outcome	Primary Endpoint (n=10)	No primary endpoint (n=39)	Hazard ratio (95% CI)	p-value
6MWD%, %	55 ±23	74 ±19	0.95 (0.91-0.99)	0.006
6MWD% <63%, n (%)	8 (80)	12 (31)	7.51 (1.59-35.5)	0.011
Age at DCM diagnosis ≥6 years, n (%)	6 (60)	18 (46)	2.02 (0.57-7.24)	0.27
LVEDD z-score	7.0 ±4.2	4.5 ±2.7	1.25 (1.02-1.53)	0.032
Fractional shortening, %	14 ±5	19 ±6	0.86 (0.75-0.97)	0.016
LV ejection fraction, %	21 ±8	36 ±11	0.88 (0.81-0.96)	0.003

6MWD% indicates 6-minute walk distance as % of predicted; DCM, dilated cardiomyopathy; LVEDD, left ventricular end-diastolic dimension

DISCUSSION

In this prospective study we demonstrate that the 6-minute walking distance expressed as a percentage of predicted was associated with prognosis in children with DCM. A higher total distance walked in 6 minutes resulted in a lower risk of death and heart transplantation. This is important because markers that identify children with a good or bad prognosis during follow-up are essential to guide clinical management in this patient group.

The study group had a mean age of 11.9 years and a median time since DCM diagnosis of 3.6 years, representing children with chronic heart failure. Although DCM has high incidence rates at young age,[14] the age-restriction for the test resulted in a relatively older group. An earlier study investigating the predictive value of CPET included patients with a mean age of 13.5 years, reflecting the somewhat older age at which CPET can be performed.[6] All study patients who reached an endpoint, underwent transplantation after a median time of almost 4 years from diagnosis. This is in contrast to 7 patients who were not able to perform a 6MWT and died or were transplanted within 2 months of diagnosis. Apparently, the 6MWT is not feasible in this severely ill subgroup reaching an endpoint shortly after diagnosis. Earlier studies in children followed from DCM diagnosis have revealed predictors at diagnosis to identify these patients, such as older age, low fractional shortening, intensive care unit admission with prolonged inotropic support or mechanical circulatory support.[14, 15] On the other hand, the present prospective study showed that 88% (49/56) of an unselected DCM cohort was able to perform a 6MWT during follow-up. The test was only done for research purposes and the treating physicians were blinded to the results. Consequently, the 6MWT results have not influenced transplantation decisions. Therefore, the 6MWT can be used as predictor for deterioration of the disease during follow-up in children with DCM.

After 4.5 years of patient inclusion and almost 3 years of follow-up the number of endpoints was limited and multivariable analysis was not allowed. The predictive value of other variables on outcome were assessed to characterize our patient population and we showed that besides the 6MWD%, LVEDD z-score, LVEF and LVFS were predictive. Considering the univariable results after correcting for multiple testing, a p-value of <0.0083 would be significant. At this level the 6MWD% and LVEF would remain significant. LVEF has been shown to be predictive in earlier pediatric reports and has also been valuable in predicting prognosis in adults.[16, 17] The 6MWD% is a new finding in children and is likely a valuable tool in predicting outcome in this patient group. Further investigation in a larger population needs to establish whether the 6MWT holds as an independent marker in multivariable analysis.

Exercise testing is one of the cornerstones in predicting prognosis in ambulatory heart failure patients.[1-4] Specifically, peak VO_2 measured with CPET has a prominent role in heart transplantation guidelines.[4, 5] A peak VO_2 <12-14 mL/kg/min in adults and <50% of predicted in children has been accepted as a Class I indication for heart transplantation. In addition, the 6MWT has been shown to be a predictor for mortality and hospitalization for adults with chronic heart failure.[7, 8, 18, 19] Although it seems that CPET results are superior to 6MWT results in order to predict prognosis,[18, 20] the 6MWT has major advantages, such as its simplicity and its inexpensiveness. Therefore, it is particularly relevant as follow-up and screening tool.

As CPET measures maximal exercise capacity, the 6MWT measures submaximal exercise capacity. This is also reflected by the maximal heart rates reached with the 6MWT. Post

6MWT, we found a mean heart rate of 62% of the maximum, while this was around 70% in the norm population.[12] In patients with heart failure chronotropic incompetence has been described as a result of beta-receptor down-regulation and desensitization of the beta-receptors.[21] Moreover, beta-blocker therapy may affect the ability to reach the maximal heart rate as predicted for age. A prevalence of 37% of chronotropic incompetence has been described in a cohort of children with chronic DCM.[6] Thus, maximal heart rates may well have been lower in patients in our study. By assuming a maximal heart rate of 200 bpm, the submaximal heart rate as percentage of the maximum may have been underestimated.

We studied almost all eligible children (88%) in the Netherlands during a 4 year-period, but the sample size was small. Nevertheless, we were able to show that the 6MWT is feasible and easy to perform in children with DCM and is a valuable predictor for outcome. Therefore, 6-minute walk testing should be implemented in this patient group to estimate the patients' risk and to analyze these results in future studies using multivariate analysis. Furthermore, we used an 8 meter track to obtain the results, rather than a 30 meter track as is recommended in the American Thoracic Society guidelines.[11] Because 6MWTs were performed at seven different centers and not all had a quiet 30 meter corridor available, we decided to use an 8 meter track in all centers to minimize test variation. We recognize that the use of a shorter track has led to more turning points and may have led to a small reduction of the total distance walked. However, because patients walked slower than healthy children, this would have had less impact. To interpret our recommended cut-off to a population walked on a 30 meter track, the cut-off may become slightly higher. Finally, the cut-off is based on our dataset and may differ in another population. Therefore it needs to be validated externally.

CONCLUSIONS

In the present study we demonstrate that the six-minute walk test is feasible and has predictive value in children with DCM ≥ 6 years. A lower distance walked, expressed as percentage of predicted, was associated with a higher risk of death and heart transplantation. A cut-off of 6MWD% <63% identified patients at highest risk of an endpoint.

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Chapter 8

Parent reports of health-related quality of life and heart failure severity score independently predict outcome in children with dilated cardiomyopathy

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ABSTRACT

Introduction

Dilated cardiomyopathy (DCM) in children causes heart failure and has a poor prognosis. Health-related quality of life (HRQoL) in this patient group is unknown. We hypothesized that HRQoL questionnaires, which provide detailed information of parents' sense of their child's functioning, have predictive value on outcome. Furthermore, we hypothesize that the pediatric heart failure score, as assessed by the physician, has also predictive value on outcome.

Methods

In this prospective study HRQoL was assessed by parent-reports: the Infant Toddler Quality of Life questionnaire (0-4 years) or Child Health Questionnaire-Parent Form 50 (4-18 years) at 3-6 months intervals. Results at DCM diagnosis and ≥ 1 year after diagnosis were compared with Dutch normative data. For risk factor analysis, results were transformed to percent of predicted using Dutch norms. Physicians completed the New York University Pediatric Heart Failure Index (NYU PHFI). Univariable and multivariable time dependent Cox regression were used to identify risk factors for the combined endpoint of death and heart transplantation.

Results

We included 90 children (median age 3.8 years, IQR 0.9-12.3) who completed 515 questionnaires. After median follow-up of 3 years (IQR 2-4), 15 patients underwent transplantation. HRQoL was severely impaired at diagnosis (0-4 years: 7/10 subscales and 4-18 years: 8/11 subscales) and ≥ 1 year after diagnosis (3/10 and 6/11). Older children were more impaired. "Physical functioning" subscale and NYU PHFI were independently predictive for the risk of death and heart transplantation (hazard ratio 1.24 per decrease of 10% of predicted, 95% CI 1.06-1.47 and hazard ratio 1.38 per unit, 95% CI 1.19-1.61, respectively).

Conclusion

Physical impairment rated by parents and heart failure severity assessed by physicians independently predicted the risk of death or heart transplantation in children with DCM.

INTRODUCTION

Dilated cardiomyopathy (DCM) in children causes heart failure and may have a poor prognosis. After diagnosis, one-year transplant-free survival rate has been reported between 69-82%, and five-year transplant-free survival rate between 54-72%.[1, 2] However, around 35% of the children develop chronic DCM and around 35% recover, with highest recovery rates in children aged 1-6 years at diagnosis.[1]

To assess the impact of disease on patients' life, functional status assignment by a physician and patient-reported health-related quality of life (HRQoL) have been used, and may contain important prognostic information. In adults, the New York Heart Association (NYHA) Classification is used to categorize heart failure functional class and has been strongly associated with outcome.[3, 4] Furthermore, in adults with heart failure, HRQoL is affected as compared to healthy age-matched controls, but also as compared to other chronically ill patients.[5-7] In addition, HRQoL has been shown to be an independent predictor for mortality.[8]

In children with heart failure secondary to DCM, such data are largely lacking. To assess functional class, the New York University Pediatric Heart Failure Index (NYU PHFI) has been developed.[9] However, this score has not been related to clinical outcome in DCM yet. In children, the effect of DCM on HRQoL is largely unknown. An explorative study investigating parent-reported HRQoL in children visiting the pediatric cardiology clinic for various diseases, reported on a small subgroup of 17 children with cardiomyopathy.[10] Using the Child Health Questionnaire Parent-Form 50 (CHQ PF50), cardiomyopathy patients scored worse compared to all other patients attending the cardiology clinic on "physical functioning", "general health perceptions" and "parental impact emotional".

The use of HRQoL questionnaires in children enables a structural assessment of patient's physical and psychosocial functioning reported by parents. Since parents "know their child best", we hypothesize that parents' assessment of their child's HRQoL, on internationally validated questionnaire, provides valuable information about a child's functioning, which may have prognostic value. Furthermore, we hypothesize that a physicians' assessment of heart failure severity, using a validated heart failure severity score, also provides prognostic information.

The present study had two aims. First, to evaluate HRQoL in children with DCM. Second, to assess the predictive value of HRQoL subscales and the heart failure severity score on the risk of death and heart transplantation at diagnosis and during follow-up.

METHODS

The institutional review boards of seven participating centers approved the study protocol. Parents and children ≥ 12 years gave written informed consent.

From 1 October 2010 until 1 March 2015 all eligible children were asked to participate in this prospective study. Children were either included at DCM diagnosis, or were followed-up for a previously diagnosed DCM in one of the participating tertiary pediatric cardiology centers. DCM was defined as fractional shortening (FS) ≤25% and left ventricular end-diastolic dimension (LVEDD) >2 z-score for body surface area. DCM could be idiopathic or secondary to other causes. Patients with congenital heart disease, neuromuscular disease or with parents who were unable to read the Dutch language were excluded.

Study entry was defined as the first time that a HRQoL questionnaire was completed. Patients were seen at 3-6 months intervals. At each visit, parents were asked to complete a HRQoL questionnaire and during the same visit the pediatric cardiologist completed the New York University Pediatric Heart Failure Index (NYU PHFI).[9] This index assesses heart failure severity based on symptoms and medication used. The score ranges from 0-30, a higher score represents more severe heart failure. Demographics were recorded and the socioeconomic status (SES) was determined using parents' occupation and categorized into: low (elementary occupations), middle (middle occupations) or high (high scientific occupations), conform the Dutch classification system.[11] The highest occupation of either parent was recorded. Follow-up ended either at 15 September 2015 or when a patient reached the age of 18 years, or reached the combined primary endpoint of death and heart transplantation.

HRQoL questionnaires

HRQoL was assessed by age-specific questionnaires: the Infant-Toddler Quality of Life (ITQoL) questionnaire for patients 0-4 years old and the Child Health Questionnaire Parent-Form 50 (CHQ PF50) for patients 4-18 years old. Both questionnaires consist of subscales (Table 2a and 2b). Subscale scores range from 0 to 100, a higher score represents better quality of life. Normative data from Dutch healthy children are available for both questionnaires.[12, 13]

HRQoL was evaluated on two different time points in the disease. First, in patients at DCM diagnosis, and second in patients who were 1 year or more after diagnosis. These time points were chosen, because event-rates in pediatric DCM differ markedly between the first year of diagnosis and from 1 year after diagnosis onwards,[14] and HRQoL may differ in parents and patients who need to cope with a recent diagnosis, compared to patients who have been diagnosed longer time ago.

To compare both age-groups (0-4 years and 4-18 years) and to predict outcome, individual subscale scores were transformed to a percentage of predicted using the mean of

the corresponding norm population. For example, if a patient had a score of 85 on the CHQ PF50 physical functioning subscale (mean norm: 99.1), then this was transformed to a score of (85/99.1) * 100% = 85.8% of predicted. A score of 85 on the ITQoL physical functioning subscale (mean norm: 97.2), resulted in a score of 87.4% of predicted ([85/97.2] * 100%). Using this transformation, only scores on comparable subscales from both questionnaires were combined, i.e. ,"physical functioning", "bodily pain", "general behavior", "general health perception", "parental impact – time", "parental impact – emotional" and "family cohesion".

Statistical analysis

The distribution of continuous variables was tested using the Kolmogorov-Smirnov test. Almost all HRQoL subscales were non-normally distributed and are therefore reported as median and interquartile range (IQR). The medians of patients were compared with the norm using the one-sample Wilcoxon Signed Rank Test. To compare age-groups, medians (as percentage of predicted) were compared using the Mann-Whitney U test. Using univariate time-dependent Cox regression analysis, we assessed the predictive value of the HRQoL subscales (as percentage of predicted) and the NYU PHFI on the endpoint. For this analysis, data of all visits were included (n= 515 in 90 different patients). The maximal number of covariates used in multivariate time-dependent Cox regression analysis was the number of events divided by ten. Proportional hazard assumptions were tested and were not violated. The hazard ratios (HRs) of the HRQoL subscales were calculated per 10% of predicted (10 units of the original scale). For readability, HRs of HRQoL subscales were transformed to values > 1.00, using the formula: 1/HR. For descriptive data analyses we used IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). For advanced statistical analyses of repeated measurements and survival data the R environment was used (R version 3.1.1, 2014-07-10). Testing was performed two-sided and statistical significance was defined as $p < 0.05$.

RESULTS

We included 90 children (median age 3.8 years, IQR 0.9-12.3, Table 1) of whom parents reported the child's HRQoL at several time points during follow-up, and at the same visit the physician scored heart failure severity on the NYU PHFI. In total, 515 HRQoL questionnaires were completed over 4.5 years, 226 ITQoL and 312 CHQ PF50 questionnaires, a median of 6 per patient (range 1-13). Accordingly, 498 NYU PHFI were completed, 3.3% were missing. To analyze HRQoL at two time points in the disease, we describe the results of two cross-sectional groups, 1. 46 questionnaires of children included at DCM diagnosis, and 2. 77 children of whom parents completed the first questionnaire at least 1 year after diagnosis; 34 children were represented in both groups.

Table 1: Cross-sectional characteristics of children with dilated cardiomyopathy at study entry (n=90), diagnosis (n=46) and ≥ 1 year after diagnosis (n=77).

	All patients, study entry n = 90	**At diagnosis n = 46**	**≥ 1 year after diagnosis * n = 77**
Gender, male, n (%)	48 (53)	24 (52)	39 (51)
Age, years	3.8 (0.9-12.3)	1.3 (0.4-7.0)	5.2 (1.8-12.7)
Time since DCM diagnosis, years	0.5 (0.1-3.4)	0.1 (0.1-0.3)	1.5 (1.1-3.7)
Socioeconomic Status, n (%) †			
Low	18 (22)	8 (19)	14 (19)
Middle	26 (32)	12 (29)	23 (32)
High	37 (46)	22 (52)	35 (49)
NYU PHFI	8 (6-11)	9 (6-11)	7 (4-9)
Follow-up time since first questionnaire, years	2.8 (1.5-3.8)	2.5 (1.6-3.6)	3.0 (2.1-4.0)
Number of questionnaires per patient	6 (4-7)		
Number of ITQoL; number of CHQ PF 50		33; 13	36; 41

* 34 children were also represented in the group 'at diagnosis'. † SES was missing in 9 cases; Continuous variables are represented median (IQR). CHQ PF 50 indicates Child Health Questionnaire-Parent Form 50; DCM, dilated cardiomyopathy; NYU PHFI, New York University Pediatric Heart Failure Index; ITQoL, Infant Toddler Quality of Life questionnaire

HRQoL results at diagnosis

Of the 90 children, 46 were newly diagnosed with DCM (median age 1.3 year, IQR 0.4-7.0). Their first questionnaire was completed at a median of 1.4 months after diagnosis (IQR 1.1-3.1). Thirty-three children were between 0-4 years old (Table 2A) and 13 children were between 4-18 years (Table 2B).

Comparison with the norm

At diagnosis, results of almost all subscales on both age-specific questionnaires were significantly lower than the norm population (ITQoL: 7/10, and CHQ PF50: 8/11). Parents

of children aged 0-4 years showed the largest difference to the norm on "general health perception". Notably, better "family cohesion" was reported in this age-group (Table 2A). Parents of children aged 4-18 years showed largest differences on "physical functioning", "role functioning – physical", "parental impact – emotional", and "parental impact – time" (Table 2B).

Table 2A: HRQoL by parent reports. Results of infants and toddlers, 0 - 4 years old, with DCM at diagnosis and ≥ 1 year after diagnosis.

ITQoL subscales	**At diagnosis n = 33**	**≥ 1 year after diagnosis n = 36**	**Norm n = 410**
Physical Functioning	**90** (77-100) †	98 (79-100)	97.2 ±9.8
Growth & development	**75** (66-85) ‡	**79** (73-91) *	86.5 ±10.6
Bodily pain	**67** (35-83) ‡	**75** (58-90) †	83.8 ±16.8
Temperament & moods	**69** (60-76) †	79 (67-86)	77.2 ±10.5
General behavior	81 (67-89)	**78** (70-91) *	72.8 ±12.7
Getting along	69 (62-80)	**78** (69-86) *	71.4 ±8.8
General health perceptions	**39** (23-52) ‡	**40** (33-59) ‡	79.0 ±14.5
Parental impact - emotional	**71** (57-89) ‡	89 (82-96)	92.1 ±10.5
Parental impact - time	**76** (67-86) ‡	93 (82-100)	93.0 ±11.0
Family cohesion	**85** (85-100) *	85 (60-100)	75.3 ±18.8

Higher scores represent better functioning. Patient values are presented as median (IQR), norm values as mean ±SD. P-value for comparison with age-specific norm values, * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$. ITQoL indicates Infant-Toddler Quality of Life.

Table 2B: HRQoL by parent reports. Results in children 4 - 18 years old with DCM at diagnosis and ≥ 1 year after diagnosis.

CHQ PF50 subscales	**At diagnosis n = 13**	**≥ 1 year after diagnosis n = 41**	**Norm n = 353**
Physical Functioning	**50** (39-69) †	**83** (61-100) ‡	99.1 ±4.3
Role Functioning - Emotional	61 (25-100)	100 (78-100)	97.9 ±7.2
Role Functioning - Physical	**33** (33-67) †	**100** (67-100) *	95.8 ±15.6
Bodily pain	**50** (20-65) †	80 (60-100)	85.7 ±17.2
General behavior	81 (68-85)	77 (66-85)	78.5 ±13.1
Mental Health	**65** (58-78) †	**75** (65-90) *	81.4 ±12.1
Self-esteem	**58** (54-79) *	**71** (58-83) †	79.2 ±11.0
General health perceptions	**60** (38-69) †	**43** (31-56) ‡	82.9 ±13.4
Parental impact - emotional	**42** (17-75) †	**67** (58-83) ‡	86.3 ±15.2
Parental impact - time	**44** (28-61) †	89 (67-100)	94.0 ±13.0
Family cohesion	60 (60-96)	**60** (60-85) *	72.2 ±19.4

Higher scores represent better functioning. Patient values are presented as median (IQR), norm values as mean ±SD. P-value for comparison with age-specific norm values, * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$. CHQ PF50 indicates Child-Health Questionnaire Parent-form 50.

Comparison between age-groups

At time of diagnosis, we found that parents of older children (4-18 years) scored significantly worse than parents of young children (0-4 years) on the subscales "physical functioning", "parental impact – emotional", and "parental impact – time" (Figure 1).

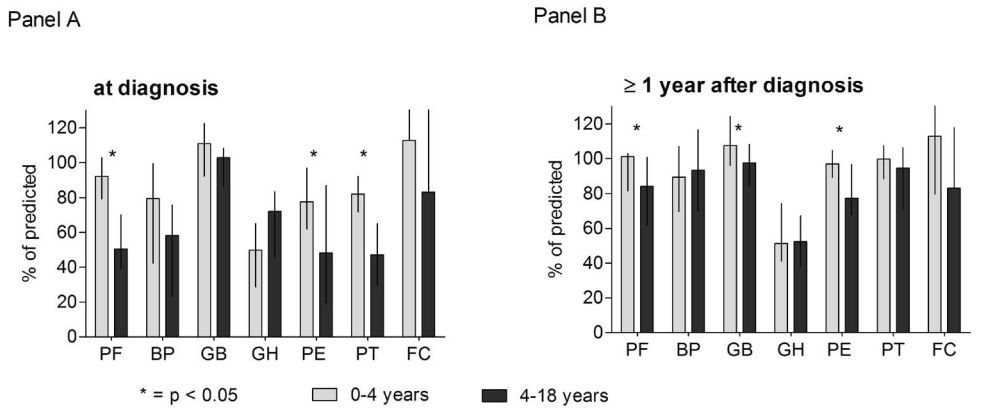

Figure 1: Differences between age groups
PANEL A: Differences in HRQoL at diagnosis between 33 infants and toddlers (0-4 years old) and 13 children (4-18 years old), results as percentage of predicted.
PANEL B: Differences in HRQoL ≥ 1 year after diagnosis between 36 infants and toddlers (0-4 years old) and 41 children (4-18 years old), results as percentage of predicted.
PF indicates "physical functioning"; BP, "bodily pain"; GB, "general behavior"; GH, "general health perceptions"; PE, "parental-impact – emotional"; PT, "parental-impact – time"; FC, "family cohesion".
* = p < 0.05 between age groups.

HRQoL results ≥ 1 year after diagnosis

Of the 90 children, parents of 77 children completed a HRQoL questionnaire at least 1 year after diagnosis, at a median time of 1.5 years after diagnosis (range 1-16 years, Table 1). Between age-groups, the time since diagnosis was significantly different; patients 0-4 year were 1.2 years after diagnosis (IQR 1.0-1.6), while patients 4-18 years were 3.4 years after diagnosis (IQR 1.3-7.8, p=0.004).

Comparison with the norm

Parents of children aged 4-18 years scored lower on more than half of the subscales (6/11), with the largest difference from the norm on "general health perceptions". In contrast, parents of children aged 0-4 years, had lower scores on three subscales, i.e. "growth and development", "bodily pain" and "general health perceptions". Parents of young children with DCM scored their children better than the norm population on "general behavior" and "getting along". The other subscales were comparable to the norm.

Comparison between age-groups

At least 1 year after diagnosis, we found that parents of older children scored their children significantly worse than younger children on “physical functioning”, “general behavior”, and “parental impact – emotional” (Figure 1). Notably, parents of young children scored their children higher than the norm on “general behavior”, and parents of older children scored them comparable to the norm.

Cardiac outcome and follow-up

In the children included at diagnosis, n = 46, the median NYU PHFI was 9 (IQR 6-11). For children who subsequently reached an endpoint (n=4) the median NYU PHFI was 11 (IQR 9-14) compared to 9 (IQR 6-11) for those without an endpoint. At least 1 year after diagnosis, the median NYU PHFI was 7 (IQR 4-9). For children who subsequently reached an endpoint (n=15), the median NYU PHFI was 11 (IQR 8-12) compared to 6 (IQR 3-9) for those without an endpoint (n=62).

The median follow-up time since the first questionnaire to the end of the study or an endpoint was 2.8 years (IQR 1.5-3.8). During the study, 15 patients reached an endpoint, all were transplanted (1.3 years [IQR 0.9-2.2] since first questionnaire; 3.2 years [IQR 2.5-6.2] since diagnosis). All 15 children are included in the cross-sectional group > 1 year after diagnosis (n=77). In the group of newly diagnosed children (n=46), 4 children reached an endpoint, all of whom more than 1 year after diagnosis.

Predictors for outcome

For predicting the risk of death and transplantation, all available measurements were used, i.e. 515 HRQoL questionnaires and 498 NYU PHFI results in 90 different patients including 15 endpoints. Using univariable time-dependent Cox regression, the subscales “physical functioning”, “bodily pain”, “parental impact – emotional”, “parental impact – time” and the NYU PHFI were each significant predictors for the risk of death and heart transplantation. For the multivariable model, “physical functioning” was used since it reflects the child’s actual physical ability and had the highest hazard ratio in univariable analysis. The multivariable model showed that “physical functioning” and the NYU PHFI were both independently predictive for the risk of death and heart transplantation (Table 3). A decrease in physical functioning of 10% of predicted resulted in a HR of 1.24 (95% CI 1.06-1.47), indicating a 24% higher risk for a patient with a score of 80% versus a patient with a score of 90% of predicted. One point higher score on the NYU PHFI was related to a 38% higher risk of death and heart transplantation (HR 1.38, 95% CI 1.19-1.61)

Table 3: Results of univariable and multivariable time dependent Cox regression analysis

Model	Variable	B	HR	(95% CI)	p-value
Univariable model					
	NYU PHFI, per unit	0.40	1.49	(1.32-1.67)	< 0.001
HRQoL subscales, per 10% of predicted *					
	Physical Functioning	- 0.42	1.53	(1.38-1.69)	< 0.001
	Bodily pain	- 0.38	1.46	(1.26-1.68)	< 0.001
	General behavior	0.01	0.99	(0.75-1.30)	0.95
	General health perceptions	- 0.68	1.97	(0.98-4.00)	0.06
	Parental impact- emotional	- 0.39	1.48	(1.32-1.68)	< 0.001
	Parental impact - time	- 0.35	1.42	(1.29-1.58)	< 0.001
	Family cohesion	- 0.12	1.13	(0.91-1.41)	0.27
Multivariable model					
	Physical Functioning *	- 0.22	1.24	(1.06-1.47)	0.01
	NYU PHFI, per unit	0.32	1.38	(1.19-1.61)	< 0.001

* For readability, 1/HR are presented.
CI indicates confidence interval; HRQoL, health-related quality of life; NYU PHFI, New York University Pediatric Heart Failure Index

DISCUSSION

This is the first study that systematically investigated HRQoL and the NYU PHFI in a relatively large cohort of children with DCM. It clearly demonstrates that HRQoL is severely impaired and that parent-reported “physical functioning” and the heart failure score as assessed by the physician are independently predictive for the risk of death and heart transplantation.

At diagnosis, patients of both age-groups scored worse on physical, psychosocial and parental impact subscales compared to norm values. Older children scored significantly worse than younger children. More than 1 year after diagnosis, HRQoL was still impaired, but to a lesser extent than at diagnosis, and again was more impaired in older than in younger children.

The differences between age-groups may have several explanations. First, impairments may be more obvious in older than in younger children because their daily-life activities and range of skills are more diverse. Moreover, older children are normally more independent, but when they become ill, parents need to accept their care-taking role and be more in control again, which may be disruptive for family routines. In contrast, parents of young children are used to an active caregiving role during daily-life, whether children are healthy or diseased. This shift in the locus of control has been described as a normal change in older children with chronic illnesses.[15] Secondly, older children are cognitively able to realize and experience the impact of the disease themselves, as demonstrated by the lower scores on “mental health” and “self-esteem”. Thus, parents of older children have to cope

with more physical and psychosocial impact than parents of young children.[16] This effect was demonstrated by the larger effect on parental impact in patients 4-18 years, both at diagnosis and ≥ 1 year after diagnosis. Thirdly, ≥ 1 year after diagnosis, older patients had DCM for a longer period and may have been "growing into deficit". This phenomenon has been described in children with other diseases, and means that psychological problems on higher cognitive functions, such as emotion regulation, may develop over time, because these functions need to mature.[17] Finally, it may also be related to the severity of heart failure. Of the 77 children measured ≥ 1 year after diagnosis 15 reached the endpoint of whom 10 were > 4 years old. Furthermore, highest recovery rates have been described in children aged 1-6 years,[1] thus the group with younger children may include more children that eventually recover. Considering these results, patients at highest risk for psychological problems, i.e. those at diagnosis and older children with chronic disease (≥ 1 year after diagnosis) may benefit most from timely referral to a psychosocial support team.

Since we described two cross-sections in which we had no complete cases, we cannot draw firm conclusions about the development of HRQoL from diagnosis to > 1 year after diagnosis. Nevertheless, we speculate that HRQoL improves after the first year of diagnosis. Our data clearly showed the severe impairment at diagnosis. Scores on several subscales were also impaired ≥ 1 year after diagnosis, but then the difference from the norm was less extreme and especially in the young age-group several subscales were comparable to the norm. This improvement was not explained by the number of children who reached an endpoint, because all 15 children with adverse outcome were represented in the group ≥ 1 year after diagnosis. This indicates that parents may be adapting to the knowledge that their child has DCM and may rate their child's disabilities with different intensity. This phenomenon may be explained by response shift, which means that parents change their internal standards towards HRQoL in case of chronical illness.[18] This has also been described in children with sequelae of complex congenital heart disease who rate their HRQoL on some subscales as normal as compared to healthy controls.[19] Another factor, which may contribute to the improvement of HRQoL scores in the young age-group is a high recovery rate. Previously, we reported a recovery rate of 69% in 1-6 year olds at a median time of 1 year after diagnosis.[1] We suspect that the improvement in clinical condition accompanying this recovery is also reflected in the HRQoL scores in the young age-group.

Previous studies in adults with heart failure have shown that self-reported HRQoL was predictive of mortality.[8] As far as we know, this is the first study in children with DCM showing that HRQoL, as reported by parents, was predictive for the risk of death and heart transplantation. Moreover, we demonstrated for the first time that the NYU PHFI, as assessed by the physician, was predictive for the risk of death and heart transplantation. Earlier reports in adults and children have shown that the presence of congestive heart failure and higher NYHA functional class were related to adverse outcomes.[2, 20] The direct association between

NYHA and physical HRQoL is a limitation for the use of both markers in the prediction of outcome.[8] The NYU PHFI may be a more discriminative measure of functional status in children, because it is a 30-points index focusing on heart failure symptoms and medication use, rather than patients' physical functioning.[9] Here, we demonstrate in multivariable analysis that both the NYU PHFI as well as the HRQoL parameter "physical functioning" independently predicted outcome. We obtained HRQoL and the NYU PHFI frequently during follow-up and found that its predictive value was constant over time. Therefore, these two predictors can be used from diagnosis onwards and during follow-up in pediatric DCM.

The few studies that have been performed concerning HRQoL in children with DCM included mainly small cohorts.[10, 21-23] The group of Menteer found reduced HRQoL in two small subgroups of children with heart failure (n=15 and n=11), but used another HRQoL questionnaire, which limits comparison with our results.[21, 22] Walker et al. performed an explorative study in the out-patient clinic and included a subgroup of 17 children with cardiomyopathy aged 5-17 years.[10] They found significantly lower scores on "physical functioning", "general health perception", and "parental impact – emotional", in line with our findings. They reported a significantly higher score on "family cohesion", which is in contrast with the results in the older age-group in our cohort. Nevertheless, "family cohesion" was better in infants and toddlers in our study. Clinical experience learns that the seriousness of the disease may either "bring families closer together" or "tear them apart". Finally, the Pediatric Cardiomyopathy Registry (PCMR) reported limited results on the CHQ PF50 in children with cardiomyopathy.[23] On average, they reported impaired HRQoL, with more physical problems than psychosocial problems, and suggested improvement over time in functional status. Finally, they suggested that poorer functional status might be a risk factor for subsequent death and heart transplantation. Our study adds to the existing data by clearly demonstrating the predictive value of functional status on outcome, by demonstrating improvement over time, but less in older children and by demonstrating the independent predictive value of a pediatric heart failure score on outcome.

Limitations

This study had some limitations. Firstly, the number of events was only 15, limiting the number of variables in multivariable analysis. The "physical functioning" subscale was most relevant, but it would be interesting to test other significant subscales. Secondly, the median follow-up time was almost 3 years. Therefore, the outcome results need to be interpreted on a mid-term follow-up time. Finally, the treating physicians who recorded the NYU PHFI scores were not blinded to the results. However, these were not registered in the clinical file of the patients, and were not part of the clinical evaluation and treatment decisions. Therefore, it is unlikely that this has caused bias in eligibility for transplantation decisions.

CONCLUSIONS

In children with DCM, HRQoL is severely impaired at diagnosis and ≥ 1 year after diagnosis. Children ≥ 4 years old had lower HRQoL than children < 4 years old. "Physical functioning" as reported by parents and heart failure severity using the NYU PHFI are independent predictors for death and heart transplantation.

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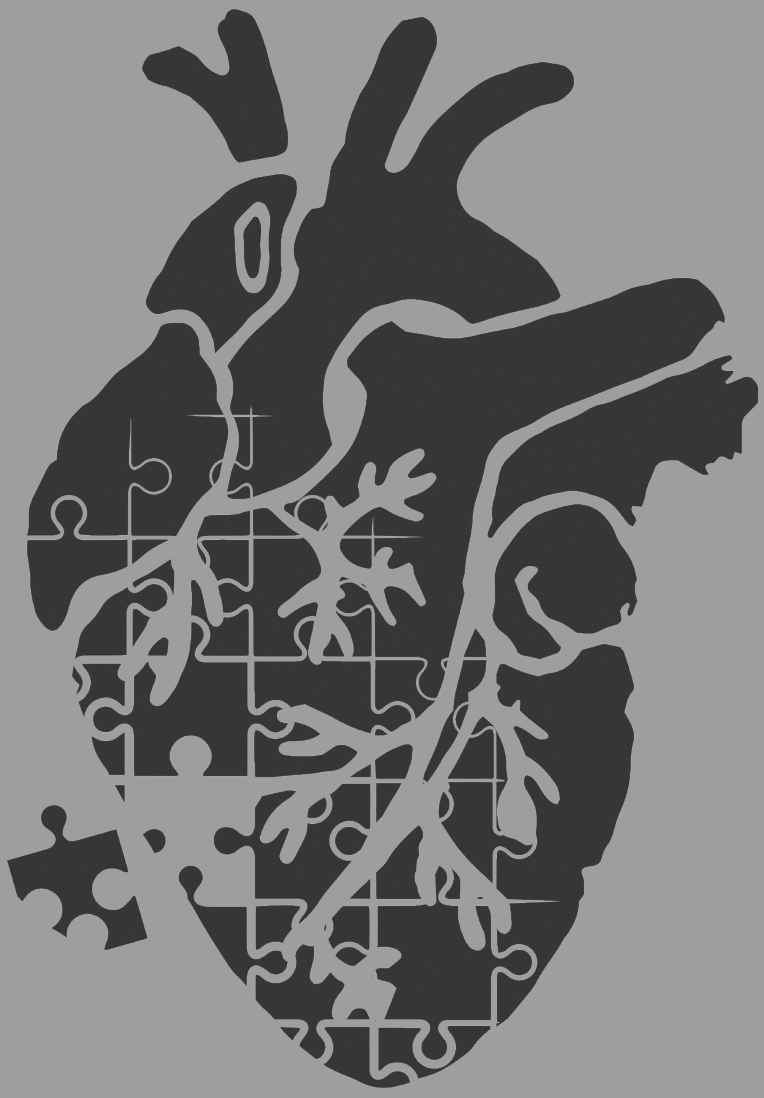
PART IV

Discussion and Summary



Chapter 9

General discussion

The results of the CArdiomyopathy Registry Study (CARS) are described in this thesis. CARS started between the end of 2010 and the beginning of 2011 in seven pediatric cardiology departments in the Netherlands (Academic Medical Center, Erasmus Medical Center, Free University Medical Center, Radboud University Medical Center, and the University Medical Center of Groningen, Leiden and Utrecht). CARS is a prospective, longitudinal, observational study in children with dilated cardiomyopathy (DCM). The aim of the study was to determine risk factors that predict outcome at diagnosis and during follow-up. We hypothesized that, beside cross-sectional data, the collection of longitudinal data to study alterations within individual patients, would provide valuable information to predict outcome.

Conducting CARS over the past years has moved the field of pediatric DCM in the Netherlands forward in several respects. First, children who participated in the study have been systematically evaluated. Since the inclusion rate was around 90%, almost all children with DCM have been systematically followed. This has resulted in an overview of pediatric DCM in the Netherlands, including the incidence, patient characteristics and the outcome. Second, the multicenter design of the study gave rise to a network enhancing communication between physicians from different centers, about patients and DCM in general. Although not confirmed by research results, we suspect that CARS has led to a more uniform approach to diagnose and treat children with DCM.

ETIOLOGY

Analysis of the etiology of DCM showed that 55% of the children had no specified cause and were labeled as idiopathic disease, and 14% of the cases were labeled as having myocarditis (Chapter 3). However, after systematically analyzing all available viral test results and uniformly interpreting these results, 8% of the patients with a diagnosis of myocarditis or idiopathic DCM were not classified consistently.

The diagnosis of myocarditis is difficult to make in children. The gold standard, an endomyocardial biopsy (EMB), has a low sensitivity.[1, 2] In a study using 14 hearts with histologically proven myocarditis (ex-vivo), biopsy sampling was simulated and showed a sensitivity around 50% using 4-5 samples per patient.[2] This could be increased to 78%, but required on average 17 samples per patient. This illustrates that by performing an EMB, a negative result will not preclude the diagnosis of myocarditis. Furthermore, a high complication risk (11%) of this procedure has been reported in children,[3] and this is probably the main reason that biopsies are not often performed in the pediatric population.[4-6] In clinical practice, most pediatric DCM cohorts report the 'clinical diagnosis of myocarditis'.[4, 5, 7] In Chapter 3, we demonstrated that the diagnostic approach and the interpretation of the test results differed markedly between physicians. These results from our study, may be

representative for other cohort studies. Outcome analysis of the Pediatric Cardiomyopathy Registry (PCMR) showed that children with biopsy-proven myocarditis had a favorable outcome as compared to those with idiopathic DCM.[8] Three years after presentation with myocarditis 6% died, 19% underwent transplantation and 54% showed echocardiographic normalization, while in the idiopathic group, 17% died, 33% underwent transplantation and 22% recovered. Furthermore, the diagnosis myocarditis (mixed population of biopsy-proven and suspected myocarditis) has been associated with increased mortality after heart transplantation.[9] These results suggest that a more accurate diagnosis of myocarditis may lead to better risk stratification in children with DCM.

The rapid developments unraveling the genetic causes underlying various forms of cardiomyopathy have indicated that a considerable number of children labeled as having idiopathic DCM, may in fact be index patients in familial disease. Systematic echocardiographic screening of 225 asymptomatic relatives (mean age 35 ±15 years) of 110 adult patients with idiopathic DCM identified 65 (29%) relatives with asymptomatic left ventricular (LV) dysfunction: 3% had DCM, 20% had LV enlargement and 6% depressed fractional shortening.[10] Notably, after a median follow-up of 3.2 years, almost one-third of the cases with LV enlargement developed DCM, and 2% of the patients who were initially normal had developed LV enlargement. These results indicate a high prevalence (~30%) of familial disease in initially idiopathic patients. Furthermore, new cases emerged during the follow-up period, suggesting the need for frequent consultation of relatives with idiopathic DCM. In adults, consultation every 3-5 years has been suggested.[11] Since adults with familial DCM commonly present with symptoms around the age of 50 years,[12] children who are diagnosed with symptomatic familial disease may have a more severe phenotype. In these cases, genetic counseling and screening of relatives may even be more relevant. As the results from studies in adults suggest, not only relatives from children with 'familial disease', but also relatives of children with idiopathic disease need to be screened. As idiopathic disease has been identified as a risk factor for adverse outcome in pediatric DCM,[7] further refining the underlying causes within this group, may allow future studies to identify the highest-risk phenotypes and genotypes.

The question remains whether asymptomatic relatives who are identified by screening require treatment. In adults, it has been recommended to prescribe angiotensin-converting enzyme (ACE) inhibitors and beta-blockers for stage B heart failure (structural heart disease without signs and symptoms).[11] Moreover, the use of ACE inhibitors has also been recommended in children with echocardiographic signs of heart failure without symptoms.[13] Furthermore, preventive treatment with ACE inhibitors in boys with Duchenne Muscular Dystrophy with normal LV ejection fraction showed delayed onset of LV dysfunction in short-term and reduced mortality in long-term follow-up.[14, 15] These data suggest that in the pediatric population, at least the prescription of ACE inhibitors may be advocated.

In conclusion, a uniform approach to the diagnostic work-up and interpretation of the results, as well as expanding the knowledge of underlying genetic causes, may improve the diagnostic classification in a large majority (65-75%) of the children with DCM. At the present time, identification of myocarditis patients may lead to better risk stratification, and identification of familial disease may lead to better treatment and to early diagnosis of other family members. Although, the definite etiology in a considerable amount of patients might remain unknown, structural diagnostic assessment may be the first step to elucidate some of the pathophysiology of DCM and to study pharmacological treatment in more homogeneous groups. More than a century ago William Osler stated: "there are three phases to treatment: diagnosis, diagnosis and diagnosis", implicating that the best management starts with the most accurate diagnosis.[16]

OUTCOME

In almost all risk factor analyses described in this thesis, the combined endpoint of death or heart transplantation was used (Chapters 2, 5, 6, 7, and 8). It is clear that 'death' is a hard endpoint. For 'heart transplantation', it is assumed that without transplantation patients otherwise would have died. However, the time of transplantation depends on listing criteria, as well as on the time on the waiting list. Listing criteria will vary across centers, and the availability of donor hearts will vary across organ sharing organizations. Reviewing the clinical condition of the patients who underwent transplantation > 1 year after diagnosis, we found that 88% was listed as Class I and 12% as Class IIa; one-third had Stage D heart failure (dependent on inotropic medication) according to the classification of Canter et al.[17] During the time on the waiting list another 13% progressed to Stage D heart failure; 50% of the Stage D patients were on MCS at the time of transplantation. The median time on the waiting list was 61 days (IQR 31-182 days), 80% was transplanted within 1 year of listing. These data underscore the severity of heart failure both at the time of listing and at the time of transplantation.

Analysis of endpoints of 120 prospectively included patients in the CARS database showed similar findings as the retrospective cohort (2005-2010) as has been described in Chapter 2. After a median follow-up time since diagnosis of 3.2 years (IQR 1.3-6.1), 31 children (26%) reached an endpoint: 11 deaths and 20 transplantations. Within the first year of diagnosis, almost all endpoints were death (9/13), and > 1 year after diagnosis almost all endpoints were transplantation (16/18). The median time from diagnosis to death was 1.1 months (IQR 0.5-8.2), and 9/11 deaths occurred within the first year. Similar to the retrospective cohort, evaluation of the patients who died, identified children who died soon after presentation, had contra-indications for transplantation, were on MCS or

were young infants. As described earlier, the outcome of children reaching an endpoint seems dichotomous. The large majority who die, do so early after presentation accounting for approximately 15% of the initial population, a number that has been reported in several other large cohort studies worldwide.[4, 7] Critical analysis of the profiles of children dying early after diagnosis suggests that mortality is unlikely to be considerably reduced by a more aggressive approach to listing children for transplantation.

In contrast to the short median time to death, the median time from diagnosis to transplantation was 2.9 year (IQR 1.5-5.9), only a few transplantations were performed within the first year of diagnosis. In the prospective CARS cohort, 4 patients were transplanted within the first year of diagnosis, all of whom were > 10 years of age and 50% were on left ventricular assist device. This is in contrast to other cohorts, like the PCMR, in which 77% of the endpoints in the first year are transplantation, with a median time from diagnosis to listing of only 1.4 months.[18] Although patient characteristics may differ, we showed in Chapter 2 that baseline characteristics of our cohort were quite similar to that of others. Differences in genetic background and environmental exposures may be present and have not been looked at.

We demonstrated that with our listing strategy, the transplantation rate in our cohort was relatively low in the first year after presentation as compared to other cohorts, without an obvious increase in mortality. Thus, the 1-year transplant-free survival in the Netherlands was higher (82%) than has been previously reported (65-72%).[4, 5, 7, 19] This difference remained after the first year, and also higher 2-year (76%) and 5-year (72%) transplant-free survival rates were found than for example in the PCMR (61% and 54%, respectively).[7] Furthermore, we, and also other cohorts, have described recovery rates around 33-38% (median time to recovery: 1 year) and the highest recovery rates in children between 1-6 years at diagnosis.[20] Particularly in that age group, a conservative approach early after diagnosis, may be justifiable.

In conclusion, our outcome analysis suggests that a conservative approach to listing for heart transplantation early after diagnosis may be justified in a considerable amount of children. Outcome results of the past ten years in the Netherlands showed comparable survival and a higher transplant-free survival rate. Therefore, interpreting the risk factor analyses in part III of this thesis, we assume that patients who underwent heart transplantation, urgently needed one. Long-term follow-up of the Dutch cohort should be performed to monitor and compare the transplant-free survival over a longer time. Furthermore, identification of the subgroup of children that deteriorates quickly after diagnosis and > 1 year after diagnosis is needed to further improve outcome.

RISK FACTORS FOR ADVERSE OUTCOME

Analyses of several risk factors for adverse outcome have been described in this thesis. The design of CARS was to include all patients who were diagnosed with DCM and to include all children with a prior DCM diagnosis who were still followed-up for DCM in one of the participating centers. After 3 years of CARS, around 55% of the study population consisted of newly diagnosed children and 45% had a prior diagnosis of DCM. Of the prior cases, the median time from diagnosis to study inclusion was 3.3 years, range 0.4 – 16.3 years. Considering the outcome of pediatric DCM, ~20% death or transplantation within the first year of diagnosis, the majority of the prior-presentation group are biased by a positive selection, i.e. they have survived the first critical year after diagnosis. The results of our study should be interpreted taking this characteristic into consideration.

One of the purposes of CARS was to study risk factors during follow-up that identified patients with increased risk of death or transplantation. To account for the difference in time-since-diagnosis within the CARS population, we made subgroups. First, patients followed from diagnosis onwards, and second patients who at least survived the first year after diagnosis. The latter were considered 'chronic DCM patients' with a markedly lower event-rate than children within the first year of diagnosis. The results of the risk factor analyses will be evaluated in the light of 'time since diagnosis'.

At diagnosis

Admission to the intensive care unit and MCS during first hospitalization were, in fact, risk factors for death within the first year. Of the patients reaching an endpoint in the first year, 80% died and another 15% were bridged to transplantation on MCS. Furthermore, we found that age > 6 years was a risk factor to reach an endpoint > 1 year after diagnosis, which was transplantation in the large majority of cases. Although, age > 6 years may increase the risk of a poor long term outlook, the fact that it was not associated with early mortality may justify to take some time to explore the response to pharmacological therapy early after diagnosis. Other cohort studies, such as the PCMR and the NACCS, also investigated risk factors for adverse outcome. They reported that at diagnosis, presence of congestive heart failure, age > 5-6 years, reduced fractional shortening and an idiopathic and familial origin were risk factors for the combined endpoint of death or heart transplantation.[5, 7] However, in the PCMR, 77% of the endpoints within the first year was transplantation. Thus, these risk factors may largely reflect the risk of being selected for transplantation, rather than the risk of dying.[18] Recently, researchers performed a competing risk analysis on the PCMR data to separate the effect of the risk factors according to their impact on death and heart transplantation.[18] For idiopathic DCM they reported that the presence of congestive heart failure, as well as age > 6 years were independent risk factors for both death and heart

transplantation. In contrast, they found that higher LV end-diastolic dimension z-score was associated with an increased risk of transplantation, but a decreased risk of death. Furthermore, lower height-for-age z-score was associated with increased risk for death, but not for transplantation. These results suggest that the presence of some markers (wide LV) drive heart transplantation decisions, while other markers, such as short length, are not recognized as high-risk markers and do not lead to listing for transplantation.

Early after diagnosis

High NT-proBNP values that do not decline and/or are > 7990 pg/mL at 1 month after diagnosis were associated with a higher risk of death, heart transplantation or MCS (cardiac death). The 1-year event rate was 23% in those with a value > 7990 pg/mL as compared to 4% in those with a value below that threshold. The events that occurred during the first year after diagnosis were either death or start of MCS. During the first year after diagnosis, we also measured the New York University Pediatric Heart Failure Index (NYU PHFI), physical functioning using health-related quality of life (HRQoL) questionnaires and 6-minute walking distance. All of these were predictive for the endpoint. However, all endpoints occurred after the first years of diagnosis and were all transplantations.

So, as far as we can conclude using our data, these markers are related to transplantation > 1 year after diagnosis, but its relation to death within the first year is unknown. NT-proBNP may be the only marker to identify patients at risk for early death or the need for MCS. As we encountered during CARS, some children reached the endpoint too soon to be included in the study, or were too ill to perform tests, such as the six-minute walk test. Therefore, laboratory parameters, such as NT-proBNP, and the evolution of these parameters in response to treatment may be the key to risk prediction in this group.

At least 1 year after diagnosis

At least ≥ 1 year after diagnosis, relevant markers associated with a higher risk of death or transplantation were: lower mean global longitudinal peak strain, higher NYU PHFI, lower physical functioning score, higher NT-proBNP, increasing NT-proBNP over time, and a lower distance walked in 6 minutes. But, since 75-100% of the endpoints were transplantation, these markers were, in fact, related to heart transplantation. These parameters were all collected according to the study protocol, and were not used in making clinical decisions about listing for transplantation.

For all these markers it was the first time that the predictive value in children with DCM was demonstrated. Previous studies in adults with heart failure, showed similar findings. Mean global longitudinal peak strain,[21] physical functioning score as reported on HRQoL questionnaires,[22] and the distance walked in 6 minutes [23] were all predictive for mortality and morbidity in adults with heart failure. Furthermore, in adults a NT-proBNP value > 1000

pg/mL has been classified as 'high-risk'.[24] We demonstrated that in children approximately the same cut-off resulted in a 2-year event-rate of 32% as compared to 0% in those below the threshold. So, we found that many markers that have been shown to have predictive value in adults were also predictive in children.

Markers that showed no predictive value

In contrast to the similarity that we found for several markers between adults and children, there were also differences. Particularly, for the presence of central sleep apnea (CSA) and dyssynchrony.

CSA was present in 19% of the children, in whom 1.2 - 4.5 apneas per hour of sleep were detected. Moreover, we detected in 3 patients a cyclic pattern of apneas and hypopneas mimicking Cheyne-Stokes respiration. We did not demonstrate a relation between CSA and the severity of heart failure. In contrast, in adults with heart failure, a high prevalence of CSA has been described (35-40%) with a much higher number of apneas per hour of sleep (mean 30 per hour).[25, 26] Furthermore, in adults the presence of CSA and Cheyne-Stokes respiration has been associated with the severity of heart failure and with higher mortality rates.[25, 26] Thus, in children, the presence of CSA was rare and the severity seemed relatively mild. Nevertheless, these mild abnormalities might suggest that the scoring rules for adults do not fit children to detect CSA and Cheyne-Stokes respiration.

In Chapter 6, we assessed dyssynchrony using quantitative and qualitative speckle-tracking analyses on echocardiography. In children, we demonstrated that the quantitative analysis, time to peak and intraventricular time differences, showed poor reproducibility. This precludes its use in clinical practice. The qualitative pattern analysis has been shown highly sensitive to predict response to cardiac resynchronization therapy (CRT), in adults with heart failure with left bundle branch block (LBBB) or QRS duration > 130 ms.[27, 28] In contrast, the patterns that were associated with response to CRT, were rarely found in children with DCM. Moreover, adults responding to CRT had all LBBB or prolonged QRS duration, however, these characteristics are very rare in children.[29, 30] Therefore we suspect that the role of CRT in children with DCM will be limited.

Univariable and multivariable analysis

In our studies, almost all risk factor analyses were univariable. This was due to a low number of endpoints and the assumption that approximately 10 endpoints were needed to allow 1 variable in multivariable analysis. In adults, incidence rates of heart failure are high, resulting in high number of patients included in studies and endpoints are more prevalent, which enable multivariable testing.[31] An example of a multivariable model is the Heart Failure Severity Score (HFSS), which includes (1) the presence of ischemic cardiomyopathy, (2) resting heart rate, (3) LV ejection fraction, (4) mean blood pressure, (5) peak VO_2, (6)

presence or absence of intraventricular conduction delay, QRS > 120 ms, (7) serum sodium.[32, 33] All these factors were independently predictive for mortality. The resultant, the HFSS, used in a population with advanced heart failure, assigned patients in one of the 3 risk groups: low, medium and high risk, with corresponding mean 1-year survival rates of 93 ±2%, 72 ±5%, and 43 ±7%, respectively. This illustrates that, in adults, several markers have been shown to be independently predictive, and by establishing such a score this may help prognostication.

The validation of such a heart failure score in pediatric DCM might not be attainable. To test the independent value of the risk factors that we found to be valuable > 1 year after diagnosis (mean global longitudinal peak strain, NYU PHFI, physical functioning score, NT-proBNP, the slope of NT-proBNP, and distance walked in 6 minutes), we need a pediatric DCM population, at least > 1 year after diagnosis, having 60 endpoints. For sample size calculation, we used all patients who were newly diagnosed since 2005, who survived at least 1 year after diagnosis without an endpoint, and were not lost to follow-up. This resulted in 168 cases with 26 events > 1 year after diagnosis, during a total follow-up time of 517 patient years (calculated from 1 year after diagnosis). Thus, ~20 patient years were needed for 1 endpoint. To collect 60 endpoints, ~1200 patient years of follow-up since 1 year after diagnosis are needed, which correspond with: 300 patients followed for 4 years. Applied to the Dutch population, we would have to collect data for 23 years. This underscores that large multicenter collaborations are required to validate a multivariate heart failure score or to demonstrate a beneficial effect of alternative treatment strategies on outcome.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

At DCM diagnosis, patients who need to be admitted to the intensive care unit are at highest risk for early adverse outcome and need critical appraisal. Especially, those who need MCS represent a critically ill subgroup requiring (urgent) listing for transplantation. Except for those with (probable) fulminant myocarditis in whom MCS may be applied as a bridge to recovery.

NT-proBNP, which remains high in the first weeks after diagnosis, is a risk marker that identifies those at highest risk of death or MCS. Considering the results described in this thesis, a conservative approach towards early listing for transplantation may be justifiable in all others, in order to explore the potential for pharmacological therapy and the potential for complete recovery. Particularly, in children aged 1-6 years at diagnosis, as recovery rates were high in this subgroup.

For children who survive the first year after diagnosis, we advise to use the following markers to make a risk profile: (1) clinical assessment using the NYU PHFI; (2)

echocardiography including speckle-tracking of the LV 4-chamber view; (3) NT-proBNP measurements; (4) HRQoL assessment using an age-specific questionnaire; (5) six-minute walk test if the patient is ≥ 6 years. We found that a higher NYU PHFI, lower mean global longitudinal strain, higher NT-proBNP, increasing NT-proBNP over time, lower physical functioning score and lower distance walked in 6 minutes were all associated with increased risk of death or heart transplantation.

Physicians should be aware of the risk of potential psychological problems. According to parent-reports, HRQoL was severely impaired in all age groups at diagnosis. Moreover, HRQoL was still impaired in children aged ≥ 4 years more than 1 year after diagnosis. Therefore, some families may benefit from psychosocial support from early after diagnosis onwards.

Future studies should focus on detecting new DCM genotypes and delineating genotype-phenotype relationships in those with genetic/familial disease. This may further contribute to defining high-risk profiles in a subgroup of children currently labeled as idiopathic or genetic/familial disease, who seem to be at higher risk for an unfavorable outcome.

For children with an unfavorable profile, optimizing heart failure therapy may be the best chance to improve outcome. Current treatment strategies for children with heart failure secondary to DCM are directly translated from adult treatment protocols. There is a paucity of data demonstrating efficacy of these treatment protocols in children. The only randomized controlled trial in children could not demonstrate efficacy for carvedilol, although subgroup analysis for LV dysfunction tended to favor carvedilol.[34] Furthermore, it has been suggested that in the young age group dose requirements may be considerably higher.[34, 35] Future studies directed at delineating dose-exposure relationships in children may help to define optimal dosing strategies. Furthermore, in order to improve efficacy of heart failure therapy in children, using NT-proBNP guided therapy in subgroups with a high risk profile may be a worthwhile strategy. This thesis provides some guide for the definition of high-risk subgroups as well as for target levels for NT-proBNP. In order to prove definite efficacy a decrease in adverse events needs to be demonstrated, which requires a large multicenter set-up in order to obtain sufficient power.

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Chapter 10

Summary / Samenvatting

SUMMARY

The aims of this thesis are to evaluate the epidemiological aspects of pediatric dilated cardiomyopathy (DCM) in the Netherlands, including the incidence, causes and outcome; and to determine risk factors for outcome at diagnosis and during follow-up in this patient group.

PART I. Introduction

Chapter 1 provides an overview of DCM. DCM in children is rare and the underlying etiology is frequently unknown. Prognosis is poor, and if pharmacological treatment fails, heart transplantation is a last-resort therapy. It is important to identify patients with a poor prognosis to intensify treatment and to select for transplantation. In contrast to children, DCM is common in adults and previous studies have revealed risk factors that predict adverse outcome. Although the pathophysiology of DCM in children may not be identical to adults, these risk factors may also provide valuable prognostic information in children. Therefore, we studied some of these factors in this thesis.

PART II. Epidemiological aspects

In **chapter 2** we study the outcome of DCM in children in the Netherlands. The policy for listing and transplantation in children in the Netherlands has been conservative because of low donor availability. In this nationwide study we included all children with DCM diagnosed between 2005 and 2010 (n = 148). In the first year after diagnosis, we found a low transplantation rate, and after the first year, the transplantation rate was similar to other cohorts. Moreover, the survival rates at 1- and 5-year were similar to other cohorts. We also studied risk factors in our patient group and found that patients who were admitted to the intensive care unit and needed mechanical circulatory support were at highest risk for an endpoint in the first year after diagnosis. Moreover, age > 6 years at diagnosis was associated with a poor prognosis > 1 year after diagnosis. Furthermore, we found that 38% of the patients recovered, 50% within the first year of diagnosis. Recovery was associated with younger age. We conclude that the conservative approach to list children early after diagnosis may be justifiable, except for those admitted to the intensive care unit and in need for mechanical circulatory support. These findings are important and help us to interpret the results of the studies on risk factors as described in Part III.

Etiology of DCM is one of the prognostic markers that have been described in other pediatric cohorts, with a favorable outcome of myocarditis versus idiopathic DCM. However, a definite diagnosis of myocarditis is difficult to make and a ‘clinical diagnosis’ is commonly used. In **chapter 3** we evaluated the diagnostic approach to find the cause of DCM in 150 children and the interpretation of the diagnostic test results. We found that the number

and kind of tests that were performed to find the cause of DCM as well as the interpretation of the results varied among patients. We propose to use viral tests in several steps and classified the probability of myocarditis as 'definite', 'probable', 'possible' and 'unlikely'. This approach may lead to a more uniform interpretation.

PART III. Risk factors

In this part we describe several risk factors that we have studied in children with DCM. **Chapter 4** describes a retrospective analysis of all available NT-proBNP values in 115 children. Using a mixed modeling approach, we found that the actual NT-proBNP level as well as the change of NT-proBNP over time was predictive for the risk of death, heart transplantation and mechanical circulatory support. Two cut-off values were defined. At 30 days after diagnosis, NT-proBNP ≥ 7990 pg/mL showed a 1- and 2-year event-free survival of 77% and 73%, and > 1 year after diagnosis NT-proBNP ≥ 924 pg/mL showed a 2- and 4-year event-free survival of 68% and 64%, while values below both thresholds showed excellent outcomes (95-100%). In **chapter 5, 6, 7 and 8,** results from the prospective cardiomyopathy registry study (CARS) are described. In **chapter 5** the predictive value of central sleep apneas is evaluated. Central sleep apneas were present in 19% of the patients. No relation with the severity of heart failure could be detected. In a small subset of children (n = 3) we registered a respiration pattern mimicking Cheyne-Stokes respiration, which however, has been associated with adverse outcome in adults with heart failure. In **chapter 6** the predictive value of speckle-tracking echocardiography and the presence of dyssynchrony are assessed. We show that speckle-tracking echocardiography is feasible in children with DCM and that global longitudinal strain is predictive for death and heart transplantation. Quantitative dyssynchrony parameters were not reproducible, which precludes its use in children with DCM. In contrast to adults, qualitative pattern analysis showed predominantly reduced strain, instead of dyssynchrony patterns, suggesting that dyssynchrony may be a minor problem in these children than in adults. **Chapter 7** describes the results of the 6-minute walk test in children ≥ 6 years. Transformed to a percentage of predicted, we found that a lower 6-minute walk distance resulted in a higher risk of death and heart transplantation. Patients who walked below the cut-off of 63% of predicted had a significant higher risk of death and heart transplantation than those who walked farther than this cut-off. Finally, in **chapter 8** we describe the health-related quality of life as reported by parents. Furthermore, we hypothesize that parents' assessment, using health-related quality of life questionnaires, provides valuable information about their child's functioning and may contain prognostic value. In addition, we hypothesize that a physician's assessment to score the severity of heart failure, using the New York University Pediatric Heart Failure Index (NYU PHFI), may also provide prognostic information. We conclude that physical functioning as reported by parents and heart failure severity as assessed by physicians were independently predictive for the risk of death and heart transplantation.

PART IV. General discussion

In **Chapter 10** we discuss the studies in this thesis in the light of current literature, and describe clinical implications and future directions.

The main conclusions are:

1. A uniform approach to the diagnostic work-up and interpretation in cases of suspected myocarditis, as well as expanding the knowledge of underlying genetic causes, may improve the diagnostic classification in a large majority (65-75%) of children with DCM. This will lead to earlier identification of familial cases, to better risk stratification and better treatment.

2. Outcome analysis suggests that a conservative approach to listing for heart transplantation early after diagnosis may be justified in a considerable subgroup of children.

3. Early listing for transplantation is warranted in children who were admitted to the intensive care unit at diagnosis, and who needed mechanical circulatory support during first hospitalization, since these were risk factors for death within the first year after diagnosis.

4. Age > 6 years at diagnosis was a risk factor for reaching an endpoint > 1 year after diagnosis, which was transplantation in a large majority of the cases.

5. High NT-proBNP values that do not decline early after diagnosis and/or are ≥ 7990 pg/mL at 1 month after diagnosis, are associated with a higher risk of death, heart transplantation and mechanical circulatory support (cardiac death).

6. At least 1 year after diagnosis, relevant markers associated with a higher risk of death and transplantation were: lower mean global longitudinal peak strain, higher NYU PHFI, lower physical functioning score, higher NT-proBNP, increasing NT-proBNP over time, and a lower distance walked in 6 minutes. It would be difficult to study the independent value of these markers, because DCM is rare and hard endpoints are relatively low > 1 year after diagnosis.

SAMENVATTING

In dit proefschrift richten we ons enerzijds op de epidemiologische aspecten van gedilateerde cardiomyopathie (DCM) bij kinderen in Nederland, zoals incidentie, de oorzaken en de uitkomst; en anderzijds op het vinden van risicofactoren op het moment van diagnose en tijdens de follow-up, die iets zeggen over de uitkomst van het ziekteproces(prognose) van kinderen met DCM.

DEEL I. Introductie

Hoofdstuk 1 geeft een introductie van DCM. Het voorkomen van DCM bij kinderen is zeldzaam, en de oorzaak is vaak onbekend. De prognose is slecht, en als medicamenteuze therapie niet meer (voldoende) werkt, is harttransplantatie de enige therapeutische optie. Het is belangrijk om patiënten met een slechte prognose te identificeren, zodat medicamenteuze therapie kan worden geïntensiveerd en patiënten op tijd geselecteerd kunnen worden voor transplantatie. In tegenstelling tot kinderen, komt bij volwassenen DCM regelmatig voor. Eerdere studies bij volwassenen hebben een aantal risicofactoren opgeleverd die een slechte uitkomst kunnen voorspellen. Ondanks dat de pathofysiologie van DCM tussen kinderen en volwassenen zou kunnen verschillen, zouden de risicofactoren die bij volwassen gevonden zijn, ook bij kinderen voorspellend kunnen zijn voor de prognose. Daarom hebben we enkele van deze risicofactoren ook bestudeerd bij kinderen. De uitkomsten hiervan beschrijven we in dit proefschrift.

DEEL II. Epidemiologische aspecten

In **hoofdstuk 2** bestuderen we de prognose van kinderen met DCM in Nederland. Mede doordat donorharten schaars zijn, zijn we in Nederland terughoudend met het plaatsen van kinderen op de wachtlijst voor harttransplantatie. In deze landelijke studie betrekken we alle kinderen die tussen 2005 en 2010 met DCM werden gediagnosticeerd (n=148). Het aantal transplantaties dat werd verricht in het eerste jaar na diagnose was laag ten opzichte van andere internationale groepen kinderen met DCM. Het aantal transplantaties ná het eerste jaar was vergelijkbaar met deze andere groepen. Ondanks het relatief lage aantal transplantaties in het eerste jaar na diagnose, was de overleving 1 en 5 jaar na diagnose vergelijkbaar met deze andere groepen. Verder bestudeerden we in deze onderzoeksgroep ook risicofactoren voor het halen van een eindpunt (overlijden of harttransplantatie). Hieruit bleek dat kinderen die bij diagnose moesten worden opgenomen op de intensive care en kinderen die tijdens de eerste opname mechanische ondersteuning van de circulatie nodig hadden, het hoogste risico hadden om een eindpunt te halen in het eerste jaar na diagnose. Verder bleek de factor leeftijd bij diagnose > 6 jaar geassocieerd met een hoger risico op overlijden of transplantatie op de langere termijn (> 1 jaar). In tegenstelling tot de

slechte prognose, vonden we ook dat 38% van de kinderen met DCM herstelde, de helft van hen binnen het eerste jaar na diagnose. Herstel was geassocieerd met jongere leeftijd bij diagnose. We concluderen dat het gerechtvaardigd is om vroeg na diagnose terughoudend te zijn met het plaatsen van kinderen op de wachtlijst voor transplantatie. Dit geldt echter niet voor kinderen die opgenomen zijn op de intensive care en mechanische ondersteuning van de circulatie nodig hebben. De bevindingen omtrent de prognose zijn belangrijk en helpen ons om de studies in deel 3 te interpreteren.

Andere studies bij kinderen met DCM, hebben laten zien dat 'de oorzaak van DCM' een prognostische factor is, waarbij kinderen met myocarditis een betere prognose hadden dan kinderen met idiopathische DCM (onbekende oorzaak). Echter, het is moeilijk om met zekerheid de diagnose myocarditis te stellen, en daarom wordt vaak een 'klinische diagnose' gebruikt. In **hoofdstuk 3** evalueren wij welke diagnostiek naar de oorzaak is uitgevoerd bij 150 kinderen met DCM en hoe de testresultaten zijn geïnterpreteerd. We vonden dat het aantal en het soort testen dat was gedaan per patiënt, alsmede de interpretatie van de testresultaten varieerden. We doen een voorstel om de virale diagnostiek stapsgewijs aan te pakken. Afhankelijk van de resultaten kan de waarschijnlijkheid van myocarditis worden geclassificeerd als 'zeker', 'waarschijnlijk', 'mogelijk', en 'onwaarschijnlijk'. Deze aanpak zou tot een meer uniforme interpretatie kunnen leiden.

DEEL III. Risicofactoren

We bestuderen verschillende risicofactoren voor uitkomst bij kinderen met DCM. De resultaten hiervan worden in dit deel beschreven. **Hoofdstuk 4** beschrijft een retrospectieve analyse van alle beschikbare NT-proBNP waarden van 115 kinderen. NT-proBNP is een stofje dat, in geval van hartfalen, door het hart wordt uitgescheiden en gemeten kan worden in het bloed. De resultaten werden geanalyseerd met behulp van een "mixed modeling" methode. Dit geeft aan dat het actuele NT-proBNP level, alsmede de verandering van NT-proBNP door de tijd, gerelateerd zijn aan het risico op overlijden, harttransplantatie of mechanische ondersteuning van de circulatie. Twee afkapwaardes werden gedefinieerd. Van de kinderen met een NT-proBNP ≥ 7990 pg/mL op 30 dagen na diagnose was 77% "event-vrij" in leven na 1 jaar, en 73% na 2 jaar ("event-vrij" betekent in leven zonder dat mechanische ondersteuning nodig was of transplantatie). Van de kinderen met een waarde ≥ 924 pg/mL minimaal 1 jaar na diagnose, was na 2 jaar 68% event-vrij in leven en na 4 jaar 64%. Dit in tegenstelling tot de kinderen met NT-proBNP waarden onder deze afkappunten; zij hadden een uitstekende event-vrije overleving (95-100%). In **hoofdstuk 5, 6, 7, en 8** worden resultaten van de prospectieve cardiomyopathie registratie studie (CARS) beschreven. In **hoofdstuk 5** wordt de voorspellende waarde van de aanwezigheid van centrale apneus (ademhalingsstilstand) geëvalueerd. Bij 19% van de kinderen werden centrale apneus geregistreerd. Er werd geen relatie gevonden met de ernst van het hartfalen. Bij een kleine groep kinderen (n = 3) werd

een ademhalingspatroon geregistreerd dat sterk lijkt op Cheyne-Stokes ademhalingen, welke zijn geassocieerd met een slechte uitkomst van hartfalen bij volwassenen. In **hoofdstuk 6** wordt de voorspellende waarde van speckle-tracking echocardiografie en de aanwezigheid van dyssynchronie onderzocht. We laten zien dat speckle-tracking een bruikbare en reproduceerbare techniek is bij kinderen met DCM. Globale longitudinale peak strain, hetgeen bepaald kan worden met speckle-tracking echocardiografie, blijkt voorspellend te zijn voor het risico op overlijden of harttransplantatie. Verder bleken kwantitatieve dyssynchronie parameters niet reproduceerbaar te zijn, en raden wij daarom af deze parameters te gebruiken bij kinderen met DCM. In tegenstelling tot volwassenen, toonde kwalitatieve patroonanalyse voornamelijk het patroon van 'afgenomen strain' in plaats van dyssynchrone patronen. Dit suggereert dat dyssynchronie een kleinere rol speelt bij kinderen dan bij volwassenen met DCM. In **hoofdstuk 7** worden de resultaten van de 6-minuten wandeltest beschreven. De 6-minuten wandeltest werd uitgevoerd bij kinderen ≥ 6 jaar, en de afstand die in 6 minuten werd afgelegd werd omgerekend naar een percentage van de voorspelde afstand van een gezonde populatie. We vonden dat een kortere afstand afgelegd in 6 minuten resulteerde in een hoger risico op overlijden of harttransplantatie. Patiënten die minder dan 63% van de voorspelde afstand liepen, hadden een hoger risico op een eindpunt dan kinderen die een afstand boven dit afkappunt haalden. In **hoofdstuk 8** beschrijven we, tot slot, wat de kwaliteit van leven is van kinderen met DCM, zoals deze door ouders werd gerapporteerd. Verder onderzoeken we de hypothese dat het functioneren van het kind, zoals het door de ouder gerapporteerd wordt met behulp van kwaliteit van leven vragenlijsten, belangrijke prognostische informatie bevat. Bovendien veronderstellen wij dat het gebruik van een gestandaardiseerde hartfalen scorelijst (New York University Pediatric Heart Failure Index) door de dokter ook bruikbare prognostische informatie oplevert. We concluderen dat 'fysiek functioneren' gerapporteerd door ouders en de ernst van het hartfalen gerapporteerd door de dokter, onafhankelijk van elkaar, voorspellend zijn voor de hoogte van het risico op overlijden of harttransplantatie.

DEEL IV. Algemene discussie

De studies zoals beschreven in dit proefschrift, worden in **hoofdstuk 10** bediscussieerd in het licht van de huidige literatuur. Verder beschrijven we de klinische implicaties van onze bevindingen en geven we richting voor toekomstig onderzoek.

We concluderen dat:

1. Door uniforme diagnostiek en interpretatie van de resultaten bij de verdenking op een myocarditis en vooruitgang in de wetenschap over onderliggende genetische oorzaken van DCM, zou de diagnostische classificatie kunnen verbeteren bij de meerderheid (65-75%) van de kinderen. Dit zou kunnen leiden tot het eerder diagnosticeren van patiënten met een familiaire DCM, het verbeteren van de risico inschatting en de behandeling van DCM.

2. De prognostische analyse van DCM bij kinderen in Nederland suggereert dat het gerechtvaardigd is om vroeg na diagnose, bij een aanzienlijk deel van de kinderen, terughoudend te zijn met plaatsing op de wachtlijst voor transplantatie.

3. Plaatsing op de wachtlijst voor transplantatie vroeg na diagnose is alleen legitiem voor hen die bij diagnose op de intensive care worden opgenomen en mechanische ondersteuning van de circulatie nodig hebben, aangezien dit risicofactoren zijn voor overlijden in het eerste jaar na diagnose.

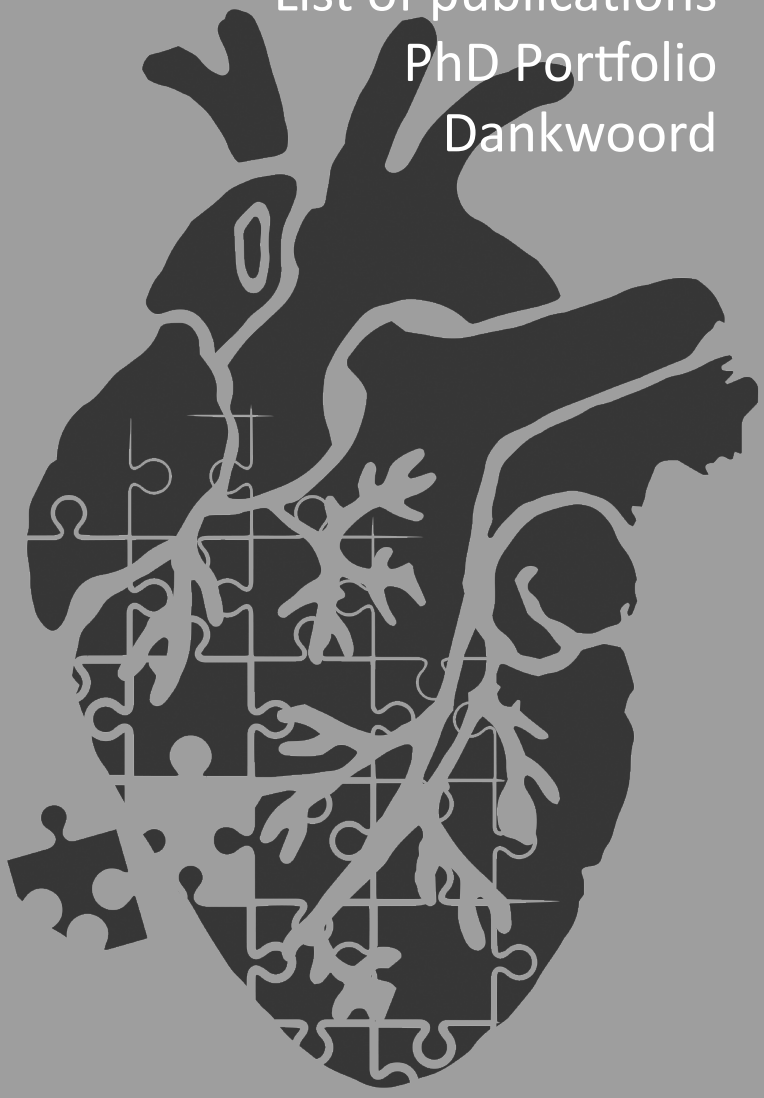
4. Leeftijd bij diagnose > 6 jaar was een risicofactor om een eindpunt te halen na het eerste jaar na diagnose; dit was in de meerderheid van de gevallen transplantatie in plaats van overlijden.

5. Hoge NT-proBNP waarden, welke vlak na diagnose niet dalen en/of hoger zijn dan 7990 pg/mL op 1 maand na diagnose, zijn geassocieerd met een verhoogd risico op overlijden, harttransplantatie of mechanische ondersteuning van de circulatie.

6. Bij DCM patiënten zijn, minimaal 1 jaar na diagnose, verschillende markers geassocieerd met een verhoogd risico op overlijden of harttransplantatie, namelijk: lagere globale longitudinale peak strain, hogere hartfalen score (NYU PHFI), lagere score voor fysiek functioneren op de kwaliteit van leven vragenlijst, hogere NT-proBNP waarde, stijgende NT-proBNP door de tijd, en een korter gewandelde afstand in 6 minuten. De onafhankelijke bijdrage van elk van deze factoren ten aanzien van het risico op een eindpunt is moeilijk het te onderzoeken, doordat DCM een zeldzame ziekte is (lage patiënt aantallen in een studie) en aantal harde eindpunten (overlijden en transplantatie) relatief laag is in de groep kinderen > 1 jaar na diagnose.

APPENDICES

List of co-authors and affiliations
Curriculum Vitae
List of publications
PhD Portfolio
Dankwoord



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CURRICULUM VITAE

Suzanne den Boer was born on 16 July 1984, in 's-Gravenzande, the Netherlands. She attended pre-university education at the "Interconfessionele Scholengemeenschap 't Westland" in 's-Gravenzande and received her certificate in 2002. Thereafter, Suzanne started medical training at the University of Utrecht. In the first years of this education, she worked as a nurse in a research institute and trained her young student colleagues in physical examination. She followed her internships in several hospitals in The Netherlands, and abroad in Nepal and Zambia. Besides her interest in patient care, she focused on medical research in the Meander Medical Center Amersfoort, Wilhelmina Children's Hospital in Utrecht and St. Antonius Hospital in Nieuwegein. She received her medical degree in 2009, and started working as a pediatric resident (ANIOS) at the St. Antonius Hospital in Nieuwegein. After a year, she decided that she wanted to expand her knowledge of medical research and got into contact with Dr. Michiel Dalinghaus. She got the opportunity to start a PhD in June 2010 at the department of Pediatric Cardiology in the Sophia Children's Hospital, Erasmus Medical Center in Rotterdam (supervisors Prof. Dr. WA Helbing and Dr. M Dalinghaus). Her study focused on potential prognostic factors in children with dilated cardiomyopathy and has resulted in this thesis.

In leisure time, Suzanne loves to cycle and to sail. She lives together with Mark and their son Coen (2014).

LIST OF PUBLICATIONS

den Boer SL, van Osch-Gevers M, van Ingen G, du Marchie Sarvaas GJ, van Iperen GG, Tanke RB, Backx APCM, ten Harkel ADJ, Helbing WA, Delhaas T, Bogers AJJC, Rammeloo LAJ, Dalinghaus M. Management of children with dilated cardiomyopathy in The Netherlands: Implications of a low early transplantation rate. *Journal of Heart and Lung Transplantation* 2015; 34(7): 963-969.

den Boer SL, Meijer RPJ, van Iperen GG, Ten Harkel ADJ, du Marchie Sarvaas GJ, Straver B, Rammeloo LAJ, Tanke RB, van Kampen JJA, Dalinghaus M. Evaluation of the diagnostic work-up in children with myocarditis and idiopathic dilated cardiomyopathy. *Pediatric Cardiology* 2015; 36(2): 409-416.

den Boer SL, Joosten KFM, van den Berg S, Backx APCM, Tanke RB, du Marchie Sarvaas GJ, Helbing WA, Rammeloo LAJ, ten Harkel ADJ, van Iperen GG, Dalinghaus M. Prospective Evaluation of Sleep Apnea as Manifestation of Heart Failure in Children. *Pediatric Cardiology* 2015; Oct 16: *epub ahead of print*.

den Boer SL, Du Marchie Sarvaas GJ, Klitsie LM, van Iperen GG, Tanke RB, Helbing WA, Backx APCM, Rammeloo LAJ, Dalinghaus M, ten Harkel ADJ. Longitudinal Strain as Risk Factor for Outcome in Pediatric Dilated Cardiomyopathy. *JACC: Cardiovascular imaging* 2015; Dec 6: *epub ahead of print*.

den Boer SL, Rizopoulos D, Du Marchie Sarvaas GJ, Backx APCM, Ten Harkel ADJ, van Iperen GG, Rammeloo LAJ, Tanke RB, Helbing WA, Dalinghaus M. Serial N-terminal pro-B-type natriuretic peptide measurements predict cardiac death in acute and chronic pediatric dilated cardiomyopathy. *Submitted*

den Boer SL, Flipse DHK, Van der Meulen MH, Backx APCM, Du Marchie Sarvaas GJ, Ten Harkel ADJ, van Iperen GG, Rammeloo LAJ, Tanke RB, Helbing WA, Takken T, Dalinghaus M. Six-minute walk test as predictor for outcome in children with dilated cardiomyopathy. *Submitted*

den Boer SL, Baart SJ, van der Meulen MH, van Iperen GG, Backx APCM, Ten Harkel ADJ, Rammeloo LAJ, Du Marchie Sarvaas GJ, Tanke RB, Helbing WA, Utens EMWJ, Dalinghaus M. Parent reports of health-related quality of life and heart failure severity score independently predict outcome in children with dilated cardiomyopathy. *Submitted*

den Boer SL, Schipper JA. Feeding and drinking skills in preterm and low birth weight infants compared to full term infants at a corrected age of nine months. *Early Human Development* 2013; 89(6): 445-447.

den Boer SL, Pasmans SG, Wulffraat NM, Ramakers-Van Woerden NL, Bousema MT. Bullous lesions in Henoch Schonlein Purpura as indication to start systemic prednisone. *Acta Paediatrica* 2010; 99(5): 781-783.

den Boer SL, Ramakers-Van Woerden NL, Pasmans SG, Wulffraat NM, Lagendijk JH, Bousema MT. [Bullae bij Henoch-Schönlein purpura; indicatie voor systemische behandeling met prednison]. *Nederlands Tijdschrift voor dermatologie en venereologie* 2009; 19(1): 10-15.

PHD PORTFOLIO

Name PhD student:	S.L. den Boer
Erasmus MC Department:	Pediatrics, division Pediatric Cardiology
Research School:	COEUR
PhD period:	2010 – 2015
Promotor:	Prof. Dr. W.A. Helbing
Copromotor:	Dr. M. Dalinghaus

	Year	Workload (ECTS)
General academic skills		
- BROK (Basiscursus Regelgeving Klinisch Onderzoek	2011	1.0
- Research Integrity	2012	2.0
- Biomedical English Writing and Communication	2013	4.0
Research skills		
- Nihes – Principles of Research in Medicine and Epidemiology	2010	0.7
- Nihes – Introduction to data-analysis	2010	1.0
- Nederlandse Hartstichting – Cardiac Function and Adaptation	2010	2.0
- COEUR – Cardiovascular Pharmacology"	2010	1.5
- COEUR – Coarctation of the aorta	2010	0.4
- Nihes – Regression analysis for clinicians	2011	1.9
- Nihes – Clinical Decision Analysis	2011	0.7
- Nihes – Case-control Studies	2011	0.7
- Nihes – Causal inference	2011	0.7
- Nihes – Markers and prognostic Research	2011	0.7
- COEUR – Research Seminar "Congenital Heart Disease"	2011	0.4
- Nihes – Biostatistical methods: basic principles	2012	5.7
- Biostatistics – Introduction to the joint modelling of longitudinal and survival data	2013	0.7
- COEUR – Cardiovascular imaging and diagnostics	2013	1.5
- COEUR – Translational Electrophysiology	2013	0.4
Seminars, workshops and other		
- COEUR PhD day	2010	0.4
- Karel V Symposium: Cardiomyopathy and Follow-up Fontan	2011	0.3
- Jonge Onderzoekersdag NVK 2011	2011	0.3
- Echocardiography course: Myocardial Velocity and Deformation Imaging, Leuven	2012	0.6
- Organizer annual CARS meetings – all study collaborators	2010-2014	1.0

	Year	Workload (ECTS)
(Inter)national conferences and presentations		
- Refereeravond Kindergeneeskunde UMCG, Groningen (*oral presentation*)	2010	0.3
- Landelijk overleg Werkgroep erfelijke hartziekten, Utrecht (*oral presentation*)	2011	0.3
- ALADIN meeting, Blijdorp, Rotterdam (*oral presentation*)	2011	0.3
- 1st European Meeting Pediatric Heart Failure & Transplantation, London, England	2011	0.6
- ESPNIC annual congress 2011, Hannover, Germany (*oral presentation*)	2011	1.2
- 1st European Workshop on Pediatric Exercise Testing, Utrecht (*poster presentation* - first prize)	2012	0.9
- 6th World Congress of Pediatric Cardiology and Cardiac Surgery, Cape Town, South Africa (*3 poster presentations*)	2013	2.4
- Vergadering Sectie Kindercardiologie, Utrecht (*oral presentation*)	2013	0.3
- Sophia Research Day (*poster presentation*)	2013	0.3
- ISHLT 35th annual meeting and scientific sessions	2015	0.9
- Vergadering Sectie Kindercardiologie, Utrecht (*oral presentation*)	2015	0.3
Teaching activities: supervising Master's theses		
- Diagnostics in dilated cardiomyopathy in children. RPJ Meijer (*published article*)	2012 2013	1.5 0.6
- The value of exercise training on risk stratification in children with dilated cardiomyopathy. DHK Flipse (*submitted article*)	2013	0.6
- Inventarisatie van de voedingstoestand, groei, energiebehoefte en energie-inname van kinderen in Nederland tussen 0 en 18 jaar met gedilateerde cardiomyopathie, MJ Vrijmoeth en NM Schotman		

ECTS – European Credit Transfer and Accumulation System
1 ECTS represents 28 hours

DANKWOORD

En dan is het zover; ik mag mijn dankwoord schrijven. Zo vaak heb ik er al over nagedacht, en toch heb ik het voor het allerlaatst bewaard.

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Dilated Cardiomyopathy in Children

UNRAVELING THE DETERMINANTS OF DISEASE PROGRESSION

Suzanne den Boer