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ORIGINAL ARTICLE

Is Endomyocardial Biopsy a Safe and Useful Procedure in Children with Suspected Cardiomyopathy?

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Abstract Endomyocardial biopsy (EMB) is a common procedure used to aid in the diagnosis, prognosis and treatment of suspected pediatric cardiomyopathy. In suspected cardiomyopathy, no multicenter experience has previously reported on the safety and utility of EMBs. Retrospectively, adverse event (AE) and patient and procedural characteristics were obtained at seven institutions participating in the Congenital Cardiac Catheterization Outcomes Project for both a cardiomyopathy ($n = 158$) and a post-transplant surveillance ($n = 2665$) cohort. Descriptive information regarding biopsy indication, pathology and clinical management based on EMB findings were retrospectively obtained. High-severity AEs were more common in the cardiomyopathy cohort when compared to the post-transplant surveillance cohort. The cardiomyopathy cohort was younger, more hemodynamically vulnerable and required more cardiorespiratory support during the procedure. The eight high-severity AEs in the cardiomyopathy group included one myocardial perforation, two ECMO cannulations and three deaths following the EMB. Factors associated with high-severity AEs included performing another catheter-based intervention during the EMB and longer fluoroscopy time. Notably, an increased number of biopsy attempts did not increase the risk of an AE. Suspected myocarditis was the most common indication. Diagnostic EMB pathology and thus alteration to clinical management based on pathology occurred more frequently in patients with suspected myocarditis. In conclusion, there is an increased incidence of high-severity AEs in patients undergoing EMB for suspected cardiomyopathy. EMB may be more clinically useful in the management of suspected myocarditis. The increased risk of high-severity AEs when additional interventions are performed highlights the hemodynamic vulnerability in patients with suspected cardiomyopathy.

Keywords Endomyocardial biopsy · Cardiomyopathy · Pediatric cardiology · Myocarditis

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Introduction

Cardiomyopathies are a heterogeneous group of myocardial diseases that alter systolic or diastolic performance as a result of mechanical or electrical dysfunction of the heart [1]. Although cardiomyopathies can be classified by echocardiography into dilated (DCM), restrictive (RCM), hypertrophic (HCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC), identifying the specific etiology of heart failure can guide management and provide important prognostic information [2]. Depending upon the etiology of the diagnosis, the clinical outcomes of children

with cardiomyopathy are highly variable with 5-year transplant-free survival ranging from 20 to 94 % [3].

Endomyocardial biopsy (EMB) is a common cardiac interventional procedure used to aid in the diagnosis, prognosis and treatment of cardiomyopathies [4]. However, due to the lack of prospective studies describing the utility of EMB, current recommendations are based on case–control series and expert opinion [4]. In 2007, the American Heart Association (AHA), the American College of Cardiology (ACC), and the European Society of Cardiology (ESC) endorsed a scientific statement outlining clinical scenarios in which EMBs are recommended [4]. The consensus statement highlighted the paucity of published literature addressing the safety and efficacy of EMB in children. Due to the lack of studies defining the utility and risks of EMB in pediatric cardiomyopathy patients, practitioners must rely on clinical judgment when deciding to refer their patient for an EMB [5].

Several single-center case series have retrospectively reviewed the safety of EMB in children. The studies report serious adverse event (AE) rates between 1 to 10 % and myocardial perforation rates as high as 5.2 % in children undergoing EMB [5–8]. Utilizing the Congenital Cardiac Catheterization Outcomes Project (C3PO) database, Daly et al. previously reported a 1 % rate of high-severity AEs associated with performing EMBs in the post-transplant surveillance population. These studies are often cited when describing the risk and utility of EMB in children with suspected cardiomyopathy; however, they are limited in either their retrospective nature, long periods of data collection or over-representation of post-transplant surveillance EMBs in the study population.

In this study, we queried the C3PO database to comprehensively examine risk factors associated with EMBs that resulted in AEs during cardiac catheterization procedures in pediatric patients with a suspected cardiomyopathy. We also sought to describe the utility of EMB in the management of pediatric cardiomyopathy by examining the influence pathology results had on the diagnosis and clinical management.

Methods

Congenital Cardiac Catheterization Outcomes Project (C3PO) Database

The C3PO is a multi-institutional, collaborative database of patient, procedural, and AE characteristics collected in a cross-sectional manner via a Web-based data entry tool [9]. Following IRB approval with a waiver for informed consent at each center, data collection began on February 1, 2007 at six institutions and two additional centers were incorporated in April 2008 and June 2009 ("Appendix"). All eight centers concluded data collection on June 30, 2010. As previously described, the occurrence of an AE was documented at the time of the procedure and updated for late AEs by the operating physician following the case [9]. Detailed data collection, validation and auditing have been previously published and demonstrated reliable capture of high-severity AEs (Level 3, 4, or 5) [10]. Classification of AE severity (ranging from Level 1–5) and attributability were based on established nomenclature (Supplemental Table 1) [9, 10].

Study Cohort

A retrospective review of all consecutive cases collected in the C3PO database between February 1, 2007 and June 30, 2010 was performed. The first case for any given patient recorded in the C3PO database with an intervention code listed as "RV biopsy diagnostic" or "Biopsy site not RV" was identified and cross-referenced with the indication for cardiac catheterization to ensure all suspected myocarditis, cardiomyopathy and new-onset heart failure biopsies were captured. One of the eight C3PO study centers did not perform any EMBs in subjects with a suspected cardiomyopathy during the study period, thus only seven centers were included in our cohort. A contemporaneous post-transplant cohort captured in the C3PO database that had undergone surveillance EMBs to screen for allograft rejection was used as a comparison group. The characteristics of the contemporaneous post-transplant surveillance population have been previously described in detail by Daly et al. [11].

Collected Data

Variables acquired included patient characteristics (age, weight, gender, diagnosis), case descriptions (admission status, case type, respiratory support, inotropic support, use of extracorporeal membrane oxygenator, case length, fluoroscopy time), hemodynamic parameters (mixed venous saturation, cardiac index, left ventricular end diastolic pressure or mean pulmonary capillary wedge pressure) and AE data (severity level, attributability). A separate IRB was approved with a waiver for informed consent at six of the seven participating centers where an attending pediatric cardiologist retrospectively reviewed each subject's medical record to collect further data regarding the EMB. Objective data acquired included the EMB pathology interpretation, the type of special stains used on the EMB and whether a viral PCR was performed. Subjective data obtained included determining if the primary indication for cardiac catheterization was the EMB itself, if the EMB pathology was diagnostic and if the EMB changed the

clinical management of the patient subsequently. Finally, in order to understand practice variability among the participating centers, we completed a post hoc online survey examining the reasoning behind indications for endomyocardial biopsy and additional diagnostic testing the centers performed.

Primary Outcome Variables

The primary endpoint for the safety analysis was defined by the occurrence of high-severity AEs associated with an EMB. We hypothesized that EMBs could be safely performed in children with a low rate of total and high-severity AEs. In addition, we hypothesized that the incidence of cardiac perforation associated with performing an EMB was appreciably lower than previously reported by Pophal et al. [7] (0.9 % overall, 5.4 % in children less than 10 kg). The utility of obtaining an EMB in pediatric cardiomyopathies was descriptive in nature and highlighted the diagnostic and clinical management strategies among centers based on the results of the EMB.

Statistical Methods

Categorical variables were summarized as frequencies and percentages. Comparisons between categorical variables were made utilizing Chi-square analysis or Fisher's exact test, as appropriate. Continuous variables were presented as mean ± standard deviation or median with interquartile ranges [25th %, 75th %]. Comparisons among continuous variables were made either by the student *t* test or the Wilcoxon rank-sum test, depending upon the normality of distribution. Univariate analyses were performed and a two-sided *p* value of <0.05 was considered statistically significant. Multivariable modeling was not performed because the high-severity AE rate was too low to support such a model. Statistical analysis was performed using SAS v9.3 (SAS Institute Inc., Cary, NC).

Results

Patient and Procedural Characteristics

Overall, 158 individual subjects with a suspected cardiomyopathy underwent cardiac catheterization involving an EMB at seven C3PO centers over the course of the 40-month study period. Compared to the previously published cohort of 2665 cardiac transplant recipients who underwent surveillance post-transplant EMB, the cardiomyopathy cohort was younger (12.6 years old [4.8, 16.7] vs. 10.6 [1.8, 15.9]; $p < 0.01$), had a lower cardiac index (3.3 L/min/m^2 ± 1.2 vs. 3.7 ± 1.2; $p < 0.01$), and a higher left-sided filling pressure (14.8 mmHg ± 7.9 vs. 10.8 ± 4.4; $p < 0.01$; Table 1). EMBs in the cardiomyopathy group were more likely to be performed on an urgent or emergent basis when compared to the post-transplant group (63.3 vs. 7.2 %; $p < 0.01$; Table 1). Cardiac catheterizations performed in the suspected cardiomyopathy group were more likely to be performed with the assistance of inotropic agents (37 vs. 3 %; $p < 0.01$), mechanical circulatory support (9 vs. 0.4 %; $p < 0.01$) and mechanical ventilation (68 vs. 49 %; $p < 0.01$) when compared to the post-transplant surveillance cohort (Table 1). In addition to performing an EMB, additional interventions at the time of cardiac catheterization were more likely to occur in the cardiomyopathy cohort when compared to the post-transplant surveillance group (78 vs. 2 %; $p < 0.01$; Table 1). The indications for EMB in the cardiomyopathy cohort were suspected myocarditis in 36 %, new-onset heart failure in 14 %, dilated cardiomyopathy in 22 %, restrictive cardiomyopathy in 10 %, hypertrophic cardiomyopathy in 5 %, arrhythmia in 7 %, and other in an additional 7 % (Table 2).

Patient and Procedural Risk Factors for High-Severity Adverse Events

Within the cardiomyopathy cohort, 16 total AEs occurred during or following 10 % of EMB cases, which is three times the rate seen in the post-transplant surveillance cohort ($p < 0.01$; Table 1). Half of the AEs were classified as high-severity and occurred during 5 % of suspected cardiomyopathy EMB cases, a much higher incidence than the 1.1 % observed in the post-transplant surveillance population ($p < 0.01$; Table 1). Highlighting the disproportionate occurrence of AEs between the two groups, there were a total of three catastrophic (Level 5) AEs in the cardiomyopathy EMB cohort, all of which resulted in death of the patient, in comparison to no deaths in the post-transplant surveillance group ($p < 0.01$; Table 1).

Performance of an additional catheter-based intervention was the characteristic most significantly associated with high-severity AEs with none occurring in cases where the EMB was the only intervention ($p < 0.01$; Table 3). The most common additional intervention performed was creation or dilation of an atrial septal defect ($n = 15$). Longer fluoroscopy time was associated with those who experienced a high-severity AE (23 min [15, 53] vs. 13 [9, 21]; $p = 0.03$); however, corrected case length (which represents total case length minus the time added to manage an adverse event) was not significantly longer than those who experienced a high-severity AE (109 min [47, 195] vs. 65 [42, 86]; $p = 0.09$; Table 3). While cardiac index was lower (3.3 L/min/m^2 ± 1.1 vs. 3.7 ± 2.5; $p = NS$), and left-sided filling pressure was higher

Table 1 Comparison of patient and procedural characteristics between post-transplant and suspected cardiomyopathy EMB cohorts

	Post-transplant EMB ($n = 2665$)	CM EMB ($n = 158$)	p value
Age (year)	12.6 [4.8, 16.7]	10.6 [1.8, 15.9]	<0.01
Weight (kg)	36.5 [16.7, 56.8]	35 [11, 60]	NS
Male (%)	1447 (54)	89 (56)	NS
Admission status (%)			
Elective	2475 (93)	58 (37)	<0.01
Urgent	185 (7)	84 (53)	
Emergent	5 (0.2)	16 (10)	
Cardiorespiratory support (%)			
Mechanical ventilation	1305 (49)	109 (69)	<0.01
Inotropes	70 (2.6)	59 (37)	<0.01
ECMO	11 (0.4)	15 (9)	<0.01
Case type (%)			
EMB only	2611 (98)	36 (23)	<0.01
EMB + intervention	54 (2)	122 (77)	
Cases with any AE (%)	88 (3.3)	16 (10)	<0.01
Cases with high-severity AE (%)	28 (1.1)	8 (5)	<0.01
Death related to AE (%)	0	3 (2)	<0.01
Hemodynamic parameters			
Cardiac index (L/min/m^2)	3.7 ± 1.2	3.3 ± 1.2	<0.01
Mixed venous saturation (%)	71 ± 7	66 ± 9	<0.01
LVEDp or mPCWP (mmHg)	10.8 ± 4.4	14.8 ± 7.9	<0.01

EMB endomyocardial biopsy, *CM* cardiomyopathy, *ECMO* extracorporeal membrane oxygenator, *AE* adverse event, *LVEDp* left ventricular end diastolic pressure, *mPCWP* mean pulmonary capillary wedge pressure

Table 2 Indication for EMB, utility in diagnosis, and effect on clinical management

Indication for EMB	*n* (%)	EMB was the primary indication for catheterization *n* (%)	EMB resulted in a clinical diagnosis *n* (%)	EMB changed clinical management *n* (%)
Overall	141 (100)	82 (58)	65 (46)	45 (32)
Suspected myocarditis	50 (36)	37 (74)	31 (62)	25 (50)
New-onset heart failure	21 (15)	11 (55)	5 (25)	4 (21)
Dilated CM	30 (21)	13 (43)	8 (27)	3 (10)
Restrictive CM	14 (10)	7 (50)	6 (43)	6 (43)
Hypertrophic CM	7 (5)	3 (43)	4 (57)	1 (14)
Arrhythmia	9 (6)	0	3 (33)	1 (11)
Miscellaneous	10 (7)	4 (44)	3 (33)	1 (11)

Results from 141 of the 158 cases in the study cohort were obtained

EMB endomyocardial biopsy, *CM* cardiomyopathy

(14.6 mmHg ± 7.7 vs. 19 ± 11; $p = NS$), in subjects experiencing a high-severity AE, this difference did not reach statistical significance (Table 3). There were no other differences in rate of high-severity AEs relative to other collected patient or procedural variables, including number of biopsy attempts (Table 3).

Adverse Event Description and Attributability: Cardiomyopathy Cohort

During the study period, one Level 1 and seven Level 2 AEs occurred. The Level 1 AE involved a circumferential balloon rupture while placing an atrial septal stent

Table 3 Cardiomyopathy patient and procedural characteristics

	CM EMB without AE ($n = 150$)	CM EMB with high-severity AE ($n = 8$)	p value
Age [year (%)]			
<1	26 (17)	1 (13)	NS
1–9	44 (29)	4 (50)	
≥10	80 (53)	3 (38)	
Weight [kg (%)] ($n = 157$)			
<4	5 (3)	1 (13)	NS
4–9	23 (15)	1 (13)	
10–19	30 (20)	2 (25)	
≥20	91 (60)	4 (50)	
Male (%)	84 (55)	5 (63)	NS
Admission status (%)			
Elective	56 (37)	2 (25)	NS
Urgent	82 (54)	4 (50)	
Emergent	14 (9)	2 (25)	
Cardiorespiratory support (%)			
Mechanical ventilation	101 (66)	8 (100)	NS
Inotropes	55 (36)	4 (50)	NS
ECMO	14 (9)	1 (13)	NS
Case type (%)			
EMB only	36 (24)	0	<0.01
EMB + intervention	116 (76)	8 (100)	
Hemodynamic parameters			
Cardiac index (L/min/m^2)	3.3 ± 1.1	3.7 ± 2.5	NS
Mixed venous saturation (%)	66 ± 9	62 ± 15	NS
LVEDp or mPCWP (mmHg)	14.6 ± 7.7	19 ± 11	NS
Number of biopsy attempts ($n = 65$)	6 [4, 7]	5 [4, 6]	NS
Number of biopsy specimens ($n = 65$)	5 [4, 6]	4 [4]	NS
Case length (min)	65 [42, 86]	109 [47, 195]	NS
Fluoroscopy time (min)	13 [9, 21]	23 [15, 53]	0.03

CM cardiomyopathy, *EMB* endomyocardial biopsy, *AE* adverse event, *ECMO* extracorporeal membrane oxygenator, *LVEDp* left ventricular end diastolic pressure, *mPCWP* mean pulmonary capillary wedge pressure

(Table 4). The Level 2 AEs included an atrial tachyarrhythmia related to performing an EMB, transient hypotension attributed to anesthesia, transient ST-T wave changes, pulse loss at the vascular access site, and thrombus noted on the right atrial side of an atrial septal defect closure device post-cardiac catheterization. Two Level 3 AEs occurred and included a patient with repeated episodes of hemodynamically significant supraventricular tachycardia requiring electrical cardioversion and malposition of an atrial septal defect stent that was ultimately repositioned in the inferior vena cava. Three Level 4 AEs occurred and included ventricular fibrillation during catheter manipulation requiring defibrillation, interruption in an extracorporeal membrane oxygenator (ECMO) circuit during transport requiring volume resuscitation and a single myocardial perforation following EMB that required treatment with pericardiocentesis.

The subject who suffered a myocardial perforation during the EMB was the only high-severity AE directly attributed to the EMB intervention itself (Table 4). The patient was a 12.5-kg, 12-month-old with suspected myocarditis secondary to complete heart block. Hypotension was noted following acquisition of the third biopsy sample and a pericardial effusion was confirmed by echocardiography. The perforation was treated with emergent pericardiocentesis, protamine for heparin reversal and fluid resuscitation. The patient was stabilized, transferred to the intensive care unit for monitoring and the pericardial drain was uneventfully removed the following day.

Table 4 Adverse event attributability

Adverse event characteristic	All levels ($n = 16$)	Level 1 ($n = 1$)	Level 2 ($n = 7$)	Level 3 ($n = 2$)	Level 4 ($n = 3$)	Level 5 ($n = 3$)
Biopsy	2	–	1	–	1	–
Atrial arrhythmia	1	–	1	–	–	–
Myocardial perforation	1	–	–	–	1	–
Coronary angiography	–	–	–	–	–	–
Sedation or airway	1	–	1	–	–	–
Hypotension	1	–	1	–	–	–
General catheterization	8	–	3	1	2	2
Asystole	1	–	–	–	–	1
Atrial arrhythmia	2	–	1	1	–	–
Non-specific ST-T change	2	–	2	–	–	–
Other equipment problem	1	–	–	–	1	–
Ventricular arrhythmia	2	–	–	–	1	1
Access	1	–	1	–	–	–
Pulse loss	1	–	1	–	–	–
Angioplasty	1	1	–	–	–	–
Circumferential balloon rupture	1	1	–	–	–	–
Stent	2	–	–	1	–	1
Stent malposition	1	–	–	1	–	–
Ventricular arrhythmia	1	–	–	–	–	1
Device	1	–	1	–	–	–
Device thrombus	1	–	1	–	–	–

Finally, there were three catastrophic, Level 5 AEs (2 % of total cases) that resulted in the death (Table 4). One death occurred in a 12-year-old diagnosed with restrictive cardiomyopathy that developed complete heart block following reversal of anesthesia and was unable to be resuscitated despite attempts at ECMO used to support cardiopulmonary resuscitation (E-CPR). A second death occurred in a patient brought to the catheterization lab with incessant and medically refractory ventricular arrhythmias secondary to suspected myocarditis. Upon placement of a right subclavian sheath, the patient developed sustained ventricular tachycardia that degenerated into ventricular fibrillation. The patient was subsequently cannulated onto ECMO, but attempts at resuscitation were unsuccessful. The third death occurred in a patient with new-onset heart failure who was subsequently found to have left main coronary artery (LMCA) stenosis that was stented during the same procedure as the EMB. The following day, the patient became hypotensive and bradycardic requiring initiation of E-CPR. While the patient was in ventricular fibrillation, subsequent angiography revealed partial thrombosis of the recently placed LMCA stent prompting transfer of the patient to the operating room where attempts at surgical repair were unsuccessful. The patient subsequently suffered a catastrophic stroke while on ECMO and the parents ultimately decided to redirect care with removal of life-sustaining therapies.

Practice Variation in the Performance of Endomyocardial Biopsy

Five of the seven centers that contributed cases responded to our post hoc practice variation survey. Based on the survey, the most common indication for referral for EMB was suspected myocarditis, though 3 of the 5 centers estimated that less than 33 % of the patients with suspected myocarditis were referred for EMB. These centers reported that patients with suspected myocarditis always had an echocardiogram performed and usually had a molecular marker of cardiac damage (i.e., troponin-T, CK-MB) performed. Three of the five centers performed cardiovascular magnetic resonance imaging (CMR) exclusively in patients with suspected myocarditis and all of the responding centers believed that CMR was performed more often than EMB in patients with suspected myocarditis.

Utility of Endomyocardial Biopsy in New-Onset Cardiomyopathy

Among the entire study cohort and in agreement with the survey results, EMB was the primary indication for cardiac catheterization most often in patients with suspected myocarditis (Table 2). EMB was most likely to be diagnostic in patients with either suspected myocarditis, hypertrophic or restrictive cardiomyopathy (Table 2). Of the 50 patients who had undergone EMB for suspected myocarditis, a pathologic diagnosis was made in 31 patients (62 %); 29 with a final diagnosis of acute myocarditis and the other 2 diagnosed with dilated cardiomyopathy. The 19 non-diagnostic EMBs for suspected myocarditis consisted of 4 subjects whose final clinical diagnosis were acute myocarditis and 6 subjects ultimately diagnosed with dilated cardiomyopathy. The remaining diagnoses included congenital complete heart block, myocardial infarction, and multisystem organ failure secondary to bacterial sepsis. The results of the EMB changed clinical management 50 % of the time in patients with suspected myocarditis and 43 % of the time in patients with restrictive cardiomyopathy (Table 2).

Discussion

Safety of Endomyocardial Biopsy in Children with Cardiomyopathy

Our study is the first multicenter experience to report on the safety and diagnostic yield of EMB in children with cardiomyopathy, myocarditis and/or new-onset heart failure. The study illustrates that the risk of AEs during cardiac catheterization procedures involving EMB in children with suspected cardiomyopathy is substantially higher than the risk of AEs in the post-transplant population. The 2665 patients who underwent EMB for post-transplant surveillance within the C3PO database only experienced a 1.1 % rate of high-severity AEs and had no documented cases of cardiac perforation or death [11]. Conversely, our study demonstrated a 5 % rate of high-severity AEs in subjects who underwent EMB for suspected cardiomyopathy at the same centers and during the same time period within the C3PO database. In addition, there was a single occurrence of cardiac perforation and three catastrophic events within our suspected cardiomyopathy cohort.

Comparing our findings to previously published single-institution case series is challenging since most reports do not separate out the cardiomyopathy patients and the majority of the reported procedures were performed in heart transplant recipients [6–8, 11–16]. However, Pophal et al. [7] presented approximately 150 children who had undergone an EMB to diagnose cardiomyopathy among a larger cohort of 1000 total EMB procedures. Sub-analysis of the non-transplant cohort demonstrated a 9 % incidence of serious complications, compared to an overall incidence of serious complications in 2 % of the study population when the transplant cohort was included. In addition, cardiac perforation occurred in 5 % of the non-transplant biopsy cases [7]. Cowley et al. described 1051 EMBs performed in children of which 8 % were conducted to aid in the diagnostic workup of cardiomyopathy [4]. The overall AE rate was 1 % and sub-analysis of the cardiomyopathy cohort found only one of the 82 EMBs (1.2 %) resulted in a serious AE [14]. In both studies, procedural complications were defined as an AE that required additional treatment or observation, a similar definition to our own high-severity AEs. The variability in the rate of high-severity AEs between the contemporary data and these two studies may be due to differences in patient selection for EMB, changes in EMB technique, and availability of new equipment [7].

The increased incidence of total and high-severity AEs in the suspected cardiomyopathy cohort compared to the post-transplant population is undoubtedly influenced by the underlying severity of illness. Poor hemodynamic parameters, the need for additional cardiorespiratory support and a substantial percentage of patients undergoing supplementary catheter-based interventions at the time of the EMB highlight the population's fragile physiologic state. Univariate analysis within our study identified additional catheter-based interventions and longer fluoroscopy time as factors associated with the occurrence of a high-severity AE. Other associations may exist but may not have been elucidated due to our small patient population and low number of high-severity AEs resulting in limited power. Only one of the eight high-severity AEs within our cohort was attributed to the EMB itself. Thus, the need and performance of additional catheter-based interventions appears to raise the occurrence risk of a high-severity AE. However, only 52 percent of the catheterizations (64 out of 124) were performed with the primary indication of obtaining an EMB. The most common additional catheter-based intervention was the creation or dilation of an atrial septal defect, most likely for left atrial decompression while on ECMO. Similar to Eastaugh et al., we had only one high-severity AE that was attributed to left atrial decompression while on ECMO [17]. Finally, the association of high-severity AEs with longer fluoroscopy times is likely due to either the performance of additional catheter-based interventions that require fluoroscopy to complete or that additional fluoroscopy was necessary to manage an adverse event that occurred during the case. It is unlikely that longer fluoroscopy time itself results in a high-severity AE. Finally, it is important to note there were no reported

episodes of permanent conduction system disturbance or injury to the tricuspid valve seen in the cardiomyopathy cohort—both of which are associated with multiple EMB procedures in the heart transplant population [18, 19].

Cardiac Perforation

The danger of myocardial perforation is frequently cited as a clinical concern when assessing the risk of performing EMBs in children, specifically in patients with dilated cardiomyopathy and myocarditis. Prior reports have identified younger age, smaller size, inotrope use and suspected myocarditis to be risk factors for cardiac perforation [7]. Others have speculated that this may be due to thin ventricular walls in patients with dilated cardiomyopathy and/or myocarditis [7]. However, this hypothesis was not supported in a large adult EMB series where all of the cardiac perforations occurred in patients without a dilated phenotype [18]. A recent case series reported that cardiac perforation occurred in 4 % of EMB procedures performed in children less than 1 year of age—with a weight less than 8 kg and age less than 6 months being the primary risk factors [5]. The single cardiac perforation in our series occurred in a subject with suspected myocarditis secondary to complete heart block and precludes an independent risk factor analysis. The subject would not have been considered high-risk based on previous publications, as the patient was 12.5 kg and 12 months old [5]. In addition, nearly 20 % of our suspected cardiomyopathy cohort weighed less than 10 kg and 17 % were under a year of age. However, the low incidence may be result of a change in practice based on previously published data and improvement in biopsy equipment and techniques. Nonetheless, the risks and benefits of EMB should be carefully weighed in small infants less than 8 kg. Given the increased risk for cardiac perforation, consideration could be given in the future for the use of echocardiography to confirm bioptome position prior to each attempt in infants under 8 kg [20].

Practice Variation in EMB in Patients with Suspected Myocarditis

A recent report analyzing the Pediatric Health Information System (PHIS) database showed a clear statistical trend toward fewer EMBs and more CMRs in children with myocarditis between 2006 and 2011 [21]. The study demonstrated a fivefold increase in the use of CMR over the 5-year study period (from 5.2 to 28.1 %) with a concomitant decline in the rate of EMB (from 24.7 to 14 %) procedures [21]. Looking at the EMB case mix, the proportion of EMBs performed in children with a suspected cardiomyopathy relative to the number of total EMBs is lower in the C3PO cohort (5.6 % of biopsy cases) compared to single-center historical cohorts (Pophal et al. reported 15.4 % and Cowley et al. described 7.8 %) [7, 14]. In fact, the number of subjects with a suspected cardiomyopathy in the Pophal et al. [7] series actually exceeded the number of post-transplant surveillance subjects (123 vs. 90). In the C3PO database, 158 individual subjects underwent EMB for evaluation of a suspected cardiomyopathy and 744 individual post-transplant subjects underwent EMB for evaluation of rejection suggesting a shift in EMB utilization [11]. This shift in EMB utilization was supported by the post hoc survey of cardiologists at the participating C3PO centers that suggested that CMR was being utilized more often than EMB in patients with suspected myocarditis. Just as we found center-based variation in the number of suspected cardiomyopathy EMBs, the PHIS analysis suggested that the differences in the diagnostic approach to myocarditis were regional with EMBs performed more often in the northeastern USA compared the central USA where CMR was more commonly utilized [21].

In 1991, Gagliardi et al. [22] first described the application of CMR to aid in the diagnosis of myocarditis in children. Since then, several clinical studies have attempted to support the diagnostic utility of CMR in patients with myocarditis [23–36]. Although the publications provide evidence for the use of CMR, it is important to acknowledge most of these studies are single-center reports with small sample sizes, variable inclusion criteria, differing CMR protocols, varying diagnostic criteria and do not routinely validate the diagnosis with an EMB sample. Furthermore, the prognostic value of CMR remains unclear, as criteria have not been extensively defined to aid in predicting functional recovery in subjects with myocarditis [37]. Due to these findings, the ACC recently published a Journal of American College of Cardiology (JACC) White Paper regarding the use of CMR in myocarditis [38]. The consensus group recommended that CMR should be used as part of the comprehensive diagnostic approach to patients with suspected myocarditis [38]. In addition, the group determined that the CMR report should include information regarding left ventricular volumes, left ventricular function, and the presence or absence of markers of inflammation through the use of T2-weighted images and early and late-gadolinium enhancement [38]. The recommendation for a follow-up CMR by the consensus group was 4 weeks after the onset of symptoms to provide important prognostic information for the patient [38].

Utility of Endomyocardial Biopsy in Children with Cardiomyopathy

The workup of children with a suspected cardiomyopathy requires the integrated synopsis of serum biomarkers, noninvasive imaging, cardiac catheterization and clinical

history in order to arrive at an etiologic diagnosis, provide important prognostic information, and direct clinical decision making. As a result, there is variation in how patients are evaluated between physicians and centers. The role of EMB in determining the etiology of myocardial failure in children remains poorly defined. Although no current guidelines recommend the universal utilization of EMB in diagnosing suspected cardiomyopathies, it does remain the "gold standard" for diagnosis of myocardial disease [4]. The 2007 AHA/ACC/ESC scientific statement gave EMB a class I recommendation in patients with new-onset heart failure of <2 weeks duration with a normal-sized or dilated left ventricle and hemodynamic compromise [4]. Unexplained cardiomyopathy in children was given a class IIa recommendation with level of evidence C. Since these are important and difficult clinical questions to address, we retrospectively surveyed pediatric cardiologists to review the role of EMB in arriving at an etiological diagnosis and whether the EMB result aided in clinical decision-making. We found that for patients with suspected myocarditis and hypertrophic cardiomyopathy, the EMB resulted in a clinical diagnosis more than half of the time. The pathological results of the EMB were most useful in guiding clinical management in patients with suspected myocarditis or restrictive cardiomyopathy.

There are limitations to EMBs, however, that must be considered. First the sensitivity of EMB is limited due to sampling error [39]. Second, there is debate among several professional organizations regarding the diagnostic criteria for analyzing myocardial pathology [40]. Finally, several publications have demonstrated poor inter-observer agreement among pathology sample findings [41]. In addition, the National Australian Childhood Cardiomyopathy study found 36 % of the children presenting with a phenotypically dilated cardiomyopathy had evidence of lymphocytic myocarditis on histology [42]. This is corroborated by a publication reporting nearly 30 % of explanted hearts undergoing orthotopic heart transplantation for phenotypically dilated cardiomyopathy were also found to have lymphocytic infiltration [42]. It has been suggested that routine clinical use of EMB in children presenting with acute decompensated heart failure allows for identification of patients with myocarditis who have a better long-term prognosis and can guide listing decisions for heart transplantation as well as reducing the incidence of lymphocytic infiltrate seen at explantation [43].

Study Limitations

Our study should be considered in light of several limitations. Data analysis was performed retrospectively and thus is subject to the inherent constraints of data collection. In addition, data collection was completed 5 years prior to publication of our study; however, there has not been a programmatic change in the indication and performance of endomyocardial biopsies during this time period and thus our data likely still represents current practice. As previously published in papers utilizing the C3PO database, the reliability of event reporting varies at individual centers and random misclassification of certain data elements in the manual data entry tool can occur. Although the study represents the largest cohort of children undergoing EMB for suspected cardiomyopathy to date, there still were only eight high-severity AEs that occurred in the cohort prohibiting multi-variable analysis of risk factors. There is a selection bias in patients who underwent EMB that likely biased the study population toward sicker patients who are more vulnerable to adverse events. Thus the adverse event rates may be different in stable patients with cardiomyopathy. Finally, data collection regarding indication for biopsy, diagnostic yield, and impact on clinical management was obtained through retrospective chart review and may be subject to misclassification bias.

Conclusions

There is an increased incidence of high-severity AEs in patients undergoing EMBs for suspected cardiomyopathy when compared to the post-transplant surveillance population—highlighting the vulnerability of this patient population. High-severity AEs in the suspected cardiomyopathy cohort were associated with additional catheter-based procedures and longer fluoroscopy time. Among patients with a suspected cardiomyopathy, EMB appears to be most clinically relevant in the management of suspected myocarditis and restrictive cardiomyopathy. Since EMB has an established role in the identification and prognostic stratification of patients presenting with possible myocarditis, a prospective multicenter study of the performance characteristics of standardized CMR sequences to pathologic EMB diagnosis for myocarditis is necessary. In addition, a prospective multicenter study within the pediatric cardiomyopathy registry (PCMR) could potentially examine the rationale behind why physicians chose certain diagnostic tests when considering the diagnosis of a suspected cardiomyopathy. Our findings enhance the overall understanding of the risks and utility of EMB in the clinical management of children with suspected cardiomyopathy.

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Zuckerman, Timothy M. Hoffman, Charles E. Canter, Audrey C. Marshall, Elizabeth D. Blume helped in data collection, study design, revision of article; Lisa Bergersen contributed to overall database design, study design and critical revision of article; and Kevin P. Daly helped in study concept and design, data collection and critical revision of article.

Compliance with Ethical Standards

Conflict of interest The authors have no financial or professional disclosures to report related to any of the data presented herein.

Appendix: Study Sites and Participants

Children's Hospital Boston: Lisa Bergersen, MD, MPH, Michael Landzberg, MD, Peter Lang, MD, James Lock, MD, Audrey Marshall, MD, and Doff McElhinney, MD.

Cincinnati Children's Hospital Medical Center: Robert Beekman, MD, and Russel Hirsch, MD.

Morgan Stanley Children's Hospital of New York Presbyterian: William Hellenbrand, MD, Julie Vincent, MD, and Alejandro Torres, MD.

Nationwide Children's Hospital: John Cheatham, MD, Ralf Holzer, MD, and Timothy Hoffman, MD.

St. Louis Children's Hospital: David Balzer, MD, Susan Foerster, MD, Ramzi Nicolas, MD, and Joshua Murphy, MD.

Rady Children's Hospital—San Diego: John Moore, MD, and Howaida El-Said, MD.

Pittsburgh Children's Hospital: Jacqueline Kreutzer, MD, Sara Trucco, MD, Brian Feingold, MD, Susan Miller, MD, and Lee Berman, MD.

Oregon Health Sciences University: Grant Burch, MD, and Laurie Armsby, MD.

References

1. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D et al (2006) Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 113(14):1807–1816
2. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL et al (2000) Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 342(15):1077–1084
3. Wilkinson JD, Landy DC, Colan SD, Towbin JA, Sleeper LA, Orav EJ et al (2010) The pediatric cardiomyopathy registry and heart failure: key results from the first 15 years. Heart Fail Clin 6(4):401–413
4. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U et al (2007) The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol 50(19):1914–1931
5. Zhorne D, Petit CJ, Ing FF, Justino H, Jefferies JL, Dreyer WJ et al (2013) A 25-year experience of endomyocardial biopsy safety in infants. Catheter Cardiovasc Interv 82(5):797–801
6. Schmaltz AA, Apitz J, Hort W, Maisch B (1990) Endomyocardial biopsy in infants and children: experience in 60 patients. Pediatr Cardiol 11(1):15–21
7. Pophal SG, Sigfusson G, Booth KL, Bacanu SA, Webber SA, Ettedgui JA et al (1999) Complications of endomyocardial biopsy in children. J Am Coll Cardiol 34(7):2105–2110
8. Yoshizato T, Edwards WD, Alboliras ET, Hagler DJ, Driscoll DJ (1990) Safety and utility of endomyocardial biopsy in infants, children and adolescents: a review of 66 procedures in 53 patients. J Am Coll Cardiol 15(2):436–442
9. Bergersen L, Gauvreau K, Jenkins KJ, Lock JE (2008) Adverse event rates in congenital cardiac catheterization: a new understanding of risks. Congenit Heart Dis 3(2):90–105
10. Bergersen L, Marshall A, Gauvreau K, Beekman R, Hirsch R, Foerster S et al (2010) Adverse event rates in congenital cardiac catheterization—a multi-center experience. Catheter Cardiovasc Interv 75(3):389–400
11. Daly KP, Marshall AC, Vincent JA, Zuckerman WA, Hoffman TM, Canter CE et al (2012) Endomyocardial biopsy and selective coronary angiography are low-risk procedures in pediatric heart transplant recipients: results of a multicenter experience. J Heart Lung Transplant 31(4):398–409
12. Leatherbury L, Chandra RS, Shapiro SR, Perry LW (1988) Value of endomyocardial biopsy in infants, children and adolescents with dilated or hypertrophic cardiomyopathy and myocarditis. J Am Coll Cardiol 12(6):1547–1554
13. Chin C, Akhtar MJ, Rosenthal DN, Bernstein D (2000) Safety and utility of the routine surveillance biopsy in pediatric patients 2 years after heart transplantation. J Pediatr 136(2):238–242
14. Cowley CG, Lozier JS, Orsmond GS, Shaddy RE (2003) Safety of endomyocardial biopsy in children. Cardiol Young 13(5):404–407
15. Lurie PR, Fujita M, Neustein HB (1978) Transvascular endomyocardial biopsy in infants and small children: description of a new technique. Am J Cardiol 42(3):453–457
16. Shaddy RE, Bullock EA (1993) Efficacy of 100 consecutive right ventricular endomyocardial biopsies in pediatric patients using the right internal jugular venous approach. Pediatr Cardiol 14(1):5–8
17. Eastaugh LJ, Thiagarajan RR, Darst JR, McElhinney DB, Lock JE, Marshall AC (2015) Percutaneous left atrial decompression in patients supported with extracorporeal membrane oxygenation for cardiac disease. Pediatr Crit Care Med 16:59–65
18. Holzmann M, Nicko A, Kuhl U, Noutsias M, Poller W, Hoffmann W et al (2008) Complication rate of right ventricular endomyocardial biopsy via the femoral approach: a retrospective and prospective study analyzing 3048 diagnostic procedures over an 11-year period. Circulation 118(17):1722–1728
19. Chen RJ, Wei J, Chang CY, Chuang YC, Lee KC, Sue SH et al (2008) Tricuspid valve regurgitation and endomyocardial biopsy after orthotopic heart transplantation. Transplant Proc 40(8):2603–2606
20. McCreery CJ, McCulloch M, Ahmad M, deFilippi CR (2001) Real-time 3-dimensional echocardiography imaging for right ventricular endomyocardial biopsy: a comparison with fluoroscopy. J Am Soc Echocardiogr 14(9):927–933
21. Ghelani SJ, Spaeder MC, Pastor W, Spurney CF, Klugman D (2012) Demographics, trends, and outcomes in pediatric acute

myocarditis in the United States, 2006 to 2011. Circ Cardiovasc Qual Outcomes 5(5):622–627
22. Gagliardi MG, Bevilacqua M, Di Renzi P, Picardo S, Passariello R, Marcelletti C (1991) Usefulness of magnetic resonance imaging for diagnosis of acute myocarditis in infants and children, and comparison with endomyocardial biopsy. Am J Cardiol 68(10):1089–1091
23. Friedrich MG, Strohm O, SchulzMenger J, Marciniak H, Luft FC, Dietz R (1998) Contrast media-enhanced magnetic resonance imaging visualizes myocardial changes in the course of viral myocarditis. Circulation 97:1802–1809
24. Laissy JP, Messin B, Varenne O et al (2002) MRI of acute myocarditis: a comprehensive approach based on various imaging sequences. Chest 122:1638–1648
25. Mahrholdt H, Goedecke C, Wagner A et al (2004) Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. Circulation 109:1250–1258
26. Abdel-Aty H, Boye P, Zagrosek A et al (2005) Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: comparison of different approaches. J Am Coll Cardiol 45:1815–1822
27. Gutberlet M, Spors B, Thoma T et al (2008) Suspected chronic myocarditis at cardiac MR: diagnostic accuracy and association with immunohistologically detected inflammation and viral persistence. Radiology 246:401–409
28. Roditi GH, Hartnell GC, Cohen MC (2000) MRI changes in myocarditis—evaluation with spin echo, cine MR angiography and contrast enhanced spin echo imaging. Clin Radiol 55:752–758
29. Rieker O, Mohrs O, Oberholzer K, Kreitner KF, Thelen M (2002) Cardiac MRI in suspected myocarditis. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr. 174:1530–1536
30. Laissy JP, Hyafil F, Feldman LJ et al (2005) Differentiating acute myocardial infarction from myocarditis: diagnostic value of early- and delayed-perfusion cardiac MR imaging. Radiology 237:75–82
31. Ingkanisorn WP, Paterson DI, Calvo KR et al (2006) Cardiac magnetic resonance appearance of myocarditis caused by high dose IL-2: similarities to community-acquired myocarditis. J Cardiovasc Magn Reson 8:353–360
32. De Cobelli F, Pieroni M, Esposito A et al (2006) Delayed gadolinium-enhanced cardiac magnetic resonance in patients with chronic myocarditis presenting with heart failure or recurrent arrhythmias. J Am Coll Cardiol 47:1649–1654
33. Mahrholdt H, Wagner A, Deluigi CC et al (2006) Presentation, patterns of myocardial damage, and clinical course of viral myocarditis. Circulation 114:1581–1590
34. Schulz-Menger J, Wassmuth R, Abdel-Aty H et al (2006) Patterns of myocardial inflammation and scarring in sarcoidosis as assessed by cardiovascular magnetic resonance. Heart 92:399–400
35. Yelgec NS, Dymarkowski S, Ganame J, Bogaert J (2007) Value of MRI in patients with a clinical suspicion of acute myocarditis. Eur Radiol 17:2211–2217
36. Yilmaz A, Mahrholdt H, Athanasiadis A et al (2008) Coronary vasospasms the underlying cause for chest pain in patients with PVB19-myocarditis. Heart 94:1456–1463
37. Wagner A, Schulz-Menger J, Dietz R, Friedrich MG (2003) Longterm follow-up of patients with acute myocarditis by magnetic resonance imaging. Magma 16:17–20
38. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, White JA, Abdel-Aty H, Gutberlet M, Prasad S, Aletras A, Laissy JP, Paterson I, Filipchuk NG, Kumar A, Pauschinger M, Liu P (2009) Cardiovascular magnetic resonance in myocarditis: a JACC white paper. J Am Coll Cardiol 53:1475–1487
39. Feldman AM, McNamara D (2000) Medical progress: myocarditis. N Engl J Med 343:1388–1398
40. Baughman KL (2006) Diagnosis of myocarditis: death of Dallas criteria. Circulation 113:593–595
41. Shanes JG, Ghali J, Billingham ME et al (1987) Interobserver variability in the pathologic interpretation of endomyocardial biopsy results. Circulation 75:401–405
42. Daubeney PE, Nugent AW, Chondros P, Carlin JB, Colan SD, Cheung M et al (2006) Clinical features and outcomes of childhood dilated cardiomyopathy: results from a national population-based study. Circulation 114(24):2671–2678
43. Hill KD, Atkinson JB, Doyle TP, Dodd D (2009) Routine performance of endomyocardial biopsy decreases the incidence of orthotopic heart transplant for myocarditis. J Heart Lung Transplant 28(12):1261–1266