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Endomyocardial biopsy and selective coronary angiography are low-risk procedures in pediatric heart transplant recipients: Results of a multicenter experience

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biopsy;
coronary angiography;
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safety

BACKGROUND: No prior reports documenting the safety and diagnostic yield of cardiac catheterization and endomyocardial biopsy (EMB) in heart transplant recipients include multicenter data.

METHODS: Data on the safety and diagnostic yield of EMB procedures performed in heart transplant recipients were recorded in the Congenital Cardiac Catheterization Outcomes Project database at 8 pediatric centers during a 3-year period. Adverse events (AEs) were classified according to a 5-level severity scale. Generalized estimating equation models identified risk factors for high-severity AEs (HSAEs; Levels 3–5) and non-diagnostic biopsy samples.

RESULTS: A total of 2,665 EMB cases were performed in 744 pediatric heart transplant recipients (median age, 12 years [interquartile range, 4.8, 16.7]; 54% male). AEs occurred in 88 cases (3.3%), of which 28 (1.1%) were HSAEs. AEs attributable to EMB included tricuspid valve injury, transient complete heart block, and right bundle branch block. Amongst 822 cases involving coronary angiography, 10 (1.2%) resulted in a coronary-related AE. There were no myocardial perforations or deaths. Multivariable risk factors for HSAEs included fewer prior catheterizations ($p = 0.006$) and longer case length ($p < 0.001$). EMB yielded sufficient tissue for diagnosis in 99% of cases. Longer time since heart transplant was the most significant predictor of a non-diagnostic biopsy sample ($p < 0.001$).

CONCLUSIONS: In the current era, cardiac catheterizations involving EMB can be performed in pediatric heart transplant recipients with a low AE rate and high diagnostic yield. Risk of HSAEs is increased in early post-transplant biopsies and with longer case length. Longer time since heart transplant is associated with non-diagnostic EMB samples.

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Endomyocardial biopsy (EMB) remains the gold standard test for detection of acute cellular rejection and antibody-mediated rejection in heart transplant recipients.[1,2] As a result, surveillance for allograft rejection remains the most common indication for EMB in children.[3,4] In addition, selective coronary angiography is an important tool for monitoring of cardiac allograft vasculopathy.[5,6]

Several single-center case series have reported EMB high-severity adverse event (HSAE) rates of 1% to 2%.[4,7,8] These reports are limited by the retrospective nature of the data collection, the long data collection periods (11 and 16 years), and the overrepresentation of patients with multiple biopsy cases. Although studies of selective coronary an-

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giography in children also suggest a favorable safety profile, all of these reports are limited to small, retrospective, single-center studies.[9–11] The Congenital Cardiac Catheterization Outcomes Project (C3PO) database is a prospectively collected database of selected patient characteristics, procedural characteristics, and AE data from 8 large pediatric cardiology centers. This database provided the opportunity to examine AEs associated with catheterization procedures involving EMBs in heart transplant recipients in the current era. Additional variables were added to the database in 2009 to assess rates of technical success and identify factors associated with insufficient biopsy samples. No previous pediatric or adult studies have comprehensively addressed the technical success rates of EMB.

Methods

Population

The C3PO database is a multi-institutional database of patient and procedural characteristics collected at the time of all cardiac catheterizations performed at 8 pediatric cardiology centers (Appendix). After IRB approval was obtained, data collection commenced in February 2007 at 6 centers, in April 2008 at 1 center, and in June 2009 at another. The availability of prospectively collected data was used to define the inclusion criteria for 2 overlapping populations as follows:

- To assess procedural safety, all consecutive cases collected in the C3PO database between February 1, 2007, and February 28, 2010, with an intervention code for a post-transplant right ventricle (RV) biopsy were analyzed as part of the safety cohort.
- To assess technical success of EMB, all consecutive cases collected in the C3PO database between April 1, 2009, and February 28, 2010, with an intervention code for a post-transplant RV biopsy were analyzed as part of the diagnostic yield cohort.

All procedures containing any code for EMB were cross-referenced with the physiologic diagnosis to ensure that all post-transplant biopsies were captured.

Exclusion criteria

EMB cases performed at 1 of the original 6 centers before March 1, 2009 were excluded from the safety analysis because EMB cases were not reported to the C3PO database before that date.

Collected data

Variables collected in the C3PO database since February 1, 2007, included patient characteristics (age, weight, sex, diagnosis, time since transplant, number of prior catheterizations), case data (admission status, case type, type of anesthesia, corrected case length defined from sheath entry to sheath removal minus time spent addressing AE, fluoroscopy time, vascular access), and hemodynamic parameters (mixed venous saturation, cardiac index, left ventricular end diastolic pressure, inotropic support, use of extracorporeal membrane oxygenation [ECMO]).

In an effort to determine technical success rates of EMB cases in children and assess the ability of the procedure to provide useful, diagnostic information, the following procedural characteristics were prospectively collected in the C3PO database beginning on April 1, 2009: Size (in French) and type of biopsy forceps used, number of biopsy attempts, number and adequacy of specimens obtained, and operator obtaining the specimen (fellow, attending, or fellow and attending). The determination of whether a biopsy specimen was diagnostic was made at each institution in response to the prompt, "Result interpretable?" and entered into the C3PO database as a yes/no variable. The study plan defined a biopsy specimen as non-diagnostic if the pathologist was not able to grade the level of rejection or commented that non-diagnostic samples were obtained. A survey of pathology practices at all of the participating centers confirmed that all centers required 3 evaluable pieces of myocardium to consider a EMB sample diagnostic of non-rejection, as suggested by the 2004 revision of the International Society for Heart and Lung Transplantation guidelines.[2]

AE data

AE data were collected at the time of the procedure and updated to include any late AEs that were identified by the operating physician after the case, as previously described.[12] AEs were defined as any anticipated or unanticipated event for which avoidable injury could have occurred, or did occur, potentially or definitely as a consequence of performing the catheterization case.[12] AEs were classified according to severity and attributability (ie. EMB, access, general catheterization, etc) and reviewed by a minimum of 2 interventional cardiologists. Coronary angiography was not part of the original classification schema; therefore, the AE description was used to identify events attributable to coronary angiography. Event severity was defined on a 5-point ordinal scale and further classified into low-severity AEs (Levels 1 and 2) and HSAEs (Levels 3, 4, and 5). AE severity levels are provided with examples in Table 1.[3,12]

Primary outcome variables

The presence of any HSAE (Level 3, 4, or 5) was selected as the primary outcome variable for the safety cohort. Audits of the C3PO database have shown excellent case capture for these clinically relevant AEs.[12] A non-diagnostic EMB specimen was defined as the primary outcome variable for the diagnostic yield cohort.

Statistical methods

Categoric variables are presented as frequency and percentage. Continuous variables are displayed as mean ± standard deviation or median (interquartile range), depending on the normality of the distribution. The effect of predictor variables on the primary outcome variables of HSAE and non-diagnostic EMB was evaluated using generalized estimating equations models. Although case characteristics were felt to carry an independent risk for an AE, patient characteristics for 2 procedures performed in the same subject could not be considered independent. Generalized estimating equations models allowed us to account for the non-independence of the patient-specific characteristics. Multivariable modeling was performed for HSAEs using forward stepwise selection; predictors were retained in the model if they remained statistically

Table 1 Adverse Event Severity Level Definitions With Examples of Adverse Events That Occurred During Endomyocardial Biopsies

Severity level	Description	Example
Level 1: None	No harm, no change in condition, may have required monitoring to assess for potential change in condition with no intervention indicated.	Transient bradycardia during biopsy sampling.
Level 2: Minor	Transient change in condition, not life-threatening, condition returns to baseline, required monitoring, required minor intervention such as holding a medication or obtaining a laboratory test.	Transient ST-T wave changes after coronary angiography requiring further monitoring.
Level 3: Moderate	Transient change in condition may be life-threatening if not treated, condition returns to baseline, required monitoring, required intervention such as reversal agent, additional medication, transfer to the intensive care unit for monitoring, or moderate transcatheter intervention to correct condition.	Damage to the tricuspid valve apparatus that required unexpected hospitalization for observation.
Level 4: Major	Change in condition, life-threatening if not treated, change in condition may be permanent, may have required an intensive care unit admission or emergent readmission to hospital, may have required invasive monitoring, required interventions, such as electrical cardioversion or unanticipated intubation, or required major invasive cases or transcatheter interventions to correct condition.	Myocardial perforation requiring emergent pericardiocentesis.
Level 5: Catastrophic	Any death and emergent surgery or extracorporeal membrane oxygenation (ECMO) to prevent death with failure to wean from bypass support.	A patient who developed hemodynamic instability, was placed on ECMO, and subsequently died.

significant at the 0.05 level. Odds ratios (ORs) and 95% confidence intervals (CIs) are provided. Multivariable modeling was not performed for non-diagnostic EMB specimens because the event rate was too low to support such a model. No corrections were made for multiple comparisons. Statistical analysis was performed using SAS software (SAS Institute, Cary, NC).

Results

Patient and procedural characteristics

Overall, 2,665 cardiac catheterizations involving an EMB were performed in 744 heart transplant recipients at 8 centers over 3 years. Patient characteristics and AE rates are summarized in Tables 2 and 3. The median age was 12.6 years (IQR, 4.8, 16.7 years) with a median time since heart transplant of 1.5 years (IQR, 0.3, 4.9). Patients had undergone a median of 6 prior cardiac catheterization procedures, and cases were elective 93% of the time. An additional catheter-based intervention (CBI) was performed in 63 cases (2.3%). The additional interventions included angioplasty and stenting of a systemic vein in 24, angioplasty and stenting of another vessel in 16, atrial septal intervention in 7, elective pericardiocentesis in 6, elective pleurocentesis in 4, radiofrequency ablation in 3, and patent foramen ovale closure in 1.

The hemodynamic profile of the transplant cohort fell within normal ranges for cardiac index, mixed venous saturation, and left ventricular end-diastolic pressure or mean pulmonary capillary wedge pressure. Transplant patients rarely required inotropic support ($n = 70$; 2.6%) or ECMO ($n = 11$; 0.4%). Fifty-one percent of the EMB cases were performed with patients breathing spontaneously, and mechanical ventilation was used in the other 49%. Amongst the sub-set of cases where diagnostic yield data were collected, the median number of biopsy attempts was 5 (IQR, 4, 7), and the median number of pieces obtained was also 5 (IQR, 4, 6). The reporting centers classified 99% of the biopsy specimens as diagnostic.

AE description for post-transplant cardiac catheterization

Ninety-four AEs occurred during or after 88 catheterization cases (3.3%). Multiple AEs occurred during 6 cases. HSAEs

Table 2 Patient and Case Characteristics

Variables[a]	Result (n = 2,665)
Patient characteristics	
Age, years	
<1	138 (5)
1–9	966 (36)
≥10	1,561 (59)
Patient weight, kg	
<4	22 (1)
4–9	251 (9)
10–19	563 (21)
≥20	1,829 (69)
Male sex	1,447 (54)
Prior catheterizations	6 (0,14)
Time since heart transplant, years	1.5 (0.3,4.9)
Case characteristics	
Elective admission status	2,475 (93)
Case type	
EMB	1,843 (69)
EMB plus coronary angiography	822 (31)
Hemodynamic parameters	
Cardiac index, liters/min/m^2	3.7 ± 1.2
Mixed venous saturation, %	71 ± 7
LVEDP or mean PCWP, mm Hg	11 ± 4
On inotropic support	70 (2.6)
On ECMO	11 (0.4)
Spontaneous respiration	1,354 (51)
Corrected case length, min	39 ± 29
Fluoroscopy time, min	10 ± 8
Access	
Internal jugular vein	
Right	1,265 (47)
Left	85 (3.2)
Femoral vein	
Right	928 (35)
Left	271 (10)
Subclavian vein	
Right	113 (4.2)
Left	40 (1.5)
Other access site	11 (0.4)
Femoral artery	
Right	741 (28)
Left	143 (5)
Biopsy attempts, No. (n = 1,122)	5 (4,7)
Pieces obtained (n = 1,123)	5 (4,6)

ECMO, extracorporeal membrane oxygenation; EMB, endomyocardial biopsy; LVEDP, left ventricular end-diastolic pressure; PCWP, pulmonary capillary wedge pressure.

[a]Categoric variables are expressed as number (%), ordinal/continuous variables are expressed as median (interquartile range), and normally distributed continuous variables are shown as mean ± standard deviation.

occurred during 1.1% of cases, with center-specific rates varying between 0% and 3.9% (Figure 1). During the study period, 11 Level 1 and 53 Level 2 AEs were recorded (Table 3). Level 1 AEs included air injected into the pulmonary circulation, transient bradycardia during biopsy sampling, and inadvertent loss of venous access during a sheath exchange. Level 2 AEs included coronary air embolus that did not require intervention, spontaneously resolving heart block, hematoma at the cannulation site, and arrhythmias that were not hemodynamically significant and resolved spontaneously. A total of 21 level 3 AEs occurred, which included complications such as thrombus on the tricuspid valve, coronary artery vasospasm requiring intra-arterial nitroglycerin administration, hypotension requiring fluid resuscitation, and transient heart block treated with temporary intracardiac pacing. Major AEs (Level 4) occurred in 10 EMB cases and included left main coronary artery dissection requiring surgical intervention in 1 patient, and events requiring chest compressions in 3 and mechanical support in 3. The 3 patients who required emergent mechanical support were non-elective cases added on due to clinical urgency. Two were supported with ECMO and the other required an intra-aortic balloon pump. All survived after weaning from mechanical support.

Among these 94 events, 18 AEs (0.7% of cases) were classified as being EMB-related (Table 3). There were 3 cases of tricuspid valve damage without significant change in the degree of regurgitation or need for surgical intervention. There were 2 patients with complete heart block, which was treated with temporary pacing in 1 patient and chest compressions in the other. Both patients had AV nodal recovery within minutes, without sequelae. Seven cases of supraventricular tachycardia were noted during EMB, 2 cases of sinus bradycardia, and 1 case of non-sustained ventricular tachycardia. All of these arrhythmias resolved spontaneously or with acute treatment in the catheterization laboratory. There were 3 cases of isolated QRS widening with a right bundle branch block pattern noted during biopsy that did not require treatment.

In 10 of 822 cases (1.2%) involving coronary angiography, an AE occurred that was directly related to coronary angiography. These included coronary air embolus in 3, coronary vasospasm or ST segment changes in 4, sinus bradycardia in 1, and non-sustained ventricular tachycardia in 1. All of these events resolved within minutes without long term sequelae. One left main coronary dissection occurred after angiography of normal coronary arteries during an elective outpatient procedure. The dissection was immediately recognized and was successfully repaired with a coronary artery bypass graft. No percutaneous coronary intervention procedures were performed during any cases involving EMB. Two low-severity AEs (air embolus due to balloon rupture and esophageal hematoma caused by a transesophageal echocardiogram performed during patent foramen ovale closure) and no HSAEs were attributable to the performance of other CBIs.

Patient and procedural risk factors for HSAEs

In univariate analysis, HSAEs were more likely among patients who had undergone fewer prior catheterizations and in cases that were non-elective, performed with mechanical ventilation, involving coronary angiography, and with longer case length (Table 4). In multivariable

Table 3 Summary of Characteristics of 94 Adverse Events Which Occurred in 88 of 2,665 Endomyocardial Biopsy Cases

	All levels	Severity level[a]				
Adverse event characteristic	No. (%)	Level 1 ($n = 11$)	Level 2 ($n = 53$)	Level 3 ($n = 19$)	Level 4 ($n = 11$)	Level 5 ($n = 0$)
Biopsy related	18 (19)	5	6	6	1	0
Atrial arrhythmia	9 (10)	1	3	5	. . .	. . .
Coronary fistula	0 (0)	. . .	. . .	. . .	. . .	. . .
Complete heart block, transient	2 (2)	. . .	. . .	1	1	. . .
RBBB/IVCD, new	3 (3)	3	. . .	. . .	. . .	. . .
Tricuspid valve damage	3 (3)	. . .	3	. . .	. . .	. . .
Myocardial perforation	0 (0)	. . .	. . .	. . .	. . .	. . .
Ventricular arrhythmia	1 (1)	1	. . .	. . .	. . .	. . .
Coronary angiography related	10 (11)	1	6	0	3	0
Air embolus	3 (3)	1	2	. . .	. . .	. . .
Arrhythmia, atrial or ventricular	2 (2)	. . .	1	. . .	1	. . .
Coronary dissection	1 (1)	. . .	. . .	. . .	1	. . .
ST segment changes/coronary vasospasm	4 (4)	. . .	3	. . .	1	. . .
Sedation or airway related	19 (20)	0	11	2	6	0
Airway obstruction	1 (1)	. . .	. . .	1	. . .	. . .
Anesthesia problem	2 (2)	. . .	2	. . .	. . .	. . .
Esophageal hematoma	1 (1)	. . .	1	. . .	. . .	. . .
Hypotension	7 (7)	. . .	5	. . .	2	. . .
Hypoxia	2 (2)	. . .	. . .	1	1	. . .
Lobar collapse	1 (1)	. . .	1	. . .	. . .	. . .
Respiratory acidosis, $Pco_2 > 45$ mm Hg	1 (1)	. . .	1	. . .	. . .	. . .
Respiratory distress	4 (4)	. . .	1	. . .	3	. . .
General catheterization related	25 (27)	2	17	5	1	0
Allergic reaction	1 (1)	. . .	1	. . .	. . .	. . .
Atrial arrhythmia	6 (6)	. . .	5	1	. . .	. . .
Bradycardia, sinus	2 (2)	1	1	. . .	. . .	. . .
Cerebrovascular accident, embolic	1 (1)	. . .	. . .	. . .	1	. . .
Equipment problem, broken catheter or wire	2 (2)	. . .	2	. . .	. . .	. . .
Fever	2 (2)	. . .	1	1	. . .	. . .
Heart block, resolved	2 (2)	. . .	2	. . .	. . .	. . .
Hypoxia	1 (1)	. . .	1	. . .	. . .	. . .
Imaging equipment problem	3 (3)	1	2	. . .	. . .	. . .
Medication error	1 (1)	. . .	1	. . .	. . .	. . .
Peripheral site infection	1 (1)	. . .	1	. . .	. . .	. . .
Seizure	1 (1)	. . .	. . .	1	. . .	. . .
Ventricular arrhythmia	1 (1)	. . .	. . .	1	. . .	. . .
Vessel trauma	1 (1)	. . .	. . .	1	. . .	. . .
Access related	21 (22)	2	13	6	0	0
Bleeding after catheter removal	1 (1)	. . .	1	. . .	. . .	. . .
Hemothorax	1 (1)	. . .	. . .	1	. . .	. . .
Inadvertent arterial puncture	1 (1)	. . .	1	. . .	. . .	. . .
Inadvertent sheath removal	1 (1)	1	. . .	. . .	. . .	. . .
Local hematoma						
Groin	2 (2)	. . .	1	1	. . .	. . .
Neck	2 (2)	1	1	. . .	. . .	. . .
Pain, right lower extremity	1 (1)	. . .	1	. . .	. . .	. . .
Pneumothorax	4 (4)	. . .	1	3	. . .	. . .
Rebleed after bandages applied	6 (6)	. . .	6	. . .	. . .	. . .
Sheath placed outside vessel	1 (1)	. . .	1	. . .	. . .	. . .
Systemic arterial thrombosis	1 (1)	. . .	. . .	1	. . .	. . .
Angioplasty related	1 (1)	1	0	0	0	0
Balloon rupture with air embolus	1 (1)	1	. . .	. . .	. . .	. . .

IVCD, Interventricular conduction delay; Pco_2 Partial pressure of carbon dioxide; RBBB, right bundle branch block.
[a]Table 1 for definitions of levels of severity and examples.

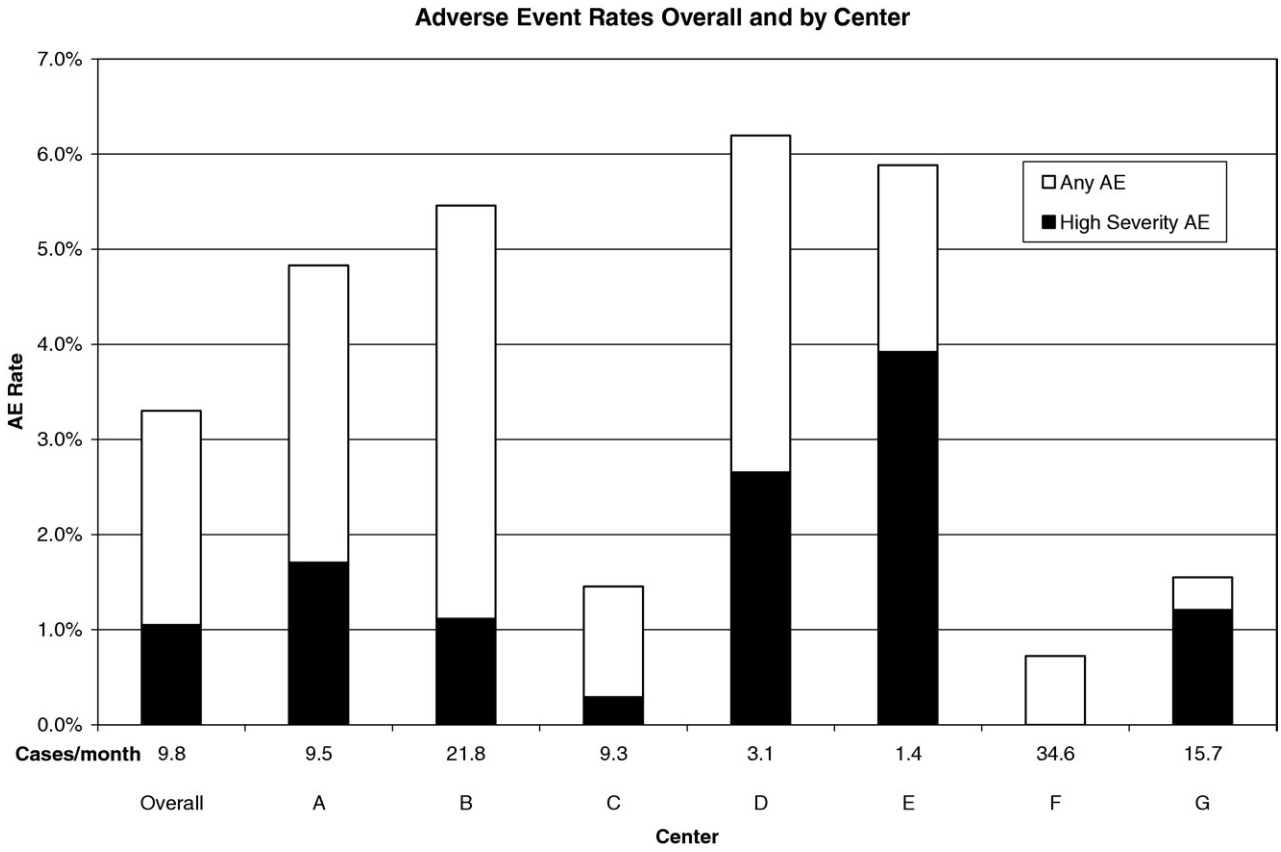

Figure 1 Rates of any adverse event (AE) and high-severity AE by center. Center volume (cases per month) is noted above each center identifier. Data from center H are not displayed because of the low case volume.

modeling, a history of fewer prior catheterization procedures (OR, 1.1 for each 1-procedure decrease; $p = 0.006$) and longer case length were associated with HSAE (OR, 1.2 for each additional 10 minutes; $p < 0.001$). In addition, there was an inverse relationship between the center-specific rate of HSAEs and the average monthly case volume by linear regression analysis ($R^2 = 0.58$; $p = 0.045$).

Procedural success and technical characteristics

Patient and case characteristics for the 1,138 EMB cases used to assess technical procedural success were not significantly different from the cases included in the combined safety cohort. Most cases (98.7%) yielded sufficient endomyocardial tissue for pathologic interpretation, with only 15 cases resulting in a non-diagnostic biopsy specimen in 14 different patients (Table 5). A 6F bioptome was used 48% of the time, whereas 5F and 7F bioptomes were used less frequently (35% and 16%, respectively). Smaller bioptomes were used infrequently. The most commonly used bioptome was the Jawz (Argon Medical, Athens, TX) forceps in 40%, whereas the Sparrow Hawk (ATC Technologies, Woburn, MA) and Procure (St. Jude Medical, St. Paul, MN) bioptomes were used in 28% and 20% of cases, respectively.

Patient and procedural risk factors for non-diagnostic biopsy specimens

In univariate analysis, patient-specific risk factors for a non-diagnostic EMB specimen included longer time since heart transplantation, age older than 10 years, and lower cardiac index (Table 5). Procedure-specific risk factors included more attempts at EMB, smaller bioptome size, use of a Sparrow Hawk bioptome, and cases performed by cardiology fellows without attending assistance. A sub-analysis of the center with the largest number of non-diagnostic EMB specimens found longer time since heart transplantation, older age, and lower cardiac index were risk factors for a non-diagnostic EMB specimen (data not shown).

Institutional variation in performance of EMB

There are important variations in how the EMB is performed at different institutions. The busiest center performed 30% of the recorded biopsy cases, whereas the 3 smallest centers each performed less than 5% of the biopsy cases (Table 6). The choice of anesthetic technique was largely related to the preference of the center performing the EMB, with 2 centers performing more than 70% of their cases under spontaneous respiration, 3 centers preferring general anesthesia in more than 70% of cases, and 2 centers being evenly split.

Table 4 Patient and Procedural Risk Factors for High-Severity Adverse Events During Endomyocardial Biopsies in Heart Transplant Recipients[a]

	HSAE		Univariable		Multivariable analysis	
Variables	Any (n = 28)	None (n = 2,634)	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Demographics						
Age, year						
<1	3 (11)	135 (5)	2.2 (0.6–8.3)	0.21		
1–9	10 (36)	956 (36)	1.1 (0.5–2.5)	0.86		
≥10	15 (54)	1,546 (59)	1.0	. . .		
Weight, kg						
<10	4 (14)	269 (10)	1.5 (0.5–4.3)	0.49		
≥10	24 (86)	2,368 (90)	1.0	. . .		
Admission status						
Elective	22 (79)	2,453 (93)	1.0	. . .		
Urgent or emergent	6 (21)	184 (7)	3.6 (1.4–9.3)	0.007		
No. of prior catheterizations[b]	3 (0,7)	6 (0,14)	1.1 (1.0–1.1)	0.009	1.1 (1.0 – 1.2)	0.006
Time since heart transplant,[c] years	3 (1,5)	2 (0,5)	1.0 (0.9–1.2)	0.49		
Case type						
EMB	11 (39)	1,832 (69)	1.0	. . .		
EMB plus coronary angiography	17 (61)	805 (31)	3.5 (1.7–7.3)	<0.001		
Airway and sedation management						
Spontaneous respiration	7 (25)	1,347 (51)	1.0	. . .		
Other mechanical support with anesthesia	21 (75)	1,290 (49)	3.1 (1.3–7.6)	0.01		
Corrected case length,[d] min	52 (36,92)	29 (20,51)	1.2 (1.1–1.3)	<0.001	1.2 (1.1 – 1.3)	<0.001
Hemodynamic parameters						
Cardiac index,[e] liters/min/m^2	3.6 ± 1.4	3.7 ± 1.2	1.0 (0.8–1.3)	0.81		
Mixed venous saturation,[f] %	70 ± 11	71 ± 7	1.1 (0.8–1.6)	0.45		
LVEDP or mean PCWP,[g] mm Hg (n = 1,081)	11 ± 3	11 ± 4	1.0 (0.9–1.2)	0.89		
On inotropic support? %	2 (7)	68 (3)	2.9 (0.7–12.9)	0.16		

CI, confidence interval; EMB, endomyocardial biopsy; HSAE, high-severity adverse event; LVEDP, left ventricular end-diastolic pressure; OR, odds ratio; PCWP, pulmonary capillary wedge pressure.

[a]Categoric variables are expressed as number (%), ordinal/continuous variables are expressed as median (interquartile range), and normally distributed continuous variables are shown as mean ± standard deviation. OR expresses risk of a HSAE calculated using generalized estimating equations models.

[b]OR for each 1-unit decrease in number of prior catheterizations.

[c]OR for each additional year since transplant.

[d]OR for each additional 10 min.

[e]OR for each 0.5 increase.

[f]OR for each 5% decrease.

[g]OR for each 2 mm Hg decrease.

The site of venous vascular access was also largely center-dependent. Although right internal jugular venous access was used in 47% of cases overall, centers D and G preferred neck access with combined right and left internal jugular access rates of 82% and 98%, respectively. Even when femoral arterial access is necessary, some centers still prefer venous access from the neck.

The type of bioptome chosen was largely center-dependent, with most centers showing a preference for one type of bioptome, although the specific type of bioptome varied considerably (Table 6). The center performing the biopsy was an important risk factor for a non-diagnostic biopsy specimen, with an OR of 9.6 (95% CI, 2.9–32.5; $p < 0.001$) for procedures performed at center B, which used a 5F bioptome exclusively.

Discussion

This multicenter report details the safety and diagnostic yield of cardiac catheterization procedures involving endomyocardial biopsy in pediatric heart transplant recipients. Overall, we found that catheterization is a safe procedure in pediatric heart transplant recipients, with a HSAE rate of 1.1% and an overall AE rate of 3.3%. Fewer prior catheterizations and longer case length were associated with HSAEs in multivariable analysis. We have also shown that centers with higher case volumes have a lower HSAE rate. Multiple studies have documented the utility of EMB in the diagnosis of post-transplant rejection.[1,7,13–21] Combined with these prior studies, our results contribute vital information to making a risk-benefit decision regarding the

Table 5 Patient and Procedural Risk Factors for a Non-diagnostic Endomyocardial Biopsy Sample in Heart Transplant Recipients[a]

	EMB Sample		Univariable Analysis	
Demographics and Clinical Predictors	Non-Diagnostic (n = 15)	Diagnostic (n = 1,123)	OR (95% CI)	p-Value
Age, year				
<1	0 (0)	40 (4)	. . .	. . .
1–9	0 (0)	386 (34)	. . .	. . .
≥10	15 (100)	697 (62)	. . .	. . .
Weight, kg				
<10	0 (0)	86 (8)	. . .	. . .
≥10	15 (100)	1,037 (92)	. . .	. . .
Time since heart transplant,[b] years	8.6 (3.3, 10.6)	1.6 (0.4, 4.5)	1.2 (1.1 – 1.2)	<0.001
Admission status				
Elective	14 (93)	1,082 (96)	1.0	. . .
Urgent or emergent	1 (7)	41 (4)	1.9 (0.2 – 14.2)	0.54
Airway and sedation management				
Spontaneous respiration	11 (73)	544 (48)	1.0	. . .
Other mechanical support with anesthesia	4 (27)	579 (52)	0.3 (0.1 – 1.1)	0.08
Hemodynamic parameters				
Cardiac index,[c] liters/min/m^2	3.0 ± 0.7	3.6 ± 1.1	2.2 (1.1 – 4.3)	0.02
Access (n = 13,1095)				
Right or left femoral vein	4 (31)	471 (43)	1.0	. . .
Right or left internal jugular vein	8 (61)	586 (54)	1.6 (0.5 – 5.7)	0.46
Right or left subclavian vein	1 (8)	38 (3)	3.1 (0.3 – 29.8)	0.33
Case performed by				
Attending	6 (40)	752 (67)	1.0	. . .
Attending and fellow	1 (7)	67 (6)	1.9 (0.2 – 16.6)	0.57
Fellow	8 (53)	304 (27)	3.3 (1.0 – 10.5)	0.04
Type of bioptome				
Sparrow Hawk	11 (73)	312 (28)	7.1 (1.9 – 27.3)	0.004
Other	4 (27)	811 (72)	1.0	. . .
Size of bioptome				
3F, 4F, or 5F	10 (67)	398 (36)	3.6 (1.1 – 12.2)	0.04
6F or 7F	5 (33)	723 (64)	1.0	. . .
No. of biopsy attempts[d]	7 (6, 9)	5 (4, 6)	1.3 (1.2 – 1.5)	<0.001
No. of pieces obtained	6 (5, 6)	5 (4, 5)	1.0 (1.0 – 1.1)	0.07
Center performing the biopsy				
Center B	10 (67)	193 (17)	9.6 (2.9 – 32.5)	<0.001
All others	5 (33)	930 (83)	1.0	. . .

CI, confidence interval; EMB, endomyocardial biopsy.

[a]Categoric variables are presented as number (%); ordinal/continuous variables are presented as median (interquartile range); and normally distributed continuous variables are presented as mean ± standard deviation Odds ratio expresses risk of obtaining a non-diagnostic sample calculated using generalized estimating equations (GEE) models.

[b]OR for each additional year since transplant.

[c]OR for each 1 liter/min/m^2 decrease in cardiac index.

[d]OR for each additional attempt.

use of EMB in the clinical management of pediatric heart transplant recipients.

Safety of EMB and coronary angiography in children

Several large single-center case series and multiple smaller series have reported on the safety of EMB in children.[4,7,8,22–26] Pophal et al[4] reported 1,000 consecutive EMB cases performed at a single institution, 85% of which were in heart transplant recipients. The overall incidence of serious complications from EMB was 1.9%, with an overall cardiac perforation rate of 0.9%.[4] This number is similar to the numbers of AEs reported in the 2 other large pediatric single-center case series.[7,8] These 3 large series are limited by retrospective collection of AE data, long study periods (10 to 16 years), and high mean case/patient ratios (5.2 to 16.1).[4,7,8]

The current study adds to the overall understanding of the risks of catheterization procedures involving EMB in pediatric patients. By using standard definitions and prospective data collection, we were able to clearly define risk

Table 6 Post-transplant Endomyocardial Biopsy Case Characteristics by Center ($n = 2,661$)[a]

Variables	Center A	Center B	Center C	Center D	Center E	Center F	Center G
Cases, No.	352	806	344	113	51	415	580
Average cases per month, No.	9.5	21.8	9.3	3.1	1.4	34.6	15.7
Patients, No.	153	131	82	39	19	160	157
Admission status							
Elective	299 (85)	707 (88)	340 (99)	110 (97)	42 (82)	411 (99)	562 (97)
Urgent and emergent	53 (15)	99 (12)	4 (1)	3 (3)	9 (18)	4 (1)	18 (3)
Case type							
EMB	224 (64)	545 (68)	227 (66)	51 (45)	25 (49)	322 (78)	445 (77)
EMB plus coronary angiography	128 (36)	261 (32)	117 (34)	62 (55)	26 (51)	93 (22)	135 (23)
Airway and sedation management							
Spontaneous respiration	255 (72)	483 (60)	276 (80)	23 (20)	0 (0)	252 (56)	81 (14)
Access							
Right or left femoral artery	135 (38)	269 (33)	128 (37)	77 (68)	30 (59)	102 (25)	138 (24)
Right femoral vein	171 (49)	304 (38)	227 (66)	20 (18)	29 (57)	167 (40)	8 (1)
Left femoral vein	71 (20)	83 (10)	52 (15)	8 (7)	7 (14)	38 (9)	12 (2)
Right internal jugular vein	36 (10)	375 (47)	39 (11)	86 (76)	16 (32)	182 (44)	530 (91)
Left internal jugular vein	2 (1)	11 (1)	0 (0)	7 (6)	1 (2)	24 (6)	39 (7)
Right subclavian vein	88 (25)	25 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other access	15 (4)	24 (3)	6 (2)	5 (4)	1 (2)	0 (0)	0 (0)
Corrected case length, min	50 ± 30	33 ± 24	35 ± 21	64 ± 41	63 ± 29	31 ± 22	43 ± 34
Fluoroscopy time, min	13 ± 8	10 ± 8	7 ± 5	20 ± 17	15 ± 9	7 ± 6	8 ± 7
Efficacy information							
Case performed by ($n = 1,145$)							
Attending	101 (88)	86 (41)	71 (61)	37 (100)	3 (25)	306 (74)	156 (66)
Attending and fellow	4 (3)	10 (5)	2 (2)	0 (0)	1 (8)	32 (8)	19 (8)
Fellow	10 (9)	115 (54)	44 (38)	0 (0)	8 (67)	77 (18)	63 (26)
Size of bioptome ($n = 1,142$)							
3F	0 (0)	0 (0)	0 (0)	5 (14)	0 (0)	5 (1)	0 (0)
5F	23 (20)	207 (99)	20 (17)	20 (54)	1 (8)	109 (26)	21 (9)
6F	9 (8)	2 (1)	96 (82)	12 (32)	11 (92)	301 (73)	114 (48)
7F	82 (72)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	103 (43)
Type of bioptome ($n = 1,145$)							
Sparrow Hawk	115 (100)	210 (99)	1 (1)	0 (0)	0 (0)	1 (0.2)	0 (0)
Argon Jaws	0 (0)	1 (0.5)	115 (98)	28 (76)	12 (100)	297 (72)	0 (0)
Cook	0 (0)	0 (0)	1 (1)	6 (16)	0 (0)	10 (2)	0 (0)
St. Jude	0 (0)	0 (0)	0 (0)	3 (8)	0 (0)	1 (0.2)	216 (91)
Schoulton	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	106 (26)	0 (0)
Fehling	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	22 (9)
Biopsy attempts, No.	5 (5, 6)	7 (6, 8)	5 (4, 6)	4 (3, 5)	5 (4, 6)	4 (4, 5)	6 (5, 8)
Maximum attempts, No.	12	15	13	14	7	27	21
Pieces obtained, No.	5 (5, 5)	6 (5, 6)	4 (4, 4)	3 (3, 4)	4 (4, 4)	4 (4, 4)	6 (5, 7)

EMB, Endomyocardial biopsy.

[a]Categoric variables are presented as number (%); ordinal/continuous variables are presented as median (interquartile range), and normally distributed continuous variables are presented as mean ± standard deviation. Center H performed 4 cases and its data were not included.

factors for HSAEs, including fewer prior catheterization procedures, longer case length, and performance at a center with a lower EMB case volume. There were no cardiac perforations in this group of post-transplant patients and no increase in procedural risk associated with patient age or size, contrary to prior studies.

The present study also highlights how the risk profile changes when coronary angiography is performed in conjunction with EMB. Coronary angiography was performed in 31% of the EMB cases in our series for the purpose of cardiac allograft vasculopathy screening. Complications of coronary angiography included left main coronary dissection, air embolus, and ST-T wave changes. Combining EMB with coronary angiography allows screening for acute cellular rejection and cardiac allograft vasculopathy during the same procedure but triples the risk of procedural AEs. The addition of other CBI resulted in a similar HSAE rate to procedures without CBI (1.6% vs 1.1%) and a marginally higher overall AE rate (4.8% vs 3.3%). Although additional CBI might be expected to confer additional risk, most appeared to be low-risk interventions to address superior vena cava stenosis. No percutaneous coronary interventions were reported in conjunction with EMB in our data set.

Tricuspid regurgitation is a well reported complication of EMB in adults.[19,27–35] Prior reports have clearly associated severe tricuspid regurgitation with an increased number of

EMB procedures and have suggested keeping the number of EMBs below 31.[33] A study of pediatric heart transplant recipients did not find an association between the number of EMBs and significant (moderate or severe) TR.[36] The lack of association between EMB and severe TR may be due to the relatively low number of EMBs performed in the pediatric transplant population, which was a median of 6 EMB in our study cohort. Echocardiography documented 3 cases of tricuspid valve damage in our cohort. This number underestimates the true incidence of tricuspid valve damage after EMB; however, no patient required operative intervention for damage to the tricuspid valve within the timeframe of this study.

Damage to the arteriovenous conduction system remains an important concern when sampling from the RV septum. We report two cases of transient complete heart block, which required cardiopulmonary resuscitation or temporary ventricular pacing before the conduction system recovered. Sampling from the RV septum can also lead to damage to the right bundle branch (RBB), a clinically recognized EMB complication that has been rarely reported.[37] Prior studies have shown an increasing prevalence of RBB block (RBBB) with increasing time after heart transplantation.[38] In our study, there were 3 cases of transient complete RBBB or intermediate RBBB. We speculate that repeated mechanical damage to the right bundle from EMB may explain the high prevalence of RBBB. No permanent complete atrioventricular block occurred in our series, and prior series report this as an extremely rare complication of EMB.[39,40]

Diagnostic yield of EMB in children

Our data show that 99% of the EMBs yielded tissue that was adequate for pathologic interpretation. This is consistent with prior reports of the yield of EMB in adults,[41–43] but is significantly better than the 92% yield reported by Braunlin et al[14] in pediatric heart transplant patients. We were able to identify longer time since heart transplant as a multivariable risk factor for a non-diagnostic biopsy specimen. Univariate risk factors for a non-diagnostic procedure included whether the procedure was performed by a fellow, the use of a smaller bioptome, and use of a Sparrow Hawk bioptome.

Clear definition of these results has some important implications: First, it may be beneficial to take more biopsy specimens in patients who are further out from heart transplant. These patients typically undergo EMB less frequently, thus making it vital to maximize yield during these cases.

Second, our data suggest that there is some operator recognition that the biopsy specimens are inadequate because more biopsy attempts were made in patients with non-diagnostic biopsy specimens. In cases such as these, the allograft may have extensive fibrosis due to a combination of chronic rejection and/or repeated EMB attempts. Switching biopsy sites may lead to increased diagnostic yield. Better operator recognition of fibrosis within the gross biopsy specimens would allow for more samples to be taken, and ultimately, might decrease the chance of a non-diagnostic biopsy procedure. At 1 of our study centers a pathologist views all gross biopsy specimens in the catheterization laboratory, with a reported 100% diagnostic yield and fewer biopsy samples taken.

The lower diagnostic yield in patients with a lower cardiac index is a concerning finding. These are typically the patients who are most in need of a diagnosis because a lower cardiac index is one of the most consistent findings seen with high-grade rejection.[18] In select patients, such as those with low cardiac output, prior non-diagnostic biopsy specimens, or patients more than 10 years out from transplant, it may be of benefit to have a pathologist evaluate the specimens in the catheterization laboratory to determine adequacy. This may help maximize diagnostic yield and patient safety in this hemodynamically vulnerable group.

The current study design has several limitations. Although pathologists at each of the centers reported that a minimum of 3 pieces of tissue were necessary to rule out rejection, pathologists may not have clearly and consistently documented the number of adequate samples submitted.[2] In this context, it is reassuring that a sub-analysis of the center with the largest number of non-diagnostic specimens identified the similar risk factors to the overall cohort, including longer time since heart transplantation and lower cardiac index. In addition, because different personnel (ie, clinical fellows, nurse practitioners, and attending physicians) at each center used a common definition to adjudicate the adequacy of the sample, it is possible that the study definition was not uniformly applied. Despite these limitations, these data are the best available to identify risk factors for a non-diagnostic EMB specimen.

In conclusion, we have found that cardiac catheterization and EMB is a safe procedure in children after heart transplantation, with a HSAE rate of 1.1% and an overall AE rate of 3.3%. The addition of coronary angiography increases the risk of AEs during an EMB. Finally, we have shown that EMB has an excellent technical success rate in children, with 99% of the cases in our series yielding sufficient tissue for pathologic interpretation.

Disclosure statement

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None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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.

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