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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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Abstract

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 over a 3 year period. Adverse events (AE) were classified according to a 5 level severity scale. Generalized estimating equation models identified risk factors for high severity adverse events (HSAE) (Levels 3-5) and non-diagnostic biopsy samples.

Results—A total of 2665 EMB cases were performed in 744 pediatric heart transplant recipients (median age 12 years [IQR: 4.8,16.7] and 54% male). AE occurred in 88 cases (3.3%), of which 28 (1.1%) were HSAE. AE attributable to EMB included tricuspid valve injury, transient complete heart block, and RBBB. 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 HSAE included fewer prior catheterizations (p=0.006) and longer case length

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(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 HSAE is increased in early post-transplant biopsies and with longer case length. Longer time since heart transplant is associated with non-diagnostic EMB sample.

INTRODUCTION

Endomyocardial biopsy (EMB) remains the gold standard test for detection of acute cellular rejection (ACR) and antibody mediated rejection (AMR) 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 coronary allograft vasculopathy (CAV).(5, 6)

Several single center case series have reported EMB high severity adverse event (HSAE) rates between 1 and 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. While studies of selective coronary angiography 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 the first 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 AE associated with catheterization procedures involving EMB 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. There are no previous pediatric or adult studies which comprehensively address 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 (10). After IRB approval was obtained, data collection commenced in February 2007 at 6 centers, in April 2008 at one center, and in June 2009 at another. Based on the availability of prospectively collected data, the inclusion criteria for two overlapping populations were defined 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 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 endomyocardial biopsy were cross referenced with the physiologic diagnosis to ensure that all post-transplant biopsies were captured.

Exclusion Criteria—EMB cases performed at one of the original six centers prior to March 1, 2009 were excluded from the safety analysis as EMB cases were not reported to the C3PO database prior to that time.

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 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 Fr) and type of biopsy forceps used, number of biopsy attempts, number and adequacy of specimens obtained, and operator obtaining the biopsy (fellow, attending, or fellow and attending). The determination of whether or not 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. Pathology practices at all of the participating centers were surveyed which confirmed that all centers require three evaluable pieces of myocardium in order to consider a EMB sample diagnostic of non-rejection, as suggested by the 2004 revision of the ISHLT guidelines.(2)

Adverse Event Data—AE data were collected at the time of the procedure and updated to include any late AE that were identified by the operating physician following the case, as previously described.(12) AE 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) AE were classified according to severity and attributability (i.e. EMB, access, general catheterization, etc.) and reviewed by a minimum of two 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 five point ordinal scale and further classified into low severity events (Levels 1 & 2) and high severity events (Levels 3, 4, & 5). Event 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 events.(12) Non-diagnostic EMB specimen was defined as the primary outcome variable for the diagnostic yield cohort.

Statistical Methods

Categorical variables are summarized with frequency and percentage. Continuous variables are displayed as mean ± standard deviation or median [interquartile range] depending upon the normality of the distribution. The impact of predictor variables on the primary outcome variables (HSAE and non-diagnostic EMB) was evaluated using generalized estimating equations (GEE) models. Although case characteristics were felt to carry an independent risk for an adverse event, patient characteristics for two procedures performed in the same subject could not be considered independent. GEE models allowed us to account for the non-independence of the patient specific characteristics. Multivariable modeling was

performed for HSAE using forward stepwise selection; predictors were retained in the model if they remained statistically significant at the 0.05 level. Odds ratios and 95% confidence intervals are provided. Multivariable modeling was not performed for non-diagnostic EMB as the event rate was too low to support such a model. No corrections were made for multiple comparisons. Statistical analysis was performed using SAS (Cary, NC) statistical software.

RESULTS

Patient & Procedural Characteristics

Overall 2665 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 old [IQR: 4.8, 16.7] with a median time since heart transplant of 1.5 years [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 2.3% (n=63) of the cases. The additional interventions included angioplasty/stenting of a systemic vein (n=24), angioplasty/stenting of another vessel (n=16), atrial septal intervention (n=7), elective pericardiocentesis (n=6), elective pleurocentesis (n=4), RF ablation (n=3), and PFO closure (n=1). The hemodynamic profile of the transplant cohort fell within normal ranges for cardiac index, mixed venous saturation, and LVEDP or mean PCWp. It was rare for transplant patients to require inotropic support (n=70; 2.6%) or ECMO (n=11; 0.4%). Half of the EMB cases were performed with patients breathing spontaneously and mechanical ventilation was used in the other half. Amongst the subset of cases where diagnostic yield data were collected, the median number of biopsy attempts was 5 [4,7], and the median number of pieces obtained was also 5 [4,6]. Ninety-nine percent of the biopsy specimens were considered diagnostic by the reporting centers.

AE Description for Post-Transplant Cardiac Catheterization

Ninety-four AE occurred during or following 88 (3.3%) catheterization cases. Multiple AE occurred during 6 cases. HSAE occurred during 1.1% of cases with center specific rates varying between 0% and 3.9% (Figure 1). There were a total of 11 Level 1 AE and 53 Level 2 AE recorded during the study period (Table 3). Level 1 events included air injected into the pulmonary circulation, transient bradycardia during biopsy sampling, and inadvertent loss of venous access during a sheath exchange. Level 2 events included coronary air embolus that did not require intervention, spontaneously resolving heart block, hematoma at the cannulation site, and arrhythmias which were not hemodynamically significant and resolved spontaneously. There were a total of 21 Level 3 AE 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 AE (Level 4) occurred in 10 EMB cases and included events such as left main coronary artery dissection requiring surgical intervention (n=1) and all events requiring chest compressions (n=3) and mechanical support (n=3). All three patients requiring emergent mechanical support were non-elective cases added on due to clinical urgency. Two were supported with ECMO and the other required an intraaortic balloon pump. All survived after weaning from mechanical support.

Among these 94 events, a total of 18 AE (0.7% of cases) were classified as being biopsy related (Table 3). There were 3 cases of tricuspid valve damage without significant change in degree of regurgitation or need for surgical intervention. There were two patients with complete heart block which was treated with temporary pacing in one case and chest compressions in the other. Both patients had AV nodal recovery within minutes without

sequelae. There were seven cases of supraventricular tachycardia noted during EMB, two cases of sinus bradycardia, and one case of non-sustained ventricular tachycardia. All of these arrhythmias resolved either spontaneously or with acute treatment in the catheterization laboratory. There were three cases of isolated QRS widening with a right bundle branch block pattern noted during biopsy which did not require treatment.

In 10 of 822 cases (1.2%) involving coronary angiography, an AE directly related to coronary angiography occurred. These included coronary air embolus(n=3), coronary vasospasm or ST segment changes (n=4), sinus bradycardia (n=1), and non-sustained VT (n=1). All of these events resolved within minutes without long term sequelae. There was one case of left main coronary dissection following angiography of normal coronaries 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 AE (air embolus due to balloon rupture and esophageal hematoma caused by a transesophageal echocardiogram performed during patent foramen ovale closure) and no HSAE were attributable to performance of other CBI.

Patient and Procedural Risk Factors for HSAE

In univariate analysis, HSAE 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 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 HSAE and 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 1138 biopsy cases used to assess technical procedural success were not significantly different from the cases included in the combined safety cohort. The majority of 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 6 Fr bioptome was used 48% of the time, while 5 Fr and 7 Fr 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% of cases, while 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 greater 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 (data not shown).

Institutional Variation in Performance of Endomyocardial Biopsy

There are important variations in how endomyocardial biopsy is performed at different institutions. The busiest center performed 30% of the recorded biopsy cases while the three 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 > 70% of their cases under spontaneous respiration, three centers preferring general anesthesia in > 70% of cases, and 2 centers being evenly split. The site of venous vascular access was also largely center dependent. Although right internal jugular venous access was used in nearly half of the cases overall (47%), several 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 a single type of bioptome, although the specific type of bioptome varied considerably (Table 6). Center performing the biopsy was an important risk factor for a non-diagnostic biopsy specimen with an OR of 9.6 (CI 2.9-32.5) ($p<0.001$) for procedures performed at Center B. Center B utilized a 5 Fr bioptome exclusively.

DISCUSSION

This is the first multicenter report on 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%. We found that fewer prior catheterizations and longer case length were associated with HSAE 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) Taken in combination with these prior studies, our results contribute vital information to making a risk-benefit decision regarding the use of EMB in the clinical management of pediatric heart transplant recipients.

Safety of Endomyocardial Biopsy and Coronary Angiography in Children

Several large single center case series and multiple smaller series have previously reported on the safety of EMB in children.(4, 7, 8, 22-26) Pophal *et al.* reported on 1000 consecutive EMB cases performed at a single institution, 85% of which were performed in heart transplant recipients. The overall incidence of serious complications from EMB was reported to be 1.9% with an overall cardiac perforation rate of 0.9%.(4) This number is similar to the numbers of AE reported in the two other large pediatric single center case series.(7, 8) All three 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 utilizing standard definitions and prospective data collection we were able to clearly define risk factors for HSAE including fewer prior catheterization procedures, longer case length, and performance at a center with 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 CAV screening. Complications of coronary angiography included left main coronary dissection, air embolus, and ST-T wave changes.

While combining EMB with coronary angiography allows screening for both acute cellular rejection and CAV during the same procedure, it triples the risk of AE during the procedure. 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%). While additional CBI might be expected to confer additional risk, most appeared to be low risk interventions to address SVC stenosis. No percutaneous coronary interventions were reported in conjunction with EMB in our dataset.

Tricuspid regurgitation is a well reported complication of endomyocardial biopsy 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 biopsies performed in the pediatric transplant population (median of 6 biopsies [1, 18] in our study cohort). Three cases of tricuspid valve damage were noted by echocardiography in our cohort. While this number underestimates the true incidence of tricuspid valve damage following EMB, no patient required operative intervention for damage to the tricuspid valve within the timeframe of this study.

Damage to the AV conduction system remains an important concern when sampling from the RV septum. We report two cases of transient complete heart block which required either CPR or temporary ventricular pacing before the conduction system recovered. Sampling from the RV septum can also lead to damage to the right bundle branch, a clinically recognized EMB complication that is rarely reported in the literature.(37) Prior studies have shown an increasing prevalence of RBBB with increasing time after heart transplantation.(38) In our study there were three cases of transient complete RBBB or intermediate right bundle branch block. We speculate that repeated mechanical damage to the right bundle from EMB may explain the high prevalence of RBBB. There are no cases of permanent complete AV Block in our series and prior series report this as an extremely rare complication of EMB.(39, 40)

Diagnostic Yield of Endomyocardial Biopsy in Children

Our data show that 99% of the EMB cases yielded tissue that was adequate for pathologic interpretation. This is consistent with prior reports of the yield of endomyocardial biopsy in adults.(41-43) However it is significantly better than the 92% yield reported by Braunlin *et al.* in pediatric heart transplant patients.(14) 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 several important implications. First is that 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. Our data suggest that there is recognition on the part of the operator that the biopsy specimens are inadequate since 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 recognition of fibrosis within the gross biopsy specimens on the part of the operator would allow for more samples to be taken, and ultimately may decrease the chance of a non-diagnostic biopsy procedure. One of our study centers utilizes a pathologist to visualize 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 as 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 both diagnostic yield and patient safety in this hemodynamically vulnerable group.

There are several limitations seen with the current study design. While pathologists at each of the centers reported that a minimum of three pieces of tissue are necessary to rule out rejection, pathologists may not clearly and consistently document 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 biopsies identified the similar risk factors to the overall cohort including longer time since heart transplantation and lower cardiac index. In addition, since different personnel (i.e. clinical fellows, nurse practitioners, and attending physicians) at each center adjudicated the adequacy of the sample based on a common definition, 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 non-diagnostic EMB specimen.

CONCLUSION

We have found that cardiac catheterization and endomyocardial biopsy is a safe procedure in children after heart transplantation with a HSAE rate of 1.1% and an overall AE rate of 3.3%. Addition of coronary angiography increases the risk of adverse events during an EMB procedure. 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.

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Appendix 1. Study Sites and Participants

Children's Hospital Boston (Lisa Bergersen, M.D., M.P.H., Michael Landzberg, M.D., Peter Lang, M.D., James Lock, M.D., Audrey Marshall, M.D., Doff McElhinney, M.D.)

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St. Louis Children's Hospital (David Balzer, M.D., Susan Foerster, M.D., Ramzi Nicolas, M.D., Joshua Murphy, M.D.)

Rady Children's Hospital – San Diego (John Moore, M.D., Howaida El-Said, M.D.)

Pittsburgh Children's Hospital (Jacqueline Kreutzer, M.D., Sara Trucco, M.D., Brian Feingold, M.D., Susan Miller, M.D., Lee Berman, M.D.)

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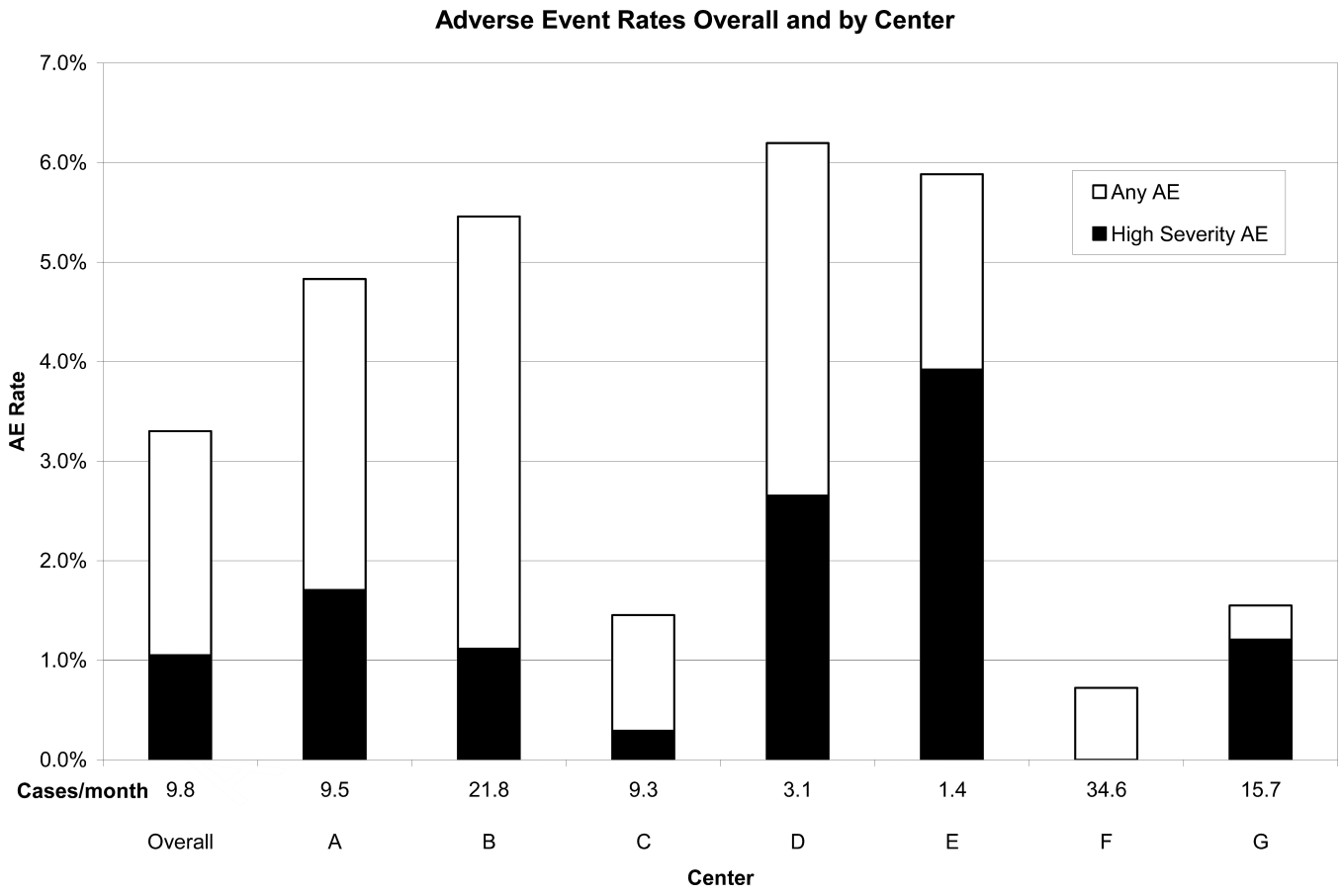

Figure 1.
Rates of any AE and HSAE by center. Center volume (Cases per month) is noted above each center identifier. Data from center H are not displayed because of the low case volume.

Table 1

Adverse event severity level definitions with examples of adverse events which occurred during endomyocardial biopsy procedures.

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.

Table 2

Patient and case characteristics. N (%) is provided for categorical variables and mean ± s.d. or median [IQR] is provided for continuous variables.

Patient or Case Characteristic (n=2665)	
Patient Characteristic	
Patient Age	
< 1 year	138 (5)
1-9 years	966 (36)
≥ 10 years	1561 (59)
Patient Weight	
< 4 kg	22 (1)
4-9 kg	251 (9)
10-19 kg	563 (21)
≥ 20 kg	1829 (69)
Patient Sex: Male	1447 (54)
Number of prior caths	6 [0, 14]
Time since heart transplant (years)	1.5 [0.3, 4.9]
Case Characteristic	
Admission Status: Elective	2475 (93)
Case Type	
EMB	1843 (69)
EMB plus coronary angiography	822 (31)
Hemodynamic Parameters	
Cardiac index (L/min/m2)	3.7 ± 1.2
Mixed venous saturation (%)	71 ± 7
LVEDP or mean PCWp (mmHg)	11 ± 4
On inotropic support	70 (2.6)
On ECMO	11 (0.4)
Spontaneous respiration	1354 (51)
Corrected Case Length (minutes)	39 ± 29
Fluoroscopy Time (minutes)	10 ± 8
Access	
Right internal jugular vein	1265 (47)
Left internal jugular vein	85 (3.2)
Right femoral vein	928 (35)
Left femoral vein	271 (10)
Right subclavian vein	113 (4.2)
Left subclavian vein	40 (1.5)
Other access site	11 (0.4)
Right femoral artery	741 (28)

Patient or Case Characteristic (n=2665)	
Left femoral artery	143 (5)
Number of biopsy attempts (n=1122)	5 [4, 7]
Number of pieces obtained (n=1123)	5 [4, 6]

EMB, Endomyocardial biopsy; LVEDP, Left ventricular end-diastolic pressure; PCWp, Pulmonary capillary wedge pressure; ECMO, Extracorporeal membrane oxygenation;

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Table 3

A total of 94 AE occurred in 88 of 2665 EMB cases. Event characteristics are summarized below.

Adverse Event Characteristic	All Levels *n* (%)	Severity Level (*n*)				
		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, pCO2 > 45 mmHg	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	—	—	—

Adverse Event Characteristic	All Levels *n* (%)	Severity Level (*n*)				
		Level 1 (*n*=11)	Level 2 (*n*=53)	Level 3 (*n*=19)	Level 4 (*n*=11)	Level 5 (*n*=0)
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 line 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	—	—
Local hematoma, 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	—	—	—	—

AE, Adverse events; EMB, Endomyocardial biopsy; RBBB, Right bundle branch block; IVCD, Interventricular conduction delay;

Table 4

Patient and procedural risk factors for high severity adverse events during EMB procedures in heart transplant recipients

N (%) is provided for categorical variables, median [interquartile range] is provided for ordinal/continuous variables, and mean ± s.d. is provided for normally distributed continuous variables. OR expresses risk of a HSAE calculated using generalized estimating equations (GEE) models.

Demographic / Clinical Predictors	High Severity AE		Univariate		Multivariable Analysis	
	Any HSAE (n=28)	No HSAE (n=2634)	Odds Ratio (95% CI)	P value	Odds Ratio	P value
Age						
< 1 year	3 (11)	135 (5)	2.2 (0.6, 8.3)	0.21		
1-9 years	10 (36)	956 (36)	1.1 (0.5, 2.5)	0.86		
≥ 10 years	15 (54)	1546 (59)	1.0	—		
Weight						
< 10 kg	4 (14)	269 (10)	1.5 (0.5, 4.3)	0.49		
≥ 10 kg	24 (86)	2368 (90)	1.0	—		
Admission Status						
Elective	22 (79)	2453 (93)	1.0	—		
Urgent or Emergent	6 (21)	184 (7)	3.6 (1.4, 9.3)	0.007		
No. of prior caths; OR for each 1 unit decrease in No. of prior caths	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 (years); OR for each additional year since transplant	3 [1, 5]	2 [0, 5]	1.0 (0.9, 1.2)	0.49		
Case Type						
EMB	11 (39)	1832 (69)	1.0	—		
EMB plus coronary angiography	17 (61)	805 (31)	3.5 (1.7, 7.3)	<0.001		
Airway & Sedation Management						
Spontaneous respiration	7 (25)	1347 (51)	1.0	—		
Other mechanical support with anesthesia	21 (75)	1290 (49)	3.1 (1.3, 7.6)	0.01		
Corrected Case Length (minutes); OR for each additional 10 minutes	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 (L/min/m2); OR for each 0.5 increase	3.6 ± 1.4	3.7 ± 1.2	1.0 (0.8, 1.3)	0.81		
Mixed venous saturation (%); OR for each 5% decrease	70 ± 11	71 ± 7	1.1 (0.8, 1.6)	0.45		
LVEDP or mean PCWp (mmHg) (n=1081); OR for each 2 mmHg decrease	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		

HSAE, High severity adverse event; EMB, Endomyocardial biopsy; LVEDP, Left ventricular end-diastolic pressure; PCWp, Pulmonary capillary wedge pressure;

Table 5

Patient and Procedural Risk Factors for a Non-Diagnostic EMB Sample in Heart Transplant Recipients

N (%) is provided for categorical variables, median [interquartile range] is provided for ordinal/continuous variables, and mean ± s.d. is provided for normally distributed continuous variables. Odds ratio expresses risk of obtaining a non-diagnostic sample calculated using generalized estimating equations (GEE) models.

Demographic / Clinical Predictors	EMB Sample		Univariate Analysis	
	Non-Diagnostic Sample (n=15)	Diagnostic Sample (n=1123)	Odds Ratio	P value
Age				
< 1 year	0 (0)	40 (4)	—	—
1-9 years	0 (0)	386 (34)	—	—
≥ 10 years	15 (100)	697 (62)	—	—
Weight				
< 10 kg	0 (0)	86 (8)	—	—
≥ 10 kg	15 (100)	1037 (92)	—	—
Time since heart transplant (years); OR for each additional year since transplant	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)	1082 (96)	1.0	—
Urgent or Emergent	1 (7)	41 (4)	1.9 (0.2, 14.2)	0.54
Airway & 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 (L/min/m^2); OR for each 1 L/min/m^2 decrease in CI	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				
3, 4, or 5 Fr	10 (67)	398 (36)	3.6 (1.1, 12.2)	0.04
6 or 7 Fr	5 (33)	723 (64)	1.0	—
Number of biopsy attempts; OR for each additional attempt	7 [6, 9]	5 [4, 6]	1.3 (1.2, 1.5)	<0.001

Demographic / Clinical Predictors	EMB Sample		Univariate Analysis	
	Non-Diagnostic Sample (n=15)	Diagnostic Sample (n=1123)	Odds Ratio	P value
Number 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	—

EMB, Endomyocardial biopsy; CI, Cardiac Index; Fr, French;

Table 6

Post-Transplant EMB Case Characteristics by Center (n=2661)

N (%) is provided for categorical variables, median [interquartile range] is provided for ordinal/continuous variables, and mean ± s.d. is provided for normally distributed continuous variables. Center H performed 4 cases and was not included in the table.

Patient and Case Characteristic	Center A	Center B	Center C	Center D	Center E	Center F	Center G
Number of cases	352	806	344	113	51	415	580
Average number of cases per month	9.5	21.8	9.3	3.1	1.4	34.6	15.7
Number of Patients	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 & 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 & 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 (minutes)	50 ± 30	33 ± 24	35 ± 21	64 ± 41	63 ± 29	31 ± 22	43 ± 34
Fluoroscopy Time (minutes)	13 ± 8	10 ± 8	7 ± 5	20 ± 17	15 ± 9	7 ± 6	8 ± 7
Efficacy Information							
Case performed by (n=1145)							
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)

Patient and Case Characteristic	Center A	Center B	Center C	Center D	Center E	Center F	Center G
Fellow	10 (9)	115 (54)	44 (38)	0 (0)	8 (67)	77 (18)	63 (26)
Size of bioptome (n=1142)							
3 Fr	0 (0)	0 (0)	0 (0)	5 (14)	0 (0)	5 (1)	0 (0)
5 Fr	23 (20)	207 (99)	20 (17)	20 (54)	1 (8)	109 (26)	21 (9)
6 Fr	9 (8)	2 (1)	96 (82)	12 (32)	11 (92)	301 (73)	114 (48)
7 Fr	82 (72)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	103 (43)
Type of bioptome (n=1145)							
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)
Number of biopsy attempts	5 [5, 6]	7 [6, 8]	5 [4, 6]	4 [3, 5]	5 [4, 6]	4 [4, 5]	6 [5, 8]
Maximum number of attempts	12	15	13	14	7	27	21
Number of pieces obtained	5 [5, 5]	6 [5, 6]	4 [4, 4]	3 [3, 4]	4 [4, 4]	4 [4, 4]	6 [5, 7]

EMB, Endomyocardial biopsy; Fr, French;