

Safety of endomyocardial biopsy in children

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Abstract Endomyocardial biopsy in children remains important in the evaluation of cardiomyopathy, myocarditis, and rejection following cardiac transplantation. We sought to evaluate the morbidity associated with endomyocardial biopsy on the basis of a large experience from a single institution.

We reviewed records of all endomyocardial biopsies performed at our institution. Complications were defined as adverse events resulting from the biopsy requiring intervention or additional observation. We also reviewed the most recent echocardiogram from all the patients for the presence and severity of tricuspid valvar regurgitation.

Between November 1986 and April 2002, we performed 1051 endomyocardial biopsies in 135 patients ranging in age from 9 days to 18 years. The internal jugular vein was the site of vascular access in 68% of the procedures. There were 10 acute procedural complications requiring intervention or additional observation. Severe tricuspid regurgitation developed in two patients who had undergone multiple biopsies after cardiac transplantation, one of whom underwent subsequent replacement of the tricuspid valve. There were no deaths or cardiac perforations. The total incidence of morbidity was 1.1%. No demographic or procedural factors were identified to be predictive of complications.

In experienced hands, therefore, endomyocardial biopsy can be safely performed in children with very low morbidity.

Keywords: Interventional procedures; morbidity; safety; paediatric; cardiac transplantation

ENDOMYOCARDIAL BIOPSY REMAINS IMPORTANT in the evaluation of cardiomyopathy, and in detecting allograft rejection following cardiac transplantation in children. This invasive diagnostic method is associated with vascular and other potentially life-threatening complications. To assess the frequency of such complications, we evaluated the morbidity associated with endomyocardial biopsy based on a large experience from a single institution.

Methods

Using the database from our catheterization laboratory, we identified all endomyocardial biopsies performed at our institution between November 1986

and April 2002. We then reviewed the records of the identified patients to retrieve demographic data, to establish the indications for biopsy, whether seen as inpatients or outpatients, vascular access, type of anesthesia, number of tissue samples obtained, the ventricle sampled, and procedural complications. We also reviewed the most recent echocardiographic reports to establish the presence, if any, and severity of tricuspid regurgitation.

Right and left ventricular biopsies were obtained using either a Cordis (Cordis Corp, Miami, FL) or Scholten (Scholten Surgical Instruments, Inc., Redwood City, CA) bioptome. The bioptome was introduced into the right internal jugular vein through a short sheath and then uncovered directly into the right ventricle. Alternatively, the tip of a long Mullins sheath (Medtronic, Inc., Minneapolis, MN) was positioned within the right ventricle from the femoral vessels, through which the bioptome was passed. One cardiologist consistently cut 2 cm

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Table 1. Demographics of 135 children undergoing 1051 procedures.

Procedures per child	7.8 ± 10.5 (1–46)
Samples per procedure	5.1 ± 1.2 (2–14)
Patient age in years	11.8 ± 5.4 (9 days–18 years)
Patients under 1 year at biopsy	48 (4.6%)
Patient weight kilograms	33.5 ± 18.8 (2.5–108)
Male patients	80 (59%) undergoing 566 (54%) biopsies
Inpatients	164 (16.7%)*

Results reported as mean ± SD (range) or No. (percent). *Data available for 982 procedures

from the tip of the femoral sheath in an effort potentially to decrease the likelihood of pulling the wall of the ventricle against the tip of the sheath when samples were obtained. Multiple samples were obtained from the ventricular septum under fluoroscopic guidance by 5 attending pediatric cardiologists. Samples were obtained from the apex or right ventricular free wall when the bioptome could not be positioned against the septum.

Complications were defined as adverse events resulting from the biopsy requiring intervention or additional observation in the hospital. Statistical analysis was performed using Student's *t*-test for comparison between groups, Pearson's correlation for normally distributed data, and the Mann-Whitney rank sum test for abnormally distributed data.

Results

A total of 1051 biopsy procedures were performed among 135 patients over a period of 15.4 years. We have summarized the demographic data in Table 1. The mean age of the patients was 11.8 years, with a range of 9 days to 18 years, and the mean weight was 33.5 kg, with a range of 2.5 to 108 kg. There were 48 procedures performed on children under 1 year of age, 9 of which were performed to evaluate for possible myocarditis, and 31 of which were performed on inpatients. The average age of this subgroup was 5.3 months, with an average weight of 5.8 kg. The majority of procedures (83%) were performed on outpatients, who were typically discharged from 2 to 6 h following the procedure according to the data available for 982 procedures. The average number of procedures per patient was 7.8, with a standard deviation of 10.5, and a range of 1 to 46 procedures. An average of 5.1 samples was obtained during each procedure, providing a total of over 5100 samples. The indications for biopsy are summarized in Table 2. Biopsies were performed for surveillance subsequent to transplantation, or follow-up of previously demonstrated rejection, in 92% of cases. The other biopsies were obtained to evaluate for myocarditis (5.3%),

Table 2. Procedural indication.

Post-transplant surveillance	969 (92.2%)
Cardiomyopathy/myocarditis	56 (5.3%)
Arrhythmia	23 (2.2%)
Tumour	2 (0.2%)
Amyloidosis	1 (0.1%)

Results reported as No. (percent)

Table 3. Procedural details.

Vascular access (data available for 1026 procedures)	
Right internal jugular vein	700 (68.2%)
Right femoral vein	241 (23.5%)
Left femoral vein	77 (7.5%)
Left internal jugular vein	4 (0.4%)
Left subclavian vein	3 (0.3%)
Right subclavian vein	1 (0.1%)
Right femoral artery	2 (0.2%)
Left femoral artery	1 (0.1%)
Anaesthesia	
Local (with or without sedation)	1030 (98.0%)
General	21 (2.0%)
Ventricle sampled	
Right ventricle only	1045 (99.4%)
Left ventricle only	3 (0.3%)
Both ventricles	3 (0.3%)

Results reported as No. (percent)

arrhythmia (2.2%), right ventricular tumor (0.2%), and amyloidosis (0.1%).

Data on vascular access, type of anesthesia, and the ventricle sampled are summarized in Table 3. Vascular access was established directly by, or under the supervision of, the attending cardiologist in all cases. The right internal jugular vein was the most commonly used site of vascular access. It was used in 68% (700/1026) of the procedures. Internal jugular venous access was established using anatomic landmarks or ultrasonic guidance. A shortened sheath was used in 42% of the biopsies that were performed from the femoral approach. The median weight in patients in whom the internal jugular vein approach was used was 38.1 kg. This was significantly greater ($p < 0.001$) than the median weight of 24.1 kg in patients in whom other sites of venous vascular access were used. The right ventricle was exclusively sampled in all but 6 procedures. The left ventricle was entered from the femoral artery in 3 cases, and across an atrial septal defect from the femoral vein in 1 case. Information about vascular access for the other 2 left ventricular samples was not apparent from the records. The reviewing pathologist deemed samples inadequate for interpretation in 6 cases. Local anesthesia was used in the majority of procedures, sedating with benzodiazepene combined with a narcotic such as morphine or fentanyl. Ketamine and pentobarbital were also occasionally used for sedation. General

Table 4. Complications.

	Age	Wt (kg)	Access	Indication	Status	Details
Arrhythmia	2.0 y	10.5	RIJV	TX	O	Bradycardia with cardiac arrest
	12.7 y	50.0	RFV	CM	PICU	Ventricular tachycardia, received bretylium
	13.9 y	42.0	RIJV	TX	O	SVT, terminated with catheter manipulation
Sedation	5.1 y	18.3	RFV	TX	O	Adverse reaction to sedatives
	5.0 m	5.9	LFV	TX	O	Increased WOB, intubated
Vascular	13.7 y	57.0	RIJV	TX	O	RIJV injury, hemothorax
	8.5 y	16.7	RIJV	TX	I	Carotid artery injury, hemothorax
Misc	3.1 y	14.0	RIJV	TX	O	Acidosis, transferred to PICU
	7.2 y	22.0	RFV	TX	O	Acidosis, transferred to PICU
	8.2 y	26.5	RIJV	TX	O	Increased WOB, transferred to PICU

Abbreviations: CM: cardiomyopathy; I: inpatient; O: outpatient; SVT: supraventricular tachycardia; TX: post-transplant; WOB: work of breathing; LFV: left femoral vein; RFV: right femoral vein; RIJV: right internal jugular vein; PICU: Paediatric Intensive Care Unit

anesthesia was employed, at the discretion of the attending cardiologist, in only 21 (2.0%) procedures.

Acute complications occurred in 10 procedures (1.0%), and are summarized in Table 4. These occurred in 9 patients after cardiac transplantation, 6 of whom had venous access from the neck. The average age among patients with complications was 7.5 years, with a standard deviation of 4.9 years. This was significantly lower ($p = 0.006$) than the average age among patients without complications, which was 11.9 years, with a standard deviation of 5.4 years. Similarly, the average weight was 20.5 kg among patients with complications, compared to 33.7 kg among patients without procedural complications ($p = 0.02$). There were no deaths or cardiac perforations. A 2-year-old boy undergoing routine catheterization and biopsy under general anesthesia developed bradycardia that progressed to asystole. He was successfully resuscitated, observed in the intensive care unit, and subsequently discharged without additional sequels. One patient developed supraventricular tachycardia that terminated with catheter manipulation within the right atrium. One patient with suspected myocarditis developed ventricular tachycardia requiring bretylium. Complications of sedation occurred on 3 occasions. A 5-month old developed labored breathing with initial sedation and was intubated. A 5-year old became agitated and developed transient evidence of obstruction to the upper airways requiring additional observation in the hospital. Another 5-year old who had undergone neonatal cardiac transplantation developed localized hives and erythema following administration of intravenous morphine. There was no associated hemodynamic instability or airway compromise. Significant vascular complications occurred as a result of attempted internal jugular venous access in 2 procedures. The carotid artery was punctured in an 8-year-old girl, resulting in acute hemothorax necessitating placement of a chest tube and subsequent hospitalization. Establishing

internal jugular venous access in a 13-year old was initially difficult, with suspected malposition of the sheath outside the vessel lumen. A chest X-ray after the biopsy demonstrated blunting of the right costophrenic angle, presumably due to a small hemothorax. The patient was discharged to home 4 h later without intervention after a repeat chest X-ray was unchanged. Admission to the intensive care unit following biopsy was necessary due to metabolic acidosis on 2 occasions. Both patients recovered with improved hydration, and were subsequently discharged without further intervention.

Echocardiographic records were available for 131 of the 135 patients. Tricuspid regurgitation was graded as a trace to none in 91 (69.5%), mild in 20 (15.3%), moderate in 3 (2.3%), severe in 2 (1.5%), and was not mentioned in 15 (11.5%). There was a weak but statistically significant correlation between the number of biopsies and the degree of tricuspid regurgitation (correlation coefficient 0.223, $p = 0.01$). The most recent echocardiogram performed on the 18-year-old patient who had undergone 46 biopsies subsequent to cardiac transplantation, however, demonstrated only mild tricuspid regurgitation. Two recipients of transplanted hearts developed asymptomatic but progressive tricuspid regurgitation following multiple biopsies. A 6-year-old girl developed severe tricuspid regurgitation following 9 procedures. An 18-year-old girl later underwent elective replacement of the tricuspid valve prior to intended pregnancy after she developed severe tricuspid regurgitation following 33 procedures.

Discussion

Endomyocardial biopsy remains crucial to the care of children following cardiac transplantation due to the lack of reliable, non-invasive indexes of rejection. The evaluation of the patient with cardiomyopathy or myocarditis often also necessitates invasive testing

as part of an evaluation for suspected metabolic or acquired cardiac disease. Reported rates of complications range widely, from 0.1% to 12%.¹⁻³ The largest experience from a single institution dealing with children published to date reported a rate of 1.9% for complications, including 9 cardiac perforations and 1 death among 1000 consecutive procedures.⁴ These authors identified small, sick children with suspected myocarditis as the subgroup particularly at risk for complications resulting from endomyocardial biopsy. Because this subgroup is notably small in our series, we recommend particular caution when considering endomyocardial biopsy in such small and sick children with suspected myocarditis.

The incidence of acute complications in our series, at 1%, was skewed towards smaller and younger patients. The heterogeneous nature of the complications does not allow for more specific identification of risk factors. The slightly lower incidence of complications in our series compared to the study by Pophal et al.⁴ probably reflects multiple variables, including the slightly older and larger patients in our cohort with a slightly higher incidence of procedures after transplantation. The mean number of procedures for each patient, nonetheless, is nearly identical in the two studies. The other notable difference between these 2 large series was the more frequent use of the internal jugular venous approach at our institution (68% vs. 53%). While the site of vascular access was not found to be a significant variable in the study of Pophal and his colleagues,⁴ all 9 of their reported perforations occurred from the femoral vein with the use of a long vascular sheath. In our patients, a substantial number of cases using the femoral approach were performed with approximately 2 cm cut from the tip of the sheath. This minor modification may decrease the risk of perforation. In small children particularly, a standard Mullins sheath may be positioned with excessive force against the wall of the ventricle when the biptome is withdrawn.

The incidence of moderate or severe tricuspid regurgitation among our patients, at 3.8%, is comparable

to the 5.6% incidence reported among a group of adults after cardiac transplantation.⁵ While this complication can be serious, the likelihood is low, and further supports the safety of carefully performed endomyocardial biopsy in children.

This large experience from a single institution further documents the safety of endomyocardial biopsy in children, with an overall rate of complications less than previously reported. The low rate of complications reported in our series may not necessarily extrapolate to centers where endomyocardial biopsy is performed less frequently. The absence of any cardiac perforations or deaths may be in part related to the increased use of the internal jugular venous approach, and to a minor modification in the tip of long vascular sheaths when the femoral approach was used. In addition, while the likelihood of tricuspid valvular injury is weakly correlated with the number of biopsy procedures, this complication is uncommon.

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