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Decline in ventricular function as a result of general anesthesia in pediatric heart transplant recipients

Justin J. Elhoff¹, Shahryar M. Chowdhury¹, Carolyn L. Taylor¹, Marc Hassid², Andrew J. Savage¹, Andrew M. Atz¹, and Ryan J. Butts¹

¹Division of Pediatric Cardiology, Department of Pediatrics, Medical University of South Carolina, Charleston, SC, USA

²Division of Pediatric Anesthesia, Department of Anesthesia and Perioperative Medicine, Medical University of South Carolina Charleston, SC, USA

Abstract

Echocardiography is frequently performed under anesthesia during procedures such as cardiac catheterization with EMB in pediatric HTx recipients. Anesthetic agents may depress ventricular function, resulting in concern for rejection. The aim of this study was to compare ventricular function as measured by echocardiography before and during GA in 17 pediatric HTx recipients. Nearly all markers of ventricular systolic function were significantly decreased under GA, including EF ($-4.2\% \pm 1.2$, $P < .01$) and RV FAC (-0.05 ± 0.02 , $P = .04$). Subjects in the first post-transplant year ($n = 9$) trended toward a more significant decrease in EF vs those beyond the first post-transplant year ($n = 8$; $-6.0\% \pm 1.2$ vs -2.1 ± 2.0 , $P = .1$). This information quantifies a decline in biventricular function that should be expected in pediatric HTx recipients while under GA and can assist the transplant clinician in avoiding unnecessary treatment of transient GA-induced ventricular dysfunction.

Keywords

anesthesia; cardiac function; echocardiography; graft function; pediatric heart transplant

1 | INTRODUCTION

Echocardiographic measures of ventricular function are often used to assess for evidence of rejection in pediatric HTx recipients. Echocardiography is frequently performed in these patients while under GA during a concurrent procedure, such as cardiac catheterization with

Correspondence: Justin Elhoff, Sections of Critical Care Medicine and Cardiology, Texas Children's Hospital, Houston, TX, USA. jxelhoff@texaschildrens.org.

AUTHORS' CONTRIBUTIONS

Justin Elhoff: Responsible for the concept and design of the study, data collection, data analysis and interpretation, drafting article, critical revision of article, approval of article, and statistics; Shahryar Chowdhury: Responsible for data collection, data analysis and interpretation, critical revision of article, and approval of article; Carolyn Taylor: Responsible for the concept and design of the study, data collection, critical revision of article, and approval of article; Marc Hassid and Andrew Atz: Responsible for the concept and design of the study, critical revision of article, and approval of article; Andrew Savage: Responsible for concept of the study, critical revision of article and approval of article; Ryan Butts: Responsible for the concept and design of the study, data analysis and interpretation, critical revision of article, and approval of article.

EMB.¹ Anesthetic agents used to establish GA potentially cause a transient decline in ventricular function. Detecting decreased ventricular function by echocardiography in pediatric HTx recipients under GA may lead to unnecessary hospital admission and/or escalation of antirejection therapies while awaiting EMB results.

While studies have indicated a myocardial depressant effect of many anesthetic agents in animal and adult populations, there is a relative paucity of qualitative data detailing the effects of anesthetic agents on cardiac function in children.^{2–8} Additionally, echocardiographic markers of cardiac function in pediatric HTx recipients may not be comparable to those in non-transplanted patients.⁹ The aim of this study was to prospectively evaluate pediatric HTx recipients in order to quantify the effects of a standard GA regimen on ventricular function as measured by echocardiography.

2 | METHODS

Patients of age 0–21 status post-HTx presenting for routine cardiac catheterization and EMB between 1/1/2014 and 9/1/2014 were screened for participation. Exclusion criteria included emergent presentation for catheterization, unstable arrhythmia, history of condition precluding standard GA regimen (ie, malignant hyperthermia), or anesthesia decision that patient was an inappropriate candidate for standardized anesthesia regimen. Patients presenting for more than one catheterization procedure during the study period were allowed to be re-enrolled as a new subject for up to three occurrences. Informed consent was obtained for all study participants. The Institutional Review Board at the Medical University of South Carolina approved this study.

Following enrollment and prior to administration of any sedative or analgesic medication, participants underwent echocardiography by a pediatric sonographer using a standardized protocol to assess measures of systolic and diastolic functions. Subsequent to this initial echocardiogram, premedication with midazolam was utilized at the discretion of the pediatric cardiac anesthesiologist and the patient proceeded to the catheterization suite. Induction of anesthesia was achieved by inhalation of sevoflurane or intravenous administration of propofol. Maintenance of anesthesia was achieved by inhalation of sevoflurane via endotracheal tube with a goal MAC between 0.8 and 1.2. MAC is the dose of inhalational anesthetic gas that prevents motor response by 50% of patients to a standardized surgical incision. A patient receiving one MAC of anesthetic gas will demonstrate a predictable depth of anesthesia regardless of the type of anesthetic gas selected or the age of the patient. Modest doses of adjunctive agents including fentanyl or propofol were used at the discretion of the cardiac anesthesia team to achieve balanced anesthesia. All patients reached a stable maintenance phase of GA prior to repeat evaluation of cardiac function.

Following performance of right heart catheterization, cardiac output measurement, and EMB, but while still under GA, repeat echocardiography using the same protocol was performed to assess ventricular function. A minimum time of 50 minutes passed between induction and performance of repeat echocardiography. Patient and anesthesia conditions at the time of repeat echocardiography were recorded. The remainder of the case and

anesthesia regimen was at the discretion of the anesthesiologist and interventionalist. All EMBs were read per institutional protocol, including traditional hematoxylin and eosin staining with immunofluorescence for C3d and C4d deposition.

Traditional echocardiographic measures of ventricular function and TDI were analyzed by a single-blinded reviewer (CT). A separate blinded reviewer (SC) performed all assessments of myocardial strain using speckle-tracking echocardiography. All measures were made in triplicate and averaged. Echocardiograms were performed using a Philips IE33 system (Andover, MA, USA). Echocardiograms were sent uncompressed and at native frame rates to an encrypted server for analysis. Non-invasive blood pressures (systolic, diastolic, and mean) were obtained supine at the time of echocardiography by automated sphygmomanometer.

Conventional measures of LV systolic function were derived from 2D echocardiography, M-mode, and spectral TDI (Xcelera, Philips). Measurement methods conformed to recommendations by the American Society of Echocardiography.¹⁰ Measurements included EF (5/6 area length method), shortening fraction (M-mode), TDIs' velocity from the lateral and septal LV walls. Right ventricular function was assessed using tricuspid annular systolic plane excursion and RV FAC from the apical four-chamber view.

Two-dimensional speckle-tracking was performed using Cardiac Performance Analysis v. 3.0 (Tomtec Imaging Systems GmbH, Munich, Germany). Six segments from the apical four-chamber view were averaged to measure longitudinal strain, strain rate, and early diastolic strain rate of the LV and RV. Six segments each from the parasternal short-axis view at the level of the papillary muscles were averaged to obtain circumferential strain, strain rate, and early diastolic strain rate of the LV.

To investigate the interplay between changes in contractility with potential alteration in afterload, non-invasive pressure–volume loop indices were calculated. Ees is the reference standard measure of LV contractility generally derived from invasive pressure–volume loop analysis. It can be estimated non-invasively using the formula developed by Chen et al.¹¹ This formula has been validated in pediatric HTx recipients.¹² Likewise, Ea is a measure of afterload calculated using the formula = (systolic blood pressure $\times$ 0.9)/stroke volume. Ventriculo-arterial coupling is a description of the interaction between myocardial performance and the vascular tree. It is calculated with the formula Ea/Ees.

The results were tested for normality of distribution using the Shapiro-Wilk test. Data are presented as mean $\pm$ SD or as median (IQR) as appropriate. Comparison of right and LV systolic and diastolic functions before and during GA was performed utilizing paired Student's *t* tests or the Wilcoxon signed-rank test. Statistical tests were two-sided, and $P < .05$ was considered statistically significant. Statistical analysis was performed using SPSS v. 23 (IBM, New York, NY, USA).

3 | RESULTS

A total of 17 subjects comprising 12 separate patients were enrolled (Table 1). No subject had rejection (defined as International Society for Heart and Lung Transplantation grade

2R or pathological antibody mediated rejection >1). Eight subjects received premedication with midazolam. GA was induced using sevoflurane in five subjects, sevoflurane with fentanyl in five subjects, sevoflurane with propofol in four subjects, fentanyl and propofol in two subjects, and propofol alone in one subject. All subjects received sevoflurane as maintenance anesthetic throughout the case titrated to MAC of 0.7–1.0. The time from induction of GA until repeat echocardiography ranged from 50 to 165 minutes (mean 89 minutes). Eight subjects received additional fentanyl administration during their procedure. Eight subjects required phenylephrine for blood pressure maintenance during the case, although none were on vasoactive infusions at the time of echocardiography. There were no adverse events from anesthesia or EMB.

Table 2 details changes seen in echocardiographic measures of function under GA. Nearly every measure of LV systolic function decreased significantly. EF worsened by 6.8% from baseline, shortening fraction by 11.6%, longitudinal strain by 18.8%, and Ees by 30.8%. There were not significant changes in LV end-diastolic volume or Ea to suggest changes in loading conditions that could affect myocardial performance. The only preserved measure of LV function under GA was LV circumferential strain. RV FAC was also significantly reduced during exposure to GA at 10.8% below the baseline value. There was not consistent evidence of alteration of diastolic function during GA.

Approximately half (9/17) of the subjects were <1 year since transplantation. These subjects showed a trend toward a more significant decline in systolic function compared to subjects (n = 8) >1 year since transplantation in all measures of systolic function, including EF (8.6% decrease in those within the first post-transplant year compared to a 3.5% decrease in those >1 year post-transplant, $P = .17$).

4 | DISCUSSION

Reliable, non-invasive monitoring for graft rejection in pediatric HTx recipients has proven elusive.^{13–17} Therefore, the “gold-standard” for the diagnosis of allograft rejection remains cardiac catheterization with EMB. However, given the invasive nature of this procedure, serial echocardiographic assessment of cardiac function remains an important aspect of post-transplant monitoring. Potentially confounding the serial non-invasive tracking of cardiac performance in this population, echocardiograms are often performed concomitantly with procedures requiring administration of anesthetic agents. To the best of the authors’ knowledge, this study is the first to quantify the expected changes in ventricular function in pediatric HTx recipients undergoing gas-based GA. Given our findings, it should be expected that while under GA these patients would have a decline in ventricular function of 6%–10% from their baseline values when using traditional markers of function such as EF, shortening fraction, and RV FAC. The decline may be more dramatic when utilizing newer techniques such as speckle-tracking echocardiography or non-invasively measured Ees. In the absence of additional concerning signs, changes within these ranges from a patient’s baseline echocardiographic markers of function while under GA should not be seen as indication of rejection. A larger study including subjects with allograft rejection is necessary to determine a level of decline in function associated with rejection.

More recent studies have raised the suggestion that tissue Doppler and speckle-tracking strain echocardiography may have better ability to predict subclinical rejection than traditional echocardiographic markers.^{9,18–22} However, utilization of these modalities in pediatric HTx recipients requires further establishment of normative values.^{23–26} Furthermore, it is unclear in the literature how anesthetic agents may affect these measures of function. We found that GA significantly decreased LV longitudinal strain while circumferential strain was preserved. LV circumferential strain was the only measure of systolic function that did not decline under GA, potentially allowing this to be a stable marker of pre-anesthetic function that could be tracked serially. Previous work has described preservation of circumferential strain in pediatric HTx recipients.²⁷ One possible explanation for this phenomenon is that the myocardial fibers in the subendocardium, most distal in the coronary arterioles, are oriented in the longitudinal orientation. Meanwhile, the circumferentially oriented fibers are located in the middle cardiac layers where they may be less susceptible to the ischemic time associated with the transplant process. It is possible that more pronounced ischemia during the organ recovery process in the longitudinally oriented fibers results in myocardial cells more sensitive to the depressive effects of anesthetic agents.

While not powered to detect such a difference, there may be a trend toward a more pronounced decline in systolic function under GA in patients <1 year post-transplant. Similar to the above argument, it is plausible that the myocardium of the more recently transplanted heart continues to recover and remodel following the stress of ischemic time; however, more investigation into this phenomenon is necessary.

The mechanism by which anesthetic agents decrease ventricular function has not been fully investigated in pediatric HTx recipients. Due to the load dependence of traditional measures such as EF, such investigation into true myocardial contractility utilizing traditional measures such as EF has been obfuscated by inevitable changes in loading conditions. Using novel, validated measures of non-invasive pressure–volume analysis, we found that Ees, a measure of contractility, decreased with anesthesia. Measures of load such as Ea and EDV showed no change. These results suggest that decreases in EF and longitudinal strain are influenced by a decrease in contractility due to myocardial depressant effects of gas anesthesia in pediatric HTx recipients rather than changes in loading conditions. Utilization of non-invasively measured Ees in conjunction with Ea allows us to more clearly define load-independent changes in cardiac function associated with administration of anesthetic agents and may be an important mechanism to better understand how the myocardium is influenced by different agents.

5 | LIMITATIONS

Given the relatively small number of subjects enrolled in this single-center study and the fact that no subjects had allograft rejection at the time of their study, we are unable to determine whether the response to anesthetic agents is different in patients with and without rejection. To date, reliable non-invasive assessment for rejection in pediatric HTx recipients has proven to be a difficult challenge. Likewise while we noted a trend toward a more pronounced

decline in function in subjects who had undergone transplant within 1 year of the study, we did not have the power to detect such a difference.

Despite prospective enrollment of subjects and a standardized anesthetic regimen, it is possible that unmeasured confounding factors influenced the changes seen in ventricular function. Given the lack of evidence for change in preload and the utilization of and the assessment of ventricular function utilizing ventriculo-arterial coupling, we do not believe that changes in loading conditions during the procedure influenced the results. However, it is possible that slight differences in the anesthetic regimen or the irregular metabolism of drugs between patients could account for some of the differences noted, and the fact that the majority of our subjects were older children and teenagers possibly limits the ability to apply results to an even younger population. Additionally, as some individual patients were enrolled as subjects at different time points in this study, it is possible that an individual patient's response to this anesthetic regimen could have increased influence on the results.

This study utilized one possible anesthetic regimen for patients undergoing cardiac catheterization and EMB, and therefore, the results need to be taken into this context. Due to practice variation across centers as well as alternative anesthetic regimens that may be utilized in other settings for pediatric HTx recipients, additional studies will be necessary to assess for the effects of other commonly used sedative and analgesic agents.

6 | CONCLUSION

This study quantifies an expected decline in systolic function for pediatric HTx recipients without allograft rejection while undergoing volatile gas-based GA. Clinicians can use this information when evaluating an echocardiogram performed under conditions of anesthesia in these patients.

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Abbreviations

Ea	arterial elastance
EDV	end-diastolic volume
Ees	end-systolic elastance
EF	ejection fraction
EMB	endomyocardial biopsy
GA	general anesthesia

HTx	heart transplant
IQR	interquartile range
LV	left ventricle
MAC	minimal alveolar concentration
RV FAC	right ventricular fractional area change
SD	standard deviation
TDI	tissue Doppler imaging

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TABLE 1

Subject demographics and data

Subjects (n)	17
Female (n, %)	9 (53)
Age (years)	13.6 (5.4–18.4)
Weight (kg)	37.8 ± 20.7
Systolic blood pressure (mm Hg)	114 ± 17.7
Diastolic blood pressure (mm Hg)	70 ± 11.7
Time since transplant (mo)	9 (0.6–26.1)
<1 year since transplant (n, %)	9 (53)
LV end-diastolic pressure (mm Hg)	11 ± 2.6
Cardiac index (L/min/m ²)	3.0 ± 0.52
Mixed venous oxygen saturation (%)	76 ± 4.3

Data are reported as mean ± SD, median (IQR), or number (percent) as appropriate.

TABLE 2

Echocardiographic function before and during GA

	Pre-anesthesia (n = 17)	Under GA (n = 17)	P-value
EF (%)	64.2 ± 5.3	60.1 ± 7.9	<.01
Fractional shortening (%)	35.5 ± 4.6	31.8 ± 5.7	<.01
LV longitudinal strain (%)	−18.3 ± 3.1	−15.4 ± 4.1	<.01
LV longitudinal strain rate (1/s)	−1.3 ± 0.3	−1.0 ± 0.3	<.01
LV circumferential strain (%)	−22.5 ± 2.5	−21.8 ± 4.5	.92
LV circumferential strain rate (1/s)	−1.6 ± 0.3	−1.4 ± 0.4	.46
Ees (mm Hg/mL)	5.1 ± 2.3	3.9 ± 1.9	<.01
Ea (mm Hg/mL)	2.7 ± 1.1	2.5 ± 1.3	.18
Ea/Ees	0.6 ± 0.1	0.7 ± 0.2	<.01
LV end-diastolic volume (mL)	61 (43–107)	51 (40–99)	.18
RV FAC (%)	0.41 ± 0.05	0.37 ± 0.06	.04
Mitral valve E/A	2.2 ± 0.6	2.7 ± 0.9	<.01
Mitral valve annular E/e′	7.8 ± 2.2	8.2 ± 2.1	.7
Mitral valve septal E/e′	11.5 ± 4.7	10.8 ± 4.1	.5

Data are reported as mean ± SD or median (IQR) as appropriate.