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CASE SERIES

Echocardiographic evaluation after pediatric heart transplant in Chile: initial application of a functional protocol with global longitudinal strain

Evaluación ecocardiográfica de pacientes pediátricos post-trasplante cardiaco en Chile: aplicación inicial de un protocolo funcional con *strain* longitudinal global

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Abstract

Introduction: The echocardiographic evaluation of patients after heart transplantation is a useful tool. However, it is still necessary to define an optimal follow-up protocol. **Objective:** To describe the results of the application of a functional echocardiographic protocol in patients being followed after pediatric heart transplantation. **Patients and Method:** Alls patients being followed at our institution after pediatric heart transplantation underwent an echocardiographic examination with a functional protocol that included global longitudinal strain. Contemporaneous endomyocardial biopsy results and hemodynamic data were recorded. **Results:** 9 patients were evaluated with our echocardiographic functional protocol. Of these patients, only 1 showed systolic left ventricular dysfunction according to classic parameters. However, almost all patients had an abnormal global longitudinal strain. Right ventricular systolic dysfunction was observed in all patients. No epidodes of moderate to severe rejectiom were recorded. No correlation was observed between these parameters and pulmonary artery pressure. **Conclusions:** Subclinical biventricular systolic dysfunction was observed in the majority of the patients in this study. No association with rejection episodes or pulmonary hypertension was observed, which may be related to the absence of moderate or severe rejection episodes during the study period, and to the small sample size. Long term follow-up of these patients may better define the clinical relevance of our findings.

Keywords:
Heart transplantation, children, echocardiography, heart failure

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Introduction

Pediatric heart transplantation is an established therapeutic tool in cases of end-stage heart failure or congenital heart disease that is not amenable to surgical correction nor palliation. According to published data by the International Society for Heart and Lung Transplantation (ISHLT), about 500-600 pediatric heart transplants are performed every year, with a sustained increase in recent years[1]. Our institution began in 2001 the only pediatric heart transplant program in our country, with 14 patients transplanted to date.

Graft rejection is a feared complication common to almost all types of organ transplants. In pediatric heart transplant patients, the occurrence of rejection episodes has decreased in recent years due to new protocols of HLA (human leukocyte antigen) compatibility and better immunosuppression treatment protocols[2]. However, rejection episodes are still frequent, especially during the first year after transplant. Early detection and management of these episodes is of paramount importance in the management of these patients. Endomyocardial biopsy remains the gold standard for diagnosing acute cellular rejection. Consequently, endomyocardial biopsies are routinely performed or when symptoms suggestive of rejection arise (i.e. heart failure)[3]. However, since this is an invasive procedure with infrequent but potentially serious complications, it is necessary to find new noninvasive diagnostic tools in order to identify patients at risk of rejection and perform targeted confirmatory biopsies[4]. Different possible early rejection markers have been studied and the use of echocardiographic parameters of systolic function based on strain have been described[5-7]. The evaluation of myocardial strain allows quantifying the deformation of the myocardium in different axes, both in systole and diastole, in relation to time. Parameters used historically for the evaluation of left ventricular function, such as the shortening fraction (SF) and ejection fraction (EF), evaluate ventricular function globally. Unlike these classical parameters, myocardial strain allows to evaluate the regional motility and mechanical alterations of ventricular contraction, thus detecting more subtle and earlier alterations of ventricular function.

The objective of this study is to describe the initial results of the application of a functional echocardiographic evaluation protocol that includes global longitudinal strain (GLS) of the left ventricle (LV) in pediatric patients after orthotopic heart transplantation.

Patients and Method

All patients who were less than 15 years old at the moment of the study from our Pediatric Heart Transplant Program from the Hospital Clinico UC-Christus were included in the study. The Research Ethics Board at Pontificia Universidad Catolica de Chile approved this prospective study. Patients older than seven years signed an assent and the parents of all patients signed an informed consent. Between March and September 2016, a routine echocardiography study including our newly designed functional protocol were performed to all our pediatric heart transplant patients. The following data were collected: demographic data, pre-transplant hemodynamic data, most recent hemodynamic study contemporary to echocardiography (within 3 months), endomyocardial biopsy results contemporary to echocardiography and the worst historical biopsy result. The ISHLT classification of acute cellular rejection was used. According to the histological findings, endomyocardial biopsy results were classified as 0R (no rejection), 1R (mild rejection), 2R (moderate rejection) or 3R (severe rejection)[8].

2D Echocardiography - Doppler

The echocardiographic study was performed by two operators on a Vivid E9 unit (GE Healthcare, Horten, Norway). The patient was positioned in left lateral recumbent position for the acquisition of appropriate images of the functional protocol. Image processing and respective measurements were performed using EchoPAC software (GE Vingmed Ultrasound A/S Horten, Norway). A complete anatomical evaluation was performed with measurement of cardiac dimensions. All measurements were indexed by body surface using the Haycock formula and Z-scores were calculated according to reference values[9]. LV systolic function was evaluated using: SF measured on left parasternal short-axis; EF by biplane Simpson's method; corrected velocity of circumferential fiber shortening (VCFc = SF x [ejection time x interval RR^{-1}]) and GLS by speckle tracking. Abnormal values considered were: SF < 28%, EF < 55%, VCFc < 1.0 circ/s and GLS > -18%. LV diastolic function was evaluated using the E/A ratio by Doppler of mitral inflow. The maximum velocity of mitral lateral E' was measured with tissue Doppler imaging and the ratio E/E' was calculated. Abnormal values were considered to be an E/A ratio < 1 and/or an E/E' mitral lateral ratio > 10. The right ventricular (RV) systolic function was assessed using TAPSE (Tricuspid Annular Plane Systolic Excursion) and tricuspid S' velocity by tissue Doppler. The Z-Score was calculated for TAPSE[10] and for tricuspid S'[11], both being considered abnormal with a value of Z < -2.

Statistical analysis

Values are described in median and range. Using Spearman's rank correlation coefficient, the corre-

lation between mean pulmonary artery pressure or pulmonary vascular resistance (PVR) as independent variables, and the Z-Score of TAPSE and tricuspid S' as dependent variables, were analyzed.

Results

At the time of this study, 14 patients have been transplanted at our Pediatric Heart Transplant Program since 2001. Four patients have died, 3 of them because of abandonment of treatment and 1 from sepsis. Another patient was excluded from the analysis because the donor heart had a bicuspid aortic valve and has currently severe aortic disease. Nine patients were included in this study. One of these patients (patient No. 5) suddenly died during the preparation of this manuscript. The average age was 15.8 years (range 5.4-19.1). The waiting time for transplantation was 5.7 months (range 0.1 - 18.6) and the average age at transplantation was 13.3 years (range 3.3 - 14.9). Three patients used ventricular assist devices as a bridge to transplantation. Table 1 shows the demographic data of the patients studied.

In relation to the LV dimensions, all patients had a LV diastolic diameter, septal and posterior wall thickness within normal ranges (data not shown).

Evaluation of LV systolic function showed a preserved SF in all patients and a decreased EF in one out of nine patients. However, eight out of nine patients had an altered GLS. Evaluation of LV diastolic function showed an abnormal mitral E/A ratio in one out of nine patients, suggestive of mild diastolic dysfunction and two out of nine patients showed a normal E/A ratio with E/E' > 10, suggestive of pseudonormalization pattern (moderate diastolic dysfunction). There was no clear association between the presence of LV systolic or diastolic dysfunction and rejection, although no rejection (0R) or mild rejection (1R) was detected in all the biopsies contemporary to the echocardiographic study. Table 2 shows the results of LV function evaluation.

The RV systolic function was compromised in seven patients (78%) when evaluated by TAPSE and in six out of nine patients (67%) when evaluated by tricuspid S' (table 3). Thus, all patients had some degree of RV systolic dysfunction. When evaluating data from the contemporary hemodynamic study, three out of nine patients had an average pulmonary artery pressure ≥ 25 mmHg and/or PVR > 3 Wood Units/m^2, being the highest pulmonary artery pressure recorded in this group 25 mmHg and the highest PVR 3.2 Wood Units/m^2. The pulmonary artery pressure contemporary to echocardiography was close to normal in this group of patients, without an obvious association with the RV alterations described. In relation to the hemodynamic data prior to transplantation, seven out of nine patients presented pulmonary hypertension according to these criteria. No correlation was found between pre-transplant pulmonary artery pressure and PVR and contemporary echocardiographic RV function parameters.

Table 1. Demographic characteristics of patients being followed after heart transplant

Patient	Age (years)	Age at transplant (years)	Time in transplant waiting list (months)		Diagnosis	Timing of echocardiographic evaluation after transplant (months)
1	18.6	13.0	1.4	[VAD 30 days]	Dilated Cardiomyopathy	63.8
2	19.1	13.7	14.3		Restrictive Cardiomyopathy	57.7
3	15.8	12.4	7.7		Dilated Cardiomyopathy	33.4
4	15.8	13.3	18.6		Dilated Cardiomyopathy	23.8
5	5.4	3.3	11.0		Dilated Cardiomyopathy	22.8
6	16.4	14.7	3.7	[VAD 103 days]	Dilated Cardiomyopathy	12.2
7	14.5	12.9	4.6	[VAD 132 days]	Dilated Cardiomyopathy	10.1
8	15.8	14.8	0.1		Dilated Cardiomyopathy	7.5
9	15.7	14.9	5.7		Dilated Cardiomyopathy	6.6
Median	15.8	13.3	5.7			22.8
(range)	(5.4-19.1)	(3.3-14.9)	(0.1-18.6)			(6.6 – 63.8)

VAD, ventricular assist device.

Table 2. Left ventricle systo-diastolic function after heart transplant

Patient	Worst historical biopsy	Contemporaneous biopsy	Left ventricle systolic and diastolic function					
			SF (%)	EF (%)	VCFc (circ/s)	GLS (%)	Mitral E/A	Mitral E/E'
1	1R	0R	44	65	1.29	-16.2	2.5	5.2
2	1R	1R	35	55	1.13	-11.7	2.3	10.2
3	1R	0R	35	63	1.09	-15.6	1.4	5.4
4	3R	0R	44	58	1.20	-18.3	3.1	8.2
5	2R	1R	37	59	1.10	-17.4	2.5	5.1
6	2R	1R	33	55	0.95	-17.6	2.1	10.5
7	1R	0R	45	66	1.30	-10.4	2.4	5.6
8	1R	1R	40	51	1.30	-10.9	0.4	6.7
9	1R	1R	34	59	1.10	-14.0	1.5	3.9
Median			37	59	1.13	-15.6	2.2	5.6
(range)			(33 – 45)	(51 – 66)	(0.95 – 1.30)	(-10.4 – -18.3)	(0.4 – 3.1)	(3.9 – 10.5)

SF, shortening fraction; EF, ejection fraction; VCFc, velocity of circumferential fiber shortening ; SLG, global longitudinal strain.

Table 3. Right ventricle systolic function after heart transplant

Patient	TAPSE (mm)	(Z) TAPSE	Tricuspid s' (cm/s)	(Z) s'	Pre-transplant		Contemporaneous	
					mPAP (mmHg)	PVR (Wood U)	mPAP (mmHg)	PVR (Wood U)
1	21.0	-1.8	9	-2.3	16	0.7	18	2.1
2	17.6	-3.4	8	-2.3	41	4.7	25	2.4
3	16.4	-3.5	13	-2.7	27	2.1	25	2.4
4	10.7	-6.4	9	-0.5	23	2.6	17	3.2
5	13.4	-3.9	7	-2.3	36	2.5	21	1.3
6	19.4	-1.9	12	-3.1	30	4.4	13	1.3
7	15.5	-3.7	8	-1.0	49	13.0	16	1.4
8	14.3	-4.4	10	-2.5	39	4.0 - 5.8	18	1.4
9	11.0	-6.2	7	-1.8	28	4.4	18	1.8
Median		-3.7		-2.3	30	3.5	18	1.8
(range)		(-6.4 – -1.8)		(-3.1 – -0.5)	(16 – 49)	(0.7 – 13.0)	(13 – 25)	(1.3 – 3.2)

TAPSE, tricuspid annular plane systolic excursion; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance.

Discussion

The main complication that limits survival of pediatric heart transplant patients remains graft rejection, in addition to post transplant coronary artery disease (cardiac allograft vasculopathy). Follow-up studies include a routine endomyocardial biopsy protocol, especially during the first year after transplantation, to rule out cellular rejection. In the pediatric population, the frequency of the scheduled biopsies varies and depends on each center[12]. Thus, many centers have focused on identifying noninvasive echocardiographic markers to identify patients at higher risk of graft rejection, including strain-based evaluations[5].

The studied population in the current study is small, which reflects the limited organ donation in our

country, however, it also reflects the entire pediatric heart transplant experience in our country. It is important to note, that more than half of the deaths in our experience (3/5 patients) were related to drop out of treatment. This undoubtedly reinforces the need for strict multidisciplinary follow-up and support of these patients, a discussion that escapes the objectives and scope of this study. Due to the cross-sectional study design used, there is high variability in the time elapsed from transplantation to the time of echocardiography, which makes the results not necessarily comparable between patients.

With regard to the evaluation of LV function, it should be noted that only one patient had LV systolic dysfunction when evaluated using classical parameters (SF and EF), but almost all of them had an altered GLS. There was no clear association between the alteration of these parameters and the presence of rejection. This discrepancy between the assessment of global ventricular function and the regional alterations observed in the strain study has been previously described in pediatric heart transplanted patients. Evaluation of biventricular function using a longitudinal, circumferential and rotational strain of LV has demonstrated subclinical systolic dysfunction in patients without evidence of rejection[13,14]. The evaluation of rotational strain (torsion) has been related to alterations in exercise response in transplanted patients[15]. Significantly, an alteration of radial, longitudinal and circumferential strain has been observed in patients with episodes of rejection in relation to their baseline values, with recovery after the rejection episode resolves[6]. In our series, patients were asymptomatic at the time of the study and we only observed episodes of mild rejection (1R) in five out of nine patients in biopsy contemporary to echocardiography, with no episodes of moderate (2R) or severe rejection (3R), which also limits the detection of association with echocardiographic alterations. This is why the data obtained probably corresponds to "baseline data" of these patients.

Evaluation of diastolic function using Doppler of mitral inflow and tissue Doppler imaging showed the presence of mild to moderate diastolic dysfunction in three out of nine patients. In previous studies, the use of tissue Doppler imaging has demonstrated biventricular diastolic dysfunction during the first year after heart transplantation[16]. In addition, longitudinal follow-up of transplanted patients has shown that during episodes of rejection, A' and E' velocity decreases at both the septal and lateral mitral annulus[17]. The LV strain has also been used for the evaluation of diastolic dysfunction, and it has been observed that LV diastolic strain is associated with an increase in pulmonary capillary pressure during catheterization, so it has been suggested as a possible marker of rejection episodes[18,19].

Among our findings, the large proportion of patients who had RV systolic dysfunction is noteworthy. There was no clear association between RV dysfunction and the presence of pulmonary hypertension either prior to transplantation or at the moment of the study, but these results are limited by the small sample size. In this population, an alteration of RV systolic function has been described, which is maintained after the first-year after transplant when evaluated by tissue Doppler imaging[17]. Additionally, adequate RV function has been shown to have good negative predictive value for cardiac allograft vasculopathy[20]. The impact of subclinical RV dysfunction and its evolution over time in our group of patients has yet to be clarified.

The current patient series is a pilot study of the application of a functional evaluation echocardiographic protocol in our transplanted patients. The small number of pediatric patients after heart transplant in our country and the low frequency of rejection episodes makes it difficult to identify echocardiography-based predictors of rejection. However, we believe that the application of advanced echocardiographic techniques for functional evaluation, such as GLS, are useful tools in these patients' due to their ability to detect functional alterations that may go unnoticed through evaluation by classical parameters. Follow-up of these patients over time will help define if whether the alterations described are transient, sustained over time, or whether they can predict the occurrence of clinically significant heart failure, with or without the occurrence of rejection. On the other hand, our initial evaluation protocol focused mainly on the evaluation of LV systolic function. The finding of RV systolic dysfunction in all of our patients was unexpected and we have no plausible explanation for it. In this way, we consider necessary to follow-up these patients using these parameters and other indexes that were not included in our initial protocol, such as RV strain. These indexes have been used in the evaluation of right ventricular function in adult patients after heart transplantation[21]. The long-term follow-up of the patients from this study will define the clinical relevance of these findings and allow the design of an optimal follow-up and management protocol.

Conclusions

The current study reports the initial results of the application of a functional echocardiographic evaluation protocol in the pediatric heart transplanted population in Chile. Although no clear relationship was observed between the echocardiographic alterations and rejection episodes, the presence of subclinical biventricular systolic dysfunction in the majority of pe-

diatric patients after heart transplantation in our series is noteworthy. Results are limited by small sample size and low frequency of rejection episodes with current management protocols, which is unlikely to vary significantly in the near future.

Current evidence supports the need for serial functional echocardiographic follow-up in these patients that include the described parameters, as well as other parameters based on the myocardial strain.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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