Cardiology in the Young

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Original Article

Cite this article: Huertas-Quiñones VM, Mestra CF, Peña-Trujillo V, Gallo-Bernal S, Villaveces M, and Alarcón-Forero LC (2020) Paediatric cardiomyopathies: echocardiographic diagnosis, clinical profile, and demographic characteristics: the experience of a tertiary referral centre for Latin American paediatric cardiology. *Cardiology in the Young* **30**: 462–467. doi: 10.1017/S1047951120000281

Received: 5 September 2019
Revised: 17 January 2020
Accepted: 17 January 2020
First published online: 17 February 2020

Keywords:
Cardiomyopathy; paediatric cardiology; epidemiology; heart failure

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Paediatric cardiomyopathies: echocardiographic diagnosis, clinical profile, and demographic characteristics: the experience of a tertiary referral centre for Latin American paediatric cardiology

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Abstract

Background: Although multiple studies have been conducted in the adult population, there is a vast knowledge gap regarding the epidemiologic characteristics of cardiomyopathies in the paediatric population. This issue is even more crucial when the precarious situation of medical research in Latin America is considered. Given the potential impact that these disorders could have on Latin American health systems, a comprehensive epidemiologic study regarding the clinical profile and sociodemographic characteristics of these patients will influence the way we approach paediatric cardiomyopathies. *Methods:* An observational retrospective study was conducted at a tertiary referral centre for Colombian and Latin American paediatric cardiology. We analysed all cases of primary cardiomyopathies in children younger than 18 years of age who presented at our institution between 2010 and 2016. Cases of cardiomyopathies were classified according to World Health Organization guidelines. *Results:* From a total of 29,533 children who attended our institution during the study period, 89 new cases of primary cardiomyopathies were identified. The median age at diagnosis was 11 years (interquartile range 4–9). Dilated cardiomyopathy accounted for 57.3% (n = 51) of cases; hypertrophic cardiomyopathy, 12.3% (n = 11); restrictive cardiomyopathy, 8.9% (n = 8); non-compacted cardiomyopathy, 7.8% (n = 7); arrhythmogenic ventricular cardiomyopathy, 6.7% (n = 6); and unspecified cardiomyopathy, 6.7% (n = 6). Heart failure was observed in 53.93% of the patients. The overall mortality was 12.36% (n = 11), which included two of eight patients who underwent cardiac transplantation.

Cardiomyopathies are diseases involving a vast range of abnormalities of the muscle fibres, which include various structural and functional phenotypes with complex taxonomies.[1,2] They can occur in children at any age and are the most common cause of heart failure in childhood and the primary cause of heart transplantation in children under 1 year of age.[3–5] Even though cardiomyopathies in the pediatric population are uncommon and compromise a very heterogeneous group of disorders, they have an immeasurable impact on the patient's life and on the health system's economic stability.[3–5] This is especially true when taking into account that nearly 40% of children who present with symptomatic cardiomyopathy either receive a heart transplant or die within the first 2 years.[3]

In multiple population-based studies, the incidence of primary cardiomyopathies has been estimated to be 1 in 100,000 persons per year in children <20 years of age, ranging between 0.7 in 100,000 (Finnish population) and 1.24 in 100,000 (Australian population).[6–8] Dilated cardiomyopathy has the highest reported incidence, accounting for approximately 50% of all paediatric cardiomyopathies.[7,9,10] About 10−25% of cases of dilated cardiomyopathy are attributable to acute myocarditis.[10,11] Hypertrophic cardiomyopathy accounts for 35−50% of the cases and restrictive cardiomyopathy for less than 5% of the cases.[6–8,11] Despite the lack of a proper consensus regarding the exact nature of left ventricular non-compaction cardiomyopathy (no agreement on whether it is a morphological trait of hypertrophic cardiomyopathy or distinctive cardiomyopathy), it accounts for about 5% of all cases.[12–14]

In the United States alone, cardiomyopathies carry an annual cost of 200 million dollars per year, and this cost is exponentially increased when taking into account the proportion of patients who undergo cardiac transplantation.[15,16] Nevertheless, no studies have been conducted regarding the costs and financial impact of this group of pathologies in Latin America; therefore, it can be assumed that these costs are proportional to our local incidence. However, no literature regarding the incidence and prevalence of this group of diseases in our region exists until

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now; thus, extrapolation of data between Latin America and the developed world is not currently possible.

Despite the instability of our emerging economies and the precarity of national health systems, paediatric cardiology in Latin American is in line with other top facilities around the world. This can be attributed to the large number of fully equipped centres that are capable of dealing with the whole spectrum of paediatric cardiomyopathies and are able to perform a wide range of interventions, providing excellent care in keeping with the best international standards.[17,18] The Latin American Transplant Association reported that heart transplantation in the paediatric population is performed in Brazil, Argentina, Colombia, Chile, and Paraguay.[19] About 50% of all cardiac transplants are performed in three centres: The Heart Institute at the University of São Paulo in Brazil, the Hospital Garrahan in Argentina, and the Fundación Cardiovascular in Colombia. However, due to the scarcity of transplantation centers and the lack of a strong transplant legislation and culture, the waiting list for cardiac transplantation in Latin America is two times higher than in the United States and one time higher than in Europe.[19]

For these reasons and considering the lack of available studies regarding the incidence and epidemiological characteristics of paediatric cardiomyopathies in Latin America, a better understanding of the epidemiology and clinical characteristics of these pathologies would facilitate planning and provision of medical services to generate improvements in patients' quality of life and rationalisation of health resources.

Cardiomyopathies in the paediatric population

Dilated cardiomyopathy

Dilated cardiomyopathy is a myocardium disorder which produces a dilated left ventricle with systolic dysfunction, without any haemodynamic cause that explains these changes.[2,3] It is the most common form of cardiomyopathy in the paediatric population and the most prevalent type of cardiomyopathy related to heart failure in both children and adults. Its incidence in the United States is estimated to be 1.13 in 100,000 infants and children.[11] Different causes have been described, including primary (idiopathic, familial, and genetic mutations) and secondary cases (inflammatory, CHD, oncologic, toxin mediated, systemic, and syndromic), with post-myocarditis dilated cardiomyopathy being the most prevalent form.[2] To date, dilated cardiomyopathy is the most common indication for heart transplantation in the paediatric population.[20]

Diagnosis is usually made by echocardiography, electrocardiography, cardiac MRI, or cardiac catheterisation. Screening studies in children who have a familial history of dilated cardiomyopathy, an inborn error of metabolism, a neuromuscular disorder, or a sentinel phenotypic trait are especially relevant. Despite efforts to improve patient care, paediatric dilated cardiomyopathy remains a challenging disease with an estimated 50% 5-year transplant-free rate of survival.[9,10]

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a common cardiac condition characterised by left ventricular hypertrophy with septal involvement associated with non-dilated ventricular chambers in the absence of a cardiac or systemic disease, which would be capable of producing the magnitude of wall hypertrophy itself.[2,4] It has an estimated worldwide prevalence of approximately 0.2%.[4] Multiple causes have been described, including sarcomeric dysfunction in primary hypertrophic cardiomyopathy, as well as myocardial infiltration related to glycogen deposit diseases, lysosomal storage disorders, and fatty acid oxidation disorders in secondary cases.[2] In the paediatric population, familial or genetic hypertrophic cardiomyopathy has an important relevance due to the possibility of screening and identification of additional cases among family members, which can contribute to a reduced mortality risk associated with this entity.[21,22]

The hypertrophic cardiomyopathy phenotype can be obstructive or non-obstructive. This is an important distinction because each phenotype requires different therapy and confers a different risk of mortality and sudden cardiac death in relation with dynamic outflow tract obstruction.[1,4,23] In children, diagnosis of ventricular hypertrophy is made when septal wall thickness is above 2−3 times the age- and sex-adjusted standard deviations.[4] Clinical presentation is very heterogeneous, ranging from symptomatic heart failure and angina, to ventricular or supraventricular arrhythmic events, syncope, or even sudden cardiac death. The latter is particularly important, as hypertrophic cardiomyopathy is an important cause of sudden cardiac death in young athletes, which can be mitigated by prompt recognition and primary prevention by the insertion of an implantable cardioverter defibrillator.[24–26]

Restrictive cardiomyopathy

Restrictive cardiomyopathy is the rarest form of paediatric cardiomyopathy. It is characterised by the presence of a stiffened ventricle with abnormal compliance, without another predominant phenotype of right or left ventricle dilatation, hypertrophy, or systolic dysfunction.[2,3] Restrictive cardiomyopathy has an incidence of 0.03−0.04 cases per 100,000 children. It is associated with a notably poor prognosis because of its high rates of morbidity and mortality, due to an increased incidence of ventricular dysfunction and heart failure.[3,4] Several systemic and myocardial diseases have been associated with restrictive cardiomyopathy, but the idiopathic form of the disease is still the most prevalent.[4] Clinical presentation highly varies, ranging from asymptomatic patients to overt heart failure, syncope, or sudden cardiac death.[3] Age at diagnosis ranges from early infancy through late adulthood.[3] Diagnosis of restrictive cardiomyopathy is made by echocardiography, electrocardiography, cardiac MRI, and cardiac catheterisation; tools that allow physicians to distinguish restrictive cardiomyopathy from constrictive pericarditis and to determine the functional severity of the disease.[2]

Left ventricular non-compaction

In the last few years, left ventricular non-compaction (also known as ventricular non-compaction) has been at the centre of great controversy among cardiologists.[12,13] Whether left ventricular non-compaction is a distinct cardiomyopathy or just a morphologic trait shared by different types of cardiomyopathies is still under debate.[27–29] There are believers and sceptics; however, new evidence in basic and clinical science, particularly new data from genetic studies, supports left ventricular non-compaction as a distinct cardiomyopathy.[12,28,30,31] Left ventricular non-compaction in children has been described in association with complex CHDs and coronary artery anomalies and as an isolated finding, with or without musculoskeletal or other organ system abnormalities.[2,32] Current paediatric studies estimate that left ventricular non-compaction accounts for about 5–9% of newly diagnosed cardiomyopathies.[7,33]

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Left ventricular non-compaction is defined by three morphological markers: prominent left ventricle trabeculae, deep intertrabecular recesses, and a thin compacted layer.[12,34,35] These three markers are also responsible for the clinical manifestations of left ventricular non-compaction such as heart failure and thrombi formation. The spectrum of morphologic variability is extreme, ranging from hearts with a nearly absent compacted layer and an almost exclusively trabecular component in the apex to hearts with prominent trabeculae but with a well-represented compacted layer.[12,27] Identical to morphological variability, left ventricular non-compaction patients have a wide clinical spectrum, ranging from an asymptomatic subclinical state to life-threatening conditions, such as severe systolic dysfunction, heart failure thromboembolism, stroke, and malignant arrhythmias.[36] To date, there are no standardised, universal criteria (clinical or imagology) for its diagnosis. Therefore, diagnosis requires the presence of a representative layer of non-compacted myocardium in the setting of a symptomatic patient, and in the absence of an alternative diagnosis that better explains the patient's clinical manifestations.

Arrhythmogenic ventricular cardiomyopathy

Arrhythmogenic ventricular cardiomyopathy is an autosomal dominant heart disease, characterised by fibro-fatty degeneration and replacement of the myocardium, which creates an anatomic subtract for ventricular arrhythmias, as well as for systolic dysfunction and heart failure.[2,37] Progressive loss of ventricular myocardium and its replacement by fibro-fatty tissue is the pathological hallmark of the disease.[38] It was previously known as arrhythmogenic right ventricular cardiomyopathy; however, biventricular and even isolated left ventricle cases are common so that the most recent literature regarding this entity now refers to it as arrhythmogenic ventricular cardiomyopathy. The most common clinical presentation of this disease consists of ventricular arrhythmias and their spectrum of related events or symptoms (i.e., syncope, sudden cardiac death, chest pain, and palpitations).[37]

Sudden cardiac death may occur unexpectedly in previously asymptomatic individuals, mostly in young athletes.[38,39] The medium- and long-term prognosis of arrhythmogenic ventricular cardiomyopathy is related to the presence of either ventricular electric instability or electrocardiographic anomalies, which may lead to arrhythmic events, syncope and/or sudden cardiac death, or progression of ventricular muscle infiltration, resulting in systolic dysfunction and heart failure.[2,37,39] Diagnosis of arrhythmogenic ventricular cardiomyopathy involves imagenological evidence of ventricular dysfunction (echocardiography, cardiac MRI, or angiography), histological evidence of fibro-fatty replacement of myocardium on endomyocardial biopsy, depolarisation or conduction abnormalities in the electrocardiogram, personal history of arrhythmic events or sudden cardiac death, and family history. Arrhythmogenic ventricular cardiomyopathy has a reported prevalence of 1/2500−1/5000.[37,39,40]

Patients and methods

We performed an observational, retrospective, and descriptive review of children younger than 18 years of age, diagnosed with primary or secondary cardiomyopathy from January 2010 to December 2016. All patients were examined by a paediatric cardiologist, and the final diagnosis was made either by echocardiography or cardiac MRI. Clinical records were taken from the Pediatric Department, Neonatal Care Unit, and Cardiac Outpatient Clinic of the Fundación Cardioinfantil in Bogotá, Colombia, and the Implantable Cardioverter-Defibrillator-10 codification system (I42-I43) was used to select patients who met the inclusion criteria. Reported data were based on a comprehensive review of each patient's visit. Clinical presentation, aetiology, morphological characteristics, outcomes, and demographic data were assessed. During the study period, the division of paediatric cardiology at our institution offered the full range of non-invasive testing (i.e., electrocardiogram, echocardiography, and cardiac MRI, etc.), as well as diagnostic and interventional catheterisation and complex cardiac surgery, depending on each patient's need.

Heart failure was clinically defined by the presence of symptoms and signs that indicated either impaired myocardial performance (i.e., tachycardia, sweating, exercise intolerance, growth failure, etc.), respiratory/lung compromise (i.e., rales, wheezing, central cyanosis, cough, nocturnal paroxysmal dyspnea, etc.), or venous congestion (i.e., hepatomegaly, oedema, etc.). To classify heart failure severity, we used either the NYHA functional class or the Ross scoring system in the infant population.[41]

Descriptive statistics are presented for numerical variables; measures of central tendency were estimated as averages or medians. Dispersion measures are given in terms of standard deviation or interquartile ranges, depending on the normality in the distribution of quantitative data, using the Shapiro–Wilk test. For the nominal and ordinal variables, absolute and relative frequencies were estimated. Data are summarised in tables. Statistical analysis was performed using SPSS software, version 14 (SPSS, Chicago, IL, USA).

Results

During the 7-year study period, from a total of 29,533 children who attended our institution, 89 new cases of primary cardiomyopathies were identified. The medium follow-up was 14 ± 3.6 months. Fifty-one patients were males (57.3%). The median age at diagnosis was 11 years (interquartile range 4–9 years old), and almost half received a diagnosis of cardiomyopathy at age 6 years or older. Dilated cardiomyopathy made up 57.3% (n = 51) of cases, hypertrophic cardiomyopathy 12.3% (n = 11), restrictive cardiomyopathy 8.9% (n = 8), non-compacted cardiomyopathy 7.8% (n = 7), arrhythmogenic ventricular cardiomyopathy 6.7% (n = 6), and unspecified cardiomyopathy made up the remaining 6.7% (n = 6). Table 1 shows the baseline characteristics of the 89 patients who were enrolled in our study.

Almost 7% of the study population (n = 6) was treated as part of our institutional social programme "Give a Life," where free care is provided to underprivileged boys and girls with cardiac conditions who do not have access to high-quality medical services and technology. To do this, we conduct an average of 11 cardiology brigades each year in different cities across the country, in which children are examined by our specialists to identify heart diseases, and if necessary, are taken to our hospital for further treatment.

At diagnosis, about 61% of the patients were in functional class NYHA I. Only a minority of patients (n = 10) presented with a functional class NYHA III or worse. However, almost 54% of patients presented with clinical or paraclinical evidence of heart failure at least once during follow-up, with dilated cardiomyopathy being the most common cardiomyopathy related to this condition (79%), followed by hypertrophic cardiomyopathy (8.5%) and restrictive cardiomyopathy (6.25%).

Left ventricular ejection fraction measurements by echocardiography were available for all patients. Thirty-nine percent (n = 35) of

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Table 1. Base-line characteristics of the 89 children diagnosed with primary cardiomyopathies

Variables	Characteristics	n	%
Age	Less than 1 year	12	13.48
	1–2 years	17	19.10
	3–5 years	16	17.98
	6–12 years	22	24.72
	13–18 years	22	24.72
Gender	Male	51	57.30
	Female	38	42.70
Provenance	Bogotá	53	59.55
	Out of Bogotá	36	40.45
Health insurance	Private insurance	57	64.04
	Public subsidised insurance	17	19.10
	Social FCI[2]	6	6.74
	No insurance	3	3.37
	Other	4	4.49
	No data	2	2.25
Heart failure signs	Yes	48	53.93
	No	39	43.82
	No data	2	2.25
BNP[1]	Less than 100 mg/dl	8	8.99
	100–400 mg/dl	4	4.49
	401–1000 mg/dl	6	6.74
	1000–2000 mg/dl	3	3.37
	2001 mg/dl and more	13	14.61
	No data	55	61.80
Functional class	I	54	60.67
	II	21	23.58
	III	9	10.11
	IV	1	1.12
	No data	4	4.49
Genetic study	Yes	23	25.84
	No	65	73.03
	No data	1	1.12

[1]BNP = brain natriuretic peptide.
[2]FCI = Fundación CardioInfantil.

the patients had a preserved left ventricular ejection fraction (>60%) and 36% had a left ventricular ejection fraction < 40%. A total of 51 patients (58%) demonstrated left ventricular impairment, among which 45% had diastolic dysfunction, 23% systolic dysfunction, and the remaining 31% had both systolic and diastolic dysfunction.

About 24% of our population showed right ventricular impairment, with systo-diastolic dysfunction being the most common type. These patients with right ventricular compromise tended to have a worse functional class (24% of patients with right ventricular compromise were in functional class III or worse versus 16% in those with preserved right ventricular function, $p < 0.05$) and a higher incidence of respiratory complications (38% versus 20%, $p < 0.05$).

Nutritional assessment was also performed as part of a comprehensive evaluation. Thirty patients (34%) were diagnosed with chronic malnutrition (stunting), 22 patients (25%) were underweight, 5 patients were overweight (5%), 3 patients (3%) had acute malnutrition (wasting), and the remaining 29 patients (32%) were eutrophic.

With regards to the coexistence of CHDs, three patients presented with an interatrial communication, two with an interventricular communication, two had a patent ductus arteriosus, and one had dextro-transposition of the great arteries. The most common comorbidity seen in these patients was renal impairment (27%), with a direct and strong association between left ventricular ejection fraction and functional class and the degree of renal compromise. The second most prevalent comorbidity was inborn errors of metabolism (12%), with the most commonly associated diseases being glycogen deposit diseases and lysosomal diseases. However, genetic evaluation was not conducted in about 65% of those patients who were referred to our institution with a diagnosis of "secondary cardiomyopathy". Finally, the overall mortality rate was 12.36% (n = 11), including two of eight patients who underwent cardiac transplantation. The median age at death was 10.3 years; however, mortality rates were higher in patients under 2 years of age.

Discussion

Contrary to the adult population, there is a huge knowledge gap regarding the epidemiologic characteristics of cardiomyopathies in the paediatric population. This issue is even more substantial when the precarious situation of medical research in Latin America is taken into account.[42] To our knowledge, few, if any, studies have been conducted to assess the epidemiological characteristics of cardiomyopathies in the Latin American paediatric population. In the past few years, great attention has been given to adult cardiomyopathies and their epidemiological characteristics. This is mainly due to the exponential increase in overall survival of children with these conditions, following the adoption of evidence-based pharmacological treatments and the advances in surgical procedures and heart transplantation.[1,2,40] Accordingly, and given the potential impact that these disorders could have on Latin American health systems, a comprehensive epidemiologic study regarding the clinical profile and sociodemographic characteristics of these patients is necessary. This study represents the first attempt to overcome this knowledge gap.

The present study documented the characteristics of childhood cardiomyopathies from a referral centre for national and regional paediatric cardiology. Among 29,533 children that attended our institution during the study period, we identified 89 new cases of primary cardiomyopathy. Even though the design of our study did not allow us to calculate the incidence or prevalence of these cardiac conditions, our findings clearly surpassed the expected number of cases. In multiple population-based studies, the incidence of primary cardiomyopathies was estimated to be 1 in 100,000 persons in children <20 years of age, which demonstrates a higher-than-expected number of cases in our institution.[6–8] The main reason for this could be the fact that our institution represents one of the main national and regional centres for the integral treatment of cardiomyopathies.

The distribution and characteristics of cardiomyopathies in our population are in line with global trends and reported studies, with dilated cardiomyopathy being the most common type seen in more than half of the cases, followed by hypertrophic cardiomyopathy.

https://doi.org/10.1017/S1047951120000281 Published online by Cambridge University Press

Interestingly, restrictive cardiomyopathy represented almost 9% of diagnosed cardiomyopathies, exceeding the reported rates of 2.5−5%.[2,6,7] Primary restrictive cardiomyopathy was more common in our population, followed by secondary restrictive cardiomyopathy due to lysosomal storage diseases. The percentage of cases of left ventricular non-compaction and arrhythmogenic ventricular cardiomyopathy were similar to those previously reported in the literature.

Most of our patients had a preserved functional class at the time of diagnosis (60.67% of our population were in NYHA/Ross functional class I). Only a minority of patients (n = 10) presented with NYHA functional class III or worse. However, about 54% of patients presented with clinical or paraclinical evidences of heart failure during follow-up, with dilated cardiomyopathy being the most prevalent cardiomyopathy related to this condition, followed by hypertrophic cardiomyopathy and restrictive cardiomyopathy. This puts into light the high and aggressive clinical impact that these diseases have on the paediatric population and the importance of integral assessments. Once a patient with a cardiomyopathy presents signs or symptoms of heart failure, both the prognosis and overall survival are negatively impacted.[3,43]

Nutritional assessment performed in our patients demonstrated that a vast proportion had stunting, wasting, or were underweight. Little is known regarding the role of growth and nutrition in paediatric cardiomyopathy as a predictor of its outcomes.[44] However, some studies have demonstrated a negative impact of malnutrition on survival of patients with heart failure related to cardiomyopathies; this is especially relevant in the subgroup of patients who eventually undergo cardiac transplantation.[45,46] The prevalence of wasting in paediatric heart failure was reported to be as high as 86%, highlighting the importance of nutritional assessments through all stages of treatment in order to provide the appropriate energy, protein, and micronutrient intake.[47,48] The aetiology of malnutrition in paediatric heart failure is multifactorial and involves hypermetabolism, decreased intake, increased nutrient losses, inefficient utilisation of nutrients, and malabsorption.[49]

The most commonly reported comorbidity in our patients was renal impairment, with a direct and strong association demonstrated between left ventricular ejection fraction and functional class, and the degree of renal compromise (14% of the patients with left ventricular ejection fraction >50% had kidney dysfunction versus 32% in those with left ventricular ejection fraction <50%). This association has been previously outlined and it highlights the importance of kidney function monitoring in these patients, as a decrease in renal function is associated with a worse prognosis.[50] The second most prevalent comorbidity in these patients was inborn errors of metabolism, with the most commonly associated diseases being glycogen deposit diseases and lysosomal diseases. This last statement highlights the importance of an integral approach of patients with cardiomyopathies, as it can be the first manifestation of a systemic disease. Genetic evaluation was not conducted in about 65% of those patients who were referred to our institution with a diagnosis of "secondary cardiomyopathy", which demonstrates the precarity and lack of clinical standards for the attention and treatment of this type of patients in our region. This puts into relevance the necessity of regional cohesion in order to create standardised guidelines and standards of treatment to provide the best possible care for children with cardiomyopathies.

We systematically searched for articles in English, Spanish, and Portuguese languages regarding the epidemiology, clinical characteristics, and outcomes of paediatric cardiomyopathies in Latin America, without success. To our knowledge, this study represents the first attempt to epidemiologically and clinically characterised paediatric cardiomyopathies in Latin America. There are no reports in medical literature regarding the incidence and prevalence of this group of diseases in our region; thus, a comparison between Latin America and the developed world is not currently possible.

Study limitations

The present report reflects the reality of the referral network at our tertiary centre, by representing an overview of paediatric cardiomyopathies in our country. Our study is limited by design, due to its observational and retrospective nature and due to the fact that we only considered data from our institution. In addition, it is possible and certainly probable that some eligible children were not included in our registry, secondary to the way data were collected.

Acknowledgements. We would like to thank the Fundación Cardioinfantil and the Universidad del Rosario for all their support during the development of this project.

Financial Support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Conflict of Interest. The authors certify that they have no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Ethical Standards. The research protocol was presented to the Research Committee of the Fundación Cardioinfantil for review and approval. It was approved on 27 October 2017 for its realisation. All activities and procedures included in the research development were carried out by qualified professionals.

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https://doi.org/10.1017/S1047951120000281 Published online by Cambridge University Press