Progression of Cardiovascular Manifestations in Adults and Children With Mucopolysaccharidoses With and Without Enzyme Replacement Therapy

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Background: Cardiovascular involvement is among the main features of MPS disorders and it is also a significant cause of morbidity and mortality. The range of manifestations includes cardiac valve disease, conduction abnormalities, left ventricular hypertrophy, and coronary artery disease. Here, we assessed the cardiovascular manifestations in a cohort of children and adults with MPS I, II, IV, and VI, as well as the impact of enzyme replacement therapy (ERT) on those manifestations.

Methods: We performed a chart review of 53 children and 23 adults with different types of MPS that had performed echocardiograms from January 2000 until October 2018. Standardized Z scores were obtained for heart chamber sizes according to the body surface area. When available, echocardiographic measurements that were performed before ERT and at least 18 months after that date were used for the assessment of pre- and post-treatment parameters.

Results: Left side valvular disease was a frequent finding, with mitral and aortic thickening being reported in most patients in all four MPS types. Left atrium dilatation was present in 26% of the patients; 25% had increased relative wall thickness; 28% had pulmonary hypertension. The cardiovascular involvement was, in general, more prevalent and more severe in adults than in children, including conduction disorders (40 vs. 16%), mitral stenosis (26 vs. 6%), aortic stenosis (13 vs. 4%), and systolic dysfunction (observed in only one adult patient). ERT promoted a significant reduction of the left ventricular hypertrophy parameters, but failed to improve valve abnormalities, pulmonary hypertension, and left atrial dilatation.
Conclusions: Adult patients with MPS may develop severe cardiovascular involvement, not commonly observed in children, and clinicians should be aware of the need for careful monitoring and timely management of those potentially life-threatening complications. Our results also confirm the impact of long-term ERT on left ventricular hypertrophy and its limitations in reversing other prevalent cardiovascular manifestations.

Keywords: mucopolysaccharidoses, enzyme replacement therapy, pulmonary hypertension, left ventricular hypertrophy, left atrium, heart valve disease

INTRODUCTION

The mucopolysaccharidoses (MPS) are a group of eleven disorders characterized by impaired catabolism of glycosaminoglycans (GAGs) as a consequence of a deficiency of lysosomal enzymes directly involved in their degradation, resulting in the accumulation of one or more of five different types of GAGs: heparan sulfate, dermatan sulfate, keratan sulfate, chondroitin sulfate, and hyaluronan (1). According to the accumulated substrate and clinical features, the MPS disorders are classified into seven main types (I, II, III, IV, VI, VII, and IX), with MPS III and MPS IV being further subclassified in four (IIIA, IIIB, IIIC, and IID) and two (IVA and IVB) subtypes, respectively, according to the enzymatic defect (2).

Cardiovascular involvement is among the main features of MPS disorders and it is also a significant cause of morbidity and mortality. As GAGs are a significant normal component of cardiac structures, enzymatic deficiencies related to GAG degradation result in prominent storage of undegraded GAGs in heart structures, which may cause tissue damage through the activation of cell proteases (3, 4). This results in many different manifestations, including cardiac valve disease, conduction abnormalities, hypertrophy of the left ventricle, and coronary artery disease (3).

Replacing the deficient enzyme, either through Enzyme Replacement Therapy (ERT) or Hematopoietic Stem Cell Transplantation (HSCT), is the current paradigm of targeting the primary defect in MPS. HSCT is widely used in the severe form—Hurler phenotype—of MPS I and ERT is available for the treatment of MPS types I, II, IVA, VI, and VII (5). Nevertheless, real-world experience with those disease-modifying therapies has unveiled several limitations, especially regarding their ability to reverse or even stop the progression of some cardiovascular manifestations in MPS patients (5, 6). In recent years, as the management of patients of MPS is resulting in an increased life expectancy, those progressing complications are a growing concern for healthcare providers (7).

In this study, we aimed to assess the cardiovascular manifestations in children and adults with different MPS types, as well as the impact of enzyme replacement therapy on those manifestations.

METHODS

Data Collection

Following institutional ethical approval (17-0013; Grupo de Pesquisa e Pós Graduação, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil), we performed a chart review of patients...
with MPS that had performed echocardiograms from January 2000 until October 2018. When available, electrocardiographic data were also recorded. MPS III patients were excluded from the study because there is an insufficient number of individuals in our center with available echocardiograms or electrocardiograms results.

Body surface area was calculated using the geometric method of Haycock (8). Left ventricular mass (LVM) was obtained using

| TABLE 2 | Characteristics of the subjects according to the age group. |
|---------|------------------------------------------------------------|
| Overall | Children | Adults | p-value |
| (n = 76) | (n = 53) | (n = 23) | |
| Sex (n) | M: 46 F: 30 | M: 34 F: 19 | M: 12 F: 11 | 0.444 |
| Age (years) | 11.3 (12.7) | 9.2 (7.3) | 26.7 (9.8) | <0.001† |
| Weight (kg) | 25.6 (21.0) | 21.5 (10.0) | 40.0 (32.0) | <0.001† |
| Height (cm) | 111.0 (35.0) | 104.0 (22.0) | 128.5 (42.0) | <0.001† |
| BSA (m²) | 0.9 (0.5) | 0.80 (0.29) | 1.21 (0.62) | <0.001† |
| Treated with ERT (n) | 47/76* | 32/53* | 15/23 | 0.799 |
| Age at the start of ERT (years) | 8.3 (10.1) | 6.3 (6) | 17.1 (6.25) | <0.001† |
| Time on ERT (months) | 41.0 (77.0) | 33.5 (58) | 107.06 (65) | <0.001† |

Continuous variables are reported as median and interquartile range.
*Four children who received ERT as a concomitant therapy for HSCT are not included in the ERT-treated group. Statistical analysis with chi-squared for categorical variables and Mann-Whitney U test for continuous variables.
†p < 0.05.

FIGURE 1 | Prevalence of heart valve abnormalities in MPS types I, II, IVA, and VI, including both treated and untreated subjects.
the formula of Devereaux (9). Standardized Z scores for left ventricle posterior wall thickness (LVPWT) and interventricular septum thickness (IVST) were calculated using the methods described by Lopez et al. (10), while, for the left ventricular mass (LVM) and left atrium parasternal long axis anteroposterior dimension (LAD) an online resource from Boston Children’s Hospital Heart Center was used (11, 12). Relative wall thickness was obtained using the formula \((2 \times \text{LVPWT})/(\text{LV internal diameter at end-diastole})\) and a cut-off value of 0.41 was used for classification of the left ventricle geometry, as previously described (13). Left ventricle ejection fraction (LVEF) was obtained through the method of Teichholz (14) and systolic pulmonary artery pressure was obtained with doppler flow studies. For the analysis of the prevalence of the cardiac manifestations, the last available echocardiogram was used. When available, echocardiographic measurements performed before ERT (up to 18 months before ERT was started) and at least 18 months after that date (up to 166 months after ERT was started) were used for the assessment of pre- and post-treatment measurements. Those patients who received ERT in the peri-transplant period or as a concomitant therapy after transplantation were not included in that assessment. Changes in echocardiographic measurements were also analyzed for treatment naïve patients that had at least two echocardiograms performed with a minimum interval of 18 months.

For those who also had an available electrocardiogram, the presence or absence of left atrial enlargement, repolarization disorder, and left ventricular hypertrophy according to the clinical report were recorded. Interval measurements and Z scores for heart rate vs. age were also obtained (11, 12). Corrected QT (QTc) interval was calculated using the Bazett formula (15).

**Statistical Analysis**

All data were entered into PASW Statistics 18.0 for Windows (SPSS Inc., Chicago, IL, USA) and submitted to specific statistical analysis. Graphics and part of the statistic tests were generated using the GraphPad Prism version 7.0. The normality of the samples was assessed with Shapiro-Wilk and D’Agostino and Pearson tests. Non-parametric Kruskal-Wallis and Dunn’s post-hoc tests were used for the comparison of quantitative measurements among different MPS types. Mann-Whitney U test was used for comparisons of quantitative measurements.
between adults and children. A chi-squared test was used for comparison of the frequencies of abnormalities among MPS types and between children and adults. For the comparison between baseline and follow-up parameters after ERT, the parametric paired t-test was used to assess Z-scores of cardiac structures and the Wilcoxon matched-pairs signed-rank test was used to assess cardiac valves. A p-value of <0.05 was considered significant.

**RESULTS**

A total of 76 patients (27 MPS I, 22 MPS II, 19 MPS IVA, and 8 MPS VI), 46 males and 30 females, with a mean age of 14.2 years, being 53 children and 23 adults, were included in this study (Tables 1, 2). Most of those patients were analyzed in a previous publication, which focused on the aortic root dimension (16). All MPS II patients were males. MPS IVA patients had a lower median height, when compared to MPS II patients and were less frequently treated with ERT when compared to MPS VI patients.

**Valvular Disease**

Among the 76 patients included in this study, left side valvular disease was a frequent finding, with mitral and aortic thickening being reported in most patients in all four MPS types (Figure 1). Furthermore, mitral and aortic insufficiency, mostly mild, were frequently found in patients with MPS I, II, and VI, but were also observed in a significant proportion of patients with MPS IVA. To a lesser extent, tricuspid valve thickening and insufficiency were also present in patients with MPS types I, II, and VI. Heart valve involvement was both more prevalent and more severe in adult patients (Figure 2; Table 3).

**Other Echocardiographic Parameters**

Left ventricular hypertrophy parameters, including LVPWT, IVST Z scores, and RWT, were above average in a significant proportion of patients in all subgroups (Figure 3). Nevertheless, LVM Z scores were normal in the last available echocardiogram of most of the patients (Table 2). Signs of left ventricular hypertrophy were more commonly observed in children than in adults (Table 3).

When assessed the last available echocardiogram, the median left atrium diameter (LAD) and the estimated systolic pulmonary artery pressure (SPAP) were increased in patients with all types of MPS (Figures 3D,E). A total of 26 and 28% of the patients had LAD or SPAP above normal reference limits, respectively (Table 4). The median value of SPAP was significantly lower in MPS IVA than in MPS I (Figure 3D). Left ventricular ejection fraction was preserved in most patients, except for one adult patient with MPS IVA, who also had eccentric hypertrophy, severe aortic insufficiency, and moderate aortic stenosis (Figures 2A,B, 3F).

**Electrocardiogram**

Electrocardiograms were performed in 65 patients (45 children and 20 adults) at some point during follow-up. All patients had a sinus rhythm, although transient junctional rhythm was observed for one female with MPS IVA in the middle childhood. The most frequently observed finding was the presence of repolarization anomalies (29%) (Table 5; Figure 4A). Left ventricular hypertrophy (LVH) and left atrium enlargement were present in 5 and 8% of the patients, respectively. Atrioventricular block and long QT intervals were also occasionally observed (Figure 4C), as well as intraventricular blocks. As compared to children, adults had a higher prevalence

**TABLE 3** | Prevalence of echocardiographic abnormalities in children and adults with MPS.

| Overall (n = 76) | Children (n = 53) | Adults (n = 23) | p-value |
|-----------------|------------------|----------------|---------|
| Aortic insufficiency | 32/76 (42%) | 17/53 (32%) | 15/23 (65%) | 0.011* |
| Aortic stenosis | 5/76 (7%) | 2/53 (4%) | 3/23 (13%) | 0.159 |
| Pulmonary insufficiency | 0/76 (0%) | 0/53 (0%) | 1/23 (4%) | 0.303 |
| Pulmonary stenosis | 0/76 (0%) | 0/53 (0%) | 0/23 (0%) | n/a |
| Mitral insufficiency | 50/76 (66%) | 31/53 (59%) | 19/23 (83%) | 0.064 |
| Mitral stenosis | 9/76 (12%) | 3/53 (6%) | 6/23 (26%) | 0.019* |
| Tricuspid insufficiency | 21/76 (28%) | 16/53 (30%) | 5/23 (22%) | 0.580 |
| Tricuspid stenosis | 0/76 (0%) | 0/53 (0%) | 0/23 (0%) | n/a |
| LVM Z score > 2 | 6/76 (8%) | 5/53 (9%) | 1/23 (4%) | 0.661 |
| RWT > 0.41 | 19/76 (25%) | 15/53 (28%) | 4/23 (17%) | 0.395 |
| Concentric remodeling | 16/76 (21%) | 12/53 (16%) | 4/23 (17%) | 0.622 |
| Concentric hypertrophy | 3/76 (4%) | 3/53 (6%) | 0/23 (0%) | 0.395 |
| Eccentric hypertrophy | 3/76 (4%) | 2/53 (4%) | 1/23 (5%) | 0.395 |
| LAD Z score > 2 | 20/76 (26%) | 11/53 (21%) | 9/23 (39%) | 0.155 |
| SPAP > 35 mmHg* | 11/40 (28%) | 8/28 (29%) | 3/12 (25%) | 1.000 |
| LVEF < 55% | 1/76 (1%) | 0/53 (0%) | 1/23 (5%) | 0.303 |

LAD, Left atrial diameter; LVEF, Left ventricle ejection fraction; LVM, left ventricle mass; RWT, relative wall thickness; SPAP, systolic pulmonary artery pressure. Statistical analysis with Fisher’s exact test. *p < 0.05.
of most of the ECG abnormalities (Table 6), particularly ventricular repolarization abnormalities (Figure 4A) and left atrial enlargement (Figure 4B).

**Effects of the Enzyme Replacement Therapy**

For those 19 patients whose echocardiographic measurements were available before and after ERT start (11 children and 8 adults), a significant reduction of LVH parameters (including IVST, LVPWT, and LVM) was observed after ERT was started (Figures 3G–I), a finding that was not identified in 18 patients that remained untreated with ERT (Supplementary Figure 1). However, no statistically significant changes in SPAP, LAD, or LVEF were observed after ERT (Figures 3J–L). Moreover, ERT did not lead to significant improvements in valvular disease (Figure 5).

As only 4 patients had available electrocardiograms in an adequate time frame before and after the start of ERT, we could not explore the impact of ERT in conduction anomalies.


TABLE 4 | Prevalence of echocardiographic abnormalities at the last available echocardiogram, including both ERT treated and untreated subjects.

|                          | Overall (n = 65) | MPS I (n = 20) | MPS II (n = 19) | MPS IV (n = 19) | MPS VI (n = 8) | p-value |
|--------------------------|-----------------|----------------|----------------|----------------|----------------|---------|
| LVM Z score > 2          | 6/27 (8%)       | 2/7 (7%)       | 2/22 (9%)      | 2/18 (11%)     | 0/8 (0%)       | 0.821   |
| RWT > 0.41               | 19/27 (25%)     | 7/17 (52%)     | 7/22 (32%)     | 3/19 (16%)     | 2/8 (25%)      | 0.701   |
| Concentric remodeling    | 16/27 (21%)     | 5/17 (30%)     | 6/22 (27%)     | 3/19 (16%)     | 2/8 (25%)      | 0.697   |
| Concentric hypertrophy   | 3/65 (4%)       | 0/20 (0%)      | 1/18 (5%)      | 2/19 (11%)     | 0/8 (0%)       | 0.385   |
| Eccentric hypertrophy    | 3/65 (4%)       | 2/20 (10%)     | 1/22 (5%)      | 0/19 (0%)      | 0/8 (0%)       | 0.159   |
| LAD Z score > 2          | 20/65 (31%)     | 7/20 (35%)     | 4/22 (18%)     | 7/19 (37%)     | 2/8 (25%)      | 0.605   |
| SPAP > 35 mmHg*          | 11/40 (28%)     | 6/14 (43%)     | 2/12 (17%)     | 1/9 (11%)      | 2/5 (40%)      | 0.265   |
| LVEF < 55%               | 1/65 (1%)       | 0/20 (0%)      | 0/22 (0%)      | 1/19 (5%)      | 0/8 (0%)       | 0.159   |

LAD, Left atrial diameter; LVEF, Left ventricle ejection fraction; LVM, left ventricle mass; RWT, relative wall thickness; SPAP, systolic pulmonary artery pressure.

*SPAP was measured in 40 of the total 76 available last echocardiograms of the participants. Statistical analysis with chi-squared.

TABLE 5 | Prevalence of electrocardiographic abnormalities at the last available electrocardiogram, including both ERT treated and untreated subjects.

|                          | Overall (n = 65) | MPS I (n = 20) | MPS II (n = 19) | MPS IV (n = 19) | MPS VI (n = 7) | p-value |
|--------------------------|-----------------|----------------|----------------|----------------|----------------|---------|
| Ventricular repolarization abnormalities | 19/66 (29%) | 4/20 (20%) | 6/18 (33%) | 8/19 (42%) | 1/8 (13%) | 0.311   |
| Left atrial enlargement | 5/65 (8%) | 2/20 (10%) | 2/18 (11%) | 0/19 (0%) | 1/8 (13%) | 0.514   |
| Right axis deviation    | 5/65 (8%) | 2/20 (10%) | 0/18 (0%) | 1/19 (6%) | 2/5 (25%) | 0.159   |
| Left ventricular overload | 3/65 (5%) | 1/20 (5%) | 1/18 (5%) | 1/19 (6%) | 0/8 (0%) | 0.930   |
| Right ventricular overload | 3/65 (5%) | 0/20 (0%) | 2/18 (11%) | 1/19 (6%) | 0/8 (0%) | 0.377   |
| Intraventricular block   | 3/65 (5%) | 1/20 (5%) | 0/18 (0%) | 0/19 (0%) | 2/5 (25%) | 0.025*  |
| Atrioventricular block   | 3/65 (5%) | 2/20 (10%) | 1/18 (5%) | 0/19 (0%) | 0/8 (0%) | 0.447   |
| Right atrial enlargement | 2/65 (3%) | 2/20 (10%) | 0/18 (0%) | 0/19 (0%) | 0/8 (0%) | 0.200   |
| Prolonged QRS           | 1/65 (2%) | 0/20 (0%) | 1/18 (5%) | 0/19 (0%) | 0/8 (0%) | 0.448   |

Statistical analysis with chi-squared.

*p < 0.05.

DISCUSSION

In this study, we assessed the prevalence of cardiac manifestations in a cohort of patients with MPS I, II, IVA, and VI; which included mostly patients treated with ERT. In agreement with previous reports (3, 17–20), valve involvement comprised mainly left-sided valves and affected a high proportion of patients. Mitral valve involvement was more common than the aortic valve in the four MPS types. Valve involvement, especially aortic insufficiency and mitral stenosis, was more commonly observed in older patients. We could not identify any significant worsening or improvement of valve pathology after ERT. It is widely accepted that ERT has limited impact on valve abnormalities of patients with MPS (27). In patients with ERT, an increase in echocardiographic LVH parameters may reflect storage of undegraded substrate, without actual increase to an increased workload associated with valve disease or arterial hypertension. Nevertheless, it may have a role in preventing or delaying its appearance when treatment is started very early, as suggested by studies with sibling pairs and animal models (26, 27).

In both humans and murine models of MPS, it was observed that GAG deposits occur mainly in histiocytes, while there is scant evidence of deposit in cardiomyocytes (32, 33). Furthermore, in MPS mice treated with bone marrow transplantation, no abnormal storage is detected in the heart tissue (32).

The finding of normal Z scores for LVM in a significant proportion of the patients in our cohort may reflect the effects of long-term therapy in this parameter. Accordingly, significant reductions of IVST, LVPWT, and LVM were observed in the follow-up measurements, which is in agreement to prior studies and generally acknowledged as a well-established effect of ERT (3, 5, 13, 22–24). Hypertrophic cardiomyopathy (HCM) has been described in different inherited metabolic disorders and it is relatively milder in MPS as compared to other conditions such as infantile Pompe Disease or Danon disease (13, 28, 29). In patients with MPS, an increase in echocardiographic LVH parameters may reflect storage of undegraded substrate, without actual increase in muscle mass (pseudohypertrophy) and/or the activation of complex pathways triggered by the GAG deposition, causing HCM (28–30). Moreover, LVH in MPS may also be secondary to an increased workload associated with valve disease or arterial hypertension (3, 31).

In both humans and murine models of MPS, it was observed that GAG deposits occur mainly in histiocytes, while there is scant evidence of deposit in cardiomyocytes (32, 33). Furthermore, in MPS mice treated with bone marrow transplantation, no abnormal storage is detected in the heart tissue (32). Effects of ERT in left ventricular (pseudohypertrophy) are also likely to be secondary to its ability to clear GAG storage in the heart wall, as there is no evidence of improvement of valve disease or hypertension with the treatment.
We found a high proportion of patients with left atrial diameter Z scores above normal limits (26%), but a lower prevalence of left atrial enlargement criteria on electrocardiogram (8%). This difference may be attributed to a lower sensitivity of the latter method as an indicator of left atrial enlargement (19). It is also important to notice that, while in this study no MPS III patient was included, a high prevalence of atrial enlargement (37). Left atrial enlargement was more frequently identified in adults, and the impact of ERT in the parameter has not been established.

Systolic pulmonary artery pressure (SPAP) was increased in 28% of the patients. Other authors have reported a prevalence of 36% of pulmonary hypertension (PH) in a sample of 28 pediatric patients and emphasized that it was the main cause of death in their cohort (17). Chronic hypoxemia secondary to obstructive sleep apnea is a known cause of pulmonary hypertension among MPS patients, but it cannot explain all cases, and a role for the left heart dysfunction in its pathogenesis is also likely (17, 38, 39).

When analyzing the whole sample, we could not demonstrate a statistically significant improvement or worsening of the left ventricle ejection fraction. Nevertheless, ejection fraction was already preserved in most patients. Also, the adult MPS IVA patient reported with low LVEF in Figure 3F has never received ERT. In the literature, the impact of ERT in ejection fraction is less clear, with some studies pointing to stabilization or reduction of the mean value over time (13, 40) and others showing improvements in those patients who already had reduced LVEF on baseline (41). Although those inconsistencies need further clarification, it is possible that ERT may improve LVEF in a subset of patients with prior systolic dysfunction, while not being able to prevent a slow long-term deterioration.

In our study, all subjects had a sinus rhythm and none was on pacemakers. However, our results support the conclusions of previous authors that noticed that cardiac conduction abnormalities may increase strikingly in older adult MPS patients (42). It is also important to notice that, while in this study no MPS III patient was included, a high prevalence of first-degree AV block was described in that MPS type (43). Although most MPS patients will not have a clinically significant conduction abnormality, resting electrocardiogram and 24 h Holter monitoring, when indicated, should be an integral part of the care of MPS patients, considering that the early recognition may have a high impact on morbidity and mortality (42).

This work has some limitations. The measurements were performed by more than one echocardiographer and the time frame of the study involved a period before the establishment of new guidelines for echocardiographic measurements in our center when newer quantification methods for LA size, ejection fraction, and LVM were included in the routine echocardiogram protocol. Nevertheless, by including data from a wide period of time, we were able to estimate the prevalence of cardiovascular abnormalities in a large sample of MPS patients as well as the long-term effectiveness of ERT.

In summary, we identified a high proportion of MPS patients with cardiac abnormalities, which ranged from isolated mitral or aortic thickening to a more severe clinical picture including moderate to severe valvular insufficiency or stenosis, left ventricular hypertrophy, pulmonary hypertension, and, rarely, systolic dysfunction. We also confirmed the impact

TABLE 6 | Prevalence of abnormalities in the resting electrocardiogram in children and adults with MPS.

|                  | Overall (n = 65) | Children (n = 45) | Adults (n = 20) | p-value |
|------------------|------------------|------------------|----------------|---------|
| Ventricular repolarization abnormalities | 19/65 (29%) | 7/45 (16%) | 12/20 (60%) | 0.001* |
| Left atrial enlargement | 5/65 (8%) | 0/45 (0%) | 5/20 (25%) | 0.002* |
| Right axis deviation | 5/65 (8%) | 2/45 (4%) | 3/20 (15%) | 0.165 |
| Left ventricular overload | 3/65 (5%) | 2/45 (4%) | 1/20 (5%) | 1.000 |
| Right ventricular overload | 3/65 (5%) | 3/45 (7%) | 0/20 (0%) | 0.547 |
| Intraventricular block | 3/65 (5%) | 1/45 (2%) | 2/20 (10%) | 0.222 |
| Atrioventricular block | 3/65 (5%) | 2/45 (4%) | 1/20 (5%) | 1.000 |
| Right atrial enlargement | 2/65 (3%) | 2/45 (4%) | 0/20 (0%) | 1.000 |
| Prolonged QRS | 1/65 (2%) | 1/45 (2%) | 0/20 (0%) | 1.000 |

Statistical analysis with Fisher’s exact test.

*p < 0.05.
of long-term ERT on left ventricular hypertrophy in the mucopolysaccharidoses and its limitations in reversing other cardiovascular manifestations, such as valvular involvement.

**DATA AVAILABILITY STATEMENT**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by Grupo de Pesquisa e Pós-Graduação, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. Written informed consent from the participants’ legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

**AUTHOR CONTRIBUTIONS**

FP, RG, and GB designed the study. HS and FP obtained the clinical data from chart review. AS and SB reviewed the echocardiographic and electrocardiographic data and analysis. CS reviewed the clinical data. FP drafted the manuscript. All authors read and approved the final manuscript.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.801147/full#supplementary-material

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