Original Article

How can the Echocardiogram be Useful for Predicting Death in Children with Idiopathic Dilated Cardiomyopathy?

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Objective

To determine the echocardiographic predicting factors of death in children with idiopathic dilated cardiomyopathy.

Methods

A retrospective study of 148 children with idiopathic dilated cardiomyopathy diagnosed between September 1979 and March 2003 was carried out. The inclusion criteria were as follows: heart failure and a reduction in contractility on the echocardiogram in the absence of congenital or secondary heart disease. Four hundred and seventy examinations during a period of 244.8 months of evolution were analyzed. The following parameters were assessed: left atrial dimension (LAD); left atrium/aorta ratio (LAD/Ao); left ventricular systolic (LVSD) and diastolic (LVDD) dimensions; left ventricular mass (LVmass); right ventricular dimension (RVD); left ventricular ejection fraction (LVEF); left ventricular shortening fraction (% SH); severity of the insufficiency of the atrioventricular and pulmonary valves; and right ventricular systolic (RVSP) and diastolic (RVDP) pressures. The significance level adopted was alpha < 0.05.

Results

The mean age was 2.37 years, and 35 patients died (23.7% - 95 CI = 17.1% to 31.2%). The analysis of variance showed the following: LAD (p<0.0001); LAD/Ao (p<0.0001); LVSD (p=0.0061); LVDD (p=0.0086); LVmass (p<0.0001); LVEF (p=0.0074); %SH (p=0.0072); and RVD (p<0.0001). Worsening of mitral (MI) (p=0.0113) and tricuspid (TI) insufficiencies (p=0.0044) were markers of death, and the presence of MI, TI, and moderate/severe pulmonary insufficiency were deleterious to survival. The Cox proportional hazards regression model showed the following independent predictors of death: LAD/Ao (p=0.0487); LVEF (<0.0001); and the presence of moderate/severe MI (p=0.0419).

Conclusion

Patients with a progressive increase in LAD/Ao, a reduction in LVEF, and progressive worsening of MI, regardless of the clinical treatment, should be considered for early heart transplantation.

Key words

idiopathic dilated cardiomyopathy, echocardiogram, predictors of death, children

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Received for publication: 9/9/02
Accepted for publication: 11/11/03
English version by Stela Maris Costalonga

Idiopathic dilated cardiomyopathy in children is an important cause of heart failure in the absence of congenital heart disease. It accounts for up to 29% of the medical interventions before the age of 2 years [1], and its mortality rates range from 16% [2] in 10 years to 49% [3] 66% [4], and 80% [5] in 5 years.

Cardiac transplantation is the treatment of choice in patients who do not respond to clinical treatment. The survival rates in cardiac transplantation range from 75 to 80% in 1 year, and from 60 to 75% in 5 years [6-8]. Several international studies [2-4,9-11] were carried out to determine the indicators of an unfavorable prognosis, helping in the early indication of cardiac transplantation. The echocardiogram is an important tool not only for the diagnosis and follow-up of idiopathic dilated cardiomyopathy, but also for the indication of cardiac transplantation, despite the lack of consensus in the results [12-16].

Aiming at determining echocardiographic predictors of death in children with idiopathic dilated cardiomyopathy, a retrospective study was carried out comprising all children admitted to the Instituto Nacional de Cardiologia Laranjeiras over a period of 24 years, and their evolutional echocardiographic data in the period were analyzed. Suspected risk factors were selected and submitted to statistical analysis.

Methods

The databank was consulted for the retrospective analysis of 148 consecutive patients with idiopathic dilated cardiomyopathy diagnosed between September 1979 and March 2003. The echocardiographic results of all patients were analyzed.

The criterion of inclusion was the presence of heart failure associated with cardiomegaly on chest teleradiography or left ventricular dilation, or both, with a reduction in contractility visualized on M mode echocardiography in the first 8 patients and on 2-dimensional echocardiography in the remaining 140 cases. In the latter, 5- and 7.5-MHz transducers were used to enable the visualization of the origin and initial bifurcations of the coronary arteries. Patients with the following characteristics were excluded from the study: congenital heart diseases; anomalous origin of the coronary arteries; Kawasaki's disease; ventricular arrhythmogenic cardiomyopathy; ischemic lesion due to neonatal asphyxia or following cardiopulmonary resuscitation; use of an antineoplastic drug; inborn errors of metabolism; primary arrhythmias; orovalvular lesions due to rheumatic disease; neuromuscular diseases; syste-

mic arterial hypertension; septicemia; HIV infection; Chagas' disease; and diphtheria. In patients in whom the 2-dimensional echocardiogram showed limitations in ruling out the anomalous origin of the coronary arteries and in the first 8 patients undergoing M-mode echocardiography, a hemodynamic study was performed to exclude it.

Patients with a clinical diagnosis of myocarditis were not excluded from the study. The clinical criteria suggestive of myocarditis were as follows: fever; chest pain; electrocardiogram with low-voltage QRS complex or abnormalities in conduction or rhythm; and an elevation in creatine phosphokinase (CK) and in its myocardial fraction (CK-MB) in laboratory tests [1]. Endomyocardial biopsies (EMB) were not performed for the diagnosis of myocarditis, because of the following reasons: they involve risks, especially in infants; the sample collected may represent a healthy area [1]; a portion of children with idiopathic dilated cardiomyopathy recovers spontaneously; and, up to the present time, no specific treatment is available for myocarditis or idiopathic dilated cardiomyopathy [3,17]. Currently, the endomyocardial biopsy has been successfully replaced by gallium-67 myocardial scintigraphy, which has a high correlation without the risks of endomyocardial biopsy [17]. No immunosuppressive therapy was used in the patients diagnosed with myocarditis, because the literature is still controversial in regard to its efficacy [18-20].

The medicamentous treatment used was optimized during the study period. The classical treatment for heart failure was used as follows: oral digoxin, furosemide, spironolactone, captopril, and acetylsalicylic acid for preventing thromboembolic events. The analysis of the influence of treatment in the evolution of the patient, however, was not the objective of this study.

The following parameters were analyzed: left atrial dimension (LAD); left atrium/aorta ratio (LAD/Ao); left atrium/body surface ratio (LAD/BS); left ventricular systolic (LVSD) and diastolic (LVDD) dimensions; the LVSD/BS and LVDD/BS ratios; left ventricular mass (LVmass); the LVmass/body surface ratio (LVmass/BS); right ventricular dimension (RVD); LV ejection fraction (LVEF); and the LV shortening fraction (%SH). The LVEF was obtained based on the LVSD and LVDD recordings in the transverse or longitudinal left parasternal view using the formula: $EF = \{[(LVDD)^3 - (LVSD)^3]/(LVDD)^3\} \times 100$. The %SH was calculated with the formula: $\%SH = [(LVDD-LVSD)/LVDD] \times 100$, used for analyzing all the examinations. In addition, the severity of the insufficiency of the atrioventricular and pulmonary valves was detected and assessed by using Doppler echocardiography, and classified as absent/mild lesion or moderate/severe lesion. Four hundred and seventy examinations of 148 patients performed during a period of up to 244.8 months of evolution were analyzed in this study.

The statistical analysis was performed using the Epi Info 6.04 program from the Centers for Disease Control & Prevention and the Statistica 6.0 program from Statsoft Inc. The dichotomous data were assessed by using the chi-square test, and, when applicable, the 95% confidence interval (95CI) was calculated. The descriptive data were expressed as mean ± standard deviation (SD) and range of values and analyzed with the Student *t* test. The analysis of variance (ANOVA) for repeated measures was used for comparing the groups. The analysis of survival was performed with the Kaplan-Meier method, and the groups were compared using the log-rank test. The Cox proportional hazards regression model was used for determining the independent echocardiographic predictors of death. Age was the temporal parameter for LAD, LVSD, LVDD, and LVmass. The time of evolution was used for RVD, LVEF, %SH, and for the LAD/Ao, LAD/BS, LVSD/BS, LVDD/BS, and LVmass/BS ratios. Any value was considered significant when alpha was < 0.05, and the power used was 80%.

Results

The epidemiological characteristics of the sample, the 95% confidence interval, and the significance are shown in table I. The mean age was 2.37 ± 3.46 years (1 day to 15.4 years), most patients were less than 2 years old (mean of 0.66 ± 0.44 years; P<0.0001) and were in New York Heart Association functional class III or IV (p < 0.0001). The mean follow-up lasted 3.79 ± 4.33 years (0 to 20.1 years). By the end of the study, 60 (40.5% - 95CI = 32.5% to 48.9%) patients had fully recovered, 53 (35.8% - 95CI = 28.1% to 44.1%) had evolved with chronic heart failure, and 35 (23.7% - 95CI = 17.1% to 31.2%) had died.

The mean echocardiographic values, the standard deviation, and the significance between groups are summarized in table II. The Student *t* test showed a difference between groups (survivor vs deceased) for all variables studied.

When the time factor was considered and ANOVA was perfor-

Table I - Epidemiological characteristics of the sample

		n - %	95CI	P
Sex	Girls	81 - 54.7%	46.3% - 62.9%	0.1036
Color	Not white	82 - 55.4%	47.0% - 63.6%	0.0629
Age group	< 2 years	108 - 73.0%	65.1% - 79.9%	<0.0001
	≥ 2 years	40 - 27.0%	20.1% - 34.9%	
Functional class	I - II	29 - 19.6%	13.5% - 26.9%	<0.0001
	III - IV	119 - 80.4%	73.1% - 86.5%	

n - number; % - percentage; 95CI - 95% confidence interval; FC - NYHA functional class; P - alpha value

Table II - Mean echocardiographic values and standard deviation of the survivor and deceased groups, and significance between groups

	Survivor		Deceased		P
	Mean	SD	Mean	SD	
LAD	2.40	0.69	3.42	1.30	<0.0001
LAD/Ao	1.45	0.39	1.98	0.52	<0.0001
LAD/BS	4.13	1.60	5.19	1.62	<0.0001
LVSD	3.08	1.07	4.60	1.11	0.0010
LVSD/BS	5.62	3.00	7.82	3.44	<0.0001
LVDD	4.10	1.02	5.36	1.19	<0.0001
LVDD/BS	7.35	3.10	9.09	3.82	<0.0001
LVMass	80.54	66.69	149.43	97.33	<0.0001
LVMass/BS	123.19	73.86	202.82	84.90	<0.0001
RVD	1.05	0.40	1.89	1.06	<0.0001
LVEF	56.85	18.82	36.37	13.35	<0.0001
%SH	26.10	11.25	14.49	6.54	<0.0001
RVSP	32.8	14.5	45.4	15.8	<0.0001
RVDP	14.0	9.9	25.5	8.8	<0.0001

LAD - left atrial dimension; LAD/Ao - left atrial dimension/aorta; LAD/BS - left atrial dimension/body surface; LVSD - left ventricular systolic dimension; LVSD/BS - left ventricular systolic dimension/body surface; LVDD - left ventricular diastolic dimension; LVDD/BS - left ventricular diastolic dimension/body surface; LV mass - left ventricular mass; LVmass/BS - left ventricular mass/body surface; RVD - right ventricular dimension; LVEF - left ventricular ejection fraction; %SH - left ventricular shortening fraction; RVSP - calculated right ventricular systolic pressure; RVDP - calculated right ventricular diastolic pressure; SD - standard deviation; P - alpha value

med for the repeated measures, significant differences were observed in the following parameters: LAD (p<0.0001), LAD/Ao (p<0.0001) (fig. 1), LVSD (p=0.0061), LVDD (p=0.0086), LVmass (p<0.0001), LVEF (p=0.0074) (fig. 2), %SH (p=0.0072), and RVD (p<0.0001). However, no difference in evolution was observed in the following ratios: LAD/BS (p=0.0667), LVSD/BS (p=0.5742), LVDD/BS (p=0.4752), and the LVmass/BS (p=0.1980).

The frequency of the echocardiographic alterations in regard to the severity of the atrioventricular and pulmonary valve insufficiency obtained on Doppler echocardiography in each group is shown in table III. Moderate/severe regurgitation was more frequent in the deceased group.

Valvular regurgitation was graded as absent, mild, moderate, and severe, and ANOVA was performed. Over a period of 72 months, the mitral insufficiency in the deceased group was observed to evolve from mild to moderate at the beginning of the observation to moderate to severe from the second year of observation onwards. On the other hand, in the survivor group, mitral insufficiency did not exceed the mild intensity (p = 0.0113), and no overlapping was observed in the groups, considering the 95CI (fig. 3). The tricuspid insufficiency had a similar behavior (p = 0.0044) from the 12th month of evolution onwards.

The interactions between LAD/Ao, functional class, and severity of mitral insufficiency are shown in figure 4. The increase in LAD/Ao in moderate to severe mitral insufficiency did not depend on the functional class (p = 0.7214); however, in absent or mild mitral insufficiency, the increase in LAD/Ao depended on the functional class (p = 0.0053).

Based on right valvular regurgitation, the right ventricular systolic (RVSP) (100 measurements: survivor = 63 and deceased = 37) and diastolic (RVDP) (52 measurements: survivor = 31 and deceased = 21) pressures could be calculated. The RVSP was greater in the deceased group (45.4 ± 15.8 mmHg vs 32.8 ± 14.5 mmHg) (p < 0.0001), and the same was observed in regard to RVDP (25.5 ± 8.8 mmHg vs 14.0 ± 9.9 mmHg) (p<0.0001).

According to the analysis using the Kaplan-Meier method and the log-rank test, the presence of moderate/severe mitral insufficiency (MI) (p = 0.0118), moderate/severe tricuspid insufficiency (TI) (p = 0.0007), and moderate/severe pulmonary insufficiency

Table III - Frequency of the echocardiographic alterations per group (survivor vs deceased)

	Survivor (n = 113)		Deceased (n = 35)		P
	Present	%	Present	%	
Absent/mild MI	80	70.8	16	45.7	0.0066
Moderate/severe MI	33	29.2	19	54.3	
Absent/mild TI	99	87.6	22	62.9	0.0009
Moderate/severe TI	14	12.4	13	37.1	
Absent/mild PI	110	97.3	30	85.7	0.0257
Moderate/severe PI	3	2.7	5	14.3	

MI - mitral insufficiency; TI - tricuspid insufficiency; PI - pulmonary insufficiency; P - alpha value

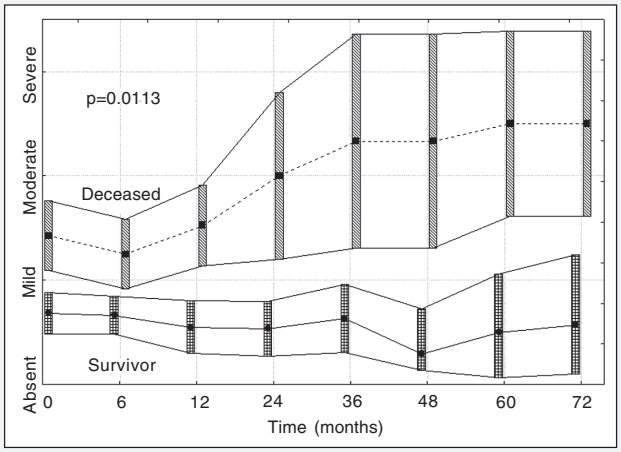

Fig. 3 - Degree of mitral insufficiency and 95% confidence interval versus the time of evolution (months) in the groups – Cox analysis: P=0.0419.

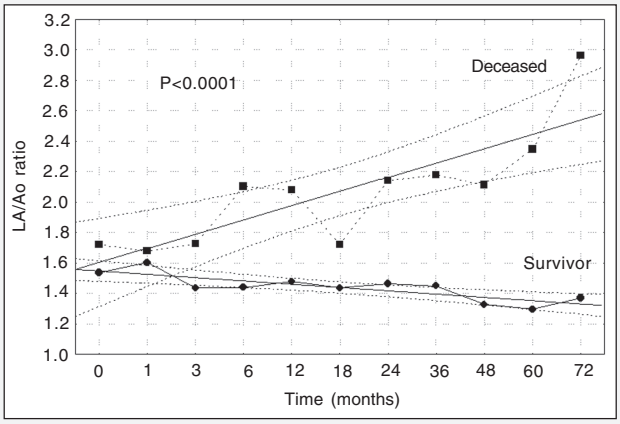

Fig. 1 - LA/Ao ratio and 95% confidence interval versus the time of evolution (months) in the groups – Cox analysis: P=0.0487.

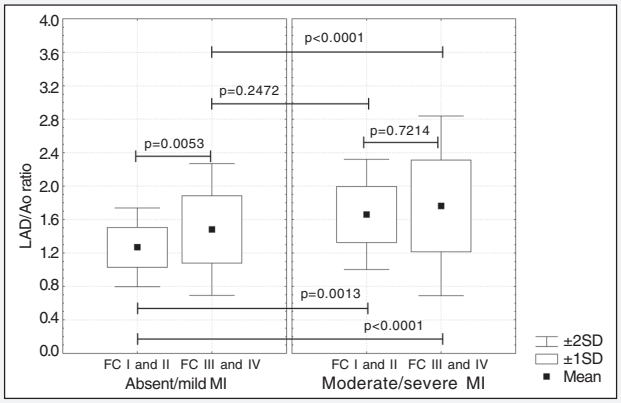

Fig. 4 - Box & Whisker Plots of the LAD/Ao ratio versus the functional class and mitral insufficiency. LAD/Ao - left atrial dimension/aorta ratio; FC - functional class; MI - mitral insufficiency; P - alpha value.

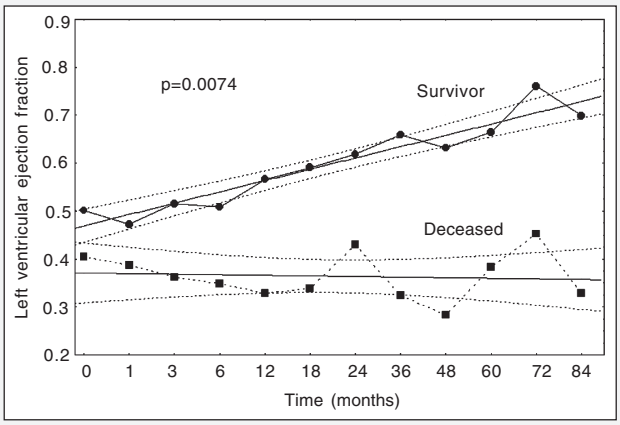

Fig. 2 - Left ventricular ejection fraction and 95% confidence interval versus the time of evolution (months) in the groups – Cox analysis: P<0.0001.

Table IV - Cox multivariate analysis of the predictive echocardiographic parameters of death

Cox analysis
Dependent variable: Time of evolution on echocardiogram
Censored data: Death
$X^2 = 99.4130$ df = 3 P < 0.0001

n = 438	β	SE	t value	β expoent	Wald Statist.	P
LA/Ao	0.41106	0.208578	1.97077	1.508414	3.88393	0.0487
LVEF	-4.32058	0.644962	-6.69897	0.013292	44.87614	<0.0001
MI	0.20838	0.102363	2.03573	1.231686	4.14420	0.0418

SE - Standard error; β - standard regression coefficient; LA/Ao - left atrium/Aorta ratio; LVEF - left ventricular ejection fraction; MI - mitral insufficiency; P - alpha value

(PI) (p = 0.0177) at any time of the evolution proved to be deleterious to survival. The regression multivariate analysis using the Cox model confirmed the predictive value of moderate/severe MI (p<0.0001) and of moderate/severe TI (p = 0.0024), but ruled out moderate/severe PI (p = 0.9037).

Cox proportional hazards regression model was performed with the following independent variables: LAD/Ao, LVmass; LVEF; LVSD; LVDD; RVD; and the presence of moderate/severe MI and TI. The dependent variable was the time of evolution until the moment of echocardiography. The analysis showed the following independent echocardiographic predictors of death: LAD/Ao (p = 0.0487); LVEF (p < 0.0001); and the presence of moderate/severe MI (p = 0.0419) (tab. IV).

Discussion

In this study, the mean age was 2.37 years [21], similar to that reported in most studies in the literature [3,4,10,22,23-28], although some authors reported greater means [2,5,14,24]. In our sample, the disease started preferably below the age of 2 years (73.0%) [21]. This trend was observed in the studies by Griffin et al [9] and Burch et al [10], but not in other reports [11,25]. This trend may be explained by the greatest susceptibility of children below the age of 2 years for having respiratory viral diseases more often than those aged 2 years or more.

No difference in incidence was observed regarding sex [21], in accordance with the literature [1-5,9,11,26-28]. Ethnicity showed no difference in regard to incidence, but no other bibliographic references were obtained.

In an early stage of diagnosis, most patients were considered severe (FC III and IV), and all 35 deaths occurred in the same group. In the study by Ciszewski et al [24], no difference was observed in the distribution of the severity of the disease (p = 0.8274), and in the study by Silva et al [11], less severely ill patients (FC I and II) predominated.

The mean LAD was greater than 42.5% in the deceased group, with a progressive increase. An increase in LAD between 43% and 54% has been reported in the literature, but no author observed any relation between LAD and death [2,4,12,29]. Arola et al [3] reported an increase in LAD in 44% of the sample weakly related to death. The mean LA/Ao ratio was greater than 36.5% in the deceased group, with a progressive increase in that group and a reduction in the survivors. Cabrera [27] reported a mean LA/Ao ratio of 1.50 ± 0.3, but did not mention its importance in the patient's evolution. The mean LA/BS ratio was greater than 25.7% in the deceased group, but no difference in evolution between the groups was observed. No analysis on the LA/BS ratio in children was found in the literature.

The LVSD (49.3%) and LVDD (30.7%) were greater in the deceased group. Hauwaert et al [30] reported increased LVSD (CHF = 70% vs recovery = 14%) and LVDD (44% vs 9%) in regard to the values expected for age. Ghafour [29] reported a 50% increase in LVSD and LVDD, while First [12] reported a 59% increase in LVDD. The mean value of LVSD reported was 3.3 ± 1.2 cm, and LVDD was between 4.2 ± 0.7cm and 7.1 ± 2.2 cm [3,27]. ANOVA showed a progressive reduction in LVSD and LVDD in the group with a good evolution and an increase in the group with a poor evolution [3,13], but these findings are not shared by all authors [24]. Lewis [25], using the "z" score of LVDD, reported a reduction in the group with good evolution and unaltered values in the deceased group. In our sample, an identical phenomenon was observed in regard to LVSD and LVDD with a progressive increase in the deceased group.

The mean left ventricular mass (85.5%) and the LVmass/BS ratio (64.6%) were greater in the deceased group, and ANOVA showed differences for the LVmass, but not for the LVmass/BS ratio. Lipshultz et al [31] reported a mean LVmass of 45.5 g at presentation, above the values expected for age. Kimball et al [13] reported a progressive, significant reduction in the LVmass/BS ratio in the survivor group (101 vs 54 g/m²) and a progressive, although not significant, increase in the group with a poor evolution (122 vs 198 g/m²). Lewis [25] reported no difference in evolution in the LVmass/BS ratio in the survivor and deceased groups.

The mean LVEF and the %SH were greater in 56.3% and 80.1% of the survivor group, respectively, the difference being confirmed by ANOVA. The mean LVEF was reported between 26 and 30% [4,22,27], and the mean %SH was between 9 and 16% [3-5,10,12,32]. In regard to evolution, Chen et al [33] reported a significant difference in the %SH at presentation in regard to death (11.5 vs 20.9%), a finding not shared by other authors [24,25,28]. Hauwaert et al [30] reported a mean %SH of 22.6% in those who evolved with heart failure and of 32.4% in those who recovered. Arola et al [3] reported a progressive increase in %SH in the group with a good evolution, and Kimball et al [13] reported a difference in the evolution of %SH: recovered (from 15% to 29%) versus poor evolution (from 17% to 20%). Nogueira et al [28] and Lewis [25] reported an increase in %SH in the survivor group 6 months after presentation.

The mean right ventricular dimension (RVD) was greater than 80.0% in the deceased group, and ANOVA showed a difference in regard to death. In the literature, only Friedman et al [2] reported an enlargement in the right ventricle.

Moderate/severe orovalvular insufficiency was a marker of death. The literature reports a varied frequency of mitral insufficiency: 23.5% [27], 48.0% [3], and 81.0% [12]; however, no author relates the presence of mitral insufficiency to death. In regard to TI, Cabrera [27] reported a 17.6% incidence of TI in his sample; however, he did not correlate it to death. Reports on the incidence and influence of PI in the evolution of patients could not be found in the literature.

It is worth questioning whether the increase in the LAD/Ao ratio occurs due to the presence of moderate to severe mitral insufficiency secondary to left ventricular dilation due to systolic dysfunction, or due to left ventricular diastolic dysfunction. In the presence of moderate to severe mitral insufficiency, the increase

in the LAD/Ao ratio did not depend on functional class; however, when mitral insufficiency was absent or mild, the increase in the LAD/Ao ratio depended on functional class. One may infer that the diastolic dysfunction was more important for determining the increase in the LAD/Ao ratio when mitral insufficiency was absent or mild, and that the systolic dysfunction was more important for determining the increase in the LAD/Ao ratio when the mitral insufficiency was moderate to severe. The increase in the LAD/Ao ratio was observed to accompany the progressive worsening of mitral insufficiency in the deceased group (fig. 1 and 3).

In regard to calculated right ventricular pressures, Cabrera [27], using hemodynamic analysis, reported a mean right ventricular systolic pressure of 96 ± 11 mmHg (4 patients), but he did not correlate it to death. Other studies assessing the calculated right ventricular diastolic pressure could not be found in the literature.

The multivariate analysis using Cox proportional hazards regression model of the echocardiographic parameters allowed for determination of the following independent predictors of death: the LA/Ao ratio ($p = 0.0487$); left ventricular ejection fraction ($p < 0.0001$); and evolution of the severity of mitral insufficiency ($p = 0.0418$). Akagi et al [5] reported a decrease in the EF as an independent predictor of death, a finding shared by Chen et al [33] and by Nogueira [28]. On the other hand, still considering the independent predictors of death, Matitiau et al [1] reported the lower EF and the spherical form of the LV; Carvalho et al [15] reported that a low LV posterior wall/LVDD ratio influences death, and Lewis [25] considered that an LV diastolic pressure above 25 torr influences death.

Considering the data analyzed, we suggest that children with these echocardiographic predictors of death, who do not respond to conventional therapy, need a closer follow-up, and, if the data suggested by these indices are confirmed through the use of clinical and new Doppler echocardiographic parameters, such as the Tei index, they should be considered for cardiac transplantation.

This study has limitations, the first being its retrospective design, with the use of data from echocardiographic results, which hindered the review of video recordings. Assessment of the myocardial performance index (Tei index) has been recently reported [34-38], and it could not be included in this study due to the lack of recordings of echocardiographic images. The diastolic function could only be indirectly assessed through the LA/Ao ratio and right ventricular diastolic pressure, because the direct assessment of diastolic dysfunction only recently received attention, when new Doppler echocardiographic parameters were introduced.

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