Evaluation of Left-Sided Heart Chambers With Novel Echocardiographic Techniques in Men With Duchenne or Becker Muscular Dystrophy

Raphael Henrique Déa Cirino, MD, PhD[a,*], Rosana Herminia Scola, MD, PhD[b], Renata Dal-Prá Ducci, MD, PhD[b,c], Ana Cristina Camarozano, MD, PhD[a], Claudia Suemi Kamoi Kay, MD[b], Paulo José Lorenzoni, MD, PhD[b,c], Lineu Cesar Werneck, MD, PhD[b], Eliane Ribeiro Carmes, MD, MSc[c], and Claudio Leinig Pereira da Cunha, MD, PhD[a]

Left ventricular systolic dysfunction (LVSD) is a common finding in patients with Duchenne (DMD) and Becker (BMD) muscular dystrophies. Novel echocardiographic techniques have been used for the detection of LVSD in several heart diseases. We aim to compare cardiac anatomic and functional data studied by three-dimensional (3DE) and two-dimensional (2DE) echocardiography and to analyze the myocardial strain for the detection of early LVSD in DMD and BMD patients. We performed a cross-sectional study of 46 DMD and 14 BMD patients. We measured left atrium volume and left ventricle volumes and ejection fraction using 3DE and 2DE techniques. Myocardial strain analysis was derived from global longitudinal strain (GLS) measurements. GLS was measured by 2DE with the speckle tracking technique. The correlation between 3DE and 2DE for the measurement of left atrium volume as well as left ventricle diastolic and systolic volumes was strong. 2DE presented larger left atrium and left ventricle volumes. Left ventricle ejection fraction was similar between the two techniques. Myocardial strain analysis was able to detect early LVSD in 50.0% of DMD patients and in 9.1% of BMD patients. In conclusion, two-dimensional echocardiography appears to be a good alternative for the anatomical and functional evaluation of the left heart chambers in DMD and BMD patients. Myocardial strain analysis detects early LVSD in a sizable portion of patients with dystrophinopathies. **(Am J Cardiol 2019;123:972−978)**

Duchenne (DMD) and Becker (BMD) muscular dystrophies are X-linked recessive diseases, both defined by specific mutations involving the dystrophin gene located at Xp21. These mutations may result in complete absence of dystrophin, which translates to the DMD phenotype, or in partial deficiency of dystrophin, which is associated with BMD.[1,2] Cardiomyopathy is a common condition in DMD and BMD patients and may manifest as heart failure, malignant arrhythmias or sudden cardiac death.[3−5] Evaluation of left ventricular volumes and systolic function (LVSF) by three-dimensional echocardiography (3DE)[6−8] and measurement of myocardial strain using the speckle tracking technique for the diagnosis of early left ventricular systolic dysfunction (LVSD)[9−13] have been used for the study of several heart diseases. The purpose of this study is two-fold: (1) to compare left atrium volume, left ventricular volume and left ventricular ejection fraction obtained through 2DE and 3DE in DMD and BMD patients and (2) to compare myocardial strain analysis with the speckle tracking technique for the detection of early LVSD between DMD and BMD patients.

Methods

This is a study of consecutive patients diagnosed with DMD and BMD followed in the Neuromuscular Disorders Service of Hospital de Clínicas of Federal University of Parana, Curitiba, Brazil, between January 2014 and June 2016. The study was conducted in accordance with ethical principles and was approved by the Ethics Committee of the Hospital de Clínicas of the Federal University of Parana. Informed consent was obtained from all patients.

The inclusion criteria included disease confirmed by a clinical course that was compatible with DMD or BMD and at least one of the following: (1) pathogenic mutation detected by Multiplex Ligation-dependent Probe Amplification (MLPA) analysis or sequencing (Sanger sequencing) of the *DMD* gene, or (2) dystrophin deficiency as determined by a muscle biopsy (immunohistochemistry).[1,3,14,15] We excluded patients who refused to participate, were unable to be present for the transthoracic echocardiogram (TTE) examination, or had a suboptimal echocardiographic view that prevented proper evaluation of two or more left ventricular endocardial segments.

TTE was performed with the Matrix probe of the Philips IE33 machine by the same researcher (RHDC). Echocardiographic measurements were made following

[a]Cardiology Division, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, Parana, Brazil; [b]Neuromuscular Service, Neurology Division, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, Parana, Brazil; and [c]Department of Internal Medicine, Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, Parana, Brazil. Manuscript received September 8, 2018; revised manuscript received and accepted December 13, 2018.

*Corresponding author: Tel: (55)4132332845; fax: (55)4133606154.

E-mail address: rapha_cirino@yahoo.com.br (R.H.D. Cirino).

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Table 1
Echocardiographic characteristics of the study population

Echocardiographic measures	Overall	DMD	BMD	p value
Left ventricular diastolic volume 2DE (mL/m^2)	51.1 (14.8)	48.3 (12.1)	60.2 (19.0)	0.009*
Left ventricular systolic volume 2DE (mL/m^2)	18.8 (9.4-82.4)	17.3 (9.4-62.1)	21.0 (15.4-82.4)	0.007†
Left ventricular ejection fraction 2DE (%)	61.5 (27.0-74.0)	62.5 (34.0-74.0)	59.5 (27.0-68.0)	0.294†
Left ventricular diastolic volume 3DE (mL/m^2)	46.0 (13.8)	43.0 (10.7)	55.4 (18.3)	0.028*
Left ventricular systolic volume 3DE (mL/m^2)	16.5 (7.3-74.5)	16.3 (7.3-69.9)	18.1 (11.5-74.5)	0.060†
Left ventricular ejection fraction 3DE (%)	60.2 (10.0)	60.6 (9.5)	59.0 (12.0)	0.604*
Global longitudinal strain (%)	−17.4 (2.8)	−17.2 (2.6)	−17.9 (3.6)	0.478*
Left atrium volume 2DE (mL/m^2)	20.6 (6.6)	19.1 (5.7)	25.6 (6.8)	0.001*
Left atrium volume 3DE (mL/m^2)	16.4 (5.8)	15.4 (5.2)	19.8 (6.5)	0.011*

Note: 2DE = two-dimensional echocardiography; 3DE = three-dimensional echocardiography.
* Student's *t* test for independent samples.
† nonparametric Mann-Whitney test.

the recommendations from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[13] 2DE left ventricular diastolic (LVDV) and systolic (LVSV) volumes were measured using the Simpson's rule. Increased 2DE LVDV and LVSV, indexed to BSA, were considered as >74.0 mL/m^2 and >31.0 mL/m^2, respectively.[13] Increased 3DE LVDV and LVSV, indexed to BSA, were considered as >60.1 mL/m^2 and >23.2 mL/m^2, respectively.[16] Left ventricle volumes obtained through 2DE and 3DE were used to estimate left ventricle ejection fraction (LVEF). LVEF <52% was considered overt LVSD.[13] Myocardial strain analysis was derived from global longitudinal strain (GLS). GLS was measured by 2DE with the speckle tracking technique. Absolute values of GLS <18% were considered abnormal. Absolute values of GLS <18% with LVEF ≥52% were considered markers of early LVSD. Absolute values of GLS ≥18% with LVEF ≥52% were considered normal LVSF.[17–20] 2DE left atrium volume was measured using the disc rule.[13] Increased 2DE left atrium volume, indexed to BSA, was considered as >38.3 mL/m^2.[21] Increased 3DE left atrium volume, indexed to BSA, was considered as >27.1 mL/m^2.[21]

Quantitative variables were described by means and standard deviations or by the median, minimum and maximum values. Qualitative variables were described by frequencies and percentages. The Shapiro-Wilk test was used to assess the variables normality. The Pearson's or Spearmańs correlation coefficient was estimated for the correlation between left atrium volumes, left ventricle volumes, and LVEF obtained by 2DE and 3DE. The Student's *t* test for paired samples, the nonparametric Wilcoxon test (quantitative variables), or the binomial test (qualitative variables) were used for the comparison of the 2 methods. The level of agreement between the 2 methods for the detection of overt LVSD and of increased LVDV, LVSV and left atrium volume was evaluated by estimating the Kappa coefficient. P values <0.05 were considered statistically significant. Data were analyzed with the computer program IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY: IBM Corp.

Results

Sixty-nine patients were eligible to enter the study. Nine patients were excluded from the study due to the inability to be present for the TTE examination (5 patients) and inadequate echocardiographic window (4 patients). Therefore, the study sample was composed of 60 male patients, 46 (76.7%) with DMD and 14 (23.3%) with BMD. The mean age of the patients was 12.8 ± 5.4 years and was specifically 11.3 ± 4.1 years for DMD and 18.1 ± 5.9 years for BMD. Thirty-two patients (53.3%) were still walking, and 43 (71.7%) used corticosteroids. Seven patients (11.7%) were using either an angiotensin-converting enzyme inhibitor or an angiotensin-II receptor blocker, and 4 (6.7%) were using beta-blockers. The echocardiographic characteristics of our population are described in Table 1.

Left ventricular diastolic volume was increased in 4 (6.7%) patients with 2DE and in 5 (8.3%) patients with 3DE, whereas 6 (10.0%) patients with 2DE and 8 (13.3%) patients with 3DE had increased LVSV. The correlation between 2DE and 3DE for the measurement of LVDV and LVSV was strong, where the correlation coefficients were 0.94 ($p < 0.001$) and 0.90 ($p < 0.001$), respectively. Figures 1 and 2 show the correlation coefficients in DMD and BMD patients separately. The agreement between the two methods for the detection of increased LVDV and LVSV was good, with an estimated Kappa coefficient of 0.88 (95% confidence interval [CI] 0.65 to 1.00) and 0.84 (95%CI 0.62 to 1.00), respectively. Resembling agreement was found when DMD and BMD patients were evaluated separately. There was no significant difference between the 2 methods for the detection of increased LVDV ($p = 1.00$) and LVSV ($p = 0.500$). Comparing the 2 methods, 3DE presented lower left ventricle diastolic and systolic volumes (Table 2). Similar results were observed when we analyzed DMD and BMD separately.

Seven patients (11.7%) presented overt LVSD with 2DE, of which 4 (8.7%) patients had DMD and 3 (21.4%) had BMD. When evaluated with 3DE, overt LVSD was present in 9 (15.0%) patients, of which 6 (13.0%) patients had DMD and 3 (21.4%) had BMD. The agreement between the 2 methods for the detection of overt LVSD was good, with an estimated Kappa coefficient of 0.71 (95%CI 0.44 to 0.98). In the subgroup of patients with DMD, the agreement between the 2 methods for the detection of overt LVSD was moderate (estimated Kappa coefficient of 0.55 95%CI 0.14 to 0.97), whereas it was good in the subgroup of patients with BMD (estimated Kappa

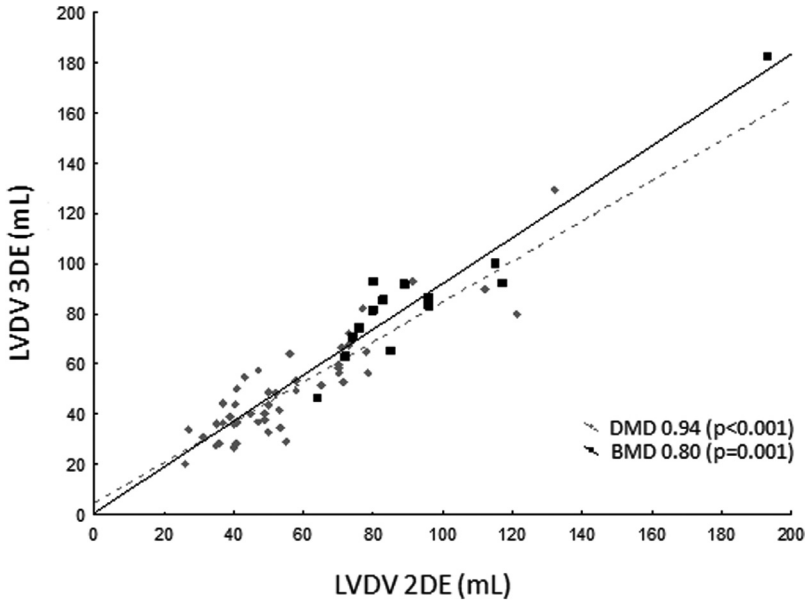

Figure 1. Correlation between two-dimensional and three-dimensional echocardiography for the measurement of left ventricular diastolic volume in Duchenne and Becker muscular dystrophies. Note: 2DE = two-dimensional echocardiography; 3DE = three-dimensional echocardiography; BMD = Becker muscular dystrophy; DMD = Duchenne muscular dystrophy; LVDV = left ventricular diastolic volume.

coefficient of 1.00). There was no significant difference between the two methods for the detection of overt LVSD ($p = 0.625$). Comparing the 2 methods, there were no significant differences in LVEF results (Table 2). When analyzed separately, DMD patients presented no significant differences in LVEF between the 2 methods, and BMD patients exhibited a slightly higher LVEF with the 3DE. Abnormal GLS (>−18%) (Figure 3) was detected in 29 (48.3%) patients, of which 25 (54.4%) had DMD and 4 (28.6%) had BMD. Early LVSD was present in 21 (35.0%) patients, of which 20 (43.5%) patients had DMD and 1 (7.1%) had BMD. Considering only patients with normal LVEF, myocardial strain analysis was able to detect early LVSD in half (50.0%) of DMD patients and in 9.1% of BMD patients.

Only 1 (1.7%) patient who had BMD presented left atrium enlargement with 2DE. 3DE revealed 3 patients (5.0%) with increased left atrium volume, of which 2 patients had BMD (14.3%) and 1 had DMD (2.2%). The correlation between 2DE and 3DE for the measurement of left atrium volume was strong, as demonstrated by a correlation coefficient of 0.87 ($p < 0.001$). Figure 4 shows the correlation coefficients

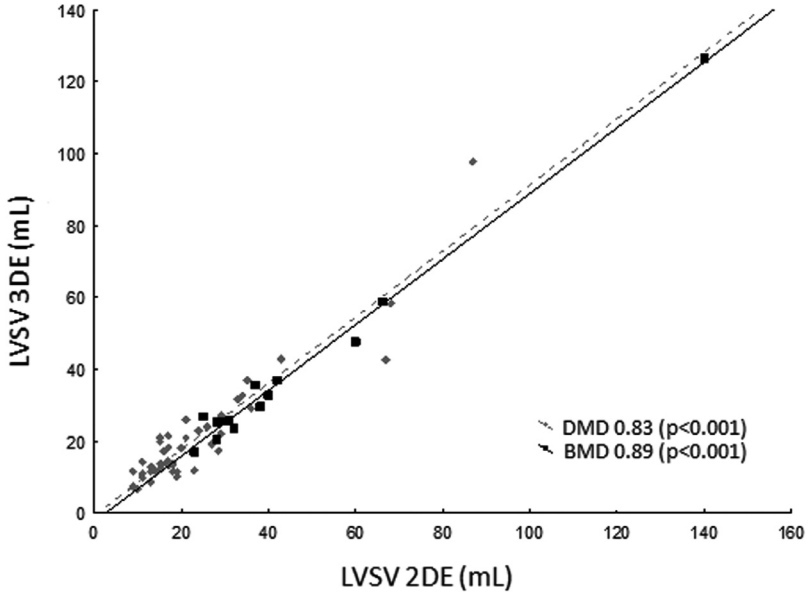

Figure 2. Correlation between two-dimensional and three-dimensional echocardiography for the measurement of left ventricular systolic volume in Duchenne and Becker muscular dystrophies. Note: 2DE = two-dimensional echocardiography; 3DE = three-dimensional echocardiography; BMD = Becker muscular dystrophy; DMD = Duchenne muscular dystrophy; LVSV = left ventricular systolic volume.

Table 2
Comparison between two-dimensional and three-dimensional echocardiography for the measurement of left ventricular volumes and ejection fraction in Duchenne and Becker muscular dystrophies

Variable (n = 60)	Method	Mean	Median	Minimum	Maximum	Standard deviation	p value
Left ventricular diastolic volume (ml)	2DE	65.6	58.0	26.0	193.0	29.9	
	3DE	58.8	53.2	20.2	182.4	28.0	<0.001*
Left ventricular systolic volume (ml)	2DE	28.5	23.0	9.0	140.0	21.7	
	3DE	25.2	20.8	6.7	126.7	20.2	<0.001†
Left ventricular ejection fraction (%)	2DE	59.5	61.5	27.0	74.0	9.2	
	3DE	60.2	61.8	24.4	75.9	10.0	0.468†

Note: 2DE = two-dimensional echocardiography; 3DE = three-dimensional echocardiography.
* Student's t-test for paired samples.
† Nonparametric Wilcoxon test.

in DMD and BMD patients separately. The agreement between the two methods for the detection of increased left atrium volume was moderate, with an estimated Kappa coefficient of 0.49 (95%CI 0 to 1.00). There was no significant difference between the two methods for the detection of increased left atrium volume (p = 0.500). Comparing the 2 methods, 3DE presented lower left atrium volumes (Table 3). Similar results were observed when we analyzed DMD and BMD separately.

Discussion

Echocardiographic evaluation is crucial for the diagnosis and management of cardiac complications in DMD and BMD patients.[22] Our results show similar LVEF between DMD and BMD patients as well as larger left ventricle and left atrium volumes in BMD patients, even when indexed to BSA. In a study that compared patients with DMD and BMD with the same age and already established cardiomyopathy, it was shown that BMD patients had larger diastolic

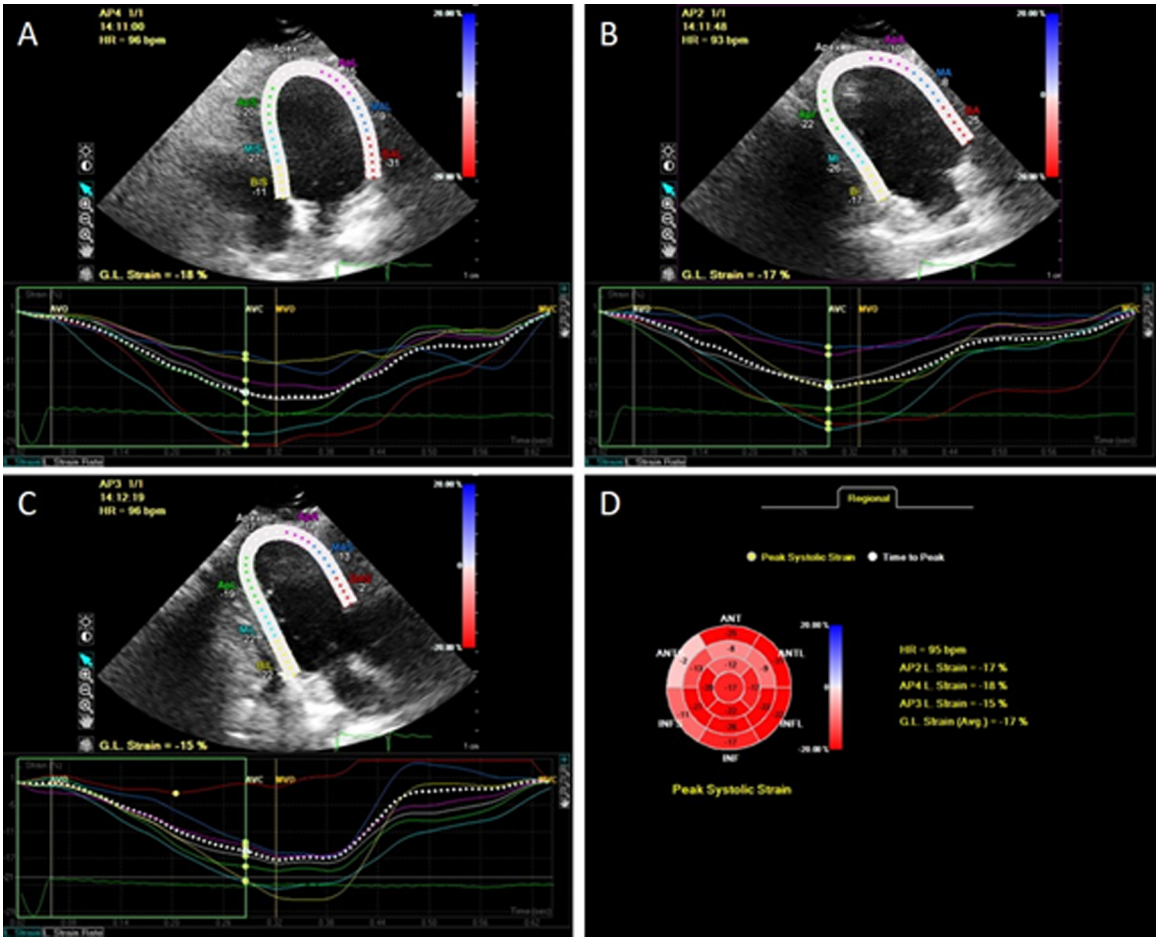

Figure 3. Measurement of the echocardiographic longitudinal strain in the apical incidences of four (A), two (B) and three (C) chambers, and the global longitudinal strain (D) in a DMD patient who showed early left ventricular systolic dysfunction (global longitudinal strain: −17%).

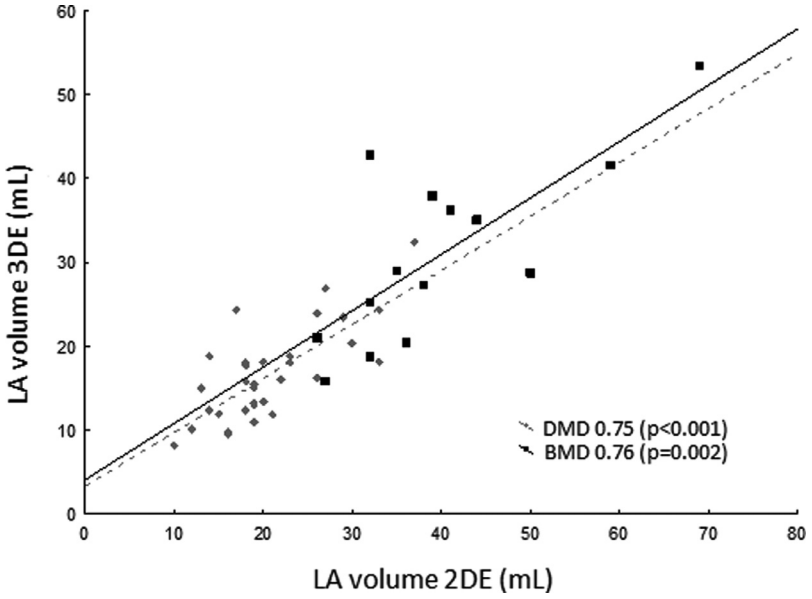

Figure 4. Correlation between two-dimensional and three-dimensional echocardiography for the measurement of left atrium volume in Duchenne and Becker muscular dystrophies. Note: 2DE = two-dimensional echocardiography; 3DE = three-dimensional echocardiography; BMD = Becker muscular dystrophy; DMD = Duchenne muscular dystrophy; LA = left atrium.

and systolic left ventricle dimensions as well as similar left ventricle fractional shortening.[23] There are no studies comparing left atrium dimensions between DMD and BMD patients.

In our study, LVDV and LVSV were larger with 2DE than 3DE, whereas LVEF was similar between the 2 methods. Ruddox et al. demonstrated that LVDV and LVSV measured by 2DE were larger than those measured by 3DE in healthy adults.[24] Although there are no studies that directly compared 2DE and 3DE techniques in the pediatric population, in our study, patients with DMD and BMD presented larger left ventricle volumes when evaluated by 2DE. This was similar to another study in the adult population that used the same software and technique for the measurement of 2DE and 3DE left ventricle volumes.[25] For the detection of increased left ventricle volumes and overt LVSD, the 2 methods were similar and had a good level of agreement. Therefore, 2DE was shown not to be inferior to 3DE for the detection of abnormalities of left ventricle size and function in patients with DMD and BMD.

Increased left atrium volume index, a reproducible measure of the left atrium volume in children,[26] was detected in a small number of patients. The left atrium volume measured with 2DE was larger when compared to 3DE, which supports the findings of Tanaka and colleagues.[21] The low frequency of left atrium enlargement in DMD patients may be related to the predominance of LVSD in relation to left ventricular diastolic dysfunction, which has already been demonstrated in other studies.[27] These results may also be related to the characteristics of our population, which was younger and did not present advanced disease for the most part.

In this study, among 51 boys with normal LVEF, 41% presented early LVSD (GLS >−18%). In DMD patients, early LVSD was detected in 50% of cases, as already demonstrated in another study of our group.[28] Other studies have demonstrated similar results, showing that echocardiographic myocardial strain can be used to detect early LVSD in DMD patients.[28-30] We evaluated the myocardial strain using the speckle tracking technique with measurement of GLS, which currently represents the most feasible and reproducible method for the evaluation of the echocardiographic myocardial strain and is recommended by the latest guidelines.[13] When compared with the study of Taqatqa and colleagues, who used the same software and technique for the GLS measurement,[29] our study included a larger number of patients. We demonstrated that these patients not only present lower GLS absolute values when compared to healthy children, but that many of them also benefit from this technique for the early detection of LVSD.

There are no studies evaluating the echocardiographic myocardial strain analysis in BMD; however, in our study,

Table 3
Comparison between two-dimensional and three-dimensional echocardiography for the measurement of left atrium volume in Duchenne and Becker muscular dystrophies

Variable (n = 46)	Method	Mean	Median	Minimum	Maximum	Standard deviation	p value
Left atrium volume (ml)	2DE	26.6	23.0	10.0	69.0	12.3	
	3DE	21.0	18.1	8.2	53.4	9.9	<0.001*

Note: 2DE = two-dimensional echocardiography; 3DE = three-dimensional echocardiography; LA = left atrium.
* Student's t-test for paired samples.

there was only one case (9.1%) of early LVSD among these patients. Therefore, the real utility of myocardial strain analysis in BMD patients remains uncertain. Nonetheless, this is a method that has been established in the context of several other cardiopathies, and thus, it is expected that there is also a benefit in some subgroup of BMD patients despite insufficient evidence in the literature to affirm this benefit.

This study has some limitations. The small number of BMD patients may have influenced the results for this subgroup. The variability of normal values of GLS is wide. The cut-off value of −18 seemed appropriate because it was derived from previous studies involving healthy children who represented the age groups of the patients included in our study.[17–20]

The results of our study suggest that 2DE is not inferior to three-dimensional analysis for the detection of overt LVSD and increased LVDV, LVSV and left atrium volume in DMD and BMD patients. Thus, it is a reliable method to be routinely used in laboratories that do not have 3DE, since the latest methods require more expensive equipment and are not available in all echocardiography laboratories. A higher percentage of DMD patients presented early LVSD when compared to BMD patients. The importance of the early detection of LVSD lies in the fact that early initiation of specific treatments could prevent the progression of cardiomyopathy and eventually improve cardiac function as well as prevent serious complications, such as sudden death, which is increasingly frequent in this population.[22,28] Further studies are required to confirm these findings and to establish their impact on the clinical management of DMD and BMD patients.

Author Agreement

None of the authors involved in this study (Raphael Henrique Déa Cirino; Rosana Herminia Scola; Renata Dal-Prá Ducci; Ana Cristina Camarozano Wermelinger; Claudia Suemi Kamoi Kay; Paulo José Lorenzoni; Lineu Cesar Werneck; Eliane Ribeiro Carmes; Claudio Leinig Pereira da Cunha) has any financial conflicts of interest.

All authors have participated in the work and have reviewed and agree with the content of the article.

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