My approach to diagnosis of and echocardiographic follow-up for muscular dystrophies

Como Eu Faço Diagnóstico e Seguimento Ecocardiográfico nas Distrofias Musculares

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Introduction

Muscular dystrophies (MD) are a group of heterogeneous diseases genetically determined and characterized by progressive muscle atrophy and weakness. Mutations in genes encoding muscle fiber proteins lead to the development of MD. MD types vary by deficient protein, each with its natural history and characteristic clinical presentation. As with other clinical aspects, cardiac involvement is also quite variable.[1,2]

This article will review the most important aspects of the clinical-echocardiographic follow-up of MD types frequently associated with cardiomyopathies, including dystrophinopathy, limb-girdle muscular dystrophy (LGMD), myotonic dystrophy, and Emery-Dreifuss muscular dystrophy (EDMD).

General aspects related to the clinical and echocardiographic diagnosis of MD

The clinical diagnosis of MD considers symptom progression, family history, and, in most cases, a genetic study and/or immunohistochemical analysis for its confirmation and classification (Table 1).[1,2] These patients usually present no cardiomyopathy-related symptoms and signs due to functional limitations caused by muscle weakness. In this context, echocardiography is an essential tool in MD management because, in addition to being widely available and of low cost, it assesses anatomic-functional characteristics of the heart and detects preclinical changes.[3]

Due to the development of new specific therapies, the increased survival of patients with some types of MD has made cardiological complications the leading cause of morbidity and mortality. For this reason, the early detection of cardiac changes and the introduction of cardiomyopathy-directed therapy have become essential.[3,4]

Keywords

Muscular dystrophies; Cardiomyopathy, dilated; Echocardiography.

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Dystrophinopathy cardiac presentation and echocardiographic findings

Duchenne MD (DMD) is the most common neuromuscular disease in children and reflects the most severe spectrum of dystrophinopathies, which also include Becker MD and asymptomatic female carriers of the DMD gene mutation[4]. Clinical cardiological presentations are characterized by dilated cardiomyopathy (DCM) and its complications and can occur in any spectrum of dystrophinopathy without a correlation with peripheral muscle involvement severity.[4,5]

In recent years, the role of echocardiography in assessing dystrophinopathies has been questioned, as some studies demonstrated the superiority of cardiac magnetic resonance imaging (cMRI).[6] Despite this, and considering the limitations inherent to cMRI, echocardiography remains valuable in the routine evaluation of these patients for being widely available, being of low cost, and presenting no severe adverse effects.[7,8] Studies comparing echocardiography with cMRI show that left ventricular (LV) fractional shortening[6,9] and LV ejection fraction (LVEF) by the area-length method[6] are the echocardiographic parameters used to assess LV systolic function that best correlate with cMRI.

Typical echocardiographic findings are LV dilation and systolic dysfunction, which define the DCM phenotype (Figure 1).[4,5] Characteristic dystrophinopathy changes include segmental contractility changes with a predilection for LV inferolateral wall involvement.[4,5] Myocardial strain evaluated by speckle tracking also shows changes versus healthy individuals, with reduced global longitudinal (GLS) (Figures 2 and 3),[4,7,10,11] global circumferential,[7,11] and global radial strains, especially the basal segments of the inferior, inferolateral, anterolateral and anterior walls.[7,11] One study also demonstrated reduced three-dimensional myocardial strain in the longitudinal, circumferential, or radial axis.[12] A recent meta-analysis determined that GLS, the most studied and most reliable echocardiographic parameter for the early detection of LV systolic dysfunction,[13] can be reduced in up to to 50% of DMD patients with a normal LVEF.[8] As for LV diastolic dysfunction, DMD patients present lower septal and lateral e' waves values and higher E/e' ratios than controls[11] but do not meet echocardiographic criteria for significant LV diastolic dysfunction. The functions of the right chambers are usually preserved.[7]

Electrocardiography and transthoracic echocardiography are recommended at diagnosis, every two years before 10 years of age, and annually thereafter. Thus, cMRI should always be considered, especially in older patients with poorer echocardiographic image quality, and

Table 1 - Genetic aspects, pathogenesis and typical echocardiographic findings typical of muscular dystrophies most often associated with cardiomyopathy.

	Classification	Inheritance	Gene	Pathogenesis	Non-Cardiac Clinical Manifestations	Typical Echocardiographic Findings
Dystrophinopathies	Duchenne Muscular Dystrophy	X-linked recessive	DMD	Total dystrophin deficiency	Delayed walking Proximal lower limb muscle weakness with onset before 5 years of age and rapid progression to walking disability (usually before 12 years of age) Proximal upper limb muscle weakness	LV dilatation LV systolic dysfunction Predilection towards impairment of the LV inferolateral wall GLS reduction, especially of the basal segments of the inferior, inferolateral, anterolateral, and anterior walls
	Becker Muscular Dystrophy	X-linked recessive	DMD	Partial dystrophin deficiency	Similar to DMD, but with onset around 10 years of age and slower progression	
Myotonic Dystrophies	Type 1	Autosomal dominant	DMPK	CTG repeat expansion	Distal muscular weakness associated with facial muscular weakness, with eyelid ptosis and myotonic phenomenon Systemic manifestations: cataract, insulin resistance, gonadal failure and baldness. It may start at birth (congenital), in childhood or in adulthood	LV systolic function Decreased GLS, especially apical longitudinal strain LV diastolic dysfunction with normal LA Mitral valve prolapse Pericardial effusion
	Type 2	Autosomal dominant	CNBP/ZNF9	CCTG repeat expansion	Proximal muscle weakness Less intense symptoms and slower progression than in myotonic dystrophy type 1. It does not start in childhood	
Limb-girdle Muscular Dystrophies	Laminopathy (LGMD1)	Autosomal dominant	LMNA	Lamin A/C deficiency	Limb-girdle muscle weakness beginning in childhood through the fourth decade of life	LV dilatation LV systolic and diastolic dysfunction
	Sarcoglycanopathies (LGMD2C-F)	Autosomal recessive	SGCG SGCA SGCB SGCD	Beta-sarcoglycan/gamma-sarcoglycan deficiency		
	Fukutinopathy (LGMD2I)	Autosomal recessive	FKRP	Fukutin-related protein deficiency		
Emery-Dreifuss Muscular Dystrophy	Type 1	X-linked recessive	EMD/FHL1	Emerin/FHL1 deficiency	Humerus-peroneal muscle weakness associated with early prominent joint contractures (neck extension, elbow flexion and ankle flexion) with onset in childhood	Predominance of biatrial dilatation over LV dilatation Atrial standstill and increased cardioembolic risk LV systolic and diastolic dysfunction
	Type 2	Autosomal dominant/ recessive	LMNA	Lamin A/C deficiency		

CNBP/ZNF9: Cellular Nucleic Acid-binding Protein/Zinc Finger Protein 9; CTG: Cytosine-Thymine-Guanine; DMD: Duchenne Muscular Dystrophy; DMPK: Myotonic Dystrophy Protein Kinase; FHL1: Four And A Half LIM Domains 1; FKRP: Fukutin Related Protein LGMD: Limb-girdle Muscular Dystrophy; GLS: Global longitudinal strain; CNS: Central Nervous System.

many clinicians advocate annual cMRI, especially in patients who already have dystrophinopathy-related cardiomyopathy.[4,6]

Cardiac presentation and echocardiographic findings in myotonic dystrophy

Myotonic dystrophies are the most common hereditary MD in adults, being characterized by multisystem involvement.[14,15] The most characteristic cardiac presentation is arrhythmia, including conduction disorders, atrial and ventricular tachyarrhythmias, sudden cardiac death, and less frequently DCM.[14,16] These complications are more common in type 1 than in type 2,[1,15,17] accounting for about 30% of deaths in myotonic dystrophy type 1 patients.[14]

Echocardiographic changes vary and may include LV dilation, systolic dysfunction, and excessive trabeculation; LV hypertrophy and diastolic dysfunction; and mitral valve prolapse.[14] Mitral, aortic, and tricuspid valve sclerosis may also be observed in addition to pericardial effusion.[14,15] The prevalence of LV systolic dysfunction is 13.8% in type 1 myotonic dystrophy.[14,15] LV systolic dysfunction presence and severity help in the decision to implant intracardiac devices, such as a pacemaker and implantable cardioverter-defibrillator as they are predictors of conduction disorders and severe tachyarrhythmias.[14] LV GLS is the most reliable parameter for the early detection of systolic dysfunction, with a reduced apical longitudinal strain being the most characteristic finding.[19]

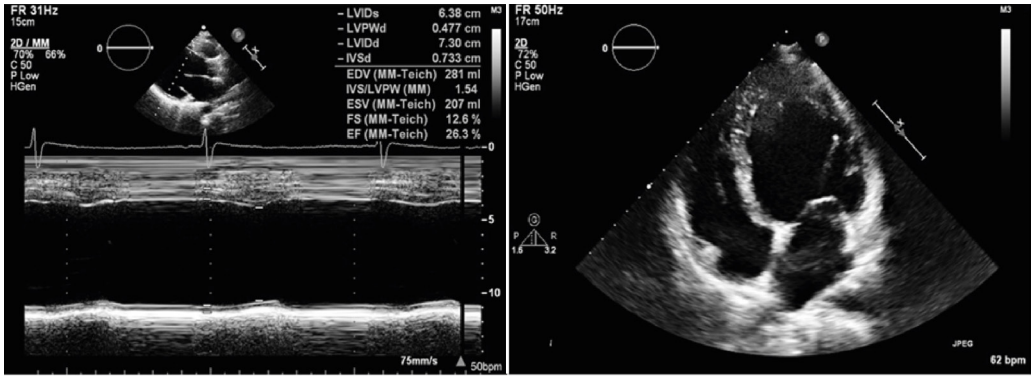

Figure 1 – *Dilated cardiomyopathy phenotype in a 15-year-old ambulatory patient with Becker muscular dystrophy.*

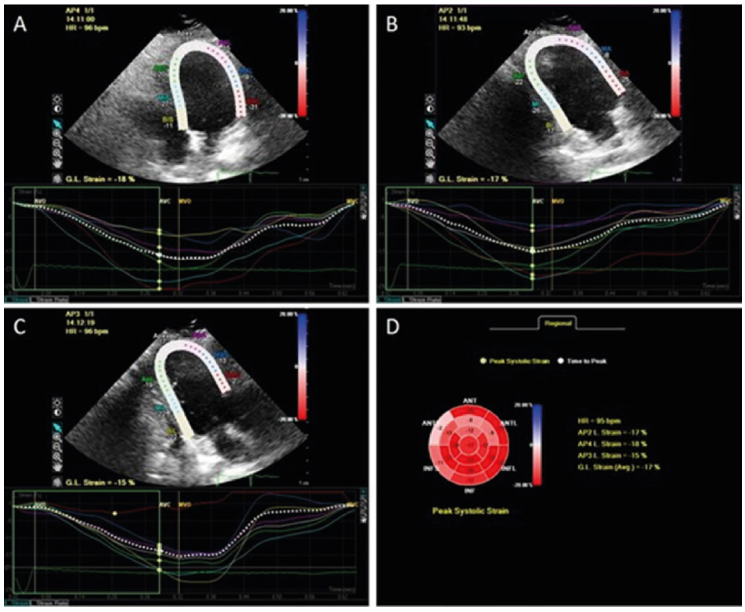

Figure 2 – *Left ventricular (LV) longitudinal strain analysis in apical four- (A), two- (B), and three-chamber (C) views, and LV global longitudinal strain (D) of a patient with Duchenne muscular dystrophy with a normal LV ejection fraction and a reduced global longitudinal strain (-17%).*

Due to the scarcity of symptoms, the high prevalence of subclinical electrocardiographic and echocardiographic changes and the worse prognosis due to these changes, we recommend assessment at the time of diagnosis followed by an annual routine assessment with ECG, 24-hour Holter monitoring, and transthoracic echocardiography and consider early primary prevention with the implantation of intracardiac devices such as a pacemaker and implantable cardioverter-defibrillator.[17,19]

Cardiac presentation and echocardiographic findings in LGMD

LGMD is a group of diseases characterized by pelvic and scapular girdle atrophy and weakness.[1,16,17] Those most frequently associated with cardiomyopathy are laminopathy (LGMD1B), sarcoglycanopathy (LGMD2C-F), and fukutinopathy (LGMD2I).[1,17,20] Cardiac clinical presentations resemble those of other MD, including DCM, cardiac arrhythmias, and sudden cardiac death.[1,17]

DCM is the most characteristic echocardiographic pattern, featuring LV dilation and systolic and diastolic dysfunction,[20] with an LVEF < 50% occurring in about 80%, 50%, and 39–45% of patients with LGMD2E (beta-sarcoglycanopathy), LGMD2C (gamma-sarcoglycanopathy), and LGMD2I, respectively.[17,21,22,23]

Recommendations about the frequency of echocardiographic assessment in LGMD are based on expert consensus.[17] In our practice, we perform ECG and transthoracic echocardiography

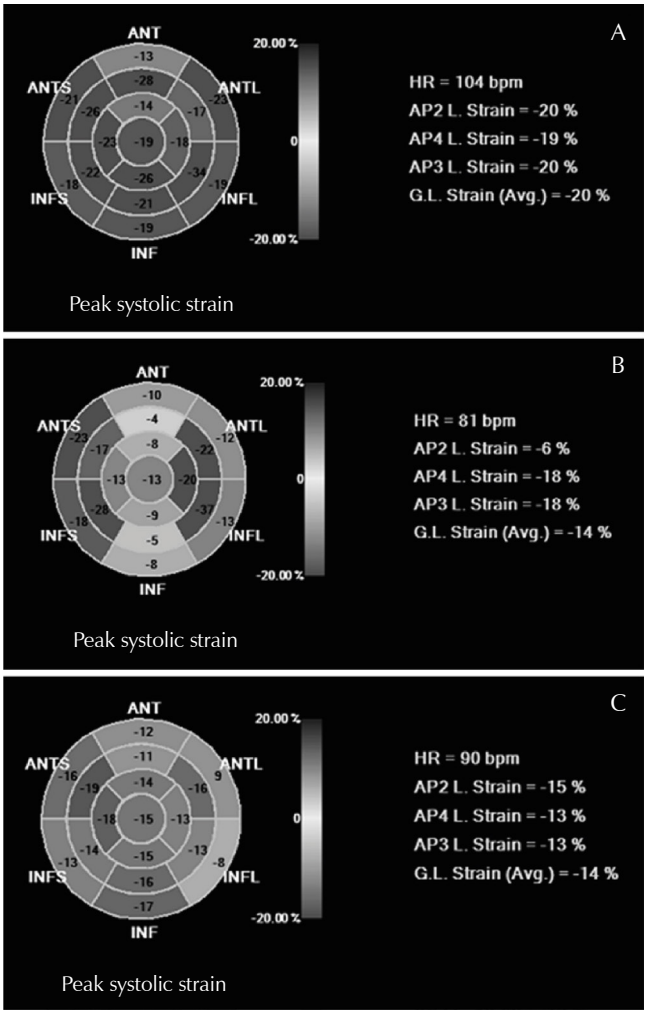

Figure 3 – *Global longitudinal strain (GLS) study of three Duchenne muscular dystrophy patients: (1) Male 10-year-old patient, symptom onset 5 years previous, ambulatory, preserved left ventricular (LV) systolic function, LV ejection fraction (LVEF) of 65%, and GLS of -20%; (2) male 12-year-old patient, symptom onset 10 years previous, wheelchair user, early LV systolic dysfunction, LVEF of 58%, and GLS of -14%; and (3) male 17-year-old patient, symptom onset 15 years prior, wheelchair user, overt LV systolic dysfunction, LVEF of 34%, and GLS of -14%.*

at diagnosis and annually thereafter. More studies are needed to investigate the benefits of myocardial strain and other recent echocardiographic techniques in LGMD.

Cardiac presentation and echocardiographic findings in EDMD

EDMD is a rare disease characterized by a high frequency of cardiac involvement that usually presents as supraventricular and ventricular arrhythmias, conduction disorders, chamber dilation, and systolic dysfunction.[1,2,16,24,25]

The most common echocardiographic findings in EDMD patients characterize the DCM phenotype and include LV dilatation and systolic dysfunction, LV diastolic dysfunction, and bi-atrial enlargement. Atrial standstill and an increased risk of embolic phenomena may also occur.[16] Marchel *et al*. demonstrated that up to 41% of EDMD patients (median age, 43 years) had LV dilation and 32% had an LVEF lower than 50%. Atrial enlargement is present in more than 2/3 of cases and predominates over ventricular dilation. Echocardiographic changes are similar in EDMD types 1 and 2 despite LMNA gene mutations being more frequently associated with DCM, heart failure and sudden cardiac death, regardless of the presence of peripheral skeletal muscle involvement.[24]

The frequency of echocardiographic assessment is not well established, but in our clinical practice, we recommend ECG, 24-hour Holter monitoring, and transthoracic echocardiography at diagnosis and annually thereafter. The

literature is scarce on the use of new echocardiographic techniques such as myocardial strain in EDMD. Due to the high risk of conduction disorders, ventricular arrhythmias, and sudden cardiac death associated with EDMD, cardiac screening of first-degree relatives and asymptomatic carriers should be performed routinely. For the same reason, an implantable cardioverter-defibrillator should be considered for primary prevention in EDMD type 2.[17]

Authors' contributions

Manuscript writing and critical review: Cirino RHD and Ducci RD.

Conflict of interest

The authors have declared that they have no conflict of interest.

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