Review

Cardiac Involvement Classification and Therapeutic Management in Patients with Duchenne Muscular Dystrophy

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Abstract. Duchenne muscular dystrophy (DMD) is an inherited myogenic disorder due to mutations in the dystrophin gene on chromosome Xp21.1. The clinical picture included peripheral muscle weakness, cardiomyopathy and chronic respiratory insufficiency. In this paper, the authors review cardiac involvement in patients with DMD, propose a cardiac impairment classification and discuss therapeutic management options.

Keywords: Duchenne muscular dystrophy, cardiomyopathy, echocardiography, classification, CMR

INTRODUCTION

Duchenne muscular dystrophy (DMD) is an inherited myogenic disorder due to mutations in the *dystrophin* gene on chromosome Xp21.1. It represents the most common and severe form of muscular dystrophy and occurs in 1 / 5000 male births [1]. The underlying gene mutations cause the absence of dystrophin, a protein located on the inner side of the skeletal and the cardiac muscle cells [2]. Symptoms include gait disturbances and difficulties in climbing stairs starting early in childhood with loss of ambulation around the age of twelve. The involvement of heart and respiratory function is classically observed in DMD and affects prognosis [2, 3]. Over the last few decades, mechanical ventilation (MV) has radically increased the survival of DMD patients by offering a way to improve respiratory functions [4, 5]. However, cardiac complications remain a serious issue impacting survival and thus requiring optimal management. In this manuscript, we review cardiac involvement in DMD patients and therapeutic management options.

PATHOPHYSIOLOGY

Dystrophin is the largest gene in the human genome with 79 exons. Mutation in the *dystrophin* gene causes the absence of dystrophin protein production because of a shift within the reading frame (out of frame) [2]. Dystrophin is a protein located in the sarcolemma and has a major structural role in muscle, as it links the internal cytoskeleton to the extracellular matrix [2]. The dystrophin contains four components: an amino-terminal domain that links the actin, a flexible rod domain, a cysteine-rich domain that links to cytoskeleton to the extracellular matrix and the carboxyl terminal domain [6]. The dystrophin protein plays a key role in the cellular stabilization [7]. It links the intracellular components (actin) with the membrane cell glycoprotein complex, giving a mechanical support during the cellular contraction [8]. In DMD, the lack of dystrophin

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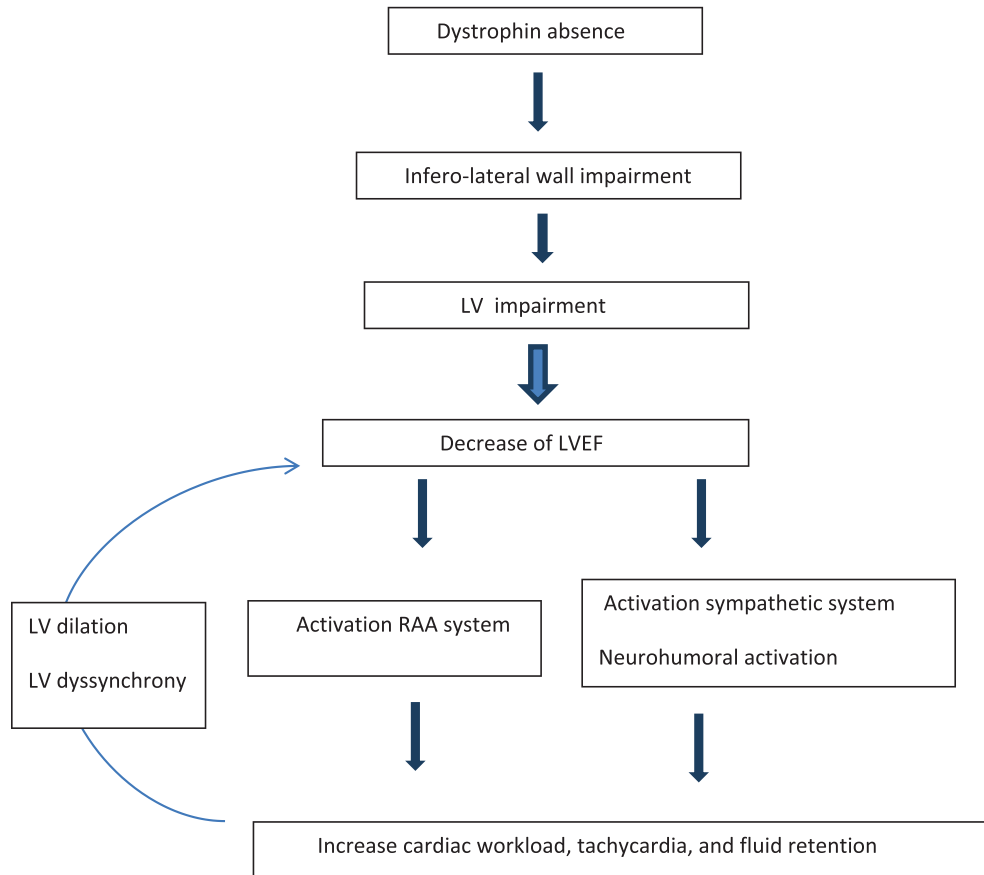
Fig. 1. Pathophysiology of heart failure in DMD. LVEF: left ventricular ejection fraction. LV: left ventricle. RAA: renin angiotensin aldosterone.

leads to intracellular mechanical destabilization that weakens the sarcolemma and progressively causes cell degeneration. Cells degeneration mechanisms are complex and involve intracellular calcium overload related to tears in the cell membrane, calcium leakage, protease activation, production of reactive oxygen species and nitric oxide pathway impairment [9]. From a mechanistic point of view, the myocardial impairment begins in the inferolateral wall, due the dystrophin absence, and progressively affects the entire left ventricle (LV) at the end of the second decade [10]. Myocardial impairment progression is associated with myocardial fibrosis [11, 12]. As myocardial fibrosis increases, the LV dilates progressively which leads to an increase in the cardiac workload and an activation of the renin angiotensin system and the sympathetic nervous system. This process worsens the heart failure, creating a vicious circle. Moreover, the high heart rate (HR) associated with the autonomous system impairment in DMD [13] and the presence of a LV dyssynchrony may worsen the LV dysfunction overtime (Fig. 1).

CLINIC

Because of limited mobility, cardiomyopathy related symptoms are often absent in DMD. In the study by Nigro et al. [2], only 28% of patients aged <18 years disclosed related symptoms. Palpitations may be related to arrhythmia [13]. Dizziness is rare. Lipothymia, an incomplete transient loss of consciousness, is rare and may be associated with conduction abnormalities. In adult patients treated with mechanical ventilation because of respiratory insufficiency, peripheral edema and ascites are classical, as is pleural effusion in end-stage disease [14]. The presence of right-sided heart failure associated symptoms and peripheral edema in patients with chronic mechanical ventilation is related to the positive intrathoracic pressures that impede the venous return [14].

ELECTROCARDIOGRAM (ECG)

ECG should be systematically included in the clinical management of DMD patients. ECG abnormalities that have been reported in DMD include sinus tachycardia, short PR intervals, and tall R wave in the right precordial leads, deep and narrow Q waves in inferolateral leads which are different from what is seen in myocardial ischemia, right bundle branch block and flat and inverted T waves [15, 16]. In a study that included 106 DMD patients, sinus tachycardia was present in 81 patients, V1 tall R waves in 79 patients and V5-V6 deep Q waves in 51 patients [17]. ECG in DMD patients may also show a Wolff Parkinson White (WPW) pattern [18]. Electrical right ventricular hypertrophy (RVH) is frequent, reaching 37% in the study by Takami et al. [16], without any correlation to LV dysfunction [19].

CARDIOMYOPATHY, ARRHYTHMIA AND CONDUCTION ABNORMALITIES

DMD is associated with a high prevalence of cardiomyopathy affecting the left ventricle and leading to chronic heart failure and heart rhythm disorders [20, 21]. Nigro et al. [2], in a pediatric population study that included 328 patients, reported that cardiomyopathy appeared as early as ten years with all DMD patients after the age of 18 years being affected. Echocardiography classically shows patterns of dilated cardiomyopathy. However, cases of left ventricle non-compaction have been reported in DMD [22]. Cardiac thrombus and cerebral infarction are rarely reported, mainly in DMD patients with severe heart failure [23]. Cardiac thrombus may be related to a significant activation of the coagulation system in DMD with heart failure [24]. Additional complications seen in DMD include arrhythmia and conduction disorder. Perloff et al. [13] reported atrial flutter in 5% of DMD patients and sinus pause in 5% of patients in a study that included 20 patients. Ventricular tachycardia was seen in 7% of patients in the study by Corrado et al. [25], reaching 16% in a study including DMD and BMD [26]. Complete atrioventricular blocks and sinus sick disease have been reported in DMD patients [27, 28]. Arrhythmia affects mainly patients with severe left ventricular dysfunction [24]. A LVEF <45% may predict the occurrence of adverse cardiac events in DMD [26].

DOPPLER ECHOCARDIOGRAPHY

Standard Doppler echocardiography should be performed according to the guidelines issued by the American Society of Echocardiography [29], using M-mode for the analysis of left atrial diameter, septal and posterior wall thickness and motion of the LV, LV end systolic and end diastolic diameters, calculation of the LV shortening fraction and LV ejection fraction (LVEF). 2D mode is used to assess cardiac anatomic structures and function by the assessment of the LV function a from 4 chambers apical view [29]. Doppler is used to assess the LV systolic function (LV aortic outflow tract systolic velocity) and the LV diastolic function (trans-mitral flow velocities, tissue Doppler imaging) and to estimate arterial pulmonary pressures [30]. However, assessment of the LV contractility by the classical LVEF analysis with standard echography is limited because in early stages, patients may have heart involvement with normal LVEF. 2D Strain imaging is a recent technology that assesses regional myocardial impairment and may detect early cardiac involvement in muscular dystrophy [31]. In early stages, subclinical diastolic function has been reported in DMD pediatric population, preceding the LV systolic dysfunction [32]. In DMD, regional myocardial abnormalities have been reported in early stages, affecting mainly the inferolateral region [33]. Mertens et al. [34] reported alteration of peak systolic and early diastolic myocardial velocities in the anterolateral and inferolateral walls in young DMD patients. In the adult population, echocardiography may show akinesia located in the LV inferobasal wall [35], LV dilation and LV systolic dysfunction. Mitral functional regurgitation may also be present, in relation with the LV and mitral annulus dilation. However, thorax deformities and difficulties to have optimal images in wheelchair- bound patients technically limit Doppler echocardiography.

CARDIAC MAGNETIC RESONANCE IMAGING

Cardiac magnetic resonance (CMR) imaging is used to assess LVEF and wall motion abnormalities. CMR may reveal early cardiac impairment in DMD with normal left ventricular ejection fraction in Doppler echocardiography [36]. Free wall segments are classically seen with late gadolinium enhancement (LGE) imaging [37]. LGE is used to assess myocardial fibrosis in CMR. In DMD, a

Table 1
Proposal for staging of heart involvement in DMD

Stage	Clinic	Echocardiography CMR	Treatment
Stage 1	Asymptomatic	Echo: LVEF>55% Possible 2D strain abnormalities CMR: Myocardium LGE often negative	ACE inhibitors
Stage 2	Tachycardia	Echo: 45%< LVEF <55% 2D strain abnormalities Infero-lateral wall impairment CMR: Myocardium with positive LGE	ACE inhibitors Beta blockers Mechanical ventilation at the end of the second decade
Stage 3	Peripheral edema Sometimes Dyspnea (patients without MV) Tachycardia	Echo 35%<LVEF <45% 2D strain abnormalities CMR: Myocardium with Positive LGE+++	ACE inhibitors Beta blockers Anti-aldosterone Diuretic (congestion) Intermittent mechanical ventilation
Stage 4	Anasarca Peripheral edema Ascites Lipothymia Tachycardia	Echo: LVEF<35% 2D stain abnormalities CRM: Diffuse myocardial LGE+++	ACE inhibitors Beta blockers Anti-aldosterone Diuretic (congestion) +- CRT or CRT-D Permanent mechanical ventilation

LVEF: left ventricular ejection fraction. CRT-D: cardiac resynchronization therapy defibrillator. CRT-P: cardiac resynchronization therapy pacemaker. ACE: angiotensin converting enzyme. LGE: late gadolinium enhancement. CMR: cardiac magnetic resonance.

transmural LGE pattern has been reported to be a prognostic factor in addition to LV systolic dysfunction [26]. In patients with LVEF ≥55%, LGE was positive in 30% of patients, particularly in the LV free wall, reaching 84% in patients with LVEF <55% [37]. Cardiac CMR may help to predict ventricular arrhythmia and cardiac remodeling in DMD [34] and may be used to assess pharmacological approach targeting myocardial fibrosis [37]. Current researches in CMR are evaluating different myocardial sequencing in dystrophinopathies.

HEART INVOLVEMENT CLASSIFICATION

With the development of new targets in Heart Failure drug treatment, heart involvement in DMD needs to be better assessed. Researches in CMR will help clinicians to better understand pathophysiology and assess therapeutic efficacies [12, 38]. In patients with advanced heart failure, clinical presentation may be atypical because of loss of global muscle strength and limitations of wheelchair-bound patients even though in end-stage cardiomyopathy, right signs have been reported and anasarca is often present [14]. Diagnosis of dyspnea is hampered by MV use, which also pro-

tects against high LV filling. Peripheral edema may be seen as a consequence of muscle loss. Adult's DMD patients may have subtle myocardial impairment whereas young DMD patients may have obvious heart failure.

Taking into account all the previous considerations, we have constructed a clinical-radiological classification of heart involvement in DMD, based on clinical, echocardiography and CMR findings (Table 1).

TREATMENT

Medical treatment

Drug treatment relies mainly on angiotensin-converting enzyme (ACE) inhibitors and beta blockers [40, 41], with the addition of aldosterone antagonists (potassium-sparing diuretic) in patients with chronic heart failure [42]. ACE inhibitors act by blocking the conversion of angiotensin I to angiotensin II, therefore leading to a decrease of arterial vascular resistance and an increase of stroke volume. In the general population, ACE inhibitors have been associated with a decrease morbidity and mortality in patients with chronic heart failure [42].

In DMD patients, ACE inhibitors (perindopril) have been shown to delay the onset of cardiomyopathy, which could be related to its anti-fibrotic properties [43, 44]. Beta-blockers act by blocking the beta-adrenergic receptors, reducing sympathetic activities, heart rate, heart contractility and relaxation. In the general population, beta blockers (bisoprolol, carvedilol, metoprolol) have been associated with a decrease morbidity and mortality in patients with chronic heart failure [42, 45, 46]. A beneficial effect of beta-blocker administration in association to ACE inhibitors has been reported for cardiac morbidity and mortality in DMD [38, 47]. According to the European guidelines [42], ACE inhibitors are recommended, in addition to a beta blocker, for symptomatic heart failure patients with reduced LVEF (*class I, level A*). Recently, in DMD pediatric population, a beneficial effect of eplerenone, an aldosterone antagonist, has been reported [48] when prescribed with either an ACE inhibitor or an angiotensin receptor blocker. Raman et al. [48], reported a lower LV circumferential strain decline after 12 months in DMD children with normal left ventricular ejection fraction and treated with eplerenone. According to the European guidelines, a MRA (mineralocorticoid receptor antagonist) is recommended in symptomatic heart failure patients with reduced LVEF despite a treatment including an ACE inhibitor and a beta blocker (*class I, level A*). Steroid therapy may also have positive impact on myocardial function, reducing mortality and new-onset cardiomyopathy [49]. Finally, idebenone administration has been associated with a slight increase of the peak systolic radial strain in the inferolateral wall of the LV that suggests a possible positive effect on LV contraction [50] using 2D strain echocardiography. Idebenone is not currently approved in this indication.

Instrumental Treatment

Instrumental treatment relies mainly on cardiac resynchronization therapy (CRT) and non-invasive ventilation. DMD patients exhibit restrictive respiratory failure, requiring long-term mechanical ventilation, which may influence cardiac function. Non-invasive ventilation (NIV) has been endorsed by the *ATS consensus* as the choice therapy in DMD for respiratory failure [48]. Positive pressure ventilation has a positive effect on LV function, resulting in a decrease in afterload [39]. In DMD, potential beneficial effects of chronic MV on cardiac function has been suggested [40]. Cardiac resynchronisation

therapy (CRT) may be beneficial to patients with symptomatic heart failure despite optimal drug therapy and a QRS duration >130 ms [51]. According to the European guidelines, CRT is recommended for symptomatic heart failure patients with QRS duration ≥150 ms, LBBB and LVEF ≤35% despite optimal medical therapy (*class I, level A*) [42]. CRT is also recommended in symptomatic patients with QRS duration of 130–149 ms, LBBB and LVEF ≤35% despite optimal medical therapy (*class I, level B*). However, Hor et al. [37] reported narrow QRS in the majority of DMD patients (97%), which reduces the number of DMD patients eligible for CRT implantation. Technical difficulties to insert CRT device and endocarditis risks also need to be taken into account [52]. An implantable cardiac defibrillator may be indicated in patients with severe LV dysfunction, particularly in case of ventricular arrhythmia events. Thus, only a minority of DMD patients may benefit from CRT. Recently, left ventricular device therapy has been proposed for DMD patients with end-stage cardiomyopathy [53] but requires further studies.

In conclusion, heart failure is a significant complication in DMD. Management relies on regular ECG, echocardiography and sometimes ECG Holter. 2D strain echocardiography and CMR may help clinicians to depict early cardiac involvement. According to the guidelines of the DMD *Care Working Group* [40], annual cardiac assessment including ECG and an echocardiography should be performed in all DMD patients aged >10 years. Pharmacological management relies mainly on ACE inhibitors, beta blockers and steroids. Electrical devices may be proposed in selected patients.

CONFLICTS OF INTEREST

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