Acta Myologica • 2019; XXXVIII: p. 1-7

ORIGINAL ARTICLES

Are there real benefits to implanting cardiac devices in patients with end-stage dilated dystrophinopathic cardiomyopathy? Review of literature and personal results

Alberto Palladino[1], Andrea A. Papa[2], Salvatore Morra[1], Vincenzo Russo[2], Manuela Ergoli[1], Anna Rago[2], Chiara Orsini[1], Gerardo Nigro[2] and Luisa Politano[1]

[1] Cardiomyology and Medical Genetics, Department of Experimental Medicine; [2] Arrhythmology Unit, Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy

Cardiomyopathy associated with dystrophinopathies – Duchenne muscular Dystrophy (DMD), Becker muscular dystrophy (BMD), X-linked dilated cardiomyopathy (XL-CM) and cardiomyopathy of Duchenne/Becker (DMD/BMD carriers – is an almost constant manifestation of these neuromuscular disorders and contribute significantly to their morbidity and mortality. Dystrophinopathic cardiomyopathy is the result of the dystrophin protein deficiency at the myocardium level, parallel to that occurring at the skeletal muscle level. Typically, cardiomyopathy begins as a "presymptomatic" stage in the first decade of life and evolves in a stepwise manner toward an end-stage dilated cardiomyopathy. Nearly complete replacement of the myocardium by fibrous and fatty connective tissue results in an irreversible cardiac failure, characterized by a further reduction of ejection fraction (EF < 30%) and frequent episodes of acute heart failure (HF). The picture of a severe dilated cardiomyopathy with intractable heart failure is typical of dystrophinopathies. Despite an appropriate pharmacological treatment, this condition is irreversible because of the extensive loss of myocites. Heart transplantation is the only curative therapy for patients with end-stage heart failure, who remain symptomatic despite an optimal medical therapy. However there is a reluctance to perform heart transplantation (HT) in these patients due to the scarcity of donors and the concerns that the accompanying myopathy will limit the benefits obtained through this therapeutic option. Therefore the only possibility to ameliorate clinical symptoms, prevent fatal arrhythmias and cardiac death in dystrophinopathic patients could be the implantation of intracardiac device (ICD) or resynchronizing devices with defibrillator (CRT-D). This overview reports the personal series of patients affected by DMD and BMD and DMD carriers who received ICD or CRT-D system, describe the clinical outcomes so far published and discuss pro and cons in the use of such devices.

Key words: dystrophinopathic cardiomyopathy, Duchenne muscular dystrophy, Becker muscular dystrophy, intracardiac devices, Duchenne/Becker carriers

Introduction

Dystrophinopathies are X-linked muscular dystrophies caused by mutations in the dystrophin gene, located at Xp21, that encodes for the sarcolemmal protein dystrophin virtually present in all tissues, but most abundant in skeletal muscle cells and heart (1, 2). Dystrophin provides the connection between the so called dystrophin-glycoprotein complex on the sarcolemma and the intracellular actin filaments, transmitting forces generated by the sarcomere contraction to the extracellular matrix (3, 4). Absence, reduced levels or abnormal structure of dystrophin lead to membrane fragility, making muscle fibres more prone to injury during contraction. As muscle disease progresses, muscle repair cannot adequately compensate for damage, leading to necrosis of skeletal and cardiac myocytes and the progressive replacement by fibrofatty tissue (5). Dystrophinopathic cardiomyopathy is the result of the dystrophin protein deficiency at the myocardium level, parallel to that occurring at the skeletal muscle level. Typically, cardiomyopathy begins as a "presymptomatic" stage in the first decade of life and evolves in a stepwise manner toward an end-stage dilated cardiomyopathy. Nearly complete replacement of the myocardium by fibrous and fatty connective tissue results in an irreversible cardiac failure, characterized by a further reduction of ejection fraction (EF < 30%) and frequent episodes of acute heart failure (HF) (6-11). Cardiac death usually occurs from systolic dysfunction, that represents the end stage of dystrophinopathic cardiomyopathy (DCM) or the onset of fatal arrhythmias.

Address for correspondence: Luisa Politano, Cardiomyology and Medical Genetics, Department of Experimental Medicine, University of Campania "Luigi Vanvitelli", I° Policlinico, piazza Miraglia, 80138 Naples, Italy. E-mail: luisa.politano@unicampania.it

Dystrophinopathies can present with four clinical pictures, Duchenne muscular dystrophy (DMD), the more severe form, Becker muscular dystrophy (BMD), the more benign form, the X-linked dilated cardiomyopathy (XL-DCM) (2, 9) and the cardiomyopathy of DMD/BMD carriers (11). They are characterised by different pathogenic conditions that result in variable degrees of skeletal muscle and myocardial dysfunction. Having a better management of the ventilatory failure led to an increase in survival rates in these patients (12-14), heart failure remains an important contributor to the mortality. Despite the high incidence of end-stage DCM, there is a reluctance to perform heart transplantation (HT) in these patients due to the scarcity of donors and the concerns that the accompanying myopathy will limit the benefits obtained through this therapeutic option (15, 16) .

In patients with New York Heart Association (NYHA) class III, ambulatory class IV systolic heart failure (HF) and recently class I and II, with electrocardiographic evidence of ventricular dyssynchrony, cardiac resynchronization therapy with defibrillator (CRT-D) has been shown to a) improve quality of life and functional status, b) reduce heart failure-related hospitalizations, and c) prolong survival (17-26). Implantable cardioverter defibrillators (ICDs) have revolutionized the primary and secondary prevention of patients with heart failure (27-30) and ventricular arrhythmias (31-33). The implantation of an ICD is considered in cases of non-sustained ventricular tachycardia unresponsive to drug treatment (usually beta-blockers) while a CRT-D system is preferred in presence of a drug-resistant heart failure associated to a left branch bundle block (LBBB), especially when conventional measures are ineffective (27). Biventricular pacing is able to synchronize left ventricular contractions, improve left ventricular function, and decrease left ventricular filling pressure. CRT-D is an adjuvant treatment for patients with post-ischemic dilated cardiomyopathy and symptomatic, drug refractory heart failure, providing both acute and long term hemodynamic and functional improvement (27, 31-33). Recent studies have reported in these patients an improvement of symptoms accompanied by the reduction of left ventricular volumes mitral regurgitation, a marker of the ventricle remodelling and the increase of LV ejection fraction (LVEF).

As tachy-arrhythmias and mechanical dyssynchrony are frequent in dystrophinopathic patients with end stage dystrophin-associated myocardial dysfunction (34-43), the implantation of ICD or CRT-D could be indicated to ameliorate clinical symptoms and prevent life-threatening arrhythmias and cardiac sudden death also in these patients.

However, few data are available about cardiac device implantation in dystrophinopathic patients. Takano et al. 44), Fassoyl et al. (45) and Kuru S et al. (46) reported on isolate cases of DMD patients receiving a pacemaker implant for complete atrioventricular block or sinus node dysfunction in 1997, in 2005 and in 2012, respectively. Stollberger et al. (47) reported a case of a 40-year-old BMD patient with severe heart failure (LVEF 25%) who benefited from CRT-D. However no amelioration was found regarding the LVEF three months after the CRT therapy and the patient died 16 weeks after implantation. Andrikopoulos et al. (48) reported the case of a BMD patient with advanced heart failure due to non-ischemic cardiomyopathy (NICM), with noncompaction morphology of the left ventricle, and associated electrical and mechanical dyssynchrony, who became nearly asymptomatic (NYHA class I) shortly after implantation, with an improvement in LV function documented by 3D-echocardiography. CRT-D has been successfully experienced in a 34 year old DMD, presenting with asthenia, leg oedema and ascites, moderate left ventricle dilation, decreased ejection fraction (30%) and a significant arterial pulmonary pressure (57 mmHg). One year before the patient was implanted of dual chamber pacemaker because of a complete atrio-ventricular block. Upgrade from a dual-chamber to a biventricular pacemaker produced, one month after, stabilization of systolic function, regression of interventricular and intra-ventricular asynchrony and decrease of pulmonary artery pressure (40 mmHg). After 5 years of follow-up, the ejection fraction improved to 45% (49).

However – except for these isolated case reports - no definitive figures exist in literature concerning the number of patients with dystrophinopathic cardiomyopathy who received ICD or CRT-D and their outcome, nor clear indications in the current guidelines that consider the use of cardiac devices as an option for dystrophinopathic patients with end-stage dilated cardiomyopathy.

Aim of this overview is to a) report the personal series of patients affected by DMD and BMD and DMD carriers who received ICD or CRT-D, b) describe the clinical outcomes so far published and c) discuss pro and cons in the use of such devices in this selected population.

Patients and methods

Patients

We retrospectively analyzed data from 18 dystrophinopathic patients followed at the Cardiomyology and Medical Genetics of the Luigi Vanvitelli Campania University, 5 affected by DMD, 10 by BMD and 3 DMD carriers, who were implanted – after informed consent - with ICDs or an CRT-Ds in the period June 2007-November 2018. The study was approved by the local ethical Committee.

Since diagnosis, based on clinical and genetic analysis, all patients undergone periodical evaluations that included cardiologic assessment, standard and dynamic

ecg, echo-color-doppler-cardiogram and electrophysiological study (SEF) when necessary. The evaluations were performed every 3-months, according to the clinical presentation. All patients were on cardiological treatment, in particular ACE-inhibitors, beta-blockers, antiarrhythmic drugs and anticoagulants.

Methods

ECG. Standard 12 lead ECG was obtained in all patients; QRS duration was measured manually. The presence of fibrosis, arrhythmias or bundle branch blocks was also noted.

24-hour Holter monitoring ECG. Hear rate (HR) and presence and type of arrhythmias were assessed by 24-hour Holter monitoring system.

Echocardiogram. Left ventricular volumes, mass and global function were assessed via standard planimetry techniques using semi automated computer software (Philips SONOS 5500 Imaging System, Netherlands) by expert readers (AP, SM). Ventricular volumes, mass, ejection fraction as far as ratio EDV/m^2 were tabulated for each subject.

The indication for a device implantation was made in presence of subjective symptoms (dyspnoea, fatigue, reduced exercise tolerance) corresponding to a III-IV NYHA class, EF ≤ 35% and/or cardiac dilation (ratio EDV / m^2 > 70) or in presence of arrhythmias. The implant of devices was performed under local anesthesia obtained by subcutaneous administration of lidocaine.

Results

The results are shown in Tables 1 and 2.

Table 1 shows the cardiological features of patients enrolled in the study, collected at the last visit before implantation. All DMD patients and 50% of BMD patients were chair-bound. The mean age of loss of ambulation (LoA) was 13.3 ± 1.6 years for Duchenne and 42.7 ± 11.2 years for Becker patients.

Not sustained ventricular tachycardia (NSVT) was reported in 7/18 (38.8%) and ventricular ectopic beats (VEB) in 4/18 (22.2%) patients considered as a whole. Atrio-ventricular blocks were observed in 3/18 patients (16.7%). Postero-lateral fibrosis was observed in all Duchenne patients and only in one Becker (patient n. 8), at the posterior level. A left bundle branch block (LBBB) was present in 6/18 patients (33.3%), 1 with Duchenne, 3 with Becker and 2 carriers. Before implantation, the mean

Table 1. Cardiological parameters of patients before implantation.

Patient number	LoA in years	Age at the device implantation	Ejection fraction in % (n.v. > 55)	EDV/m^2 (n.v. < 70)	Presence/type of arrhythmias or BBB and fibrosis	Type of device implanted
DMD n. 1	15y 10m	15y 10m	35	166	NSVT; postero-lateral fibrosis	ICD
DMD n. 2	13y	23y 6m	30	108	NSVT; postero-lateral fibrosis	ICD
DMD n. 3	13y 8m	28y 11m	33	78	None; postero-lateral fibrosis	ICD
DMD n. 4	11y 5m	15y 7m	40	91	AVB 2:1; LBBB; postero-lateral fibrosis	CRT-D
DMD n. 5	12y 6m	26y 5m	35	108	NSVT; postero-lateral fibrosis	ICD
BMD n. 1		39y 8m	32	109	VEB; LBBB	CRT-D
BMD n. 2		51y 7m	28	127	None	ICD
BMD n. 3	52y	51y 7m	30	82	AVB 3rd degree	CRT-D
BMD n. 4		56y 4m	33	91	NSVT	ICD
BMD n. 5	40y	45y	40	155	NSVT	ICD
BMD n. 6	45y 2m	51y 7m	28	127	NSVT	ICD
BMD n. 7	51y 8m	51y 3m	33	111	AVB 1st degree; AVB 2nd degree, type 1 and type 2; RBBB	PM upgraded to ICD
BMD n. 8	24y 10m	33y 2m	35	118	VEB; posterior fibrosis	ICD
BMD n. 9		58y 4m	38	139	VEB	ICD
BMD n. 10		60y 10m	35	124	NSVT, LBBB	CRT-D
DMDc n. 1		54y 6m	31	147	LBBB	CRT-D
DMDc n. 2		55y 4m	37	147	VEB	ICD
DMDc n. 3		50y 8m	30	147	LBBB	CRT-D

DMD: Duchenne Muscular Dystrophy; BMD: Becker Muscular Dystrophy; DMDc: Duchenne Muscular Dystrophy carrier; LoA: loss of ambulation; EDV: end-diastolic volume; m^2= height in meters, elevated to the square; NSVT: Not sustained Ventricular Tachicardia; AVB: atrio-ventricular block; LBBB: Left Bundle Branch Block; RBBB: Right Bundle Branch Block; VEB: Ventricular ectopic beats.

Table 2. Comparison of cardiological parameters before and after implantation.

Patient number	Ejection fraction in % before implantation (n.v. > 55)	Ejection fraction in % post-implantation (n.v. > 55)	EDV/m² before implantation (n.v. < 70)	EDV/m² post implantation (n.v. < 70)	FU in months since the implantation
DMD n.1	35	32	166	166	5
DMD n.2	30	37	108	90	40
DMD n. 3	33	38	78	99	25
DMD n. 4	40	36	91	95	5
DMD n. 5	35	25	108	97	21
Mean ± SD	34.6 ± 3.6	33.6 ± 5.4	110.2 ± 33.6	109.4 ± 31.8	19.2 ± 14.8
BMD n.1	32	20	109	153	69
BMD n.2	28	35	127	153	66
BMD n. 3	30	35	82	85	3
BMD n. 4	33	33	91	91	5
BMD n. 5	40	21	155	169	53
BMD n. 6	28	31	127	145	76
BMD n. 7	33	31	111	95	136
BMD n. 8	35	28	118	138	67
BMD n. 9	38	30	139	127	40
BMD n. 10	35	35	124	99	42
Mean ± SD	33.2 ± 3.9	29.9 ± 5.5	118.3 ± 21.5	125.5 ± 30.6	55.7 ± 38.1
DMDc n. 1	31	28	147	236	71
DMDc n. 2	37	25	147	137	41
DMDc n. 3	30	25	147	172	96
Mean ± SD	33.7 ± 3.8	26.0 ± 1.7	147.0 ± 0	181.6 ± 50.2	69.3 ± 27.5

DMD: Duchenne Muscular Dystrophy; BMD: Becker Muscular Dystrophy; DMDc: Duchenne Muscular Dystrophy carrier; LoA: loss of ambulation; EDV: end-diastolic volume; m^2: height in meters, elevated to the square.

value of ejection fraction was 34.6 ± 3.6% in Duchenne, 33.2 ± 3.9% in Becker and 32.7 ± 3.8% in DMD carriers. The mean value of VTD/m2, a parameter considered as a marker of cardiac dilation, was 110.0 ± 33.6 in Duchenne, 118.3 ± 21.5 in Becker and 147.4 ± 0.05 in DMD carriers.

Twelve out of 18 patients received an ICD as cardiac device, while 1 Duchenne patient (n. 4), 3 Becker patients (n.1, n. 4 and n. 9) and 2 carriers (n. 1 and n. 3) received a CRT-D because the contemporary presence of mechanical dyssynchrony.

The device implantation was performed at a mean age of 21.8 ± 5.9 years in Duchenne patients, 50.3 ± 8.7 years in Becker patients and 53.5 ± 2.5 years in DMD carriers. The average duration in months of the follow-up was 19.2 ± 14.8 (range 5-40 months) for Duchenne patients, 55.7 ± 38.1 (range 3-136 months) for Becker patients and 69.3 ± 27.5 (range 41-96 months) for the DMD carriers.

Table 2 shows a comparison between data obtained before and after the implantation. The ejection fraction varied on average from 34.6 ± 3.6% to 33.6 ± 5.3% in Duchenne patients, from 33.2 ± 3.9% to 29.9 ± 5.5% in Becker patients and from 32.7 ± 3.8% to 26 ± 1.7% in DMD carriers. None of the three groups recovered normal values, rather we saw a stabilization of the starting values or more often a clear deterioration, particularly in Becker patients and DMD carriers. Similarly, the mean values of VTD/m^2 changed from 110 ± 33.6 to 109.4 ± 31,8 in Duchenne patients, from 118.3 ± 21.5 to 125.5 ± 30.6 in Becker and from 147.4 ± 0.05 to 181.0 ± 50.2 in DMD carriers, values clearly indicating a progression in the heart dilation in the last two groups.

A restrictive respiratory failure was present in all DMD patients with percentage of Forced Vital Capacity (FVC) ranging from 6 to 71% compared with the expected values. Only one Becker patient had a FVC equal to 60%, while the remaining had values ranging from 71 to 100%. Two out of DMD carriers had FVC values at about 60% of the expected ones.

During the follow-up 6/18 patients (33.3%) died. Three Duchenne and one Becker patients from respiratory failure, two carriers from intractable heart failure. The death occurred on average 22 months in DMD, 50 months in BMD and 60 months after implantation, respectively.

Despite these not encouraging results, 25% of patients referred they have got something positive out of

this situation in terms of cardiac symptoms and daily life activities.

Implant-related complications

Usually two types of major implant-related complications can occur: (1) In-hospital complications and (2) complications within 90 days of discharge. In-hospital complications include: in-hospital death; re-operation including generator, lead or pocket re-operation with incision and drainage of hematoma, seroma, or abscess; post-procedural shock; pericardial or pleural drainage; and infective endocarditis.

Post-discharge complications include: death within 30 days of discharge; re-operation for reasons reported above; re-hospitalization within 90 days with a primary diagnosis consistent with a device-related complication; infection (device infection, endocarditis, systemic infection); pneumothorax or pericardial effusion; pocket-related complications such as hematoma or wound dehiscence; venous obstruction or thrombo-embolism and other admissions for potentially serious device-related complications.

The occurrence of in-hospital and post-discharge complications have been estimated in about 8-8.5% of patients, with a slight prevalence for women (50), prevalently consisting in pleural and pericardial drainage and infections (50-52).

In our cohort of patients, only 1 BMD patient had implant-related complications consisting in a healing defect of the ICD pocket.

Discussion

Cardiac dysfunction in patients with Duchenne/Becker muscular dystrophy (DMD/BMD) and in DMD/BMD carriers is a leading cause of death, together with the onset of life-threatening arrhythmias. Implantable cardiac defibrillators and cardiac resynchronization therapy with defibrillator have been shown to dramatically decrease mortality in eligible adult population with congestive heart failure. Current therapeutic options for dystrophinopathic patients presenting heart failure are limited and no established standard of care for medical or device interventions are still available. Furthermore few studies sought to determine the feasibility of ICDs or CRT-Ds in DMD/BMD population, most of whom have normal QRS complexes. The data here reported, while seem to confirm the limited benefits from the use of this therapeutic approach, on the other hand show that 25% of patients have had a subjective improvement in their daily activities. The normality of QRS complex as well as the extensive postero-lateral fibrosis associated to dystrophinopathic cardiomyopathy are likely the cause of poor response to the treatment, at least in Duchenne patients. This suggests that it would be advisable - in determining the indications for implantation of the ICD and CRT-D for primary prevention of sudden cardiac death in Duchenne patients - to take into account not only the value of left ventricle ejection fraction, but also the features of the fibrosis of the left ventricle.

Patients with severe dystrophinopathy may be at risk for respiratory insufficiency because of diaphragm involvement and chest deformities; moreover, a device implantation may be problematic in these patients because of possible and serious mechanical and infective complications. Fayssoil et al. have recently (53) reported retrospective data on the risks related to ICD in muscular dystrophy patients ventilated by tracheostomy. They found 12 device implantations performed in 9 patients (5 DMD, 1 BMD and 3 DM1), at a mean age of 39.9 years ± 13.0. All patients were wheel-chair bound and tracheotomised. Concerning the type of the device, 6 were pacemakers (PM) and 6 CRT devices, including 2 CRT-D. They observed a high prevalence of early complications (16.6% pneumothorax) and an acceptable long-term infectious risk (8.3%).

A further major risk in these patients is general anesthesia (54), so that the most part of these operations are made under local anesthesia. In cases of trans-muscle access, Froyshteter et al. have recently suggested the use of unilateral pectoralis and intercostal nerve blocks, supplemented with intravenous sedation (55).

Because data about the pros and cos in using ICD and CRT-D in dystrophinopathic patients remain controversial, specific guidelines on device therapy, similar to those established for patients with acute and chronic heart failure by the European Society of Cardiology (ESC), the Heart Failure Association (HFA) of the ESC and the European Society of Intensive Care Medicine (ESICM) (56,57) are strongly advocated to expand and support the CRT indication in dystrophinopathic patients.

Conflict of interest

The Authors declare to have no conflict of interest.

References

1. Sadoulet-Puccio HM, Kunkel LM. Dystrophin and its isoforms. Brain Pathol 1996;6:25-35.
2. Muntoni F, Torelli S, Ferlini A. Dystrophin and mutations: one gene, several proteins, multiple phenotypes. Lancet Neurol 2003;2:731-40.
3. Rafael JA, Cox GA, Corrado K, et al. Forced expression of dystrophin deletion constructs reveals structure-function correlations. J Cell Biol 1996;134:93-102.

4. Petrof BJ, Shrager JB, Stedman HH, et al. Dystrophin protects the sarcolemma from stresses developed during muscle contraction. Proc Natl Acad Sci USA 1993;90:3710-4.
5. Wallace GQ, McNally EM. Mechanisms of muscle degeneration, regeneration and repair in the muscular dystrophies. Annu Rev Physiol 2009;71:37-57.
6. Nigro G, Politano L, Nigro V, et al. Mutation of dystrophin gene and cardiomyopathy. Neuromuscul Disord 1994;4:371-9.
7. Obler, D, Wu B-L, Lip VA, et al. Familial dilated cardiomyopathy secondary to dystrophin splice site mutation. J Card Fail 2010;16:194-9.
8. Finsterer J, Stollberger C. The heart in human dystrophinopathies. Cardiology 2003;99:1-19.
9. Nigro G, Comi LI, Politano L, et al. Cardiomyopathies associated with muscular dystrophies. In: Engel AG, Franzini-Armstrong C, Eds. Myology. New York: McGraw-Hill 2004; pp. 1239-56.
10. Michele DE, Campbell KP. Cardiomyopathy in muscular dystrophies. In: Walsh RA, Ed. Molecular mechanisms of cardiac hypertrophy and failure. London: Taylor & Francis 2005, pp. 541-67.
11. Politano L, Nigro V, Nigro G, et al. Development of cardiomyopathy in female carriers of Duchenne and Becker muscular dystrophies. JAMA 1996;275:1335-8.
12. Eagle M, Baudouin SV, Chandler C, et al. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord 2002;12:926-9.
13. Passamano L, Taglia A, Palladino A, et al. Improvement of survival in Duchenne muscular dystrophy: retrospective analysis of 835 patients. Acta Myol 2012;31:121-5.
14. Koeks Z, Bladen CL, Salgado D, et al. Clinical outcomes in Duchenne muscular dystrophy: a study of 5345 patients from the TREAT-NMD DMD global database. J Neuromuscul Dis 2017;4:293-306.
15. Papa AA, D'Ambrosio P, Petillo R, et al. Heart transplantation in patients with dystrophinopathic cardiomyopathy: review of the literature and personal series. Intractable Rare Dis Res 2017;6:95-101.
16. El-Assaad I, Al-Kindi SG, Oliveira GH, et al. Implantable cardioverter-defibrillator and wait-list outcomes in pediatric patients awaiting heart transplantation. Heart Rhythm 2015;12:2443-8.
17. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873-80.
18. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.
19. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.
20. Lubitz SA, Leong-Sit P, Fine N, et al. Effectiveness of cardiac resynchronization therapy in mild congestive heart failure: systematic review and meta-analysis of randomized trials. Eur J Heart Fail 2010;12:360-6.
21. van Bommel RJ, Gorcsan J, Chung ES, et al. Effects of cardiac resynchronisation therapy in patients with heart failure having a narrow QRS complex enrolled in PROSPECT. Heart 2010;96:1107-13.
22. Ng K, Kedia N, Martin D, et al. The benefits of biventricular pacing in heart failure patients with narrow QRS, NYHA class II and right ventricular pacing. Pacing Clin Electrophysiol 2007;30:193-8.
23. Yu CM, Chan YS, Zhang Q, et al. Benefits of cardiac resynchronization therapy for heart failure patients with narrow QRS complexes and coexisting systolic asynchrony by echocardiography. J Am Coll Cardiol 2006;48:2251-7.
24. Bleeker GB, Holman ER, Steendijk P, et al. Cardiac resynchronization therapy in patients with a narrow QRS complex. J Am Coll Cardiol 2006;48:2243-50.
25. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. N Engl J Med 2007;357:2461-71.
26. Shlevkov NB, Zhambeev AA, Gasparyan AZ, et al. Characteristic of fibrotic myocardial lesions associated with life-threatening ventricular tachyarrhythmias in patients with ischemic and non-ischemic cardiomyopathies. Ter Arkh 2018;90:42-7.
27. Miller JD, Yousuf O, Berger RD. The implantable cardioverter-defibrillator: an update. Trends Cardiovasc Med 2015;25:606-11.
28. Grimm W. Clinical trials of prophylactic implantable defibrillator therapy in patients with non-ischemic cardiomyopathy: what have we learned and what can we expect from future trials? Card Electrophysiol Rev 2003;7:463-7.
29. Borggrefe M, Chen X, Martinez-Rubio A, et al. The role of implantable cardioverter defibrillators in dilated cardiomyopathy. Am Heart J 1994;127(4 Pt 2):1145-50.
30. Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol 2002;40:111-8.
31. Kurita T, Noda T, Aiba T, et al. Cardiac resynchronization therapy to prevent life-threatening arrhythmias in patients with congestive heart failure. J Electrocardiol 2011;44:736-41.
32. Sundell J, Engblom E, Koistinen J, et al. The effects of cardiac resynchronization therapy on left ventricular function, myocardial energetics, and metabolic reserve in patients with dilated cardiomyopathy and heart failure. J Am Coll Cardiol 2004;43:1027-33.
33. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329-38.
34. Fayssoil A, Abasse S, Silverston K. Cardiac involvement classification and therapeutic management in patients with Duchenne muscular dystrophy. J Neuromuscul Dis 2017;4:17-23.
35. Hor KN, Wansapura JP, Al-Khalidi HR, et al. Presence of mechani-

cal dyssynchrony in Duchenne muscular dystrophy. J Cardiovasc Magn Reson 2011;13:12.

36. Diegoli M, Grasso M, Favalli V, et al. Diagnostic work-up and risk stratification in X-linked dilated cardiomyopathies caused by dystrophin defects. J Am Coll Cardiol 2011;58:925-34.
37. Fayssoil A, Nardi O, Orlikowski D, et al. Cardiac asynchrony in Duchenne muscular dystrophy. J Clin Monit Comput 2013;27:587-9.
38. Bourke JP, Bueser T, Quinlivan R. Interventions for preventing and treating cardiac complications in Duchenne and Becker muscular dystrophy and X-linked dilated cardiomyopathy. Cochrane Database Syst Rev 2018;10:CD009068.
39. Chiang DY, Allen HD, Kim JJ, et al. Relation of cardiac dysfunction to rhythm abnormalities in patients with Duchenne or Becker muscular dystrophies. Am J Cardiol 2016;117:1349-54.
40. Segawa K, Komaki H, Mori-Yoshimura M, et al. Cardiac conduction disturbances and aging in patients with Duchenne muscular dystrophy. Medicine (Baltimore) 2017;96:e8335.
41. Fayssoil A, Ben Yaou R, Ogna A, et al. Left bundle branch block in Duchenne muscular dystrophy: prevalence, genetic relationship and prognosis. PLoS One 2018;13:e0190518.
42. Villa CR, Czosek RJ, Ahmed H, et al. Ambulatory monitoring and arrhythmic outcomes in pediatric and adolescent patients with Duchenne muscular dystrophy. J Am Heart Assoc 2015;5. pii: e002620.
43. Ishizaki M, Fujimoto A, Ueyama H, et al. Life-threatening arrhythmias in a Becker muscular dystrophy family due to the duplication of exons 3-4 of the dystrophin gene. Intern Med 2015;54:3075-8.
44. Takano N, Honke K, Hasui M, et al. A case of pacemaker implantation for complete atrioventricular block associated with Duchenne muscular dystrophy. No To Hattatsu 1997;29:476-80.
45. Fayssoil A, Orlikowski D, Nardi O, et al. Pacemaker implantation for sinus node dysfunction in a young patient with Duchenne muscular dystrophy. Congest Heart Fail 2010;16:127-8.
46. Kuru S, Tanahashi T, Matsumoto S, et al. Complete atrioventricular block in Duchenne muscular dystrophy. Rinsho Shinkeigaku 2012;52:685-7.
47. Stöllberger C, Finsterer J. Left ventricular synchronization by biventricular pacing in Becker muscular dystrophy as assessed by tissue Doppler imaging. Heart Lung 2005;34:317-20.
48. Andrikopoulos G, Kourouklis S, Trika C, et al. Cardiac resynchronization therapy in Becker muscular dystrophy. Hellenic J Cardiol 2013;54:227-9.
49. Fayssoil A, Nardi O, Annane D, et al. Successful cardiac resynchronisation therapy in Duchenne muscular dystrophy: a 5-year follow-up. Presse Med 2014;43:330-1.
50. Moore K, Ganesan A, Labrosciano C, et al. Sex differences in acute complications of cardiac implantable electronic devices: implications for patient safety. J Am Heart Assoc 2019;8:e010869.
51. Orellana-Barrios M, Sotello Aviles DA, Oyenuga O, et al. Implantable cardiac defibrillator infections: the emerging importance of Mycobacterium fortuitum. BMJ Case Rep 2017;2017. pii: bcr-2017-221934.
52. Zhu J, Yang Q, Pan J, et al. Cardiac resynchronization therapy-defibrillator pocket infection caused by Mycobacterium fortuitum: a case report and review of the literature. BMC Cardiovasc Disord 2019;19:53.
53. Fayssoil A, Lazarus A, Wahbi K, et al. Cardiac implantable electronic devices in tracheotomized muscular dystrophy patients: safety and risks. Int J Cardiol 2016;222:975-7.
54. Breucking E, Reimnitz P, Schara U, et al. Anesthetic complications. The incidence of severe anesthetic complications in patients and families with progressive muscular dystrophy of the Duchenne and Becker types. Anaesthesist 2000;49:187-95.
55. Froyshteter AB, Bhalla T, Tobias JD, et al. Pectoralis blocks for insertion of an implantable cardioverter defibrillator in two patients with Duchenne muscular dystrophy. Saudi J Anaesth 2018;12:324-7.
56. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2015;36:2793-867.
57. Lane JD, Whittaker-Axon S, Schilling RJ, et al. Trends in implantable cardioverter defibrillator and cardiac resynchronisation therapy lead parameters for patients with arrhythmogenic and dilated cardiomyopathies. Indian Pacing Electrophysiol J 2019;19:49-54.

How to cite this article: Palladino A, Papa AA, Morra S, et al. Are there real benefits to implanting cardiac devices in patients with end-stage dilated dystrophinopathic cardiomyopathy? Acta Myol 2019;38:1-7.