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

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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 myocytes. 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.
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 asthma, 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 inter-ventricular 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, anti-arrhythmic 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. Heart 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/m² 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 / m² > 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 | Ejection fraction in % (n.v. > 55) | EDV/m² (n.v. < 70) | Presence/type of arrhythmias or BBB and fibrosis | Type of device implanted |
|----------------|--------------|-----------------------------------|-------------------|------------------------------------------------|-------------------------|
| DMD n. 1       | 15y 10m      | 35                                | 166               | NSVT; postero-lateral fibrosis                    | ICD                     |
| DMD n. 2       | 13y          | 30                                | 108               | NSVT; postero-lateral fibrosis                    | ICD                     |
| DMD n. 3       | 13y 8m       | 33                                | 78                | None; postero-lateral fibrosis                    | ICD                     |
| DMD n. 4       | 11y 5m       | 40                                | 91                | AVB 2:1; LBBB; postero-lateral fibrosis           | CRT-D                   |
| DMD n. 5       | 12y 6m       | 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          | 30                                | 82                | AVB 3rd degree                                   | CRT-D                   |
| BMD n. 4       | 56y 4m       | 33                                | 91                | NSVT                                             | ICD                     |
| BMD n. 5       | 40y          | 40                                | 155               | NSVT                                             | ICD                     |
| BMD n. 6       | 45y 2m       | 28                                | 127               | NSVT                                             | ICD                     |
| BMD n. 7       | 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      | 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; m² = height in meters, elevated to the square; NSVT: Not sustained Ventricular Tachycardia; AVB: atrio-ventricular block; LBBB: Left Bundle Branch Block; RBBB: Right Bundle Branch Block; VEB: Ventricular ectopic beats.
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 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

### 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; m²: height in meters, elevated to the square.
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**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 cons 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.

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