Cardiac involvement in Becker muscular dystrophy

Josef Finsterer MD PhD¹, Claudia Stöllberger MD²

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The present review gives an overview of the clinical and subclinical manifestations of cardiac involvement (CI) in Becker muscular dystrophy (BMD), its pathophysiological background, diagnostic possibilities and therapeutic options for CI in BMD patients and carriers. CI may be subclinical or symptomatic. Up to 100% of patients develop subclinical CI. The onset of symptomatic CI is usually in the third decade of life, rarely in the first decade. One-third of patients develop dilative cardiomyopathy with concomitant heart failure. In BMD patients, CI manifests as electrocardiographic abnormalities, hypertrophic cardiomyopathy, dilation of the cardiac cavities with preserved systolic function, dilative cardiomyopathy or cardiac arrest. There is no correlation between CI and the severity of myopathy. CI is more prominent in patients than carriers. As soon as the diagnosis of BMD is established, a comprehensive cardiac examination should be performed. Because CI in BMD is progressive and adequate therapy is available, cardiac investigations need to be regularly repeated. If CI in BMD is recognized early, appropriate therapy may be applied early, resulting in a more favourable outcome.

Key Words: *Dystrophinopathy; Echocardiography; Electrocardiography; Heart; Muscular dystrophy; Myocardium; X-linked inheritance*

Cardiac involvement (CI) is a frequent feature of Becker muscular dystrophy (BMD) (1-3). CI in BMD may be subclinical (asymptomatic) and detectable only by instrumental investigations, or symptomatic. Asymptomatic CI occurs in most cases, and up to one-third of patients develop dilative cardiomyopathy (dCMP) with concomitant heart failure (4,5). The degree of symptomatic CI in BMD varies greatly between no (or hardly any) cardiac abnormalities to severe arrhythmias, hypertrophic cardiomyopathy (hCMP), dCMP, heart failure or sudden cardiac death (3,6). The present review aims to give an overview of the recent developments and current knowledge about the clinical manifestations of CI, its pathophysiological background, diagnostic possibilities, the frequency of CI and the currently available therapeutic options for CI in BMD.

Extracardiac manifestations of BMD

BMD is allelic to Duchenne muscular dystrophy (DMD) and occurs at one-tenth the frequency of DMD (1). BMD shows a more heterogeneous clinical picture than DMD and has a milder course (7,8). During the first decade of life, patients are usually free of clinical manifestations except for elevated creatine kinase (CK). Between 10 and 15 years of age, a gait abnormality, with side-to-side motion of the hips ('waddling gait'), occurs. Between 15 and 20 years of age, weakness steadily progresses, and pseudohypertrophy of the calves develops. During the third decade, patients develop difficulties in climbing stairs and performing manual work. Cardiac abnormalities start to arise during this period. There are also patients with elevated CK, muscle cramps, exertional myalgia, episodic myoglobinuria, and calf hypertrophy but without muscle weakness (2).

L'atteinte cardiaque en présence d'une dystrophie de Becker

La présente analyse donne un aperçu des manifestations cliniques et subcliniques de l'atteinte cardiaque (AC) dans la dystrophie de Becker (DB), de ses antécédents physiopathologiques, des possibilités diagnostiques et des possibilités thérapeutiques une l'AC chez les patients ou les porteurs de la DB. L'AC peut être subclinique ou symptomatique. Jusqu'à 100 % des patients développent une AC subclinique. D'ordinaire, l'apparition de l'AC symptomatique a lieu dans la trentaine, rarement dans les dix premières années de vie. Le tiers des patients développent une myocardiopathie dilatée accompagnée d'une insuffisance cardiaque. Chez les patients atteints de DB, l'AC se manifeste sous forme d'anomalies électrocardiographiques, d'une myocardiopathie hypertrophique, d'une dilatation des cavités cardiaques avec préservation de la fonction systolique, d'une myocardiopathie dilatée ou d'un arrêt cardiaque. Il n'existe pas de corrélation entre l'AC et la gravité de la myopathie. L'AC est plus marquée chez les patients que chez les porteurs. Dès que le diagnostic de DB est posé, il faudrait procéder à un examen cardiaque complet. Puisque l'AC secondaire à la DB est évolutive et qu'il existe une thérapie pertinente, il faut reprendre régulièrement les explorations cardiaques. Si l'AC secondaire à la DB est dépistée tôt, on peut entreprendre une thérapie pertinente rapidement, ce qui s'associe à une issue plus favorable.

BMD is due to deletions, duplications or point mutations in the dystrophin gene, which is the reason why, histopathologically, the muscle dystrophin isoform is reduced in amount or has an abnormal size (patchy staining of dystrophin) (7). Disease that develops earlier is said to be more severe and associated with mutations in the amino terminal (5' end), including the promoter region. Disease, which develops later, is said to be milder and associated with the preservation of the carboxy terminal. Approximately one-third of patients cannot be categorized under these terms (9-11). There is no specific genotype linked to the degree of CI in BMD (12), although this was previously believed.

BMD not only manifests in the skeletal muscle and myocardium, but also in the brain. Among 53 BMD patients, epilepsy was diagnosed in four (7.5%) (13). In some patients, intelligence may be below average (14). In some patients, BMD may be associated with macroglossia and red-green colour blindness (15).

Pathoanatomical background of CI in BMD

The pathoanatomical background of CI in BMD includes the replacement of dysfunctional cardiomyocytes and the intracardiac impulse generation and conduction system by fibrous tissue or fat (3). Extensive myocardial fibrosis in an early stage of the disease may be a surrogate marker for poor clinical outcomes (3).

Cardiac manifestations of BMD

CI in BMD is rarely completely absent throughout life or remains subclinical throughout life. Usually, CI remains asymptomatic for a longer period and becomes symptomatic thereafter. Asymptomatic CI may

¹Krankenanstalt Rudolfstiftung; ²Second Medical Department, Vienna, Austria

Correspondence: Dr Josef Finsterer, Postfach 20, 1180 Vienna, Austria. Telephone 43-1-71165, fax 43-1-4781711, e-mail ffigis1@yahoo.de

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TABLE 1
Instrumental investigations to diagnose cardiac involvement in Becker muscular dystrophy

Investigation	Finding
Blood chemical investigations	
CK, CK-MB	Myocardial cell damage
Brain natriuretic peptide	Heart failure
Electrocardiogram	Rhythm abnormalities, myocardial damage
Ambulatory electrocardiogram	Vegetative impairment
Echocardiography	hCMP, dCMP, ventricular dysfunction
Backscatter analysis	Myocardial fibrosis, arrhythmias
Thallium scintigraphy	Reduced myocardial perfusion
Technetium ventriculography	Systolic and diastolic dysfunction
MIBG-SPECT	Sympathetic hyperactivity
Cardiac magnetic resonance imaging	hCMP, dCMP, LVHT, fibrosis
Magnetic resonance spectroscopy	Reduced dystrophin expression
Endomyocardial biopsy	Fibrosis, LVHT, atrophic myocardiocytes

CK Creatine kinase; dCMP Dilative cardiomyopathy; hCMP Hypertrophic cardiomyopathy; LVHT Left ventricular hypertrabeculation; MIBG Meta-iodobenzylguanidine; SPECT Single photon emission computed tomography

manifest as asymptomatic arrhythmias, other nonspecific electrocardiogram (ECG) abnormalities or asymptomatic hCMP. Symptomatic CI may manifest as palpitations, dizziness, syncope, dyspnea at rest or during exercise, leg edema or coughing. There is no correlation between CI and the severity of skeletal muscle manifestations (14,16). There are also no correlations between the severity of CI and the deleted exons (4,17).

Asymptomatic and symptomatic CI may be detected by clinical cardiac examination, blood chemical investigations, ECG showing impulse generation or impulse conduction abnormalities, ambulatory ECG (AECG), echocardiography revealing hCMP, dilation of the cardiac cavities with preserved systolic function, dCMP, or left ventricular hypertrabeculation, myocardial scintigraphy, positron emission tomography (PET), cardiac magnetic resonance imaging (cMRI), magnetic resonance spectroscopy (MRS) or endomyocardial biopsy (Table 1).

DIAGNOSIS OF CI IN BMD

History and physical examination

BMD patients with CI may complain about palpitations, dizziness, syncope, dyspnea at rest or during exercise, leg edema or coughing. A clinical cardiac examination may reveal rhythm abnormalities, pulmonary rales, arrhythmic heart rate, leg edema, sore liver or neck vein distension. In a study of 67 BMD patients (18), heart failure was found in 3%. In a study of 59 BMD patients (19), two patients presented with exertional dyspnea before the onset of skeletal muscle manifestations. In a study of 19 patients with BMD (20), six of whom were younger than 22 years of age, two had exertional dyspnea. In a report (21) of two brothers with a deletion of exon 13, one developed heart failure at nine years of age, while the older brother was asymptomatic. The different phenotypes were attributed to the amount of dystrophin transcript in the younger brother, which was 20% of that of the older brother. In one patient, CI manifested as acute pulmonary edema (22).

Blood chemical investigations

Although CK and CK-MB may be elevated in some cases, determination of CK or CK-MB is of little help in diagnosing CI in BMD. Whether the determination of troponin T or troponin I is more helpful in this respect remains speculative, because no systematic studies on this matter have been carried out thus far. In a controlled study of 12 patients (23), prothrombin fragments 1 and 2 (F1+2) and

TABLE 2
Electrocardiogram abnormalities in Becker muscular dystrophy patients

Abnormality	References
Sinus tachycardia	18,27,33,37,39
Atrial fibrillation	28,36
Atrioventricular block type I	9
Atrioventricular block type III	34,35
Short PQ	20,27
Left anterior hemiblock	9
IRBBB or CRBBB	9,14,20,28,29,33
ILBBB or CLBBB	9,20
Prominent Q wave in leads I, II, III, aVL, aVF, V6	4,7,9,20,31,81
Tall QRS	4,7,9,33
Tall R wave in lead V1	4,7,9,20,81
Small R wave in leads I, aVL, V1, V6	4
Abnormal ST-T wave	9,31,33
Increased corrected QT and QT dispersion	32
Ventricular arrhythmias	37

IRBBB/CRBBB Incomplete/complete right bundle branch block; ILBBB/CLBBB Incomplete/complete left bundle branch block

antithrombin III were significantly increased. Ejection fraction (EF) was reduced in 50% of patients and left ventricular dilation was present in 41%. F1+2 and antithrombin III were negatively correlated with EF. In a controlled study (24) of 11 patients investigated for plasma levels of fibrinogen degradation products and D-dimer, both were increased in four patients each. The results were interpreted as enhanced coagulation and fibrinolysis secondary to muscle dysfunction (24). It has recently been reported (25) that brain natriuretic peptide is reduced in BMD patients, but these findings have been challenged (26).

Standard 12-lead or signal-averaged ECG

ECG abnormalities frequently found include sinus tachycardia at rest, atrial fibrillation (18,27,28), PQ shortening without delta wave, suggesting atriofascicular bands or accelerated conduction of the atrioventricular (AV) node (27), intraventricular conduction delay with QRS broadening (14,28,29) and a hypertrophy pattern (Table 2) (30). In a study of 68 BMD patients (31), ECG evidence of myocardial damage was found in 15% and arrhythmias in 7%. In a study of 67 patients (18), 20% had sinus tachycardia at rest or other ECG abnormalities. Among 48 patients with 'mild dystrophinopathy' (9), 54% had ECG abnormalities, 17% had an R/S ratio greater than 1 in lead V1, 15% had incomplete right bundle branch block (IRBBB), 10% had incomplete or complete left bundle branch block, 4% had ST-T wave abnormalities, 2% had AV block type I, 2% had left anterior hemiblock, 2% had an abnormal Q wave and 2% had an abnormal QS complex. In a study of 31 patients (16), ECG abnormalities were found in 68%. Life-threatening ventricular arrhythmias were detected in four patients (16). In a study of 30 patients (32), the corrected QT interval and QT dispersion were significantly increased. The authors recommended monthly AECGs if the QT dispersion increases to more than 100 ms or if there are runs. They also recommended amiodarone in such cases and, if ineffective, the use of an implantable cardioverter defibrillator. In a study of 21 patients (7), there were prominent Q waves in leads II, III, aVF, V6 or a tall R wave in lead V1, suggesting myocardial injury in the posterobasal and lateral walls. In another study of 21 patients (4), 90% showed a decreased R wave or prominent Q wave in leads I, aVL and V6, 47% had a prominent R1 wave in lead V1, and 37% had a prominent Q wave in leads II, III and aVF (4), suggesting that the lateral wall is most prominently affected in BMD. In a study of 19 patients (20), the ECG was

abnormal in 74% of patients and an intraventricular conduction delay was present in 42%. In a study of six patients (14), ECG abnormalities included IRBBB and intraventricular conduction delay. In a 10-year study of five patients (33), sinus tachycardia, ST elevation, IRBBB and, in one patient, tall R and S waves were found (33). In some patients, CI may manifest as a complete AV block early in life (34) or late in life (35). In one case (36), atrial fibrillation was observed resulting in stroke from cardioembolism. Overall, the ECG is frequently abnormal in BMD patients, and arrhythmias may contribute to these patients' reduced life expectancy.

AECG

Whether there is primary autonomic dysfunction in BMD is controversial (37,38). In a controlled study of 20 patients (37), an AECG revealed abnormal indexes of heart rate variability. The total number of premature ventricular beats was increased and inversely related to fractional shortening (FS) and EF. In addition, the corrected QT interval was inversely related to the FS. These findings were interpreted as autonomic imbalance in BMD, characterized by sympathetic predominance over parasympathetic activity, possibly accounting for sinus tachycardia and, thus, the increased number of ventricular arrhythmias, even in the absence of overt CMP (37). Adrenergic hyperactivity was regarded as a primary manifestation of the disease, and not as a reaction to other cardiac abnormalities (37). In another study of 20 patients (38), applying a battery of six tests for assessing autonomic functions did not show autonomic dysfunction in any patients. AECGs may also demonstrate sinus tachycardia (39).

Echocardiography

Depending on the stage of the disease, echocardiography may show mild to severe myocardial thickening with normal size of the cardiac cavities and preserved systolic function (6,12,40). hCMP usually evolves into dCMP within varying periods of time, showing dilation of the cardiac cavities, global hypokinesia or other wall motion abnormalities, and normal or reduced systolic function (6,30). Dilation becomes more prominent with age (7). In two patients (41,42), left ventricular hypertrabeculation, also known as noncompaction, was shown on echocardiography and cMRI. Echocardiography may also reveal apical thrombi (12,28) or secondary valve insufficiency. Severe systolic dysfunction, requiring heart transplantation, may even be the presenting manifestation of BMD (18,43). There are no reports on stress echocardiography in BMD available.

Among 48 patients, 69% had right ventricular dilation alone or in combination with left ventricular abnormalities, 35% had isolated left ventricular dilation, 29% reduced EF and 21% had left ventricular wall motion abnormalities (9,10). Fifteen per cent had CMP with episodic myoglobinuria and 19% had CMP without skeletal muscle weakness (9,10). Overall, echocardiography was abnormal in 65% of these patients. In a study of 31 BMD patients (16), echocardiographic abnormalities were reported in 62% and right ventricular involvement was detected in 52%. Among 29 patients nine to 57 years of age, one had clinical signs of heart failure and 45% had ECG abnormalities. In 17% of patients with an abnormal ECG, dCMP was diagnosed. None of the patients with a normal ECG had echocardiographic abnormalities (44). In a study of 21 BMD patients (4), mitral regurgitation was observed in 67% of those with heart failure. Among 19 patients (20), left ventricular dilation was present in 37% and 63% had FS of less than 27% (20). In one patient (45), dCMP with severe hypokinesia and reduced EF was associated with a deletion of exon 4 of the dystrophin gene.

Tissue Doppler imaging

In one study (46), myocardial ultrasound tissue characterization by integrated backscatter revealed subclinical myocardial fibrosis. Myocardial dysfunction could be reliably detected in another study of BMD patients (47) with tissue Doppler imaging.

Thallium scintigraphy

In an uncontrolled study of 14 patients (48), 201-thallium scintigraphy revealed a tracer uptake defect, which was positively correlated with left ventricular function. Dipyridamole-induced, nonreversible uptake defects were found in 50% of patients, all with depressed left ventricular function (48). All patients with subclinical CI had defects on thallium scintigraphy (48). In a study of 11 patients (49) with thallium scintigraphy and technetium 99m human serum albumin multi-gated radionuclide ventriculography, decreased systolic and diastolic function were observed in most cases (49). In two brothers with BMD, 48 and 39 years of age, thallium scintigraphy showed reduced perfusion in the anterolateral, septal and apical left ventricular walls (50).

Iodine-123 15-(p-iodophenyl)-3(R,S)-methylpentadecanoic acid scintigraphy

In one study of four patients (51), iodine-123 (I-123) 15-(p-iodophenyl)-3(R,S)-methylpentadecanoic acid (BMIPP) scintigraphy showed reduced regional uptake of BMIPP in all of them. All patients had abnormal ECG. Two of the patients had regional wall motion abnormalities.

Metaiodobenzylguanidine single photon emission computed tomography

In one patient (52), 201-thallium metaiodobenzylguanidine single photon emission computed tomography showed nonreversible myocardial perfusion defects in the anterior, inferoposterior and apical walls. I-123-metaiodobenzylguanidine single photon emission computed tomography depicted hyperactivity of the myocardial sympathetic nervous system. Only a small region of decreased sympathetic innervation was found (52).

PET

In a controlled study of eight patients (53), the coronary vasodilative reserve was normal as determined by PET with oxygen-15-labelled water. In one patient with severe left ventricular dilation (54), PET studies showed globally poor perfusion (nitrogen-13 ammonia tracer) and metabolism (fluorine-18 fluorodeoxyglucose tracer).

cMRI

cMRI has been proved to be a valid, noninvasive method for obtaining anatomical and structural information on the heart. With gadolinium-enhanced cMRI, it is also possible to identify, localize and characterize areas of myocardial fibrosis (3). Serial cMRI investigations may be helpful to recognize and monitor the development of myocardial fibrosis early (3). In one case (55), contrast-enhanced cMRI revealed subendocardial late gadolinium enhancement, resembling myocardial infarction. Coronary angiography, however, was normal in this patient, and the finding was attributed to subendocardial fibrosis, which has been repeatedly reported on autopsy.

MRS

In a study of 13 patients using phosphorus-31 MRS (56), the cardiac phosphocreatine (PCr) to ATP ratio was reduced, revealing the reduction of high-energy phosphate-containing metabolites in their myocardium. None of the echocardiographic indexes were correlated with the PCr/ATP ratio, which explains why the reduced PCr/ATP ratio was attributed to the altered dystrophin expression and the development of CMP.

Endomyocardial biopsy

At an early stage of the disease, endomyocardial biopsy may show hypertrophy of the myocardiocytes and endocardial or interstitial fibrosis (6). In the later stages of the disease, endomyocardial fibrosis prevails (6). In addition, there may be cytoplasmic lipofuscinosis, focal lymphocytic infiltration, huge, pleomorphic, bizarre myonuclei of variable size, shape and staining, and focal necrosis (8,12,28,30,57). No characteristic histological features distinguishing BMD from other

cardiac diseases have ever been described (58). Immunohistochemical staining for dystrophin may reveal continuous, discontinuous or absent membrane immunoreactivity for dystrophin along the sarcoplasmic membrane (6,58). Discontinuous immunoreactivity for cardiac dystrophin is characteristic of BMD. Absent immunoreactivity is associated with more severe cardiac dysfunction (58). Concerning the question of immunoreactivity, recent studies failed to demonstrate the value of assessing every endomyocardial biopsy specimen from dCMP patients for dystrophin (58).

CI preceding the onset of skeletal muscle manifestations is rare. The search for dystrophinopathy on endomyocardial specimens seems justified only in cases with high clinical suspicion or a family history of CMP and elevated CK (11).

Explanted hearts and autopsy

Pathology studies of explanted hearts have shown normal valvular leaflets, normal coronary arteries, but thickening of the left ventricular myocardium (30). One examination of an explanted heart showed patchy staining of dystrophin (57). Ultrastructural examinations showed foci of disorganization of myofibrils and Z bands, foci of severe clumping of intercalated discs and severe pericellular fibrosis. The sarcoplasmic reticulum and mitochondria showed dilation and disorganization (57). In another study of explanted hearts (59), utrophin appeared to be highly upregulated.

FREQUENCY OF CI IN BMD

In a study of 68 patients (31), subclinical CI was found in 67% of patients younger than 16 years of age. Subclinical CI decreased to 30% in patients older than 40 years of age. Symptomatic CMP was present in 15% younger than 16 years of age. These figures rose steadily throughout adulthood, reaching 73% by the ages of older than 40 years. As in DMD, dCMP was more frequent than hCMP. Symptomatic CI was more frequent in ambulatory patients than in patients with initial or wheelchair-bound stage disease, with severe muscle involvement. Reduced cardiac workload was considered to be responsible for the improved cardiac status in wheelchair-bound patients (31). In a study of 67 patients (18), only 20% showed CI. In a study of 27 patients (17), 71% had ECG abnormalities, 33% had dCMP with or without heart failure, 22% had borderline echocardiographic abnormalities, 22% became symptomatic and 15% died from heart failure. In a study of 14 patients (60), nonspecific myocardial involvement was described in 80%.

BMD CARRIERS

Phenotype

In a study of 56 carriers (61), 12% presented with muscle weakness, which was usually recognized by the individual, but it was mild and not substantially affecting daily activities. Depending on age and location of the mutation, CK was increased in 30% to 62% of carriers (18,29,62,63). Up to 26% of asymptomatic BMD carriers have dystrophin-negative muscle fibres (64).

CI

Symptomatic and asymptomatic CI in carriers is highly variable. In a cross-sectional study of 56 carriers (61), the prevalence of cardiac abnormalities on ECG and echocardiography was 18%. Only 7% had dCMP, defined as left ventricular dilation and decreased systolic function (61). In a study of 51 carriers (31), CI was found in 43 individuals. CI was symptomatic in 16 of these carriers, nine had dCMP and 18 had arrhythmias. In a study of 44 carriers, 27% had at least one ECG abnormality and 9% had at least two. Echocardiography was abnormal in 34%. Sixteen per cent had a dilated left ventricle but none had dCMP (29,65,66). In a study of 23 female carriers six to 16 years of age (67), none showed abnormalities on clinical examination, ECG or echocardiography. In a study of 23 carriers (68), CI was found in 63% of individuals. A CMP was found in 26% and minor

TABLE 3
Therapy of cardiac involvement in Becker muscular dystrophy

Therapy	Indication
Discontinuation of drugs	In case of QT prolongation
Avoidance of succinylcholine and volatile anesthetics	To prevent malignant hyperthermia or sudden cardiac arrest
Angiotensin-converting enzyme inhibitor	Low systolic function, sympathetic hyperactivity
Beta-blockers	Tachycardia
Digitalis	Tachycardic atrial fibrillation
Amiodarone	Tachycardic atrial fibrillation
Diuretics	Systolic dysfunction
Oral anticoagulation	Atrial fibrillation, intracardiac thrombus
Electrical cardioversion	Atrial fibrillation <1 year
Pacemaker	Atrioventricular block type III, bradycardia
Implantable cardioverter defibrillator	Symptomatic ventricular rhythm abnormalities
Biventricular pacing	Heart failure
High-frequency catheter ablation	Supraventricular re-entry tachycardia
Heart transplantation	Intractable heart failure

signs of CI were found in another 39%. Echocardiographic indexes were all within normal limits. CI was subclinical in 39% (68). In a study of 15 carriers (65), echocardiography was abnormal in 34%, dCMP was found in none, but left ventricular dilation was present in 16%. In a study of 10 carriers (56), phosphorus-31 MRS revealed an impaired energetic state of the myocardium, but the findings were independent of the echocardiographic indexes.

Overall, there is symptomatic and asymptomatic CI in BMD carriers, but it is age-dependent and highly variable. CI does not appear to develop before 16 years of age and may remain subclinical with advancing age in up to two-thirds of cases. CI in BMD carriers manifests as ECG abnormalities in two-fifths of individuals or as dCMP in up to one-fifth. There is no correlation between genotype and CI in BMD carriers (65).

TREATMENT OF CI IN BMD

Therapy of CI in BMD is not at variance with therapy of cardiac disease due to other causes (Table 3).

Prophylaxis

Medication that induces or enhances arrhythmias or heart failure needs to be strictly avoided. In particular, nonsteroidal anti-inflammatory drugs, such as diclofenac and mephenamine, may induce or deteriorate heart failure (69). In case of QT prolongation, any medication known to prolong the QT interval should be discontinued.

Drugs

If there is atrial fibrillation, patients should be anticoagulated. If atrial fibrillation is tachycardic, digitalis, amiodarone, or beta-blockers should be added. In cases of intracardiac thrombus formation, anticoagulation is indicated. Systolic dysfunction may require high-dose angiotensin-converting enzyme (ACE) inhibitors, diuretics and, in cases of tachycardia, beta-blockers in low dosages. Diastolic dysfunction may respond to ACE inhibitors. If the autonomic nervous system is affected, manifesting as sinus tachycardia, deprivation of the circadian rhythm or reduced heart rate variability, ACE inhibitors in combination with beta-blockers are recommended to reduce the cardiac autonomic nervous imbalance (39). Also, ACE inhibitors alone can reduce cardiac sympathetic hyperactivity (52).

TABLE 4
Becker muscular dystrophy patients who had undergone orthotopic heart transplantation

Author (reference)	Number of patients	Outcome
Patane et al 2006 (72)	1	Not indicated
Srinivasan et al 2005 (5)	1	Excellent
Ruiz-Cano et al 2003 (82)	3	Good
Leprince et al 2002 (83)	1	Favourable
Melacini et al 2001 (84)	Not indicated	Not indicated
Finsterer et al 1999 (43)	1	Excellent
Jones et al 1998 (11)	1	Good
Fiocchi et al 1997 (85)	1	Good
Bittner et al 1995 (86)	1	Good
Piccolo et al 1994 (12)	1	Favourable
Orlov et al 1994 (28)	1	Not indicated
Rees et al 1993 (87)	Not indicated	Good
Quinlivan et al 1992 (88)	1	Good
Sakata et al 1990 (81)	1	Not indicated
Donofrio et al 1989 (57)	1	Favourable
Casazza et al 1988 (30)	1	Good

In a study of 10 patients (70), treatment with recombinant human growth hormone for three months resulted in a hypertrophic myocardial response, associated with significant reduction of brain natriuretic peptide serum levels and slight improvement in systolic function, but no improvement of muscle performance.

Instrumental therapy

Electrical cardioversion may be tried if atrial fibrillation lasts less than one year and if the left atrial diameter is smaller than 50 mm. In cases of bradycardia, intractable to drugs, or AV block type III, a pacemaker is indicated. If there are symptomatic ventricular rhythm abnormalities, an implantable cardioverter defibrillator may be required. Supraventricular re-entry tachycardia may be treated with high-frequency catheter ablation. In one patient (71), biventricular pacing was used to treat heart failure from dCMP. In this particular patient, biventricular pacing resulted in a significant improvement of heart failure (71).

Intractable chronic heart failure may necessitate heart transplantation. Quite a number of patients have successfully undergone heart transplantation (Table 4) (5,72). Candidates are selected from a base of heart failure patients who are usually in New York Heart Association functional class III or IV (5).

General anesthesia

To avoid hyperthermia-like reactions (rhabdomyolysis, dark urine, hyperkalemia, hypocalcemia or trismus) in BMD patients and carriers during general anesthesia, succinylcholine and volatile anesthetics should be avoided (73-75). Malignant hyperthermia-like reactions should also be prevented because they may be associated with heart failure (75) or even sudden cardiac arrest (74). In a six-year-old patient (74), general anesthesia for dental treatment triggered rhabdomyolysis and sudden cardiac arrest. In a five-year-old patient (76), cardiac arrest occurred following the administration of a single dose of succinylcholine, which was assumed to have induced rhabdomyolysis with hyperkalemia.

COURSE AND OUTCOME OF CI IN BMD

CI in BMD may be totally absent throughout life, may remain subclinical throughout life or for long periods, or may become symptomatic. Overall, CI is the rule rather than the exception in BMD (17). The onset of symptomatic CI is highly variable, but most frequently

occurs in the third decade of life. In some cases, however, it may occur in the first decade of life (39). In a study of 14 patients (14), the time of onset ranged between four and 41 years of age (14). The median age of onset of FS of less than 25% was reported to be 30 years (39). In a study of 68 BMD patients (31), all showed subclinical or symptomatic CI by 30 years of age. Left ventricular dilation may begin at any time during the course of the disease. In a study of 27 patients (17), the proportion of patients with ECG abnormalities increased from 44% to 71% over 12 years; 22% became symptomatic and four died of heart failure (17). The rate of progression is unpredictable. In some cases, hCMP may rapidly progress to dCMP (6). A substantial proportion of patients develop incapacitating and life-threatening CMP (17). The most common causes of death in CI are arrhythmias or heart failure. In a study of 21 patients (4), one patient with polymorphic ventricular arrhythmias died during the observational period. Because of the progression of CI in BMD in annual clinical cardiac examinations, ECG and echocardiography are recommended as soon as CI has become symptomatic.

CI may precede affection of the skeletal muscles even by years (43,77,78). Rapidly progressive heart failure without apparent clinical signs of neuromuscular disease has been reported in a 38-year-old patient with rhabdomyolysis, which was complicated by renal failure (78), and in a 33-year-old patient in whom dCMP evolved into severe heart failure, necessitating heart transplantation six years before affecting the skeletal muscle (43). Particularly in such cases, the correct diagnosis is frequently delayed until skeletal muscle is also involved. In cases with rapidly progressive heart failure but without overt skeletal muscle involvement, a dystrophinopathy should be considered, and patients should be referred to the neurologist for further evaluation. In such cases, the family history may be helpful, which may show affected male relatives or manifesting female carriers. Severe heart failure necessitating heart transplantation may be also associated with only mild skeletal muscle involvement (30). The onset and course of CI may be largely variable, even in monozygotic triplets (79).

CONCLUSIONS

The present review shows that there is CI in BMD patients and carriers, and it is much more prominent in patients than in carriers. CI in patients manifests as arrhythmias, other ECG abnormalities, hCMP, dilation of the cardiac cavities with preserved systolic function, dCMP, heart failure or sudden cardiac death. CI is not well correlated with the severity of skeletal muscle involvement (58), as confirmed in cases in which CI preceded the onset of skeletal muscle manifestation by years, and in cases of patients who were wheelchair-bound but did not develop CI. Management of CI in BMD requires the referral of all BMD patients to the cardiologist as soon as the diagnosis has been established. CI in BMD requires adequate treatment, depending on the type of cardiac abnormality. Overall, the prognosis of CI is favourable in the majority of BMD patients if CI is recognized early and adequately treated (42,80).

REFERENCES

- Emery AE. The muscular dystrophies. *Lancet* 2002;359:687-95.
- Finsterer J, Stöllberger C. The heart in human dystrophinopathies. *Cardiology* 2003;99:1-19.
- Süselbeck T, Haghi D, Neff W, Borggreffe M, Papavassiliu T. Midwall myocardial fibrosis in Becker-Kiener muscular dystrophy. *Z Kardiol* 2005;94:465-8.
- Saito M, Kawai H, Akaike M, Adachi K, Nishida Y, Saito S. Cardiac dysfunction with Becker muscular dystrophy. *Am Heart J* 1996;132:642-7.
- Srinivasan R, Hornyak JE, Badenhop DT, Koch LG. Cardiac rehabilitation after heart transplantation in a patient with Becker's muscular dystrophy: A case report. *Arch Phys Med Rehabil* 2005;86:2059-61.
- Park OY, Ahn Y, Park WS, et al. Rapid progression from hypertrophic cardiomyopathy to heart failure in a patient with Becker's muscular dystrophy. *Eur J Heart Fail* 2005;7:684-8.

7. Saito M, Kawai H, Adachi K, Akaike M. [Clinical feature and mechanism of cardiac failure in patients with Becker muscular dystrophy.] *Rinsho Shinkeigaku* 1994;34:134-40.
8. Yoshida K, Ikeda S, Nakamura A, et al. Molecular analysis of the Duchenne muscular dystrophy gene in patients with Becker muscular dystrophy presenting with dilated cardiomyopathy. *Muscle Nerve* 1993;16:1161-6.
9. Angelini C, Fanin M, Freda MP, et al. Prognostic factors in mild dystrophinopathies. *J Neurol Sci* 1996;142:70-8.
10. Angelini C, Fanin M, Pegoraro E, Freda MP, Cadaldini M, Martinello F. Clinical-molecular correlation in 104 mild X-linked muscular dystrophy patients: Characterization of sub-clinical phenotypes. *Neuromuscul Disord* 1994;4:349-58.
11. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 22-1998. A 22-year-old man with a cardiac transplant and creatine kinase elevation. *N Engl J Med* 1998;339:182-90.
12. Piccolo G, Azan G, Tonin P, et al. Dilated cardiomyopathy requiring cardiac transplantation as initial manifestation of Xp21 Becker type muscular dystrophy. *Neuromuscul Disord* 1994;4:143-6.
13. Goodwin F, Muntoni F, Dubowitz V. Epilepsy in Duchenne and Becker muscular dystrophies. *Eur J Paediatr Neurol* 1997;1:115-9.
14. Sakata C, Yamada H, Sunohara N, Arahata K, Nonaka I. [Cardiomyopathy in Becker muscular dystrophy.] *Rinsho Shinkeigaku* 1990;30:952-5.
15. Fu HD, Tang XF, Guo YP. Becker muscular dystrophy. *Chin Med J (Engl)* 1989;102:373-7.
16. Melacini P, Fanin M, Danieli GA, et al. Cardiac involvement in Becker muscular dystrophy. *J Am Coll Cardiol* 1993;22:1927-34.
17. Hoogerwaard EM, de Voogt WG, Wilde AA, et al. Evolution of cardiac abnormalities in Becker muscular dystrophy over a 13-year period. *J Neurol* 1997;244:657-63.
18. Emery AE, Skinner R. Clinical studies in benign (Becker type) X-linked muscular dystrophy. *Clin Genet* 1976;10:189-201.
19. Comi GP, PELLE A, Bresolin N, et al. Clinical variability in Becker muscular dystrophy. Genetic, biochemical and immunohistochemical correlates. *Brain* 1994;117:1-14.
20. Steare SE, Dubowitz V, Benatar A. Subclinical cardiomyopathy in Becker muscular dystrophy. *Br Heart J* 1992;68:304-8.
21. Ishigaki C, Patria SY, Nishio H, Yoshioka A, Matsuo M. Early cardiac failure in a child with Becker muscular dystrophy is due to an abnormally low amount of dystrophin transcript lacking exon 13. *Acta Paediatr Jpn* 1997;39:685-9.
22. Borgeat A, Goy JJ, Sigwart U. Acute pulmonary edema as the inaugural symptom of Becker's muscular dystrophy in a 19-year-old patient. *Clin Cardiol* 1987;10:127-9.
23. Porreca E, Guglielmi MD, Uncini A, et al. Haemostatic abnormalities, cardiac involvement and serum tumor necrosis factor levels in X-linked dystrophic patients. *Thromb Haemost* 1999;81:543-6.
24. Saito T, Takenaka M, Miyai I, et al. Coagulation and fibrinolysis disorder in muscular dystrophy. *Muscle Nerve* 2001;24:399-402.
25. Demachi J, Kagaya Y, Watanabe J, et al. Characteristics of the increase in plasma brain natriuretic peptide level in left ventricular systolic dysfunction, associated with muscular dystrophy in comparison with idiopathic dilated cardiomyopathy. *Neuromuscul Disord* 2004;14:732-9.
26. Stöllberger C, Finsterer J. Clinical relevance of plasma brain natriuretic peptide in patients with Duchenne and Becker muscular dystrophy. *Neuromuscul Disord* 2005;15:513-4.
27. Mansur AJ. A 15-year-old male with progressive muscular dystrophy of the Becker type and severe heart failure. *Arq Bras Cardiol* 2000;74:360-4.
28. Orlov YS, Brodsky MA, Allen BJ, Ott RA, Orlov MV, Jay CA. Cardiac manifestations and their management in Becker's muscular dystrophy. *Am Heart J* 1994;128:193-6.
29. Hoogerwaard EM, Schouten Y, van der Kooij AJ, Gorgels JP, de Visser M, Sanders GT. Troponin T and troponin I in carriers of Duchenne and Becker muscular dystrophy with cardiac involvement. *Clin Chem* 2001;47:962-3.
30. Casazza F, Brambilla G, Salvato A, Morandi L, Gronda E, Bonacina E. Cardiac transplantation in Becker muscular dystrophy. *J Neurol* 1988;235:496-8.
31. Nigro G, Comi LI, Politano L, et al. Evaluation of the cardiomyopathy in Becker muscular dystrophy. *Muscle Nerve* 1995;18:283-91.
32. Nigro G, Nigro G, Politano L, et al. Is the value of QT dispersion a valid method to foresee the risk of sudden death? A study in Becker patients. *Heart* 2002;87:156-7.
33. Finsterer J, Stöllberger C, Blazek G, Kunafer M, Prager E. Cardiac involvement over 10 years in myotonic and Becker muscular dystrophy and mitochondrial disorder. *Int J Cardiol* 2007;119:176-84.
34. Akdemir R, Ozhan H, Gunduz H, et al. Complete atrioventricular block in Becker muscular dystrophy. *NZ Med J* 2004;117:U895.
35. Quinlivan R, Ball J, Dunckley M, Thomas DJ, Flinter F, Morgan-Hughes J. Becker muscular dystrophy presenting with complete heart block in the sixth decade. *J Neurol* 1995;242:398-400.
36. Atsumi M, Tanaka A, Kawarabayashi T, et al. [Cerebral embolism associated with Becker muscular dystrophy-related dilated cardiomyopathy.] *No To Shinkei* 2004;56:163-7.
37. Ducceschi V, Nigro G, Sarubbi B, et al. Autonomic nervous system imbalance and left ventricular systolic dysfunction as potential candidates for arrhythmogenesis in Becker muscular dystrophy. *Int J Cardiol* 1997;59:275-9.
38. Vita G, Di Leo R, De Gregorio C, et al. Cardiovascular autonomic control in Becker muscular dystrophy. *J Neurol Sci* 2001;186:45-9.
39. Kirchmann C, Kececioglu D, Korinthenberg R, Ditttrich S. Echocardiographic and electrocardiographic findings of cardiomyopathy in Duchenne and Becker-Kiener muscular dystrophies. *Pediatr Cardiol* 2005;26:66-72.
40. Palmucci L, Doriguzzi C, Mongini T, et al. Dilating cardiomyopathy as the expression of Xp21 Becker type muscular dystrophy. *J Neurol Sci* 1992;111:218-21.
41. Finsterer J, Stöllberger C. Spontaneous left ventricular hypertrabeculation in dystrophin duplication based Becker's muscular dystrophy. *Herz* 2001;26:477-81.
42. Stöllberger C, Finsterer J, Blazek G, Bittner RE. Left ventricular non-compaction in a patient with Becker's muscular dystrophy. *Heart* 1996;76:380.
43. Finsterer J, Bittner RE, Grimm M. Cardiac involvement in Becker's muscular dystrophy, necessitating heart transplantation, 6 years before apparent skeletal muscle involvement. *Neuromuscul Disord* 1999;9:598-600.
44. de Visser M, de Voogt WG, la Rivière GV. The heart in Becker muscular dystrophy, facioscapulohumeral dystrophy, and Bethlem myopathy. *Muscle Nerve* 1992;15:591-6.
45. Saotome M, Yoshitomi Y, Kojima S, Kuramochi M. Dilated cardiomyopathy of Becker-type muscular dystrophy with exon 4 deletion – a case report. *Angiology* 2001;52:343-7.
46. Giglio V, Pasceri V, Messano L, et al. Integrated backscatter in Becker muscular dystrophy patients with functionally normal heart: Myocardial ultrasound tissue characterization study. *J Am Coll Cardiol* 2006;47:686-8.
47. Meune C, Pascal O, Bécane HM, et al. Reliable detection of early myocardial dysfunction by tissue Doppler echocardiography in Becker muscular dystrophy. *Heart* 2004;90:947-8.
48. Mansi L, Pace L, Politano L, et al. Left ventricular function and perfusion in Becker's muscular dystrophy. *J Nucl Med* 1997;38:563-7.
49. Nagamachi S, Inoue K, Jinnouchi S, et al. Cardiac involvement of progressive muscular dystrophy (Becker type, Limb-girdle type and Fukuyama type) evaluated by radionuclide method. *Ann Nucl Med* 1994;8:71-4.
50. Lazzaroni E, Favaro L, Botti G. Dilated cardiomyopathy with regional myocardial hypoperfusion in Becker's muscular dystrophy. *Int J Cardiol* 1989;22:126-9.
51. Momose M, Iguchi N, Imamura K, et al. Depressed myocardial fatty acid metabolism in patients with muscular dystrophy. *Neuromuscul Disord* 2001;11:464-9.
52. Kaminaga T, Matsumura K, Hatanaka H, Shimizu T. Abnormality of the myocardial sympathetic nervous system in a patient with Becker muscular dystrophy detected with iodine-123 metaiodobenzylguanidine scintigraphy. *Clin Nucl Med* 2001;26:701-3.
53. Gneccchi-Ruscone T, Taylor J, Mercuri E, et al. Cardiomyopathy in duchenne, becker, and sarcoglycanopathies: A role for coronary dysfunction? *Muscle Nerve* 1999;22:1549-56.
54. Quinlivan RM, Lewis P, Marsden P, et al. Cardiac function, metabolism and perfusion in Duchenne and Becker muscular dystrophy. *Neuromuscul Disord* 1996;6:237-46.
55. Petrie CJ, Mark PB, Dargie HJ. Cardiomyopathy in Becker muscular dystrophy – does regional fibrosis mimic infarction? *J Cardiovasc Magn Reson* 2005;7:823-5.

56. Crilly JG, Boehm EA, Rajagopalan B, et al. Magnetic resonance spectroscopy evidence of abnormal cardiac energetics in Xp21 muscular dystrophy. *J Am Coll Cardiol* 2000;36:1953-8.
57. Donofrio PD, Challa VR, Hackshaw BT, Mills SA, Cordell AR. Cardiac transplantation in a patient with muscular dystrophy and cardiomyopathy. *Arch Neurol* 1989;46:705-7.
58. Maeda M, Nakao S, Miyazato H, et al. Cardiac dystrophin abnormalities in Becker muscular dystrophy assessed by endomyocardial biopsy. *Am Heart J* 1995;129:702-7.
59. Muntori F, Melis MA, Ganau A, Dubowitz V. Transcription of the dystrophin gene in normal tissues and in skeletal muscle of a family with X-linked dilated cardiomyopathy. *Am J Hum Genet* 1995;56:151-7.
60. Nigro G, Comi LI, Limongelli FM, et al. Prospective study of X-linked progressive muscular dystrophy in Campania. *Muscle Nerve* 1983;6:253-62.
61. Grain L, Cortina-Borja M, Forfar C, et al. Cardiac abnormalities and skeletal muscle weakness in carriers of Duchenne and Becker muscular dystrophies and controls. *Neuromuscul Disord* 2001;11:186-91.
62. Kingston HM, Sarfarazi M, Newcombe RG, Willis N, Harper PS. Carrier detection in Becker muscular dystrophy using creatine kinase estimation and DNA analysis. *Clin Genet* 1985;27:383-91.
63. Zatz M, Frota-Pessoa O, Levy JA, Peres CA. Creatine-phosphokinase (CPK) activity in relatives of patients with X-linked muscular dystrophies: A Brazilian study. *J Genet Hum* 1976;24:153-68.
64. Hoogerwaard EM, Ginjaar IB, Bakker E, de Visser M. Dystrophin analysis in carriers of Duchenne and Becker muscular dystrophy. *Neurology* 2005;65:1984-6.
65. Hoogerwaard EM, van der Wouw PA, Wilde AA, et al. Cardiac involvement in carriers of Duchenne and Becker muscular dystrophy. *Neuromuscul Disord* 1999;9:347-51.
66. Hoogerwaard EM, Bakker E, Ippel PF, et al. Signs and symptoms of Duchenne muscular dystrophy and Becker muscular dystrophy among carriers in The Netherlands: A cohort study. *Lancet* 1999;353:2116-9.
67. Nolan MA, Jones OD, Pedersen RL, Johnston HM. Cardiac assessment in childhood carriers of Duchenne and Becker muscular dystrophies. *Neuromuscul Disord* 2003;13:129-32.
68. Comi LI, Nigro G, Politano L, Petretta VR. The cardiomyopathy of Duchenne/Becker consultands. *Int J Cardiol* 1992;34:297-305.
69. Stöllberger C, Finsterer J. Worsening of heart failure in Becker muscular dystrophy after nonsteroidal anti-inflammatory drugs. *South Med J* 2005;98:478-80.
70. Cittadini A, Ines Comi L, Longobardi S, et al. A preliminary randomized study of growth hormone administration in Becker and Duchenne muscular dystrophies. *Eur Heart J* 2003;24:664-72.
71. 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.
72. Patanè F, Zingarelli E, Attisani M, Sansone F. Successful heart transplantation in Becker's muscular dystrophy. *Eur J Cardiothorac Surg* 2006;29:250.
73. Breuckling E, Reimnitz P, Schara U, Mortier W. [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.
74. Bush A, Dubowitz V. Fatal rhabdomyolysis complicating general anesthesia in a child with Becker muscular dystrophy. *Neuromuscul Disord* 1991;1:201-4.
75. Ohkoshi N, Yoshizawa T, Mizusawa H, et al. Malignant hyperthermia in a patient with Becker muscular dystrophy: Dystrophin analysis and caffeine contracture study. *Neuromuscul Disord* 1995;5:53-8.
76. Wu CC, Tseng CS, Shen CH, Yang TC, Chi KP, Ho WM. Succinylcholine-induced cardiac arrest in unsuspected becker muscular dystrophy – a case report. *Acta Anaesthesiol Sin* 1998;36:165-8.
77. Miyashita H, Ikeda U, Shimada K, Natsume T, Arahata K. Becker muscular dystrophy with early manifestation of left heart failure. *Intern Med* 1993;32:408-11.
78. Yokota R, Shirohara M, Kouchi I, et al. Subclinical Becker's muscular dystrophy presenting with severe heart failure. *Intern Med* 2004;43:204-8.
79. Chrzanowski L, Kasprzak JD, Trzos E, et al. Different expressions of X-linked cardiomyopathy in monozygotic triplets with Becker's dystrophy. *Int J Cardiovasc Imaging* 2003;19:377-80.
80. Doing AH, Renlund DG, Smith RA. Becker muscular dystrophy-related cardiomyopathy: A favorable response to medical therapy. *J Heart Lung Transplant* 2002;21:496-8.
81. Sakata C, Sunohara N, Nonaka I, Arahata K, Sugita H. [A case of Becker muscular dystrophy presenting cardiac failure as an initial symptom.] *Rinsho Shinkeigaku* 1990;30:210-3.
82. Ruiz-Cano MJ, Delgado JF, Jiménez C, et al. Successful heart transplantation in patients with inherited myopathies associated with end-stage cardiomyopathy. *Transplant Proc* 2003;35:1513-5.
83. Leprince P, Heloire F, Eymard B, Léger P, Duboc D, Pavie A. Successful bridge to transplantation in a patient with Becker muscular dystrophy-associated cardiomyopathy. *J Heart Lung Transplant* 2002;21:822-4.
84. Melacini P, Gambino A, Caforio A, et al. Heart transplantation in patients with inherited myopathies associated with end-stage cardiomyopathy: Molecular and biochemical defects on cardiac and skeletal muscle. *Transplant Proc* 2001;33:1596-9.
85. Fiocchi R, Vernocchi A, Gariboldi F, Senni M, Mamprin F, Gamba A. Troponin I as a specific marker for heart damage after heart transplantation in a patient with Becker type muscular dystrophy. *J Heart Lung Transplant* 1997;16:969-73.
86. Bittner RE, Shorny S, Streubel B, Hübner C, Voit T, Kress W. Serum antibodies to the deleted dystrophin sequence after cardiac transplantation in a patient with Becker's muscular dystrophy. *N Engl J Med* 1995;333:732-3.
87. Rees W, Schüler S, Hummel M, Hetzer R. Heart transplantation in patients with muscular dystrophy associated with end-stage cardiomyopathy. *J Heart Lung Transplant* 1993;12:804-7.
88. Quinlivan RM, Dubowitz V. Cardiac transplantation in Becker muscular dystrophy. *Neuromuscul Disord* 1992;2:165-7.