

Clinical Relevance of Atrial Fibrillation/Flutter, Stroke, Pacemaker Implant, and Heart Failure in Emery-Dreifuss Muscular Dystrophy

A Long-Term Longitudinal Study

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Background and Purpose—Emery-Dreifuss muscular dystrophy (EDMD) is a rare inherited disorder associated with cardiac involvement. We investigated the spectrum and relevance of the cardiac manifestations of EDMD, focusing on bradyarrhythmias and tachyarrhythmias (including atrial fibrillation/flutter), embolic stroke, and heart failure.

Methods and Results—Eighteen patients (age 42.8 ± 19.6 years) with genetically confirmed X-linked ($n=10$, including 3 carriers) or autosomal dominant ($n=8$) EDMD were followed for a period ranging from 1 to 30 years in a research center for neuromuscular diseases and in a university cardiological department. Pacemakers were required by 10 of 18 (56%) patients for bradyarrhythmia, and related complications occurred in 3 of 10 (30%) cases. Atrial fibrillation/flutter developed in 11 of 18 (61%) patients, with atrial standstill subsequently occurring in 5 of 11 (45%) cases and embolic stroke (most often disabling) in 4 of 11 (36%). Heart failure requiring transplantation occurred in 1 of 18 (6%) patients, and asymptomatic left ventricular dysfunction in a further 3 (17%). No relationship was evident between neuromuscular impairment and cardiac involvement.

Conclusions—Both X-linked and autosomal dominant EDMD patients risk not only bradyarrhythmia (requiring pacemaker implant) but also atrial fibrillation/flutter, which often anticipates atrial standstill and can cause disabling embolic stroke at a relatively young age. Antithromboembolic prophylaxis has to be recommended in EDMD patients with atrial fibrillation/flutter or atrial standstill. With careful monitoring, survival after pacemaker implant may be long. Heart failure, which seems to occur only in a minority of patients, may be severe. (*Stroke*. 2003;34:901-908.)

Key Words: atrial fibrillation ■ congestive heart failure ■ muscular dystrophy, Emery-Dreifuss ■ stroke ■ thromboembolism

Emery-Dreifuss muscular dystrophy (EDMD) is a hereditary condition characterized by the triad of (1) early-onset contractures of the elbow, ankles, and cervical spine; (2) humeroperoneal muscle wasting and weakness; and (3) cardiac involvement consisting of conduction system disease, most often heart block.¹⁻³ EDMD occurs either as an X-linked disorder (XL-EDMD) or as an autosomal dominant trait (AD-EDMD), caused by mutations in the *STA*^{4,5} and *LMNA*^{4,6} genes, respectively, which both encode for nuclear envelope proteins. Emerin, the product of the *STA* gene, is a ubiquitous protein found in the inner nuclear membrane of many cell types, including skeletal and cardiac fibers. Lamins A and C, which are encoded by the *LMNA* gene, are 2 components of the nuclear lamina that interact directly with emerin. Other pathologies caused by *LMNA* mutations in-

clude the following: dilated cardiomyopathy and conduction system disease (CMD1A), one form of limb-girdle muscular dystrophy with atrioventricular conduction disturbances (LGMD1B), a rare form of familial partial lipodystrophy (FPLD), and an autosomal recessive form of axonal neuropathy.^{7,8} Both CMD1A and LGMD1B have clinical features in common with EDMD.

In XL-EDMD, the cardiac involvement is characterized by frequent occurrence of bradycardia at a young age (early second decade to fourth decade),⁹ followed by evolution to atrial standstill and atrioventricular block requiring pacemaker implant to prevent arrhythmic death.^{1-3,10} Clinical presentation with heart failure due to dilated cardiomyopathy, which is frequent in other X-linked muscular dystrophies, such as the Duchenne/Becker form,¹¹ is rare in XL-EDMD.¹²

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TABLE 1. Patient Population

Pt no.	Sex	Gene Defect	Type of Clinical Presentation and Age	Length of Follow-Up, y	Age at End of Follow-Up	Degree of Muscular Involvement at End of Follow-Up	Arrhythmias During all the Follow-Up	Symptoms Related to Arrhythmias	EP Study	PM Implant
XL-EDMD		STA gene mutation								
1	F (carrier)	29 bp deletion	AVB III°; 67 y	9	Death, 76 y	M0	SAB, AVB III	Lightheadedness	No	Yes
2	M	"	Walking difficulties; 12 y	24	67	M2	AVB III, PAF, CAF	None (PM)	Yes	Yes
3	F (carrier)	"	SAB II°; 53 y	16	64	M0	SAB II°	None	No	No
4	M	"	AVB II°; 27 y	30	57	M0	PAF, AVB II, CAF	Stroke, palpitations	Yes	Yes
5	F (carrier)	"	PAF; 51 y	16	51	M0	PAF	None	No	No
6	M	"	Walking difficulties; 4 y	18	40	M3	CAFL, high-grade AVB	Dyspnea	Yes	Yes
7	M	"	Walking difficulties; 6 y	17	29	M2	PAF, BAV II°	None	No	Yes
8	M	"	Muscular stiffness; 5 y	6	23	M1	SAB II°, BAV I°, PAF	None	Yes	Yes
9	M	"	Muscular weakness; 8 y	5	20	M1	SAB II°	None	No	No
10	M	"	Walking difficulties; 7 y	7	24	M1	Sinus arrests, CAFL	None, palpitations	No	Yes
AD-EDMD		LMNA mutation								
11	F	R386K	Walking difficulties, contractures; 6 y	24	42	M3	BAV III°, CAFL	RVF, stroke	No	Yes
12	M	R527P	Muscular weakness; 40 y	18	Death, 73 y	M1	SAB, BAV II-III°, CAF	Stroke	Yes	Yes
13	F	R527P	Muscular weakness; 19 y	7	43	M3	SAB II, PAF	None	No	No
14	M	R527P	Walking difficulties, contractures; 3 y	7	24	M2	SAB II	None	No	No
15	M	R249Q	Walking difficulties; 1 y	1	24	M1	No	No
16	M	L140P	Walking difficulties; 3 y	1	13	M2	No	No
17	M	I63N	Asymptomatic, detected at 48 y	1	48	M0	No	No
18	M	R377L	AFL, BAV II° in DCM; 36 y	17	53	M1	BAV II°, CAFL	Stroke, HF	No	Yes

EDMD indicates Emery-Dreifuss muscular dystrophy; EP, electrophysiological; PM, pacemaker; AVB, atrioventricular block; SAB, sinoatrial block; PAF, paroxysmal atrial fibrillation; PAFL, paroxysmal atrial flutter; CAF, chronic atrial fibrillation; CAFL, chronic atrial flutter; HF, heart failure; RVF, right ventricular failure; DCM, dilated cardiomyopathy; M0, not apparent muscular involvement; M1, slight muscular involvement; M2, moderate muscular involvement; M3, severe muscular involvement (walking impairment).

Lamin A/C mutations may cause conduction system disease and dilated cardiomyopathy, which usually becomes symptomatic in the third or fourth decade of life,⁹ sometimes as an isolated manifestation of the disease without detectable skeletal muscle involvement. Although pacemaker implant is recommended as soon as bradycardia occurs, limited data are available on long-term follow-up of the cardiac involvement in the different forms of EDMD.

Herein, we describe a population of patients with different forms of EDMD and their clinical outcomes with regard to (1) arrhythmia and cardiac function evolution before and after pacemaker implant, (2) pacemaker-related complications, and (3) cardioembolic and neurological events. The population consists of 18 consecutive patients with clinical and genetically confirmed diagnosis followed at the Center for Neuromuscular Diseases of the Istituti Ortopedici Rizzoli (since 1998, all of these patients have also been prospectively studied at the Institute of Cardiology of the University of Bologna).

Methods

Between 1982 and 2001, 18 subjects affected by EDMD were referred from the Center for Neuromuscular Diseases of the Istituti Ortopedici Rizzoli to the Institute of Cardiology of the University of Bologna. Cases with an initial diagnosis of other diseases but with a final diagnosis of EDMD, as confirmed by overall clinical status and genetics, were included in the study. Full clinical, laboratory, histological (muscle biopsy), and instrumental (electromyography) findings were always available. In all cases, diagnosis of EDMD was confirmed by genetic analysis; the *LMNA* and *STA* genes were

analyzed by polymerase chain reaction, single-strand conformation polymorphism (SSSP), and sequencing.¹³ At the time of initial diagnosis (or suspicion) of EDMD, all of the subjects received a cardiological workup in the referring center (regional cardiology departments, including the University of Bologna). This always included history, physical examination, ECG, 24-hour Holter monitoring, and echocardiography. The degree of subjective functional impairment due to cardiac disease was classified according to New York Heart Association (NYHA) functional class.¹⁴ The patients' degree overall disability due to muscular dystrophy was classified according to a simplified functional scheme derived from the Walton scale.¹⁵ In brief, this M0 through M3 scale classifies disabilities according to the following 4 grades (Table 1): M0, preclinical with no evident disability (Walton grade 0); M1, mild muscular disability (grades 1 and 2), inability to run or walk normally; M2, moderate muscular disability (grades 3 to 5), difficulty in climbing stairs or rising from a chair but retained ability to walk unassisted; and M3, severe muscular involvement (grades 6 to 10) with impairment of unassisted walking.

Since 1998, all of the patients have been prospectively studied at the Cardiology Institute of the University of Bologna, with regular clinical examinations every 6 months and yearly echocardiographic and 24-hour Holter monitoring (plus additional visits in cases of change of clinical status or occurrence of symptoms suggestive of new arrhythmias or worsening heart failure). The echocardiogram is performed according to usual techniques. Left ventricular ejection fraction is calculated by the area-length method. Left and right atrial enlargement is assessed by an experienced cardiologist with a 4-chamber view (for both the left and the right atrium) and a dual-chamber parasternal view (for the left atrium). When appropriate, an electrophysiological study is performed for the assessment of sinus node and atrioventricular conduction to confirm or exclude the decision to implant a pacemaker. In case of pacemaker implant, the

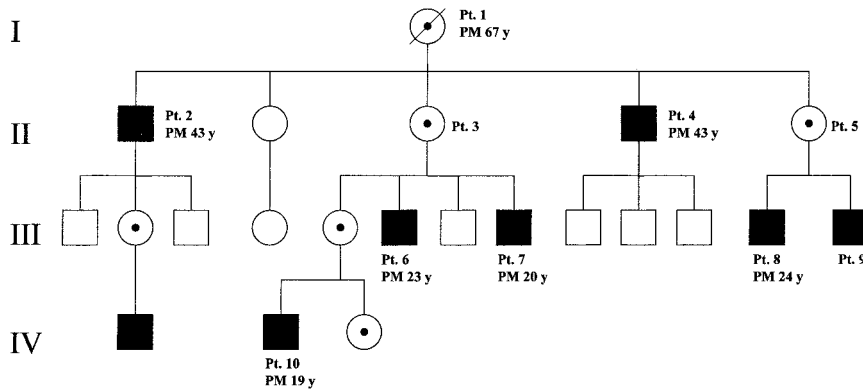


Figure 1. Genealogical tree of large XL-EDMD family, including 7 affected males and 3 female carriers. Age at pacemaker implant is reported. Pt indicates patient; PM, pacemaker; □, unaffected male; ○, unaffected female; ■, affected male; ⊙, female carrier; /, deceased.

devices are checked every 4 months at the Institute’s pacemaker clinic.

All patients released written informed consent before undergoing any invasive procedures (electrophysiological study or pacemaker implant). Prospective evaluation (from 1998 onward) was carried out according to the principles of the Helsinki Declaration.

Results

Population

The main clinical characteristics of the patient population are shown in Table 1. Ten subjects (7 affected males and 3 female carriers of the genetic defect; median age of the affected males at presentation 10 years [range 4 to 27]) had XL-EDMD and 8 (6 males and 2 females; median age at presentation 6 years [range 1 to 40]) had AD-EDMD. All of the XL-EDMD patients belong to a large family including 4 generations of affected males (Figure 1 shows the genealogical tree). Three of the 8 AD-EDMD patients (patients 12, 13, and 14) belong to 3 different generations of a single family (a father, his daughter, and his grandson, respectively); the other 5 had de novo mutations. The length of follow-up, as shown in Table 1, ranged between 1 and 30 years.

Cardiac Arrhythmias

Among the 10 subjects with XL-EDMD (7 affected men and 3 female carriers), the clinical presentation was primarily arrhythmic in 4 cases (3 female carriers and an affected male with no musculoskeletal signs) and was mainly neuromuscular in the other 6 cases (Table 1). Among the 8 patients with AD-EDMD, the clinical presentation was primarily arrhythmic in 1 case (patient 18) and mainly musculoskeletal in 6; in 1 case (patient 17), a “silent” mutation in the *LMNA* gene was discovered as a result of familial genetic screening (prompted by 2 affected daughters, who received cardiological assessment elsewhere and therefore were not included in the present series).

In 10 of 10 (100%) subjects with XL-EDMD and in 5 of 8 (63%) patients with AD-EDMD, arrhythmias were observed at presentation or during follow-up. Among the 10 XL-EDMD subjects, 6 (60%) developed both bradyarrhythmia and tachyarrhythmia, whereas 3 (30%) had only bradyarrhythmia and 1 (10%) had only tachyarrhythmia. Among the 8 AD-EDMD subjects, 4 (50%) developed both bradyarrhythmia and tachyarrhythmia, 1 (13%) had only bradyarrhythmia; 3 (25%) currently have no arrhythmia (at the ages of 13, 24, and 48 years, the last also being neurologically asymptomatic).

In our series of patients, atrial fibrillation or flutter occurred during follow-up in 11 of 18 (61%) cases and evolved to atrial standstill in 5 patients (patients 4, 6, 7, 10, and 11; see Table 2).

Pacemaker Implantation and Follow-Up

Among the 5 XL-EDMD patients who received electrophysiological examinations to assess indications for pacemaker implantation, 4 were found to have relevant electrophysiological abnormalities. In particular, 3 of the 4 patients in sinus rhythm (1 patient had atrial flutter) had sinoatrial dysfunction (expressed by a pathological corrected sinus node recovery time, ie, >525 ms). Furthermore, a pathological infra-hissian conduction delay was found in 4 patients (HV interval >55 ms).

In view of the severity of bradyarrhythmias, pacemakers (9 VVI/VVIR and 1 DDDR) were implanted in 10 patients, 7 of 10 (70%) with XL-EDMD and 3 of 8 (37%) with AD-EDMD, at ages ranging between 19 and 76 years (median 35.5 years). Pacemaker implant was performed on an elective basis in 6 cases (5 XL-EDMD and 1 AD-EDMD), and as an emergency, because of severe bradyarrhythmias, in the remaining 4 cases (2 XL-EDMD and 2 AD-EDMD). The median follow-up after pacemaker implant was 12 years (range 0 to 18 years). Pacemaker dependency (absence of a spontaneous ventricular rhythm at a rate >40 bpm) was recorded in all cases at the end of follow-up. Five (50%) of the 10 implanted patients (patients 4, 6, 7, 10, and 11) developed atrial standstill (as detected by 12-lead ECG and confirmed by cross-sectional echocardiogram) after the development of paroxysmal atrial fibrillation or flutter (Table 2). One patient (patient 2) developed permanent atrial fibrillation after pacemaker implant. Two patients with stable atrial fibrillation or flutter (patients 12 and 18, respectively) before pacemaker implant maintained this arrhythmia during follow-up. One patient (patient 8) had episodes of paroxysmal atrial fibrillation. A female carrier (patient 1) died at the age of 76 years after a stroke, 10 years after pacemaker implant, without developing atrial tachyarrhythmia. Pacemaker-related complications were observed in 3 patients. One patient (patient 6) developed early ventricular lead displacement. A further 2 patients (patients 7 and 11) experienced ventricular lead fracture with consequent loss of ventricular capture; this led to marked bradycardia and asystolia detected at Holter

TABLE 2. Evolution of Atrial Arrhythmias in Patients With or Without Pacemaker Implant and Occurrence of Stroke

Pt no.	Sex	Type of Implanted PM and Age	Occurrence of AF or AFL (age)	Occurrence of Atrial Standstill (age)	Occurrence of Stroke (age)
XL-EDMD					
1	F (carrier)	VI; 67 y			
2	M	VI; 43 y*	PAF 51 y, CAF 56 y		
3	F (carrier)				
4	M	VI; 43 y	PAF 34 y, CAF 54 y	57 y	54 y
5	F (carrier)		PAF 45 y		
6	M	VI; 23 y	CAFL 23 y	38 y	
7	M	VI; 20 y	PAF 14 y	27 y	
8	M	VI; 24 y	PAF 12 y		
9	M				
10	M	DDD; 19 y*	CAFL 22 y	22 y	
AD-EDMD					
11	F	VI; 30 y*	CAFL 26 yr	30 yr	26 yr
12	M	VI; 55 y	CAF 55 y		57 and 70 y
13	F		PAF 42 y		
14	M				
15	M				
16	M				
17	M				
18	M	VI; 41 y*	CAFL 36 y		43 and 44 y

PM indicates pacemaker; AF, atrial fibrillation; AFL, atrial flutter; PAF, paroxysmal atrial fibrillation; CAF, chronic atrial fibrillation; CAFL, chronic atrial flutter.

*Emergency.

monitoring in patient 7 (Figure 2), and to low-rate idioventricular rhythm in patient 11.

Patient 10, who had a DDD/DDDR pacemaker implanted at the age of 19 years after sinoatrial arrests in an attempt to prevent evolution to atrial fibrillation or atrial standstill, developed atrial flutter 4 years after implantation. Sinus rhythm was resumed by treatment with intravenous propafenone. Prophylaxis with oral propafenone was maintained for 1 year, but was then withdrawn because of atrial standstill found during routine follow-up. Atrial standstill persisted and was associated with the inexcitability of the atria even when the output of the pacemaker was increased (up to 5.3 V/1.0 ms).

Thromboembolic Complications

Thromboembolic complications occurred in 4 patients with an overt picture of ischemic stroke (patients 4, 11, 12, and 18), in 1 case (patient 11) after unrecognized transient ischemic attacks. All 4 patients had permanent atrial fibrillation or stable atrial flutter at the time of stroke (in 2 cases even before the event), and none was under chronic anticoagulation or aspirin treatment. As shown in Table 2, the age range at the time of stroke was 26 to 70 years; 3 of the 6 events occurred at <45 years of age. In 1 case (patient 4), cardioembolic origin of the stroke was demonstrated by transesophageal echocardiography showing a thrombus in the left atrial appendage (Figure 3). A Doppler echocardiographic

study of epiaortic vessels was performed in all 4 cases of ischemic stroke, but no significant lesion was found. Disabling consequences occurred in 3 patients; these were namely hemiparesis (patient 4, stroke at 54 years) residual hemiplegia (patient 11, stroke at 26 years), and ataxia (patient 18, cerebellar stroke at 43 years, with recurrence 1 year later).

Left Ventricular Dysfunction and Echocardiographic Findings

Table 3 summarizes echocardiographic evaluation data at the end of follow-up, together with clinical data on the presence/absence of chronic atrial fibrillation or flutter and NYHA functional class. Severe heart failure was observed in our series only in 1 patient with AD-EDMD (patient 18, Table 1), who presented with a clinical picture of limb girdle muscular dystrophy and dilated cardiomyopathy in NYHA class 3. In this patient, left ventricular dysfunction was present at first observation (left ventricular ejection fraction, 30%) and was associated with atrial flutter and atrioventricular block requiring pacemaker implant. After further worsening of heart failure (Table 3), the patient successfully underwent heart transplantation. In patient 11, the AD-EDMD presented with reversible right ventricular failure with venous congestion secondary to atrioventricular block with a low rate of escape rhythm (20 to 30 bpm). After pacemaker implant, right ventricular failure disappeared with normal biventricular function. In 3 other patients (patients 2, 4, and 12; Table 3),

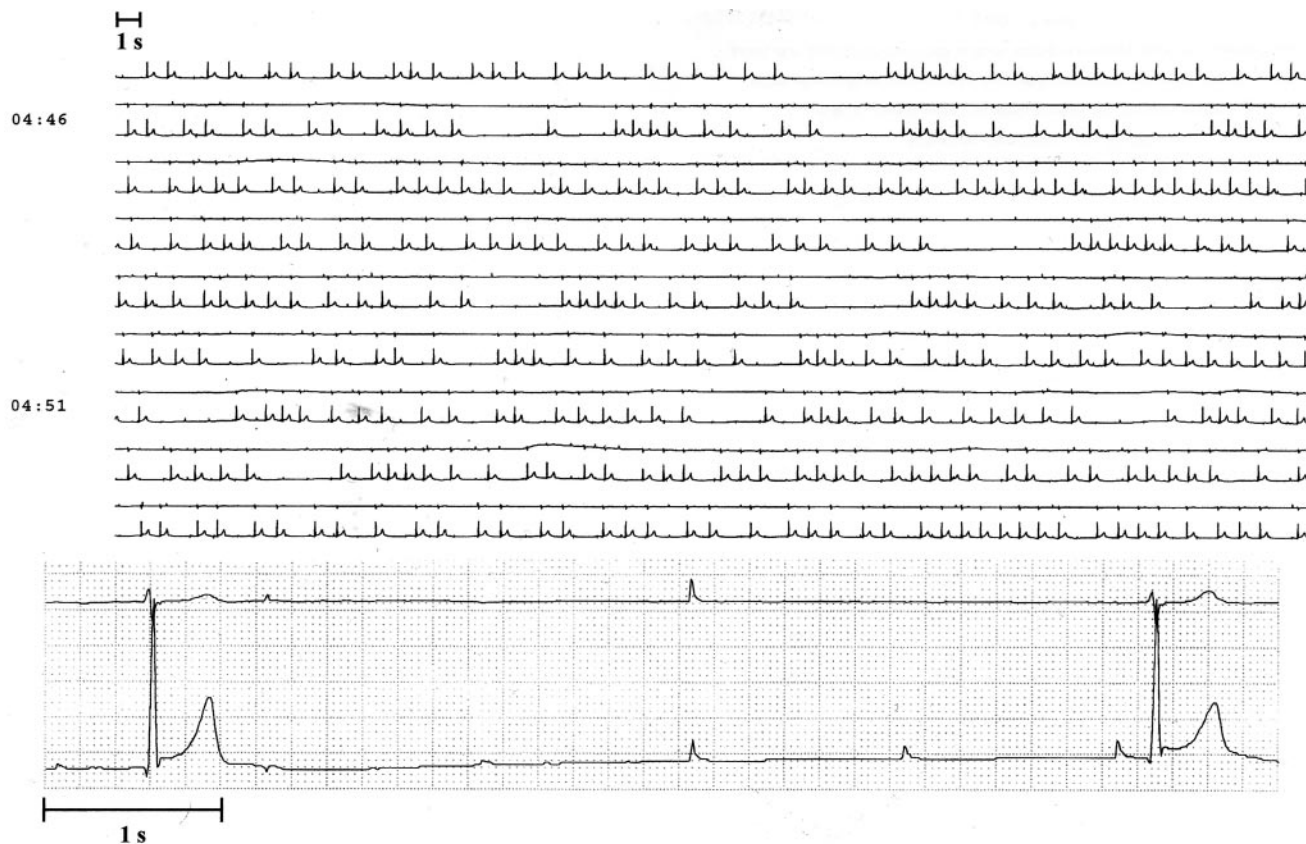


Figure 2. Electrocardiographic strips from a 24-hour Holter recording of a patient with a VVI pacemaker. Top, 3,125 mm/s recording speed; bottom, 25 mm/s recording speed. A series of asystolic pauses was found (up to 6 s); these were caused by loss of ventricular capture. Implant revision revealed break in the lead (pacemaker was implanted 10 years before).

mild to moderate left ventricular dysfunction was observed (ejection fraction, 30% to 50%), but with limited or no impairment (NYHA class 1 or 2) in daily activities.

Echocardiographically, right atrial dilation was present in 12 of 18 (67%) patients (in 8/12 [75%] cases associated with chronic atrial fibrillation/flutter or standstill); left atrial dilation was present in 7 of 18 (39%) patients and was always associated with chronic atrial fibrillation/flutter or standstill and with right atrial dilation.

Cardiac and Muscular Involvement

As shown in Table 1, the degree of cardiac involvement did not seem to be affected by the degree of muscular involvement (at the end of follow-up). Indeed, II- to III-degree atrioventricular block and/or chronic atrial fibrillation/flutter

occurred even in patients classified as M0, whereas severe heart failure was observed in 1 patient (patient 18) with M1 (Table 1).

Discussion

This long-term follow-up study on the largest longitudinal series yet reported clearly shows that atrial standstill is only 1 of the arrhythmias present in EDMD. The study also indicates that atrial fibrillation or flutter, which often precedes an eventual atrial standstill, can emerge either before or after pacemaker implantation. This implies that EDMD patients have a high risk of developing both severe bradyarrhythmias and supraventricular tachyarrhythmias, a very uncommon association in young subjects. Whereas the bra-

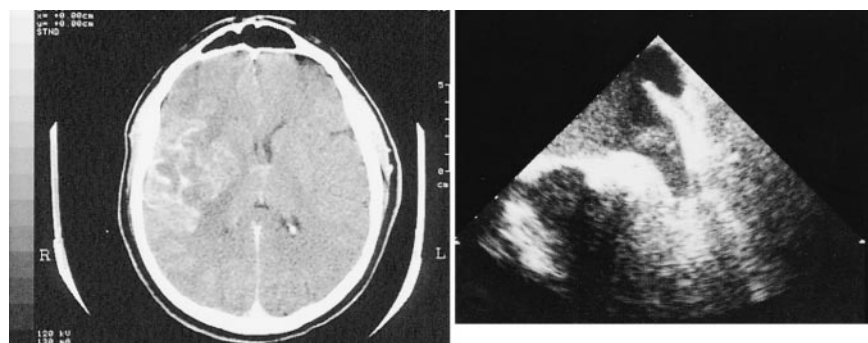


Figure 3. Cerebral CT scan (left) and transesophageal echocardiogram (TEE) (right) of patient 4. Examinations were performed some days after clinical stroke. CT scan (without contrast medium) shows a cerebral infarct; there is a hypodense area in the right fronto-temporo-parietal region with compression on the homolateral ventricle. TEE shows the embolic source of stroke; a thrombotic formation in the left atrial appendage is clearly evident.

TABLE 3. Echocardiographic Evaluation and NYHA Functional Class at the End of Follow-Up

Pt no.	LV Dilation/Hypokinesia and LVEF (%)	Left Atrial Dilation	Right Atrial Dilation	CAF or CAFL/Atrial Standstill	NYHA Class
XL-EDMD					
1	No	No	No	No	1
2	Yes (35)	Yes	Yes	CAF	2
3	No	No	No	No	1
4	Yes (45)	Yes	Yes	AS	1
5	No	No	No	No	1
6	No	Yes	Yes	AS	1
7	No	Yes	Yes	AS	1
8	No	No	Yes	No	1
9	No	No	Yes	No	1
10	No	Yes	Yes	AS	1
AD-EDMD					
11	No	No	Yes	AS	1
12	Yes (50)	Yes	Yes	CAFL	1
13	No	No	No	No	1
14	No	No	Yes	No	1
15	No	No	No	No	1
16	No	No	Yes	No	1
17	No	No	No	No	1
18*	Yes (25)	Yes	Yes	CAFL	3–4

AS indicates atrial standstill; CAF, chronic atrial fibrillation; CAFL, chronic atrial flutter; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA Class, New York Heart Association functional classification of heart failure.

*This patient has received a successful heart transplantation.

dyarrhythmias carry a risk of sudden death (because of EDMD patients' very low escape rhythm rates), atrial fibrillation/flutter seems to be associated with a particularly high risk of thromboembolic stroke in EDMD patients. These concepts were not evident from previous reports, which focused on the high risk of atrial standstill in many EDMD patients, with the consequent need for pacemaker implantation.^{2,16,17}

Eleven (61%) of our 18 patients experienced atrial fibrillation and/or flutter during follow-up. Because atrial fibrillation and flutter generally depend on atrial dilation or electrophysiological alterations in refractoriness and conduction probably as a result of histological alterations,¹⁸ they are probably an initial consequence of the marked alterations in atrial structure and function that develop in EDMD patients. Such expressions of lesser degrees of derangement in atrial morphology and function (with maintenance of some kind of conduction within the atria) may precede atrial standstill, characterized by complete loss of atrial excitability.^{19–21} Clear evidence of this sequence of events was found in 5 (28%) of our 18 patients (patients 4, 6, 7, 10, and 11; see Table 3) and in 5 of 11 (45%) of those who had atrial fibrillation or flutter. It should be noted that in our series atrial fibrillation/flutter and atrial standstill (as well as other arrhythmic complications) developed in both XL-EDMD and AD-EDMD patients, irrespective of the degree and severity of muscular disability.

Atrial fibrillation/flutter itself implies a risk of cerebral or systemic thromboembolism, and in our series of patients ischemic stroke occurred in 4 patients (patients 4, 11, 12, and 18), in 3 of whom it was the first expression of the arrhythmic manifestations of EDMD. In none of the 4 cases did subsequent Doppler evaluation of the epiaortic vessels reveal any major lesion. The consequent diagnosis was therefore embolic stroke due to atrial fibrillation or flutter. In 1 case (patient 4), direct evidence of atrial thrombi in the left atrial appendage was obtained by transesophageal echocardiography at the time of stroke. No data are currently available regarding the prophylactic efficacy of aspirin or anticoagulants for prevention of thromboembolism related to atrial fibrillation or flutter in EDMD patients, and this now requires dedicated study. Generally,²² aspirin is the prophylactic treatment of choice in young subjects without left ventricular dysfunction, but also anticoagulants have to be considered. Nevertheless, the specificity of the EDMD-related features recorded by us (high frequency of permanent atrial fibrillation, possible evolution to atrial standstill) suggests the need for prospective evaluation. Whereas atrial fibrillation is usually highly symptomatic in young patients, in EDMD it may occur even in the presence of normal or low ventricular rates, thereby hampering early detection. Regular Holter monitoring of EDMD patients could facilitate earlier detection of atrial fibrillation.

Not only atrial fibrillation per se, but also atrial standstill^{21,23} and sinus bradyarrhythmia carry substantial risks of systemic embolism. Moreover, VVI pacing (the usual pacing modality in EDMD) implies a higher risk of embolism than physiological pacing.²⁴ In a young patient (patient 10) with sinoatrial block, implantation of a DDDR pacemaker failed to prevent paroxysmal atrial fibrillation, followed by chronic flutter and eventual atrial standstill (the 1 other reported attempt of DDDR implantation¹⁸ in an EDMD patient was also unsuccessful).

Another form of cardiac involvement in EDMD is the progressive evolution of cardiac dysfunction. This kind of involvement is reported to be more frequent in AD-EDMD than in XL-EDMD.¹³ Our series includes a case of XL-EDMD with asymptomatic mild impairment of left ventricular function (patient 2) and 1 of AD-EDMD with an episode of reversible right heart failure due to severe bradycardia (patient 11). Moreover, another AD-EDMD patient (patient 18) has been successfully transplanted because of dilated cardiomyopathy and worsening congestive heart failure (NYHA class III to IV). In this patient too, there was no apparent correlation between the cardiac and muscular involvement (M1). The observation of minor impairment of left ventricular function in 3 of 18 (17%) patients suggests that echocardiographic monitoring is advisable (even though the rate of evolution to overt heart failure remains unknown).

After pacemaker implant, the long-term reliability of the pacing system has to be checked regularly. In a 10-year follow-up of a large cohort of elderly, unselected pacemaker recipients, lead failure occurred in 34% of cases.²⁵ Clearly, the risk of lead failure is particularly relevant in younger patients in whom it may severely affect quality of life and morbidity. In our series, long-term monitoring by 24-hour Holter revealed 2 cases of lead fracture (patients 7 and 11) with asystolic pauses up to 6 seconds (Figure 2, patient 7) and in 1 case confirmed loss of capture due to increased threshold (patient 10). The improved monitoring and diagnostic functions of currently available pacemakers should facilitate early detection of lead failure in the future.

The potential risk of ventricular tachyarrhythmias in EDMD has been stressed only recently,^{13,26} and the true incidence of tachyarrhythmic death in implanted EDMD patients without left ventricular dysfunction is unknown. None of our 10 implanted EDMD patients presented sustained ventricular tachyarrhythmia or sudden cardiac death. In implanted EDMD patients, no specific indication exists for upgrading to a cardioverter defibrillator. The problem of sudden tachyarrhythmic death was found to be of primary relevance in a family of heritable conduction and myocardial disease patients.²⁷ A higher incidence of ventricular tachyarrhythmia is obviously to be expected in EDMD when significant left ventricular dysfunction is present, as occurs in other heart disease patients.²⁸

The possibility of cardiac disturbances in female carriers of the X-linked gene also needs to be considered. One of the 3 carriers in our series required pacemaker implant at the age of 67 years because of atrioventricular blocks. Although sudden death²⁹ and severe heart failure requiring transplantation³⁰ have also been reported, the complete spectrum and relevance

of cardiac manifestations in female X-linked carriers remains to be defined.

In the context of such a rare disease as EDMD (with <200 cases reported in literature), it is difficult to define new specific recommendations on the basis of prospective studies. Although 13 of our patients come from 2 families (1 with XL-EDMD [n=10] and 1 with AD-EDMD [n=3]), our group currently constitutes the second largest series in literature (after that of Bonne et al,¹³ who reported a cross-sectional study on 53 patients). It is noteworthy that 1 of our patients (patient 2), who at 67 years of age is the oldest EDMD-affected subject on record, has had a pacemaker for 24 years. This indicates that with careful monitoring, survival after implantation may be long. In the last 2 years, we have started to prospectively monitor all of the surviving patients from our case series. This may also allow us to provide more information on the spectrum of asymptomatic (as well as symptomatic) arrhythmias and degrees of ventricular dysfunction, which may be underestimated in a retrospective study.

In conclusion, patients with EDMD show a broad spectrum of cardiac abnormalities and a high risk of cardiovascular events, including atrial standstill, atrial fibrillation, congestive heart failure, and cardioembolic stroke. Cardiac and muscular involvement do not appear to be closely related, and cases of severe cardiomyopathy can occur in the context of only mild muscular symptoms. Nevertheless, close collaboration between neurologists and cardiologists is essential in the regular cardiological follow-up required by subjects affected by EDMD. Early implant of a pacemaker is advisable when important bradyarrhythmias appear, irrespective of symptoms. Females with a family history of EDMD who present with arrhythmias should receive evaluation of the carrier gene and regular follow-up. Stroke can be the first clinical manifestation of EDMD in young adults, and can frequently be disabling. Thus, even though no specific guidelines for administration of aspirin or anticoagulants are currently available for EDMD, antithromboembolic prophylaxis has to be recommended even in young EDMD patients affected by atrial fibrillation/flutter or standstill.

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