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TREATMENT OF DILATED CARDIOMYOPATHY in patient with EMERY-DREIFUSS muscular dystrophy: from ablation to heart transplantation

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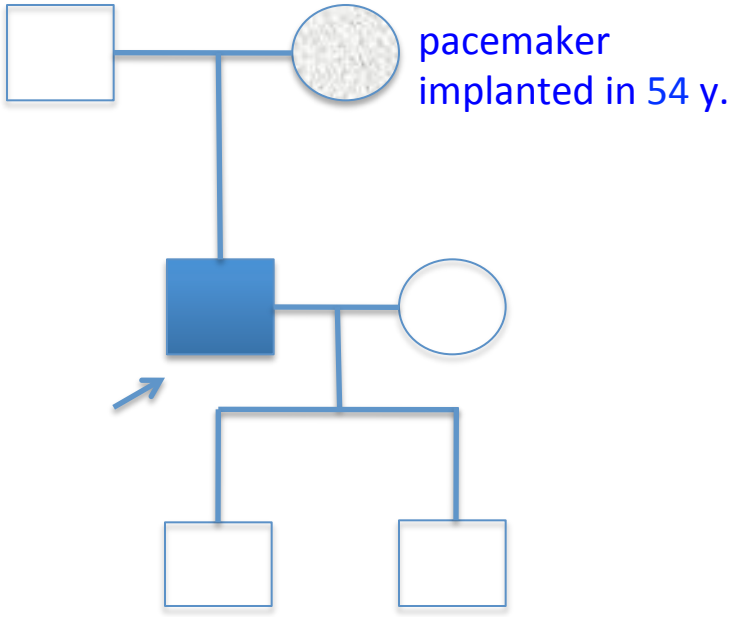
October 16-18, 2015, Venice, Italy

Male, 38 years, first visit in the clinic (June, 2012)

symptoms

- moderate general weakness
- presyncope without association with physical activity
- proximal muscular weakness
- dyspnea at moderate physical activity
- episodes of palpitation

life history



- father 66 years, history of stroke
- mother 63 years – arterial hypertension, pacemaker implantation in 54 years
- year of birth 1974
- clinically healthy sons 3 и 11 years
- profession: the lawyer
- abuse: smoking

Male, 38 years, first visit in the clinic (June, 2012)

medical history

- since 5 years – progressive muscular weakness, frequent falls
- in 6 years – the diagnosis of muscular dystrophy
- since 2006 (32 years) – palpitations, heart pain, minimal decreasing of LV EF
- 2012: increasing palpitatons, presyncope
  - ✓ Echo-CG: LV end-diastolic volume 230 ml, LV EF 40%
  - ✓ Holter monitoring without medication: sinus bradycardia, episodes of atrial flutter/ fibrillation, AV block II degree (Mobitz 1), > 4.000 PVBs, unsustained VT
  - ✓ coronary angiography: normal coronary arteries

physical examination

- height 180 cm, weight 77 kg
- walking difficulties, moderate knees and elbows contractures
- no edema
- breathing rate 18 per minute
- no wheezing in the lungs
- heart rate 56 beats per minute, premature beats 2-4 per minute
- no cardiac murmur
- blood pressure 110/70 Hg mm
- no ascites and hepatomegaly

genetics consultation

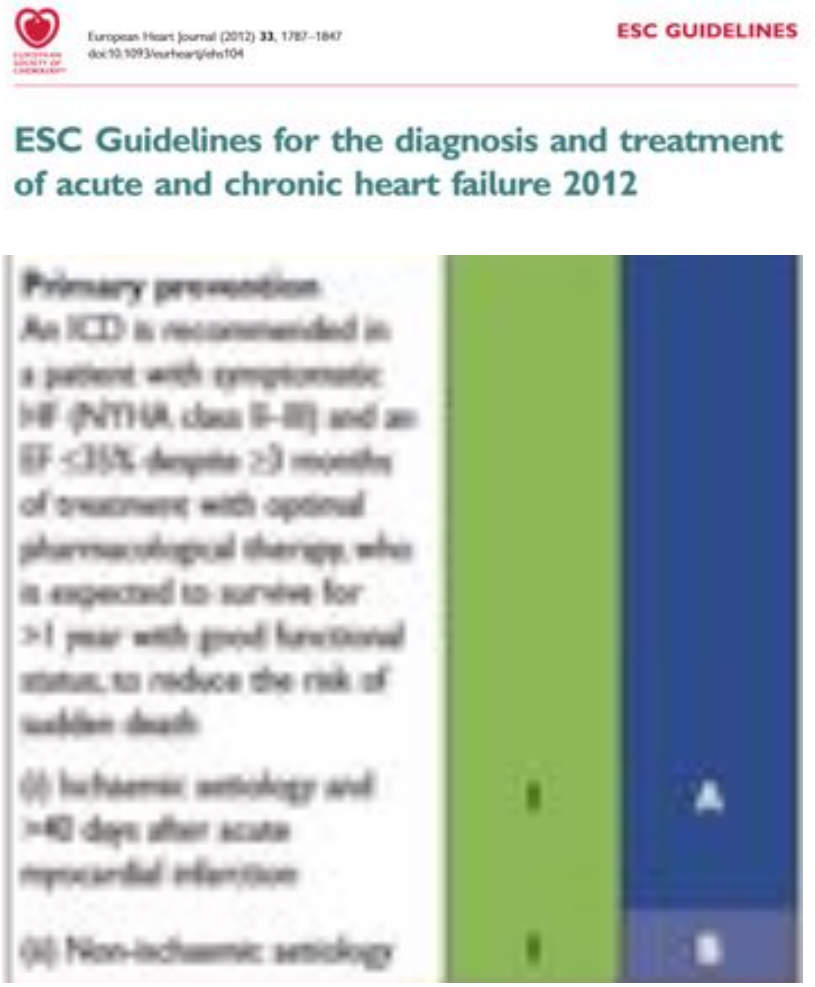
preliminary diagnosis – Emery-Dreifuss muscular dystrophy

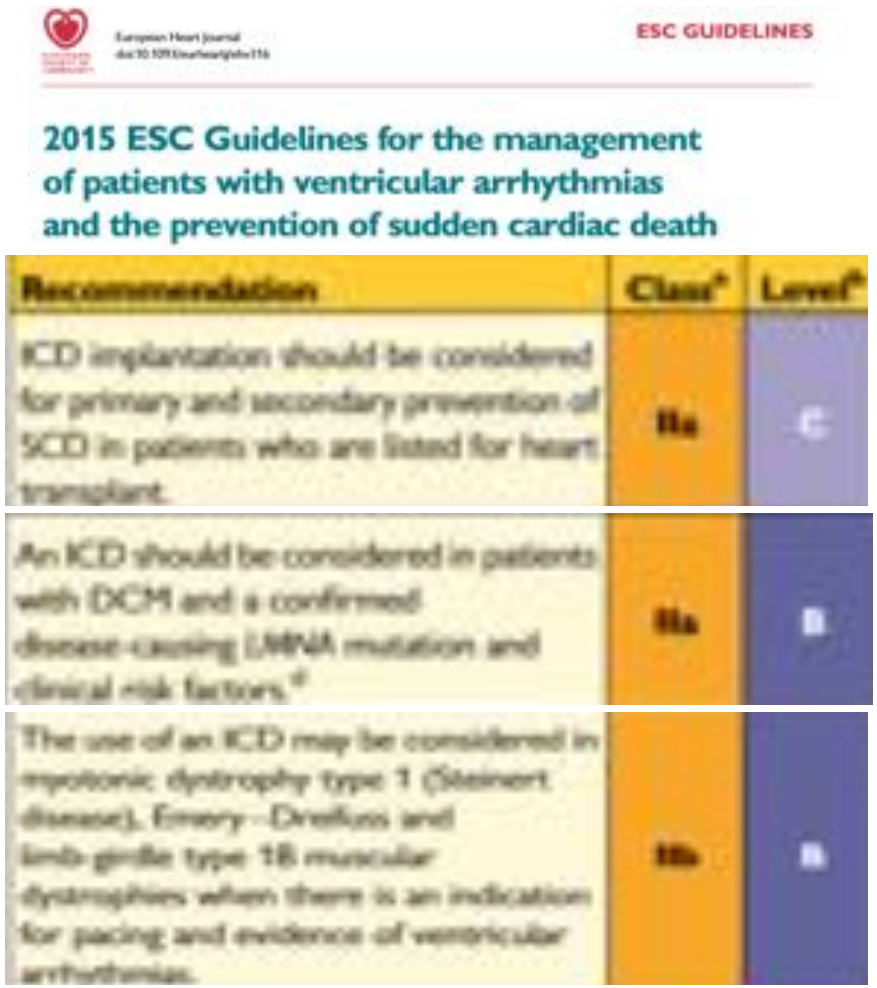
clinical signs	patient
Walking, standing up, jumping difficulties, muscular weakness	+, since 5 years
Progressive contractures	–
High level of creatin kinase	+, 576 U/l
Normal intellect	+
No pseudohypertrophies	+
Dilated cardiomyopathy	+
Arrhythmias	+

EDMD	gene	locus	protein	inheritance
EDMD1	*EDM*	Xq28	emerin	X-linked recessive
EDMD2	*LMNA*	1q22	lamin A/C	dominant
EDMD3	*LMNA*	1q22	lamin A/C	recessive
EDMD4	*SYNE1*	6q25.1	nesprin 1	dominant
EDMD5	*SYNE2*	14q23.2	nesprin 2	dominant
EDMD6	*FHL1*	Xq26.3	SLIM1	X-linked recessive
EDMD7	*TMEM43*	3p25.1	transmembrane protein 43	dominant

Possible therapeutic and diagnostic strategy

- biopsy (of the myocardium, skeletal muscle)?
- RF-ablation (pulmonary veins isolation, cavatricuspid isthmus)?
- pacemaker implantation?
- **ICD implantation and administration of amiodarone**



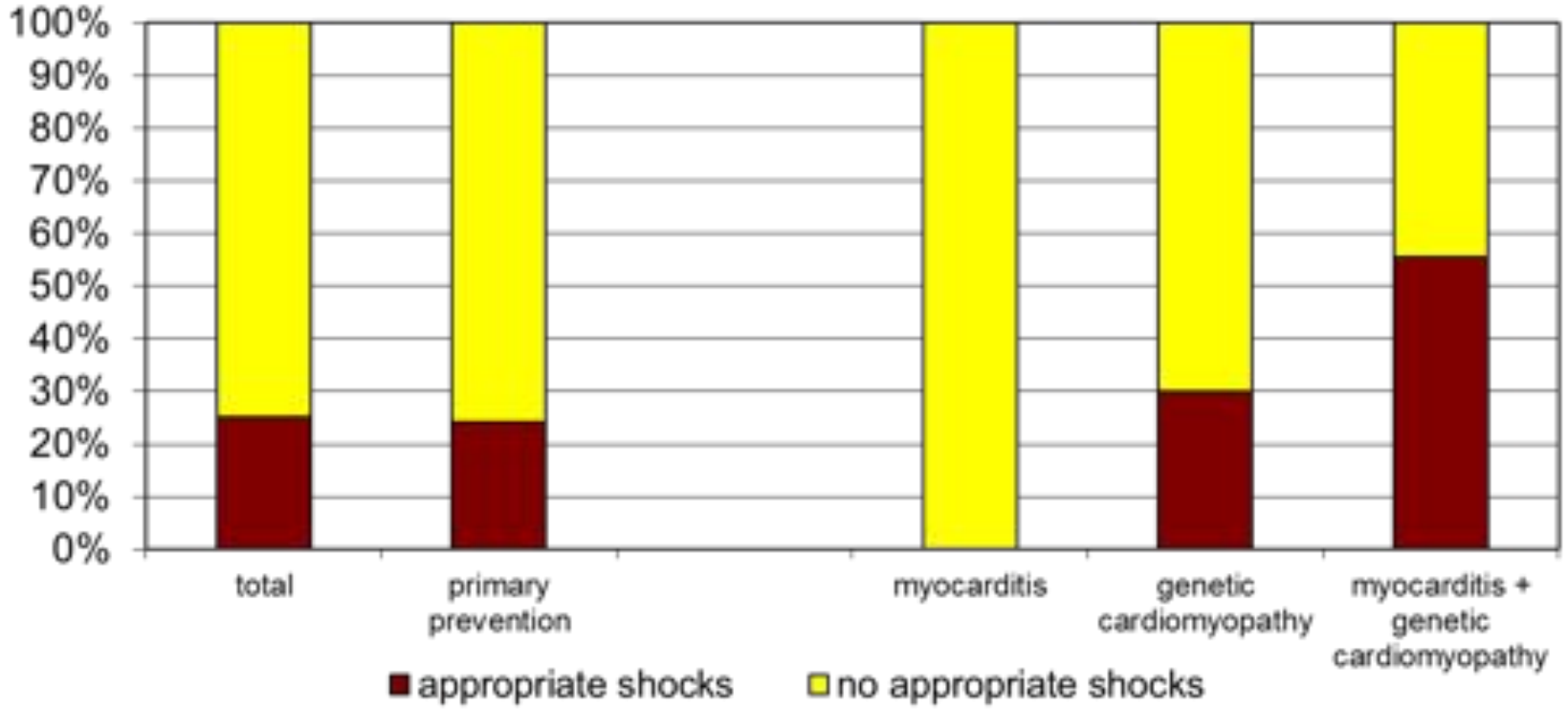


Appropriate ICD/CRTD shocks in patients with DCM depending on its aetiology (genetic or inflammatory)

32 patients (19 – ICD, 13 – CRT-D)

in 29 patients (90.6%) as a primary prevention

mean follow-up 18 month



	appropriate shocks	no appropriate shocks	p
genetic DCM	100%	41.7%	0.013
NYHA class	2.2±0.9	2.9±0.7	>0.05
LV ejection fraction	31.8±11.5%	22.8±7.9%	>0.05

Follow-up (June 2012 – January 2013)

Bakoulev Center for Cardiovascular Surgery (June 2012)

Echo-CG: LV EDD 6.7 cm, LV EDV 198 ml, LV ESV 116 ml, LV EF 43%, LA 4.2 cm, mitral and tricuspid regurgitation I degree

30.05.2012
RF ablation of isthmus

01.06.2012
dual-chamber ICD implantantion

amiodarone, warfarin

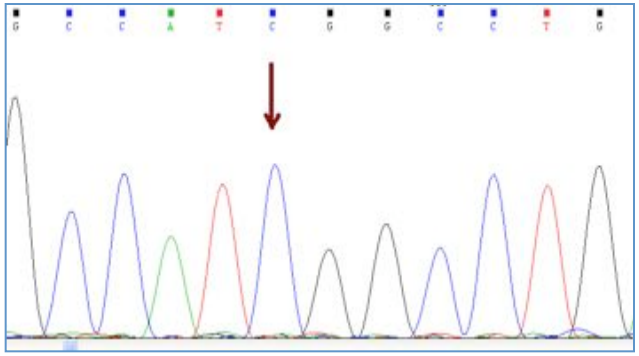
June: less than 1000 PVBs per day, no atrial flutter/ fibrillation
August: decreasing of the amiodarone dose (100 mg/ day)
November: palpitation, progressive dyspnea and edema

Hospital on a residence (January 2013)

ECG: atrial flutter with heart rate 85-110 beats/minute
Echo-CG: LV EDD 6.8 cm, LV EDV 235 ml, LV EF 16%, PA pressure 47 Hg mm, RV 2.7 cm, mitral and tricuspid regurgitation III degree
amiodarone 100 mg/day, warfarin, perindopril 2.5 mg/day, furosemide 20 mg/day

Results of PCR-based direct Sanger sequencing

December 2012



In gene ***EMD*** - frame-shift deletion c.del619C in EMD gene causing premature stop-codon appearance and protein shortening (p.236X)

In gene ***LMNA*** – intron replacement c.IVS4-13T>A, the clinical significance is not known

Homo sapiens emerin (EMD), RefSeqGene on chromosome X

Sequence ID: gi|208879448|ref|NG_008677.1| Length: 21002 Number of Matches: 1

Range 1: 11273 to 11831 GenBank Graphics

Score	Expect	Identities	Gaps	Strand
978 bits(1084)	0.0	554/559(99%)	2/559(0%)	Plus/Plus

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Sbjct  11813  GGCTGACTGCCTTAGCAGT  11831
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both variants were not found in control group of 100 healthy volunteers

Hospitalization in the clinic (February, 8, 2013)

Physical examination

- skin is pale; no edema
- breathing rate 20 per minute, no wheezing in the lungs
- heart rate 120 beats per minute, pulse irregular, deficits 10-15 beats per minute
- blood pressure 110/60 Hg mm
- no ascites; hepatomegaly +5 cm

Blood examination

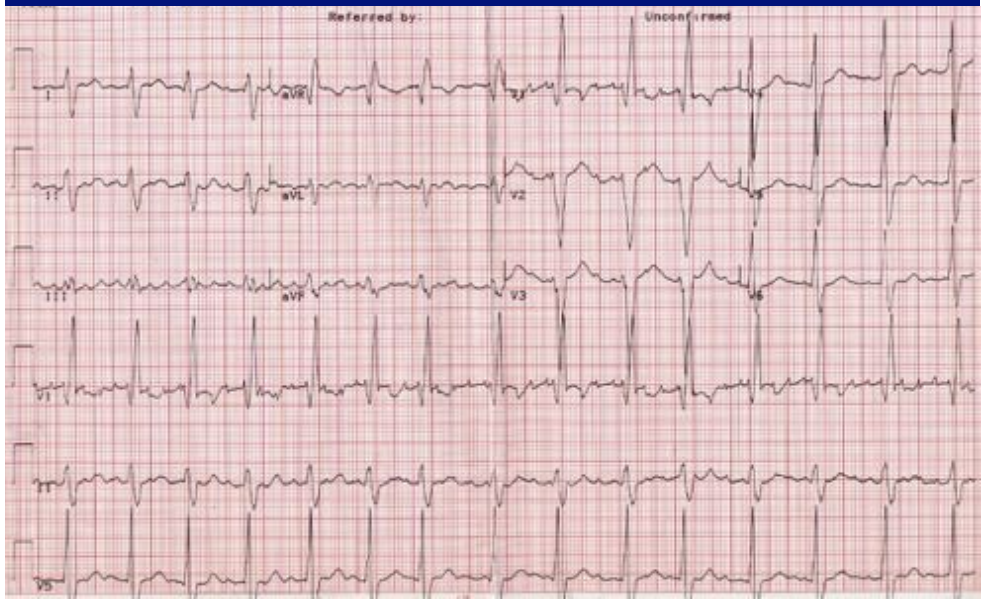
biochemistry	11.02.13	26.02.13	normal level
Creatinine, mg/dl	0.96	0.74	0.6-1.2
Potassium, mmol/l	3.4	3.6	3.5-5.0
Uric acid, mkmol/l	752.2	403.7	242-416
Bilirubin, mkmol/l	28.4	20.5	5.0-21.0
Creatine kinase, U/l	458	325	0-125
thyroid status			
	initial	**repeatedly**	**normal level**
T4 (free.) pmol/l	30.3	28.6	11.5-22.7
TTH U/l	8.3	4.4	0.35-5.5

Blood investigation for myocarditis diagnosis

Viral DNA	30.11.11
Cytomegalovirus (CMV)	no
Herpes Simplex Virus Type 1 (HSV-1)	no
Herpes Simplex Virus Type 2 (HSV-2)	no
Human Herpes Virus (HHV-6)	no
Epstain Barr virus (EBV)	no
Varicella zoster virus (V2V)	no
Parvovirus B19	no

Anti-heart antibodies		
Type of antibody	**28.02.2013**	normal level
heart-specific anti-nuclear antibodies	**no**	no
IgG to the endothelial antigens	**1:160**	1:40
IgG to antigens of cardiomyocytes	**1:80**	1:40
IgG to antigens of smooth muscle	**1:80**	1:40
IgG to antigens of conductive system	**1:160**	1:80

Initial ECG



Holter (amiodarone 400 mg/day)

- atrial flutter (2:1,3:1,4:1)
- ICD pacing VVI (20% of QRS) 75 beats/minute
- Heart rate:

day - 74-126/minute (mean 85/minute)
night - 67- 88/minute (mean 76/minute)

- PVBs, total 787 (maximal 85/minute), 18 couplets, 1 triplet
- ST-T: no changes

Echo-CG

- **LV**: end-diastolic diameter **7,0** cm; EDV 305 ml; ESV 188 ml, EF 33%
- **RV**: 2,8 cm. **LA**: 187 ml. **RA**: 148 ml
- **Mitral regurgitation** I degree. **Tricuspid regurgitation** II degree
- **PA systolic pressure** 40-46 Hg mm

Multi-slice computed tomography

- normal coronary arteries
- dilatation of the all heart chambers, LV end-diastolic diameter 80 mm
- homogenous thinning of right ventricle
- no intracardiac thrombosis

Causes of deterioration and the potential therapeutic and diagnostic tactics

- **the accession of the myocarditis?**
- **increasing of tricuspid regurgitation and asynchrony due to ICD implantation?**
- **relapse of sustained tachyarrhythmia?**
- **natural follow-up of disease?**

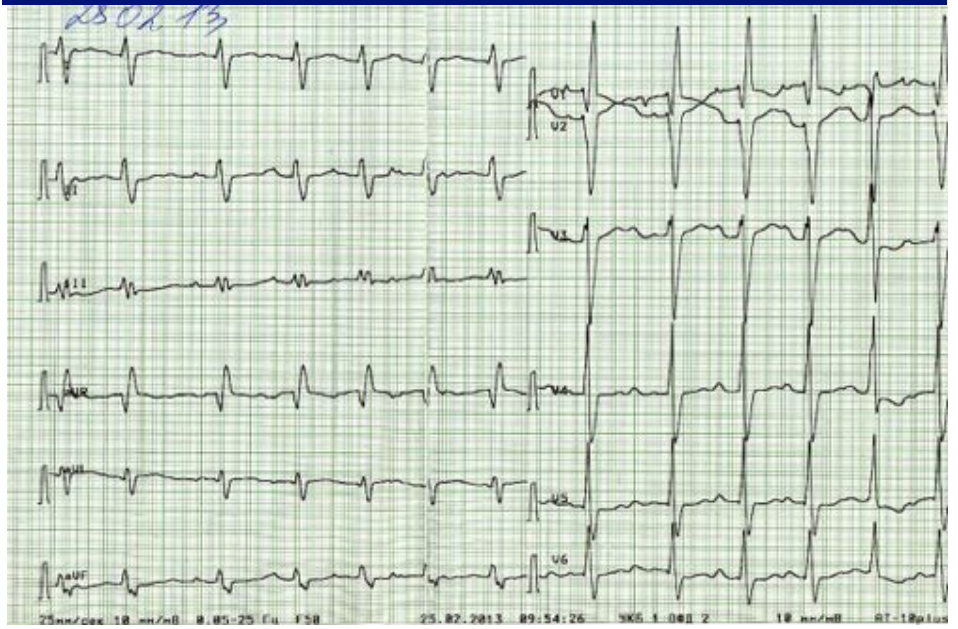
- perindopril 2.5 mg/day
- amiodarone 400 mg/day
- warfarin 2.5-3.75 mg/day
- furosemide 40-60 mg/day

➲ **CRT-D reimplantation?**

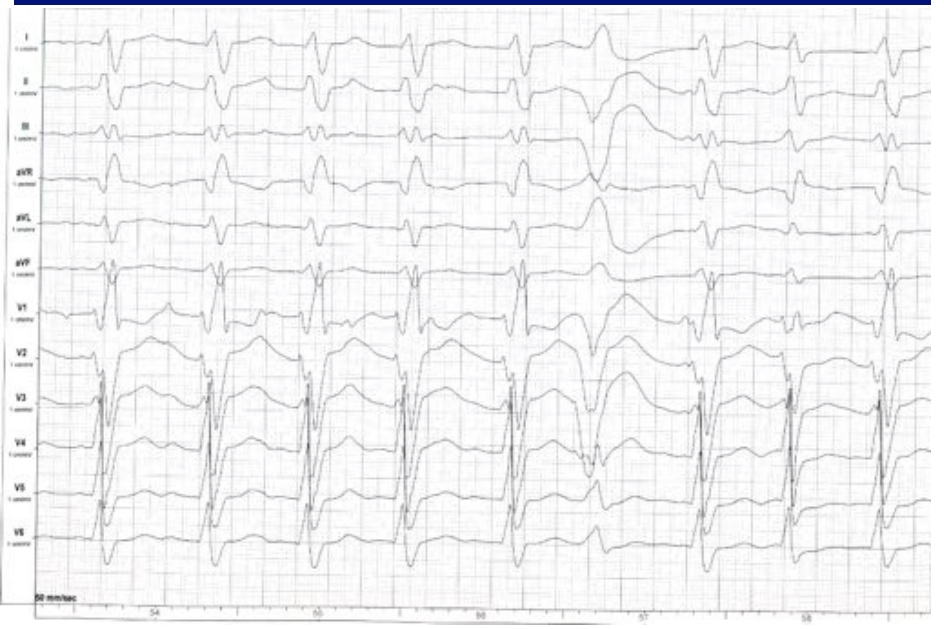
➲ **electrical cardioversion**

➲ **heart transplantation?**

ECG after cardioversion



ECG after ICD shocks

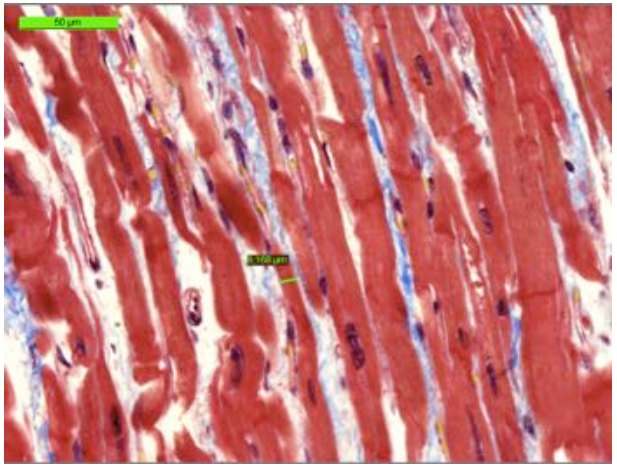
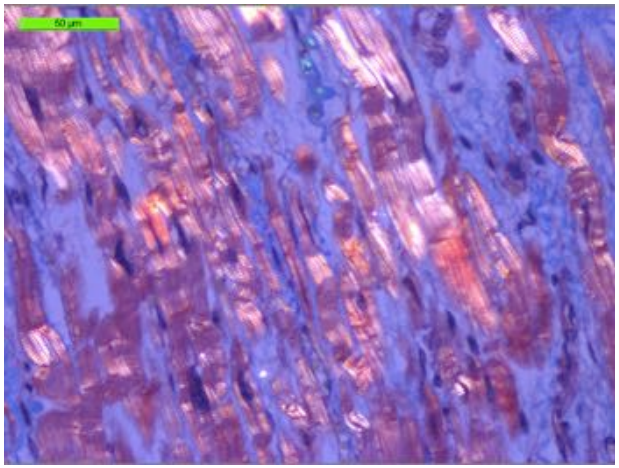
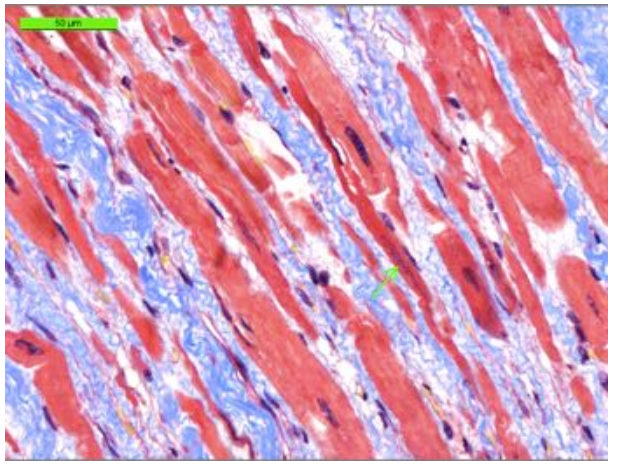


Urgency heart transplantation due to electrical storm

- **19.03.2013** – syncope, ICD shocks; emergency hospitalization in ICU
- **19.03.2013** – implantation of veno-arterial ECMO system
- **21.03.2013** - orthotopic heart transplantation; induction immunosuppression - bazoliximab
- **22.03.2013** - explantation of ECMO; tacrolimus + mycophenolic acid + methylprednisone
- **21.03.2013 – 17.04.2013:** temporary pacing 90-100/minute; rejection 0-I degree

explanted heart examination

Macroscopy: weight 470 g, sizes 11x9x4.5 cm; normal coronary arteries
myocardium flabby, homogeneous, pink-brown

Microscopy

Polymorphism of cardiomyocytes: there are atrophic, hypertrophic and normal cells with a tendency to atrophy; their relationship unequal.
Nucleus In cardiomyocytes: ugly shape with perinuclear edema; decaying nuclei (apoptosis).
Fibrosis: diffuse focal (most pronounced in the interventricular septum and the left ventricle), periarterial.
Interstitial edema.

Problems of heart transplantation in myopathies

◎ generally high perioperative risk (serious medical condition of the patients)

◎ difficulty of anesthesia due to:

- damage of respiratory muscles (long period of intubation, etc.)
- involving the back of the neck muscles (difficulty in intubation)

◎ increased risk of aspiration (gastric reflux)

◎ rhabdomyolysis

◎ the risk of malignant hyperthermia (disturbances of Ca ++ metabolism in skeletal muscle with the development of severe contractures)

- trigger are anesthetics, antidote is dantrolene
- optimal are total IV anesthesia and the use of non-depolarizing muscle relaxants

◎ worsening peripheral myopathy by the action steroids (atrophy of proximal muscle without necrosis, CK levels are normal):

- stimulation of catabolic path AKT1 / FOXO1
- decrease in protein synthesis
- hypokalemia

◎ increased risk of cardiomyopathy in the transplanted heart?

Heart transplantation in the Emery-Dreifuss muscular dystrophy and other genetic myopathies

cases report in Medline (EDMD)	**16**
first case report in EDMD	**1987 r.** *Baur X et al. Klin Wochenschr. 1987; 65 (15):738-45*
immediate success of heart transplantation in EDMD	**12 (4?)**
male/ female	**4/2 (10?)**

◎ **Italian register of LMNA-associated myopathies:** of the 78 patients, 17 (22%) had autosomal dominant Emery-Dreifuss muscular dystrophy 2 (EDMD2), ICD or pacemaker was implanted in 41 (53%) myopathic patients, heart transplantation was performed in 8 (10.3%) myopathic patients

Maggi L et al. Neurology. **2014 Oct 28;83(18):1634-44.**

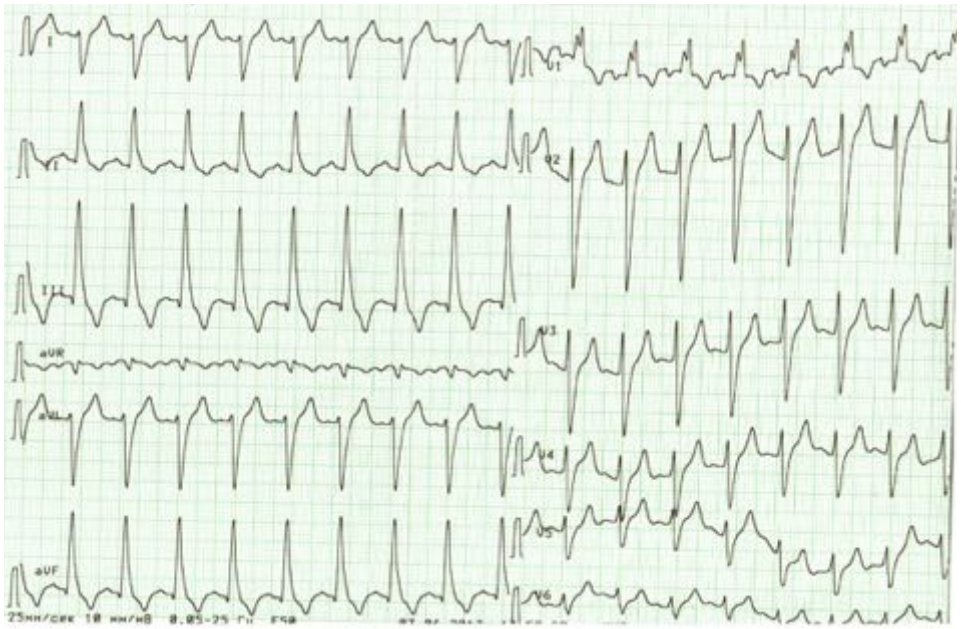
◎ **Berlin:** of 582 heart transplant recipients, six patients (1%) had muscular dystrophy associated with cardiomyopathy, all patients had an uneventful postoperative course; one patient died suddenly 27 months after operation

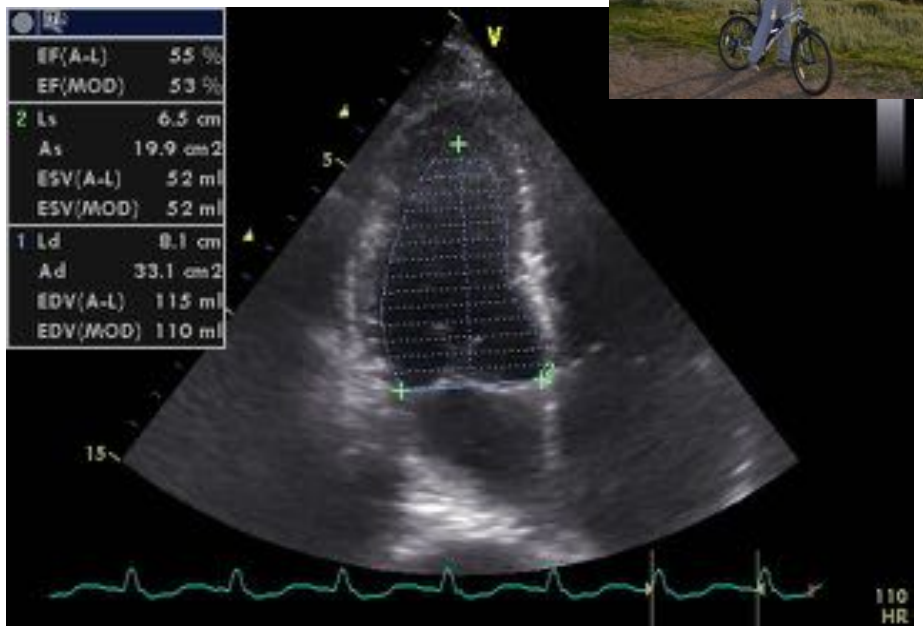
Rees W et al. J Heart Lung Transplant. **1993 Sep-Oct;12(5):804-7.**

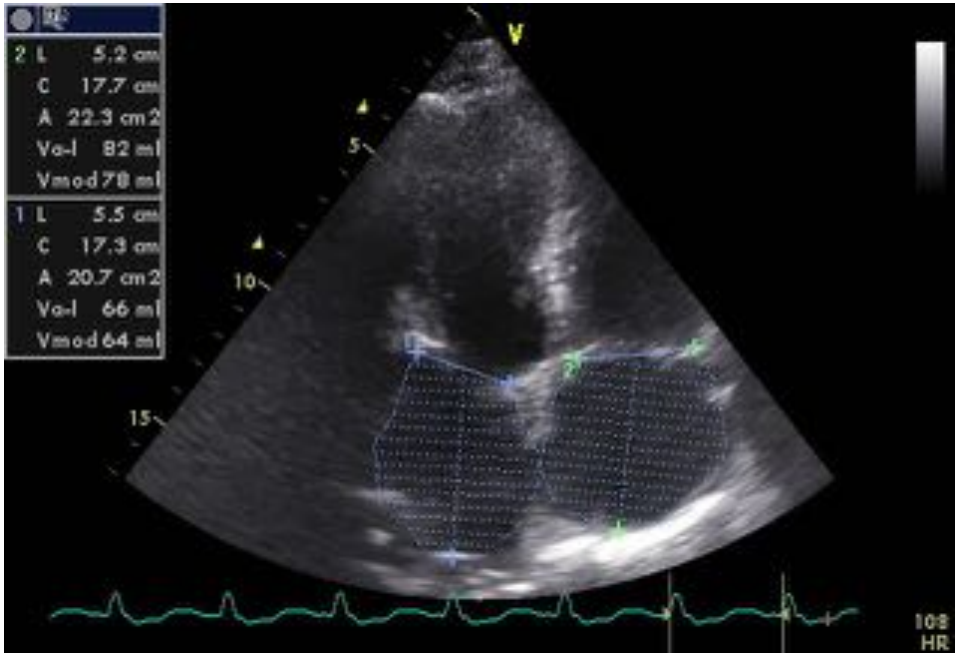
◎ **Madrid:** among 311 patients who underwent heart transplantation, five (2%) had end-stage cardiomyopathies related to inherited myopathies; mean age at the time of transplantation was 38.6 years (range from 24 to 55); all of them are alive with a good performance status

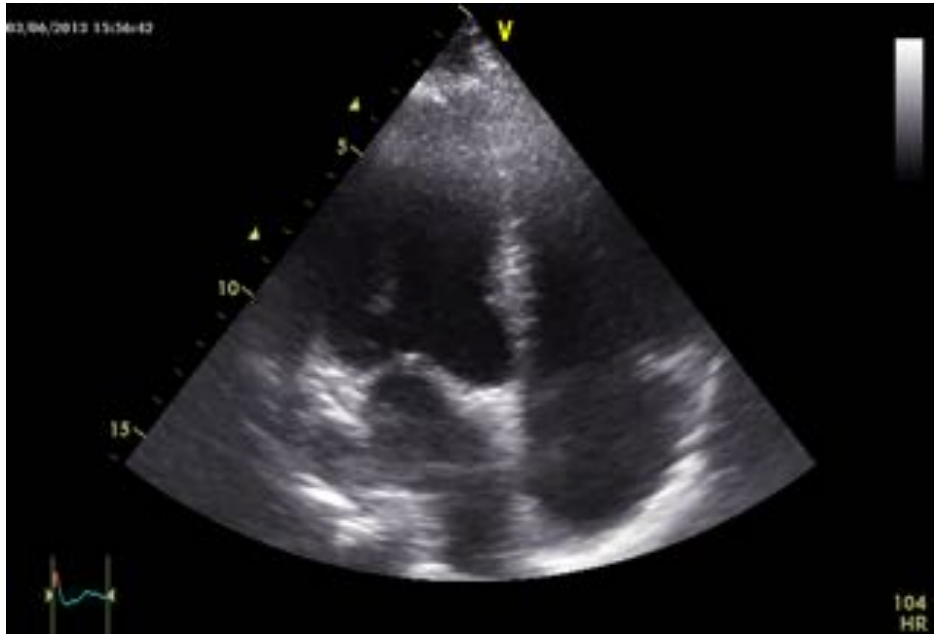
Ruiz-Cano MJ et al. Transplant Proc. 2003; 35(4):1513-5.

AFTER TRANSPLANTATION (follow-up 30 month)



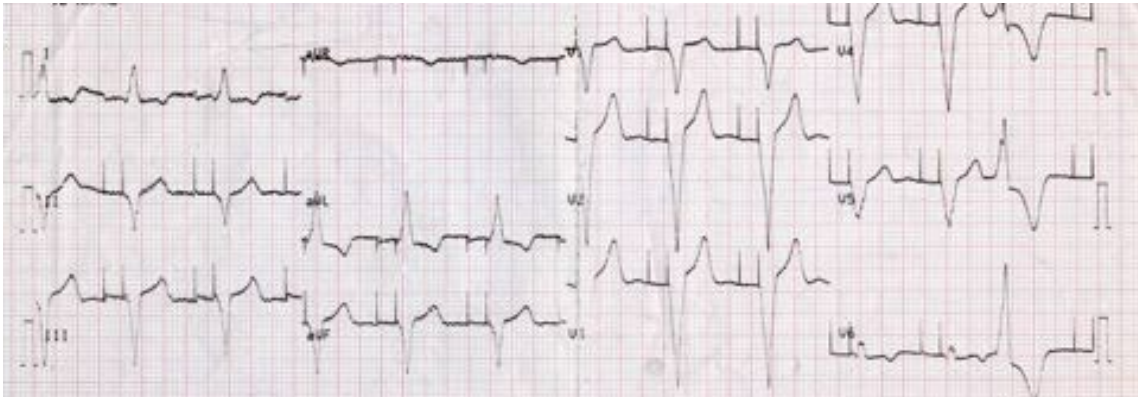






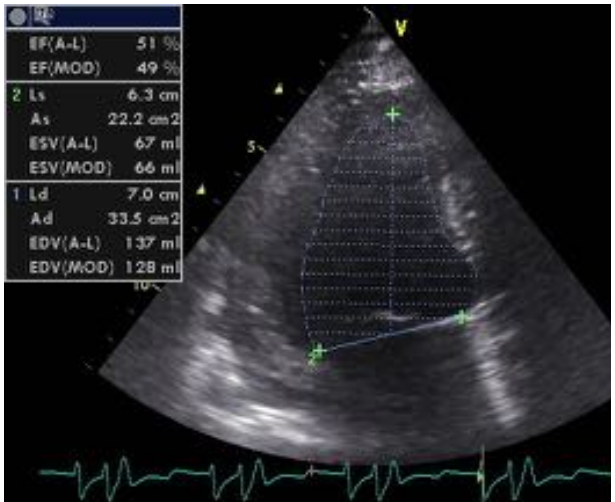
Examination of the mother of patient (63 years)

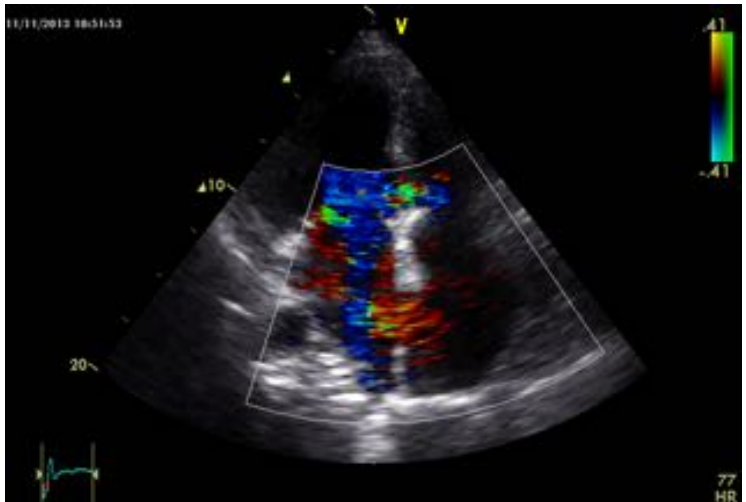
deletion c.del619C *EMD* in the heterozygous state

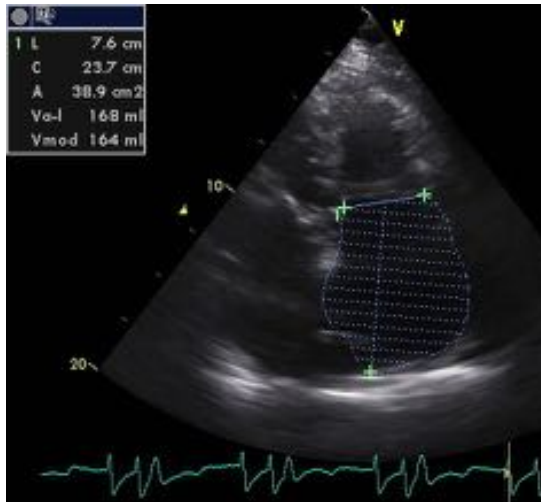


◎ **pacemaker** in 54 years due to SSS, AV block with syncope; moderate dyspnea
◎ **previous diagnoses** – arterial hypertension, coronary heart disease
◎ **Echo-CG**: LV EDD 6.4 cm, LV EF 50%, LA 164 ml, RA 150 ml, PA pressure 50 Hg mm
◎ **MSCT:** normal coronary arteries

Diagnosis: dilated cardiomyopathy (mild form of X-linked Emery-Dreifuss muscular dystrophy).







Conclusions

- cardiomyopathy in patients with primary myopathy (Emery-Dreifuss muscular dystrophy, EDMD) may progress rapidly despite earlier stable course and requires regular monitoring cardiologist

- the presence of mutations in two genes can explain unusually severe cardiomyopathy in our patient with Emeri-Dreifuss muscular dystrophy

- in all cases of «unexplained» decompensation in EDMD patients should be excluded myocarditis

- verification of a specific genetic variant of myopathy with cardiac involvement is essential to determine the treatment, including surgery

- indications to RF ablation and ICD implantation in EDMD patients should be determined considering immediate and long-term prognosis

- despite peripheral myopathy and limitations in the use of anesthetics, heart transplantation can be successfully performed in patients with EDMD using modern regimens of immunosuppression

- X-linked EDMD in women occurs in a mild form behind the masks of more frequent heart disease and may not be recognized for a long time