

**Iowa Wellstone Dystroglycanopathy  
Conference 07/17/2021:  
Cardiology Concerns in Dystroglycanopathy**

**Ferhaan Ahmad, MD, PhD, FRCPC, FAHA, FACC**

**Associate Professor of Internal Medicine, Radiology, and Molecular  
Physiology and Biophysics**

**Director, Cardiovascular Genetics Program**

**Director, Cardiovascular Disease Fellowship Program**

**Senior Associate Editor, *Journal of the American Heart Association***

**Division of Cardiovascular Medicine**

**University of Iowa Carver College of Medicine**

**Iowa City, Iowa**

**[ferhaan-ahmad@uiowa.edu](mailto:ferhaan-ahmad@uiowa.edu)**



# Disclosures

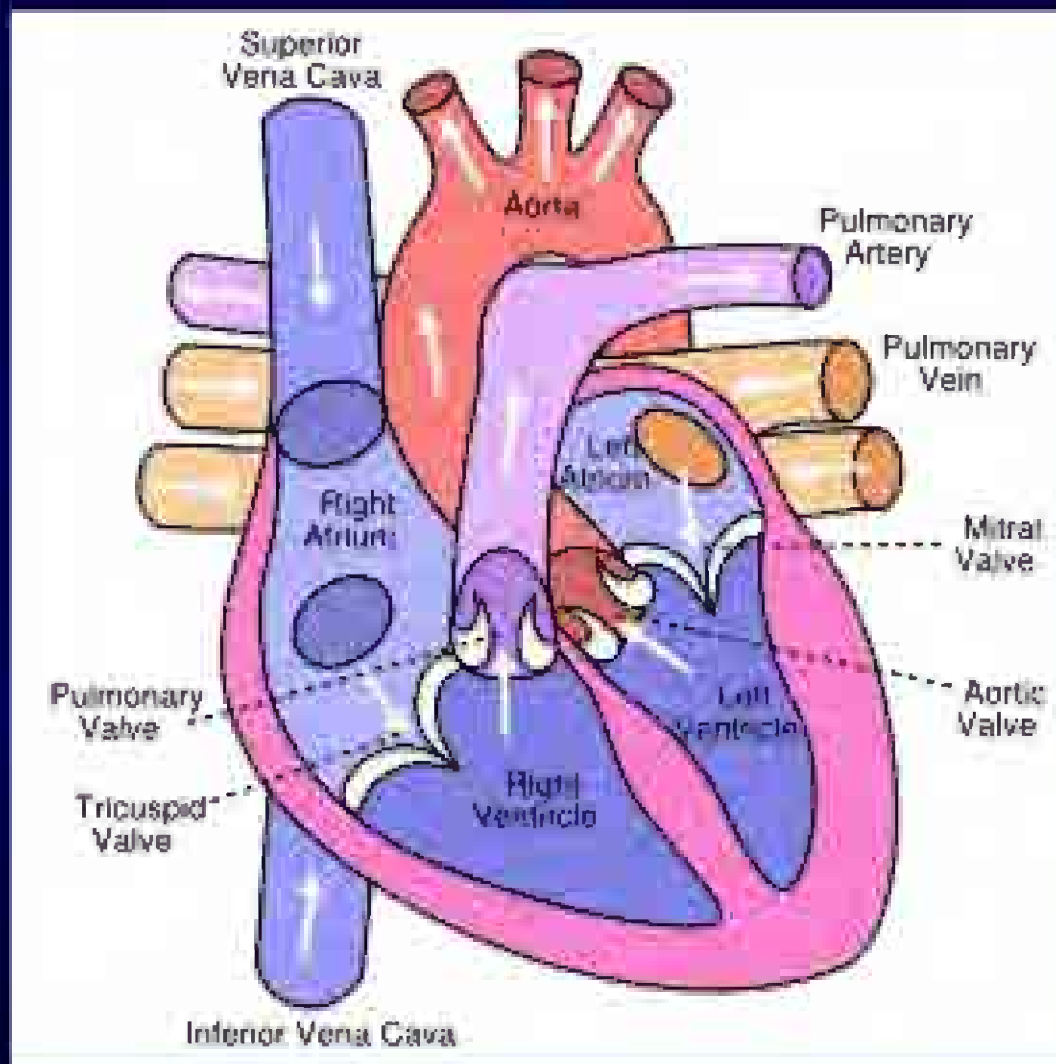
- **Research funding from Bristol Myers Squibb**

# Outline

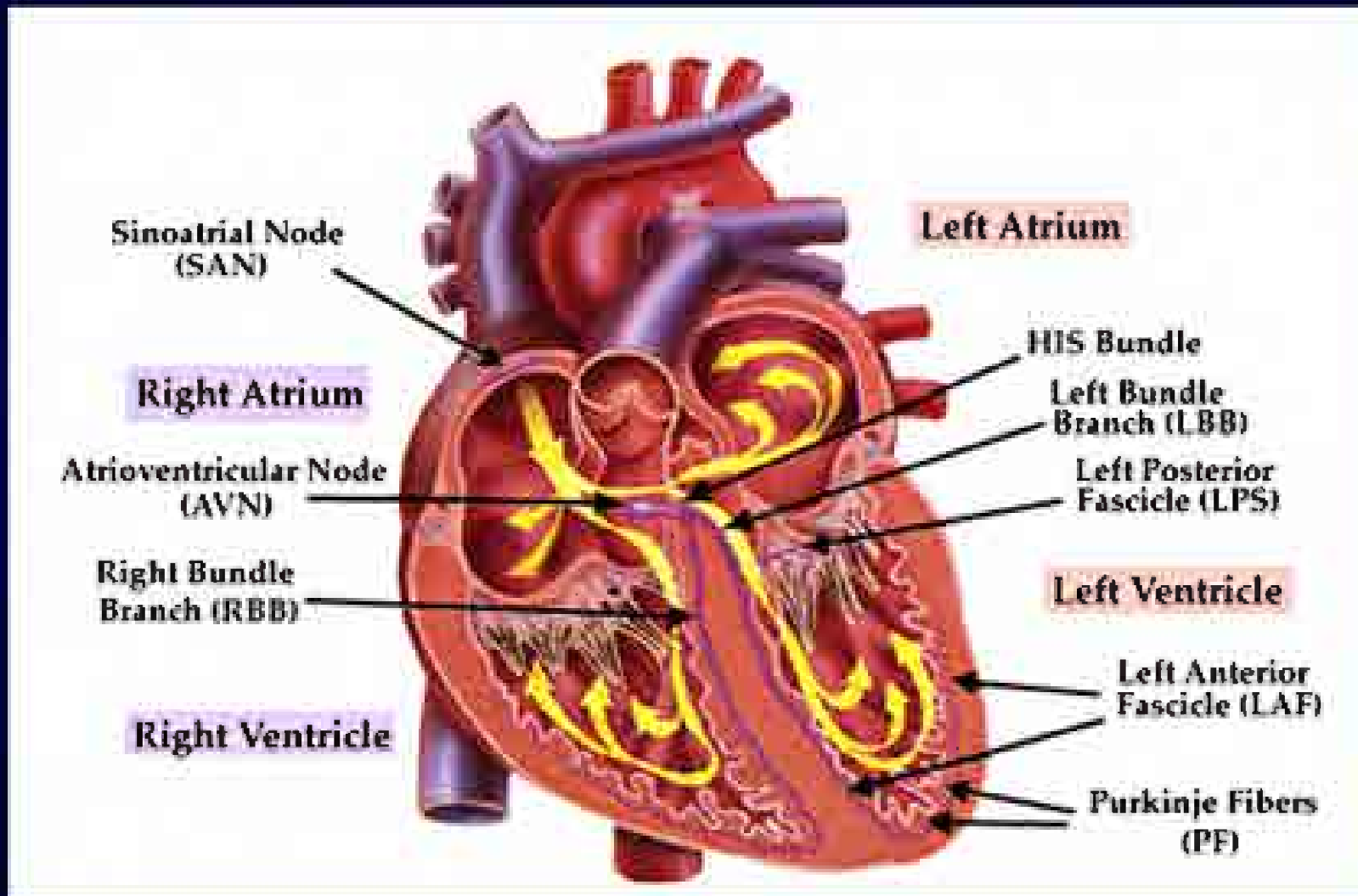
- **Review of heart structure and function**
- **Heart changes in dystroglycanopathies**
- **Evaluation and monitoring of heart problems**
- **Treatment of heart problems**

# **Structure and Function of the Heart**

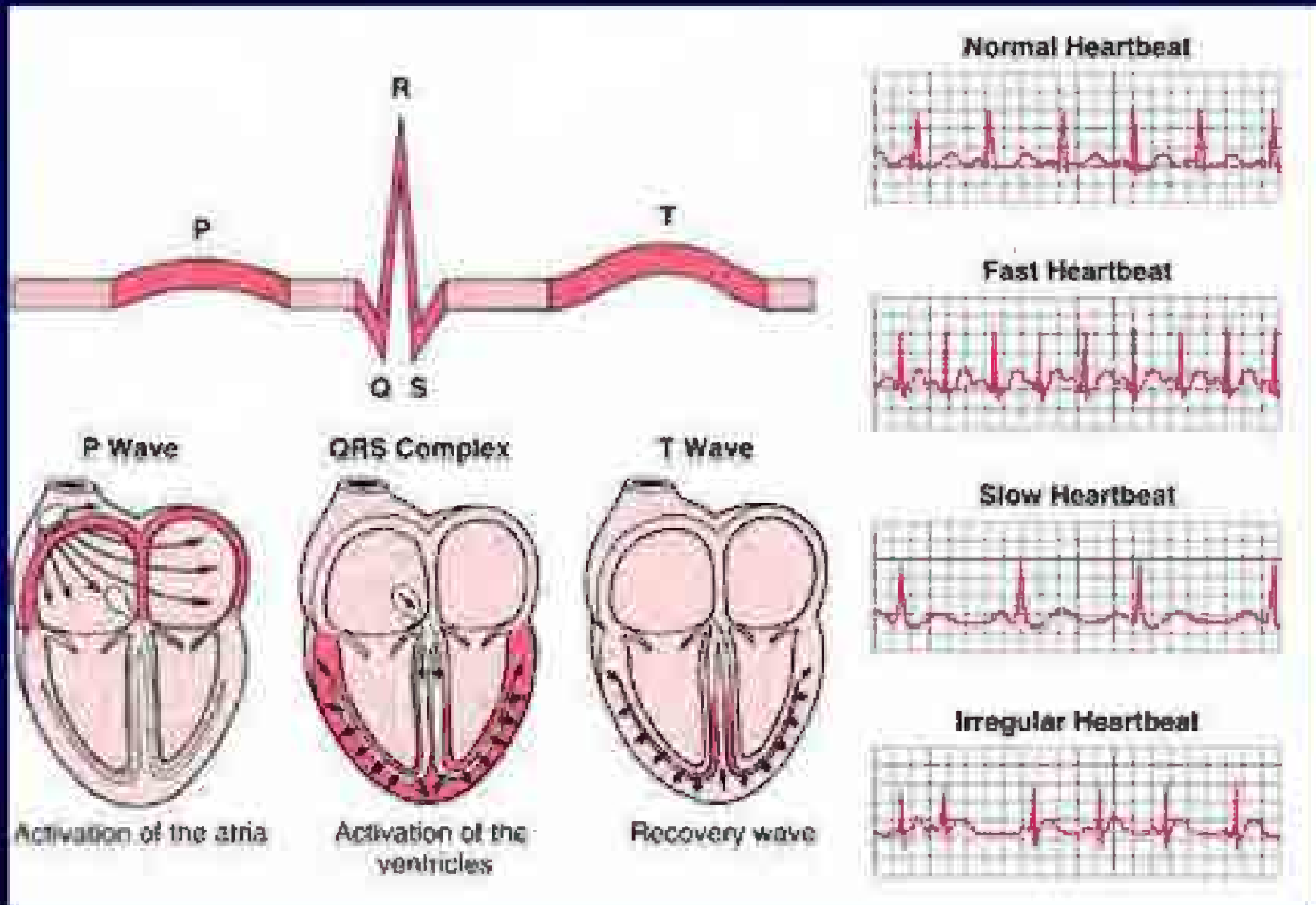
# Structure and Function of the Heart



# The Electrical System of the Heart



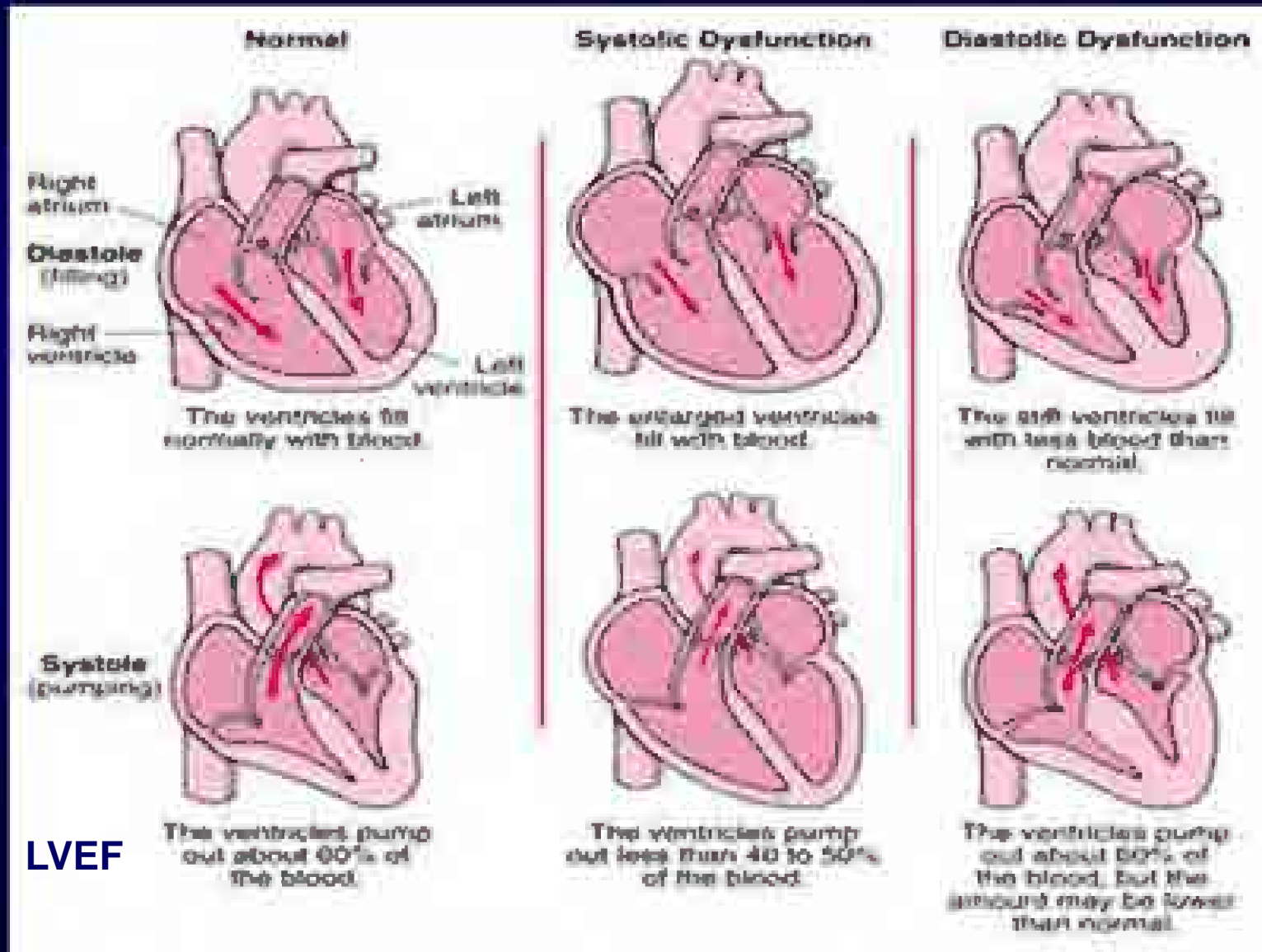
# Electrical Conduction and the Electrocardiogram (ECG)



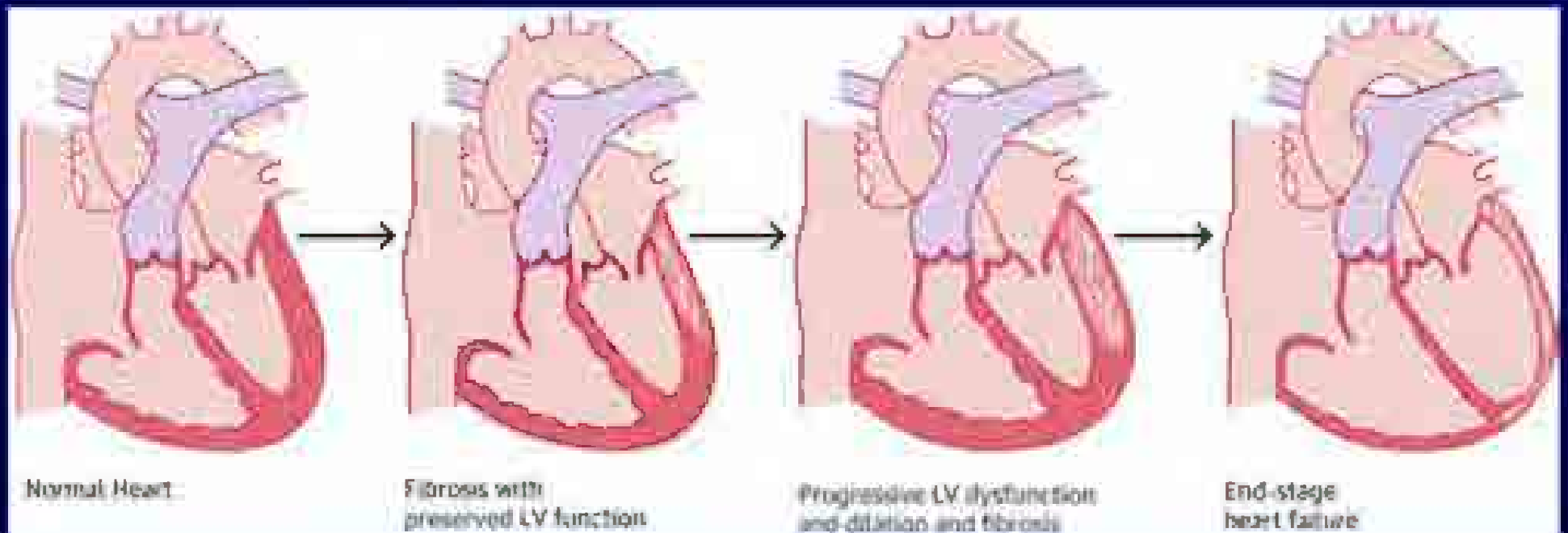
# **Heart Changes in Dystroglycanopathies**



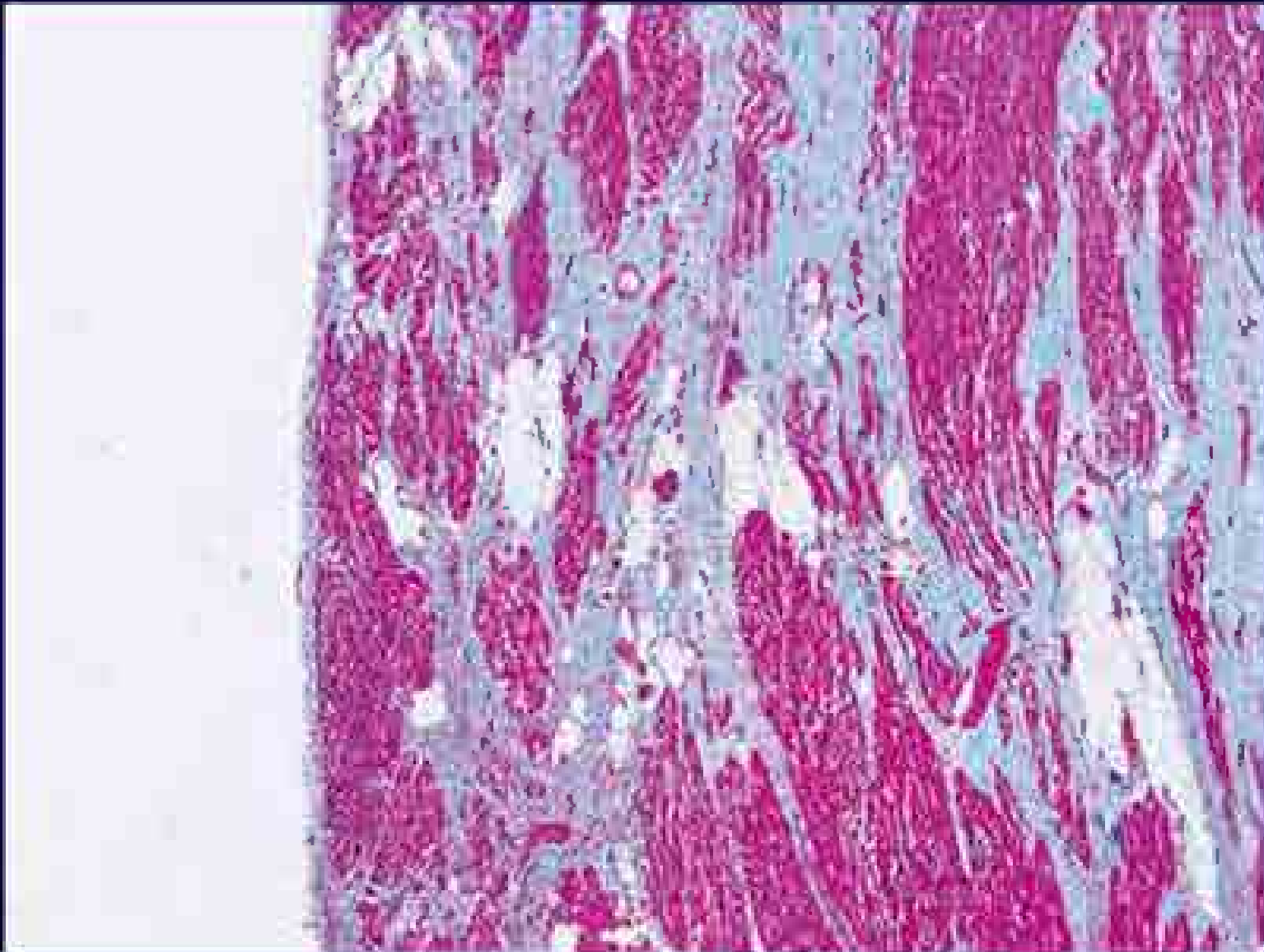
# Heart Failure



# Progression of Heart Failure in Neuromuscular Disorders

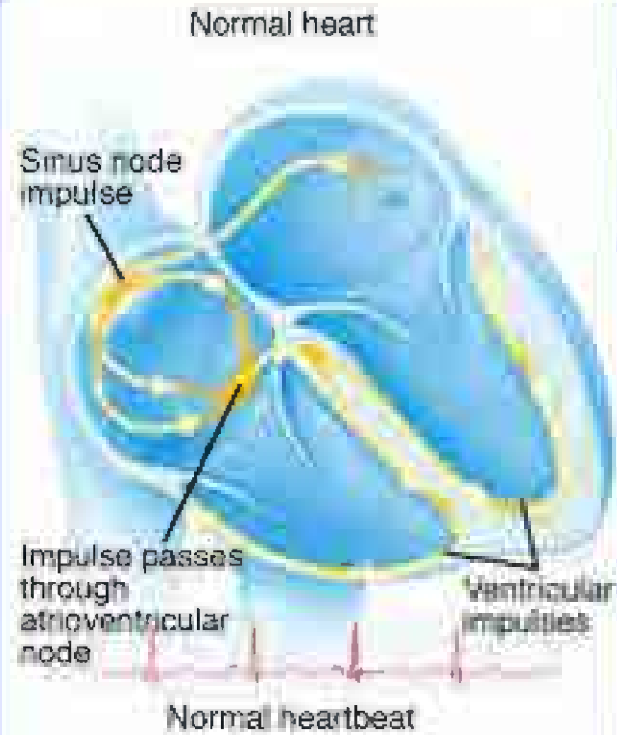


# Heart Scarring in Duchenne Muscular Dystrophy (DMD)



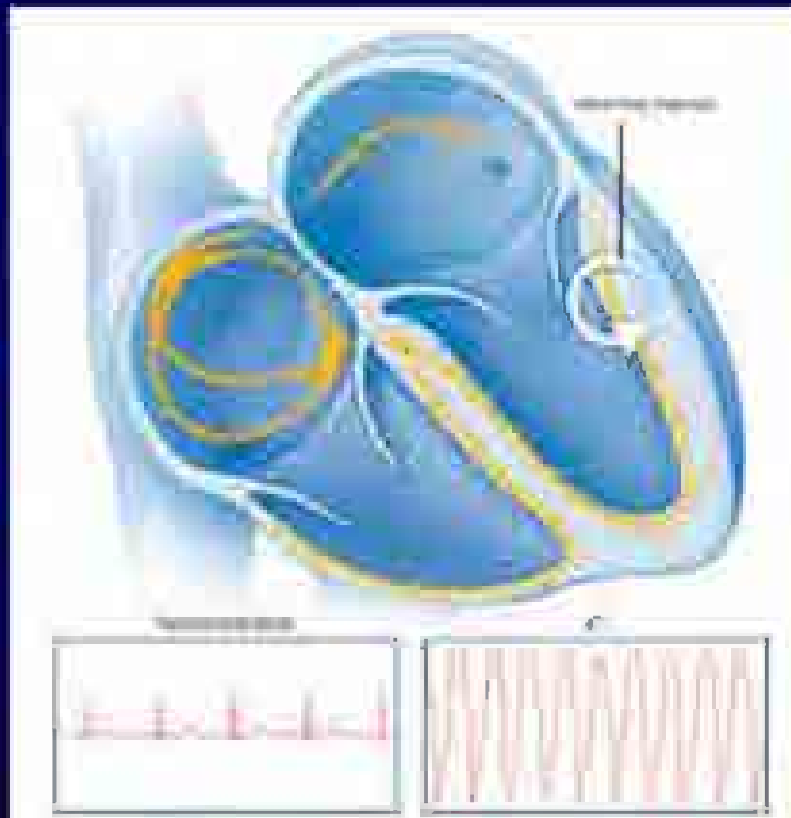
# Ventricular Tachycardia and Ventricular Fibrillation

## Normal

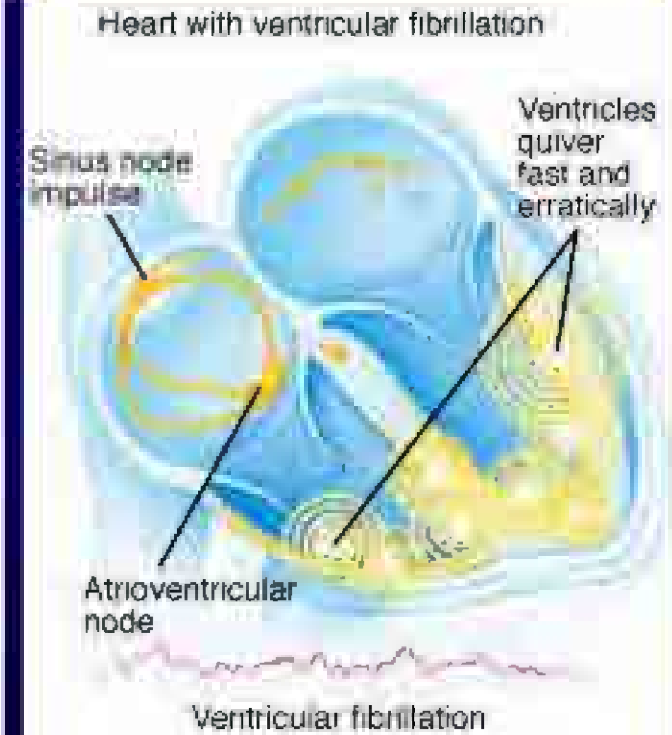


© MAYO FOUNDATION FOR MEDICAL EDUCATION

## Ventricular Tachycardia



## Ventricular Fibrillation



RESEARCH. ALL RIGHTS RESERVED.

# Arrhythmia

00 25 AP12: DIGITAL SUBSTRATE 9 20 17 7 (100 kHz)  
 01 25 AP13: LEFT ATRIUM PA-12 (100 kHz) (100 kHz)  
 02 25 AP14: DIGITAL SUBSTRATE 9 20 17 7 (100 kHz)  
 03 25 AP15: DIGITAL SUBSTRATE 9 20 17 7 (100 kHz)  
 04 25 AP16: DIGITAL SUBSTRATE 9 20 17 7 (100 kHz)  
 05 25 AP17: DIGITAL SUBSTRATE 9 20 17 7 (100 kHz)

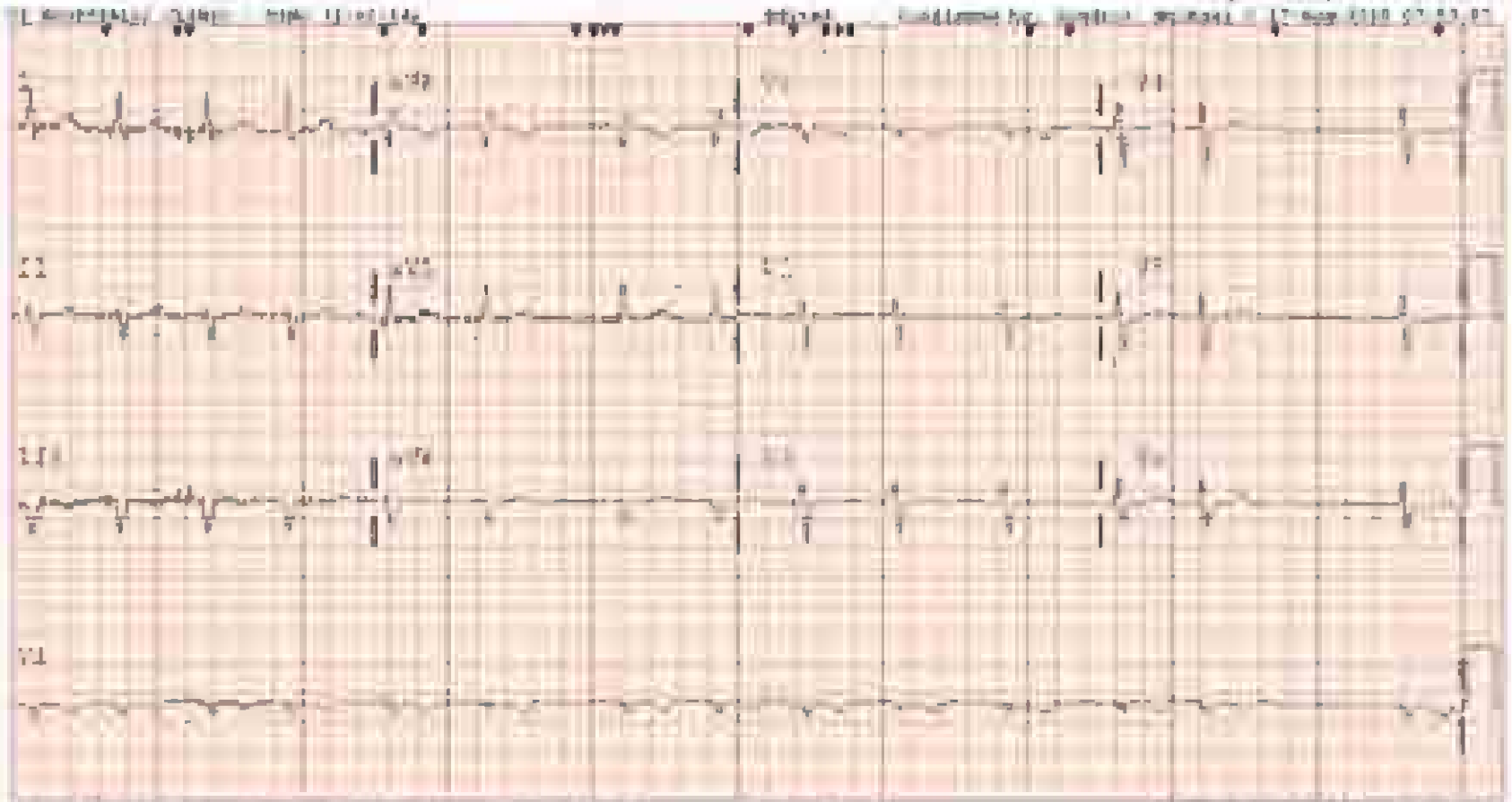
Patient Name: [REDACTED]  
 Date: 11/10/07  
 Time: 11:00

— 2.5mV —

— 2.5mV —

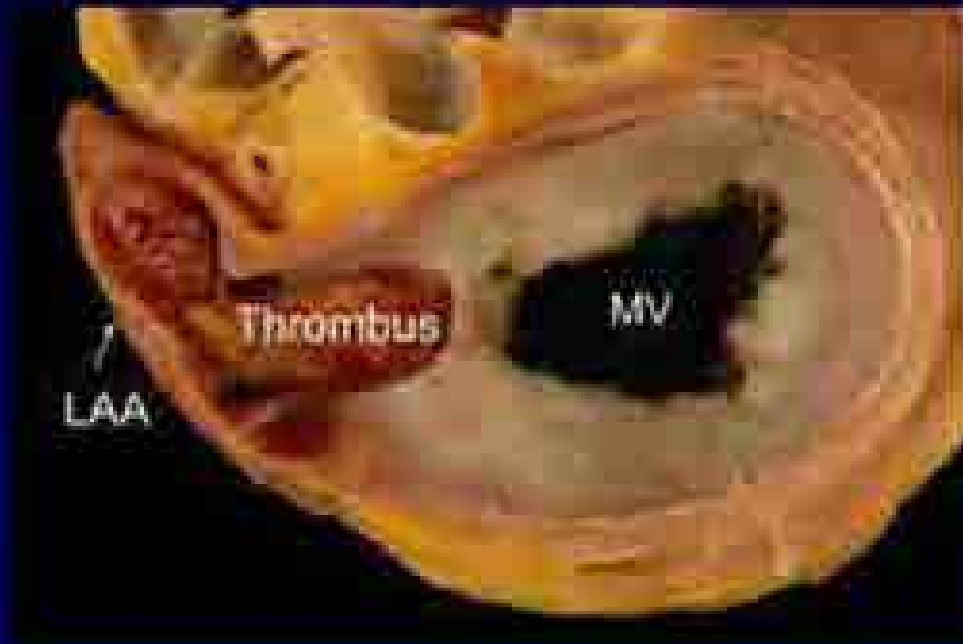
06 25 AP18: DIGITAL SUBSTRATE 9 20 17 7 (100 kHz)  
 07 25 AP19: DIGITAL SUBSTRATE 9 20 17 7 (100 kHz)  
 08 25 AP20: DIGITAL SUBSTRATE 9 20 17 7 (100 kHz)

Patient Name: [REDACTED]  
 Date: 11/10/07  
 Time: 11:00

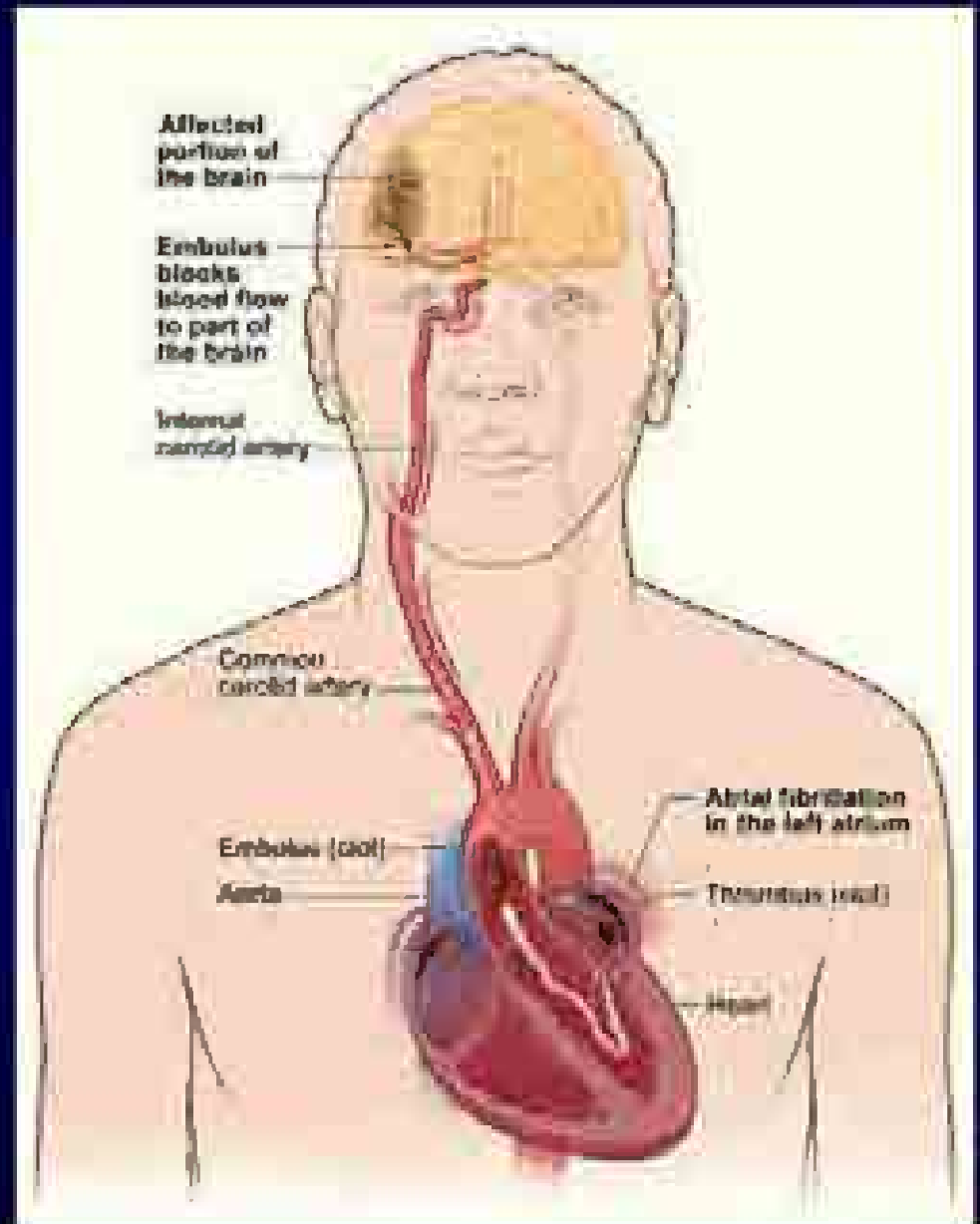


1000 2000 3000 4000 5000 6000 7000 8000 9000 10000

# Atrial clots in atrial fibrillation can cause strokes.

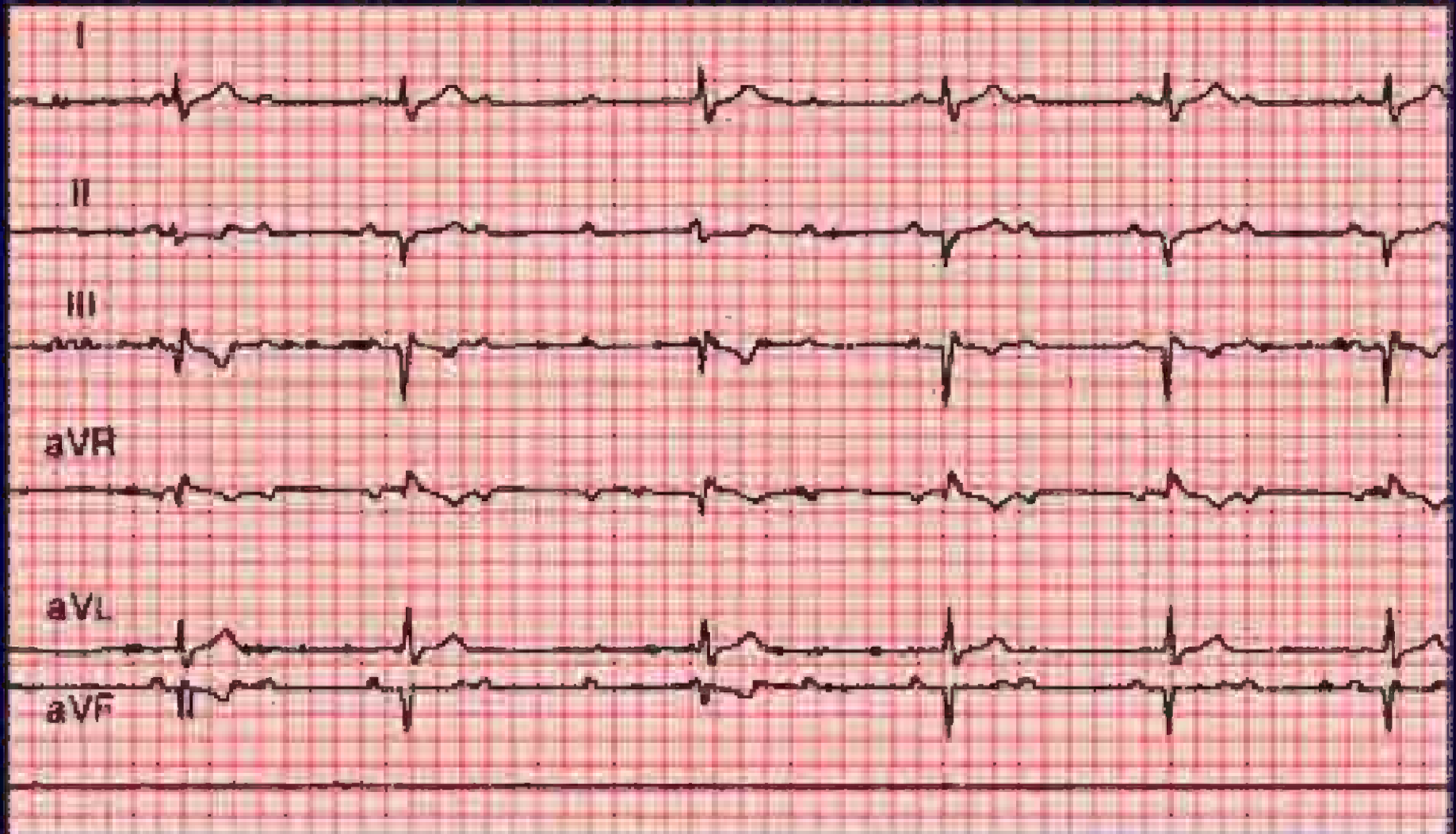


doctorstrizhak.com



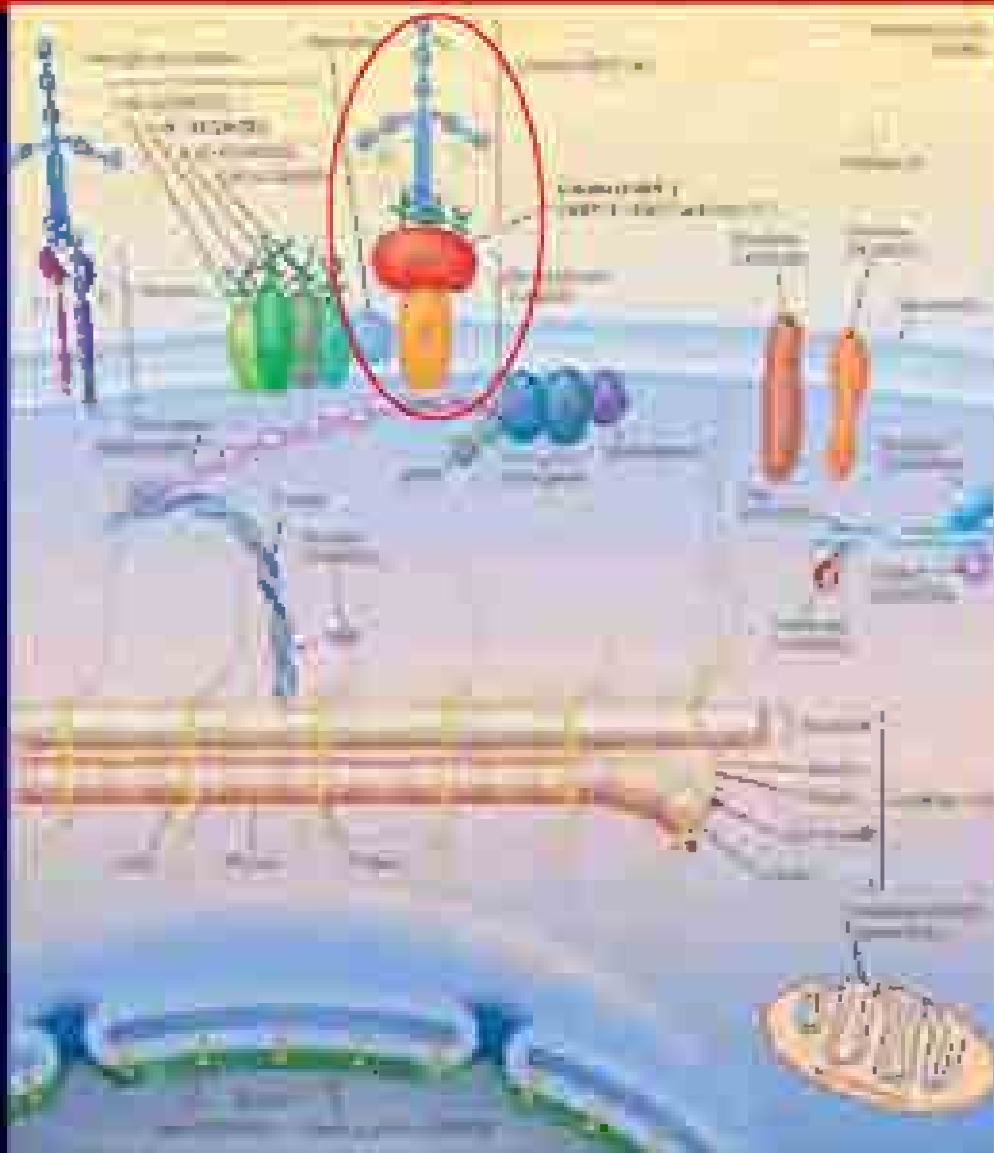


# Complete Heart Block





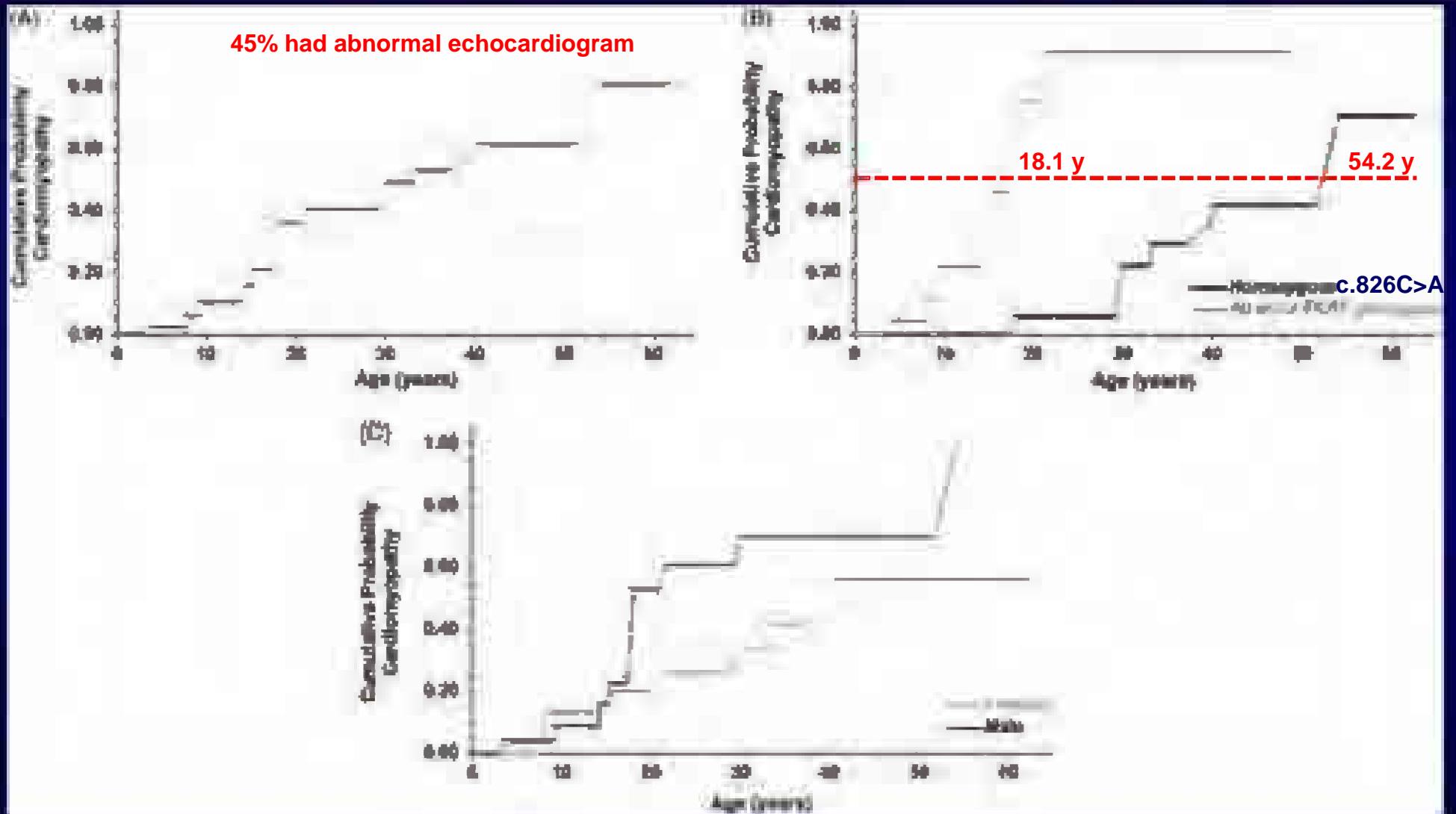
# Proteins Implicated in Neuromuscular Diseases Associated with Cardiac Involvement



# Dystroglycanopathies and the Heart

<u>Disease</u>	<u>Genes</u>	<u>Onset</u>
Walker-Warburg Syndrome and Muscle Eye Brain Disease	ALG13, B3GLNT2, B4GAT1, DAG1, <b>FKRP</b> , <b>FKTN</b> , GMPPB, ISPD, LARGE, POMGnT1, POMGnT2, <b>POMT1</b> , <b>POMT2</b> , RXYLT1/TMEM5	Birth Infancy
Fukuyama Congenital Muscular Dystrophy	<b>FKTN</b>	Birth Infancy
Congenital Muscular Dystrophy	<b>DOLK</b> , DPM1, DPM2, <b>DPM3</b> , <b>FKRP</b> , <b>FKTN</b> , <b>POMT1</b> , <b>POMT2</b> , POMGnT1	Birth Infancy
Limb Girdle Muscular Dystrophy	DAG1, <b>FKRP</b> , <b>FKTN</b> , GMPPB, ISPD, <b>POMT1</b> , <b>POMT2</b> , POMGnT1, POMGnT2	Childhood or Early Adulthood

# Echocardiography in LGMDR9 (*FKRP*)



# Arrhythmias in LGMDR9 (*FKRP*)

**Table 3**

## Holter-monitoring results

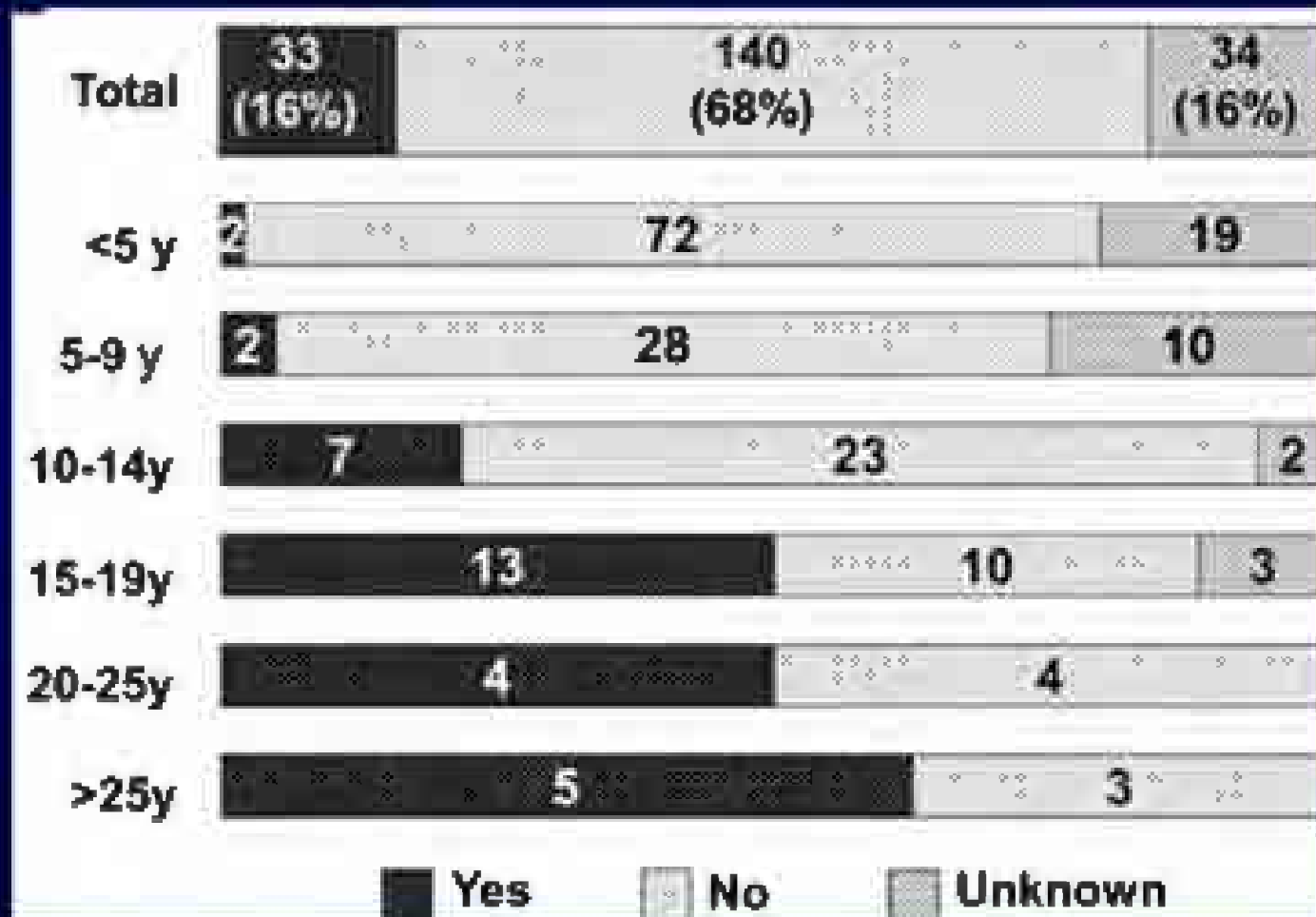
Diagnosis	LGMD2I (n = 20)
SVT, n (%)	7 (35)
VPC/h, median (range)	5 (0 – 78)
Frequent VPC, n (%)	2 (10)
NSVT, n (%)	2 (10)

Frequent VPC: >30 ventricular premature contractions/hour.

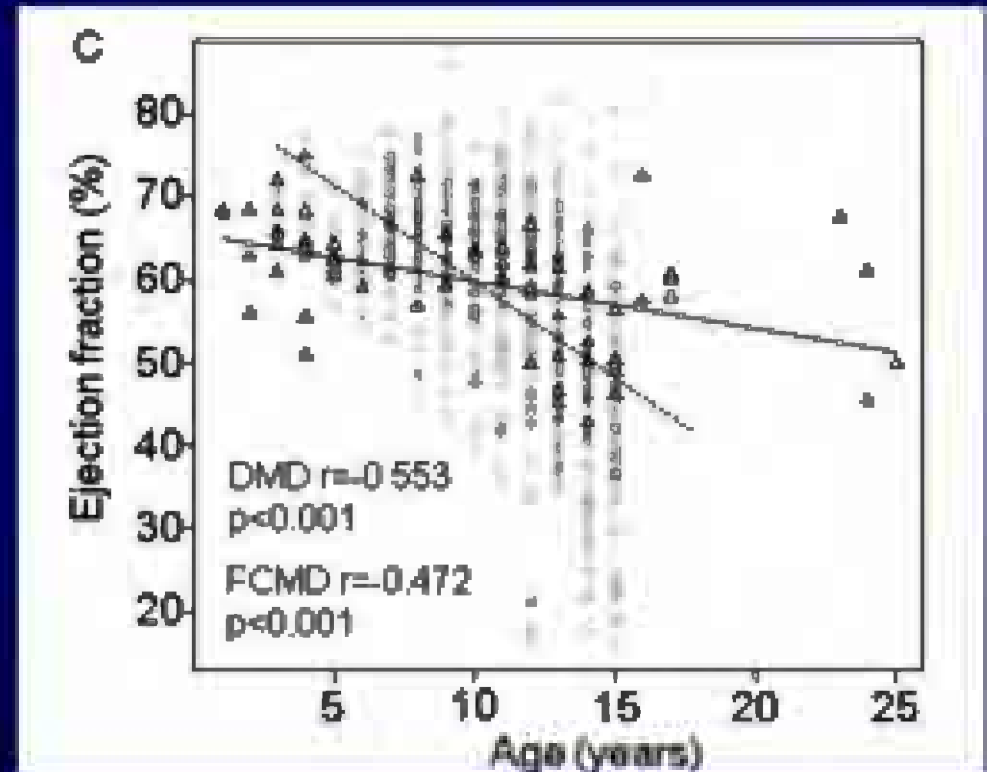
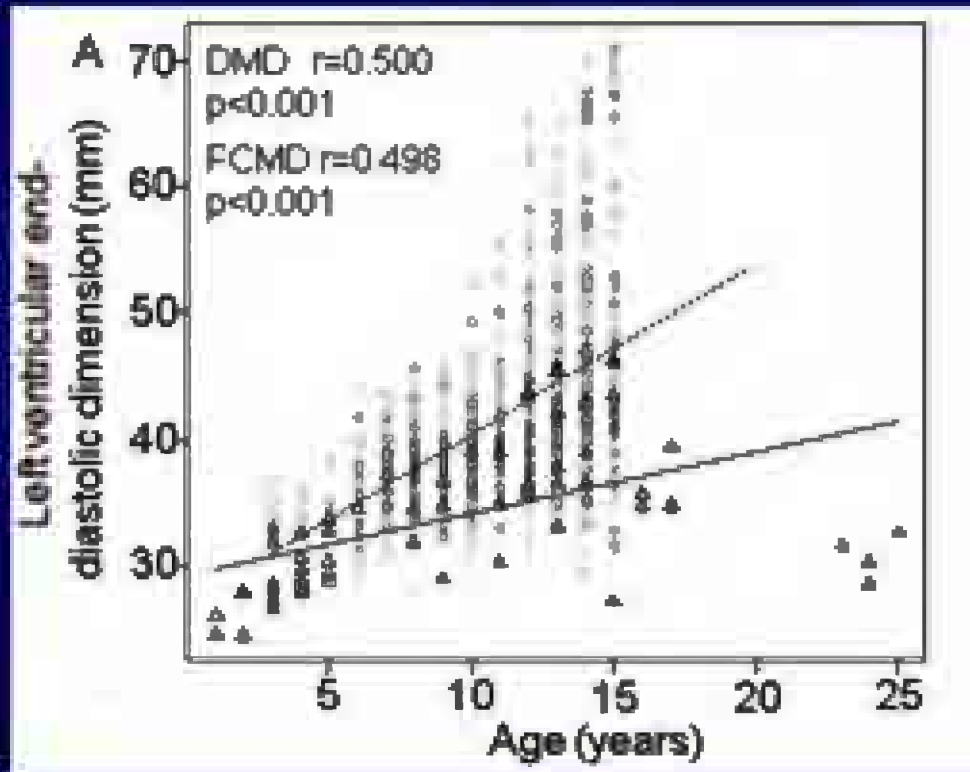
NSVT: non-sustained ventricular tachycardia.

SVT: supraventricular tachycardia.

# Heart Failure in Fukuyama Congenital Muscular Dystrophy (FCMD)



# Heart Failure in Fukuyama Congenital Muscular Dystrophy (FKTM)



# Symptoms

## Heart Failure

- Shortness of breath
  - After lying down
  - Waking you up at night
  - With exertion
- Swelling in the ankles
- Night cough
- Symptoms can be underestimated because of poor mobility and nighttime ventilation

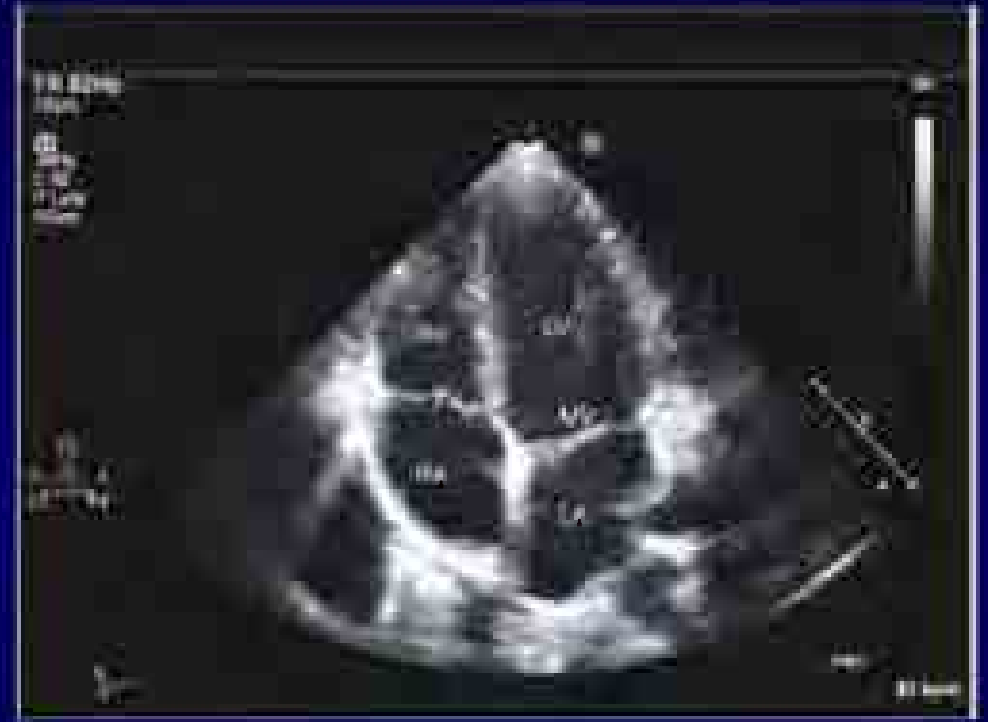
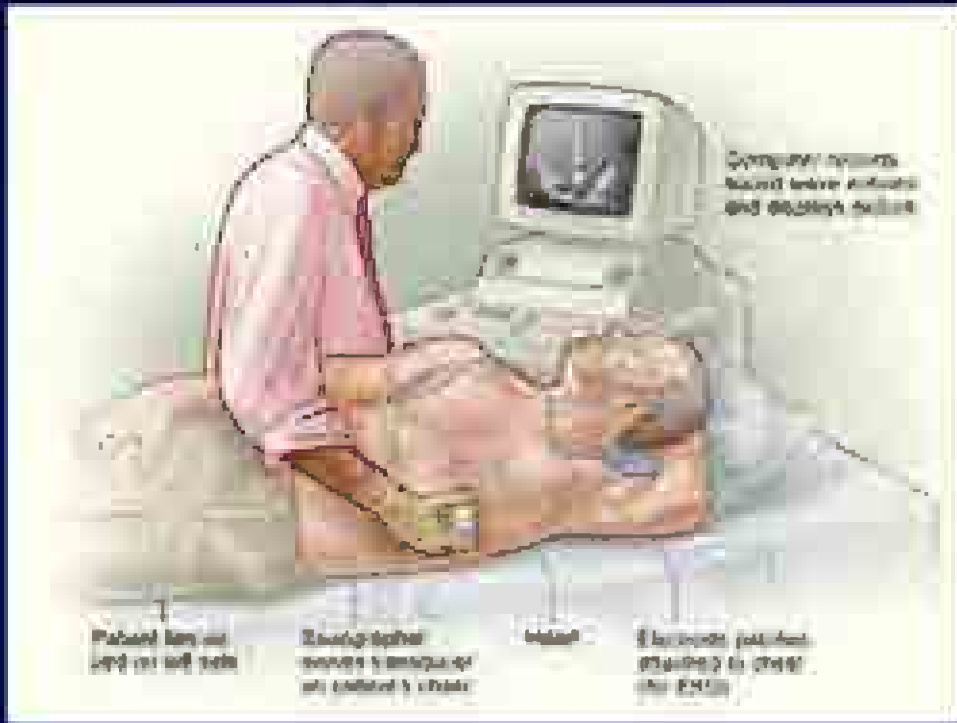
## Arrhythmias and Conduction Abnormalities

- Palpitations
- Lightheadedness
- Fainting
- Strokes or mini-strokes

# **Evaluation of Heart Problems**



# Echocardiography

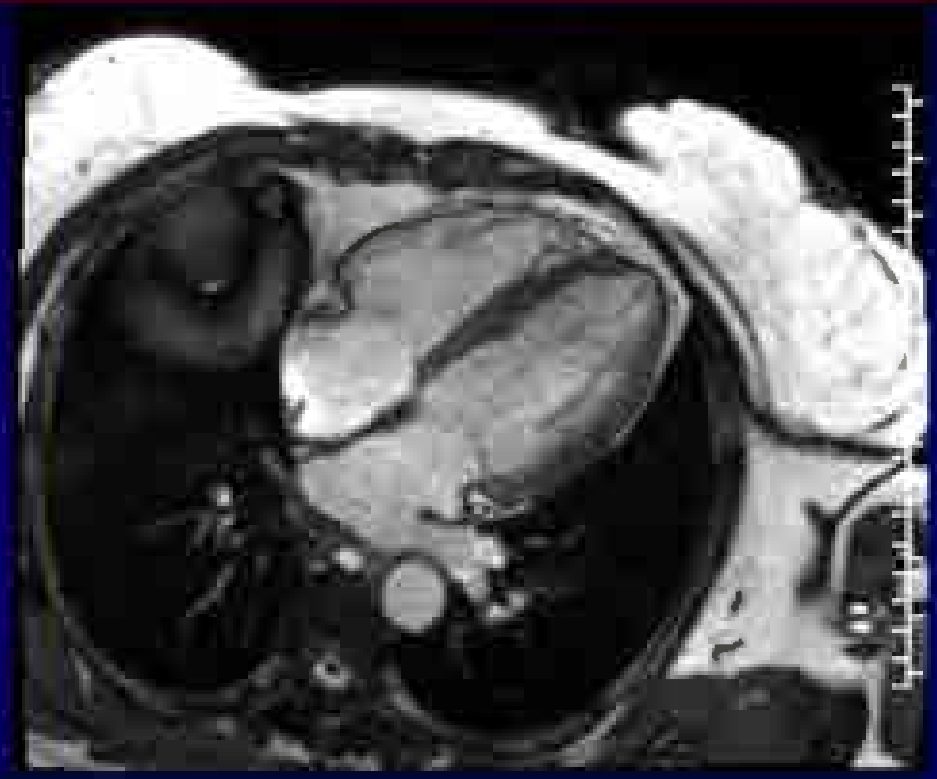


- Detects dilated heart, decreased contraction (EF, GLS)
- Widely available, relatively inexpensive
- Imaging limited by variations in body structure and respiratory dysfunction

# Cardiac MRI



Getty Images



heartmri.org

- Detects dilated heart, decreased contraction (EF, strain)
- Detects heart scarring even before other abnormalities
- Imaging limited by metal implants and motion
- May require sedation, expensive, less widely available

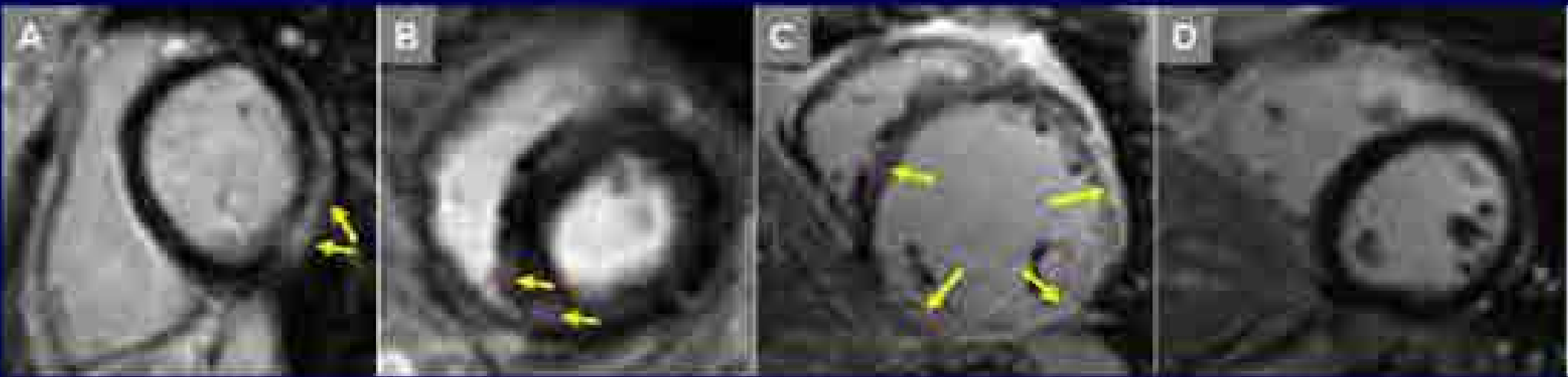
# Cardiac MRI

LGMD

LGMD

FKRP

Healthy

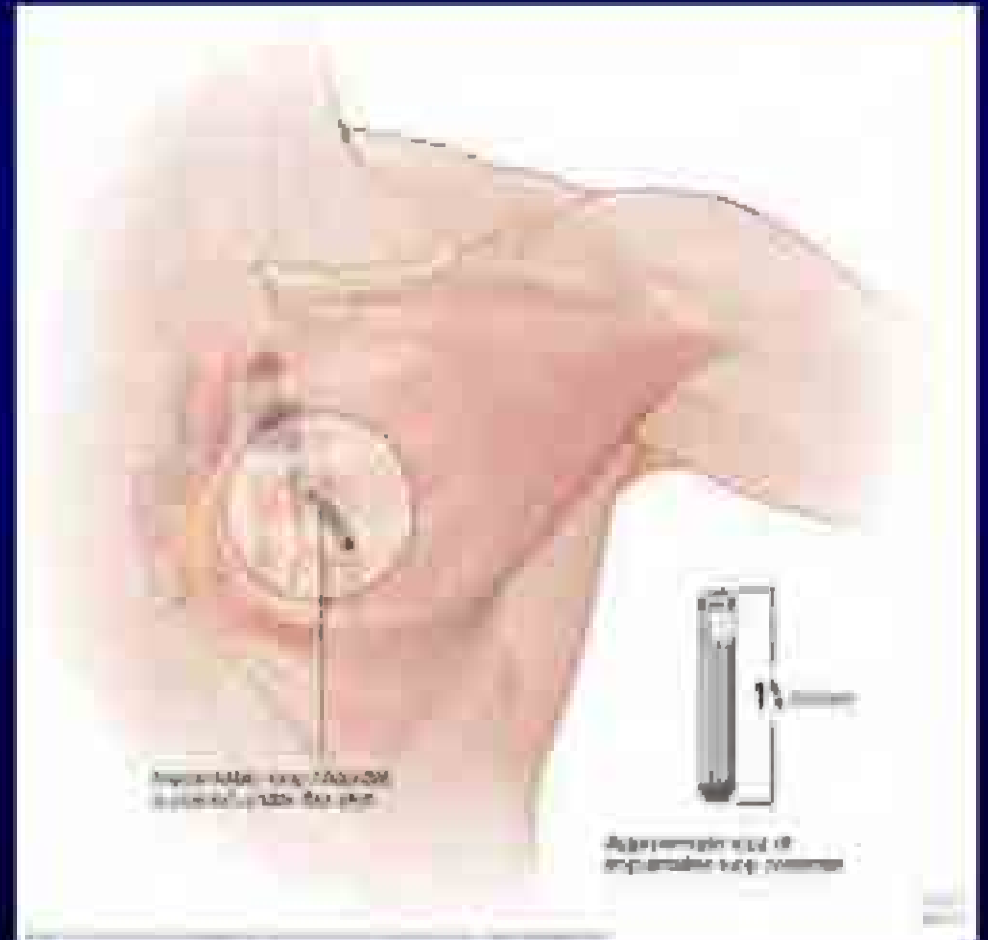


# Longer Electrocardiographic Monitoring

## Holter Monitor



## Implantable Loop Recorder (ILR)



# General Heart Recommendations

- **Proactive approach to screening, diagnosis, and management of cardiovascular complications.**
- **Cardiac evaluation should be performed before anesthesia or sedation in any patient at risk for cardiac involvement.**
- **For patients believed to be at increased cardiac risk during surgery, cardiac monitoring by an anesthesiologist experienced in the care of patients with neuromuscular disorders should occur, and the procedure should take place in a center with appropriate intensive care facilities.**

# Intervals for Heart Evaluation

- **Initial heart evaluation at diagnosis.**
- **Every 2 years if normal heart findings and no symptoms.**
- **At least every year if abnormal heart findings.**
- **More frequently if heart failure.**

# **Treatment of Heart Problems**

## **Evidence in dystroglycanopathies is limited.**

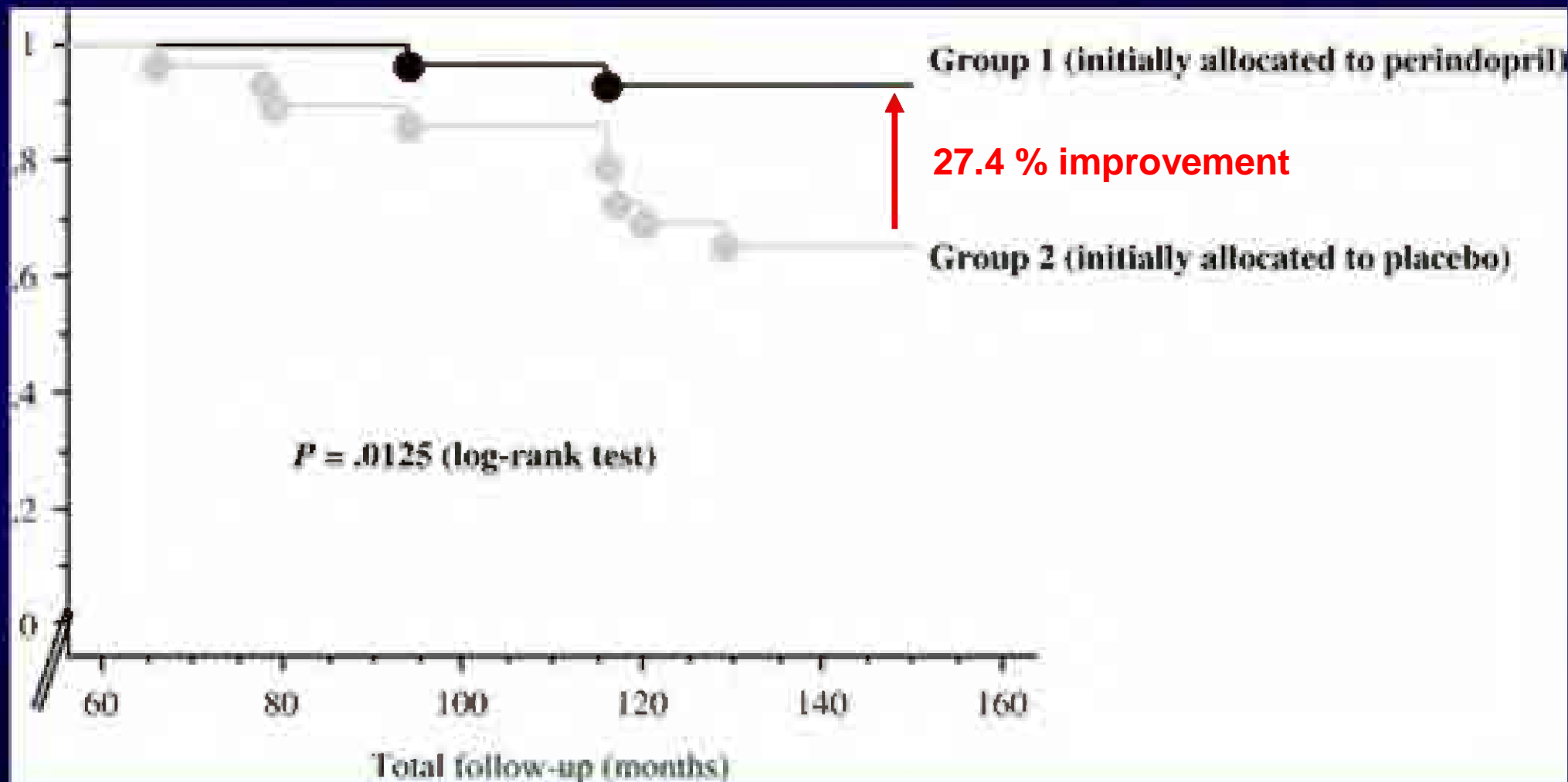
- **Almost no randomized controlled clinical trials**
- **Most studies are in Duchenne muscular dystrophy (DMD)**
- **Must extrapolate from studies in adults with heart failure from other causes**



# Graded Therapy for Heart Failure

- ACEI / ARB

# Survival of Duchenne Muscular Dystrophy (DMD) Patients Initially Randomized to Perindopril versus Placebo



# **ACE Inhibitors (ACEIs) or Angiotensin Receptor Blockers (ARBs)**

- **ACEI or ARB with a reduced left ventricular ejection fraction (LVEF) in all patients.**
- **Perhaps start earlier in patients at high risk of heart failure.**

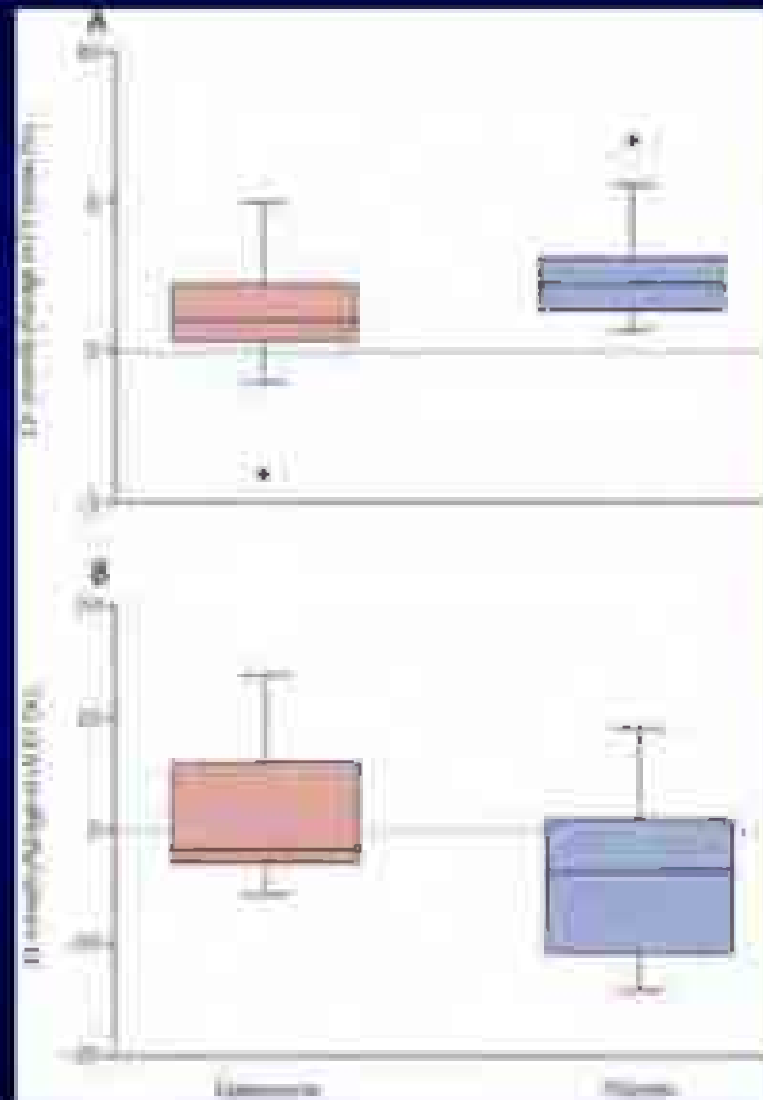
# Graded Therapy for Heart Failure

- ACEI / ARB

- MRA

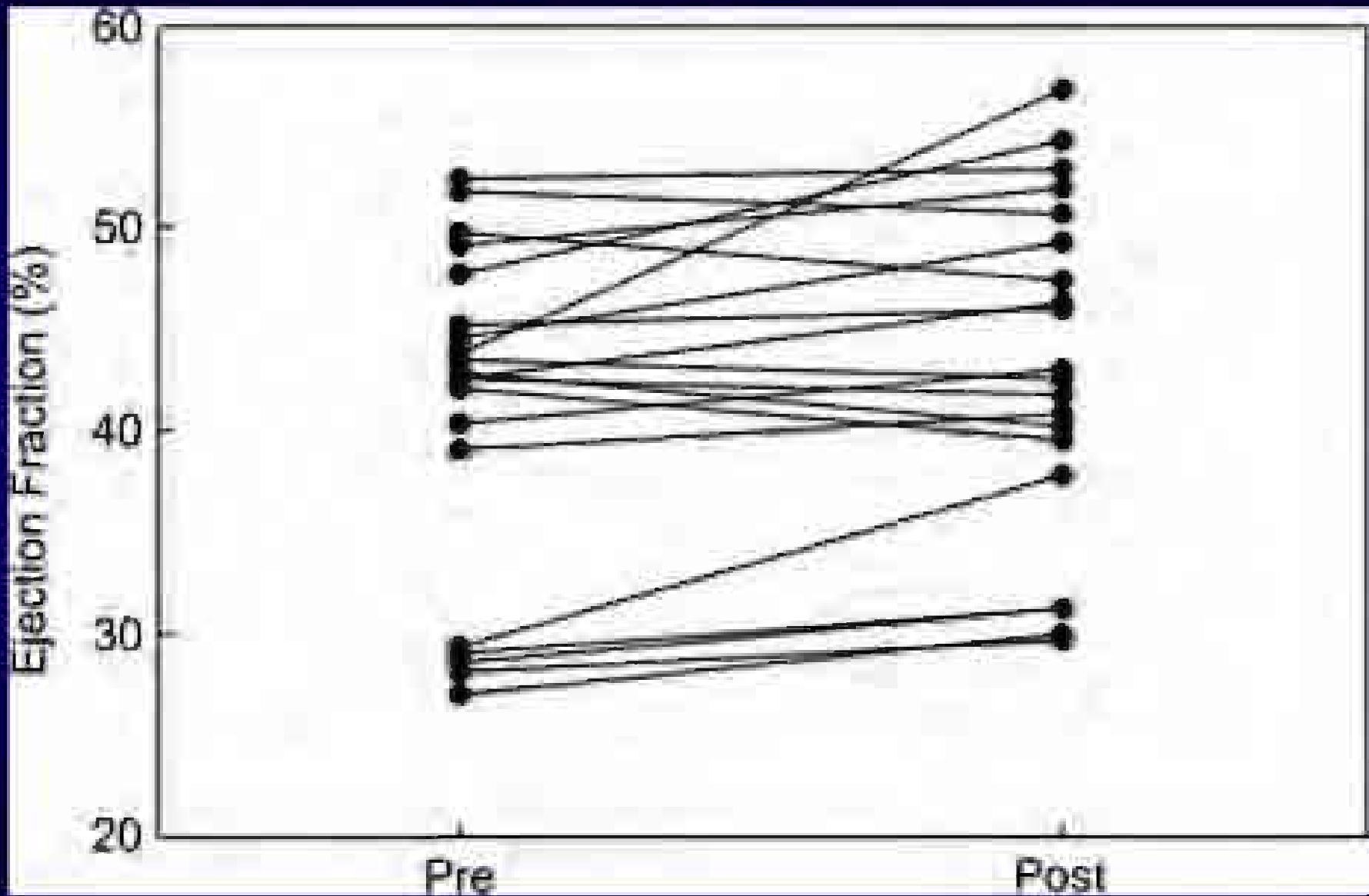
Heart scarring

# Eplerenone (MRA) in DMD Patients with Heart Scarring





# Carvedilol (Beta Blocker) in DMD Patients with Heart Failure

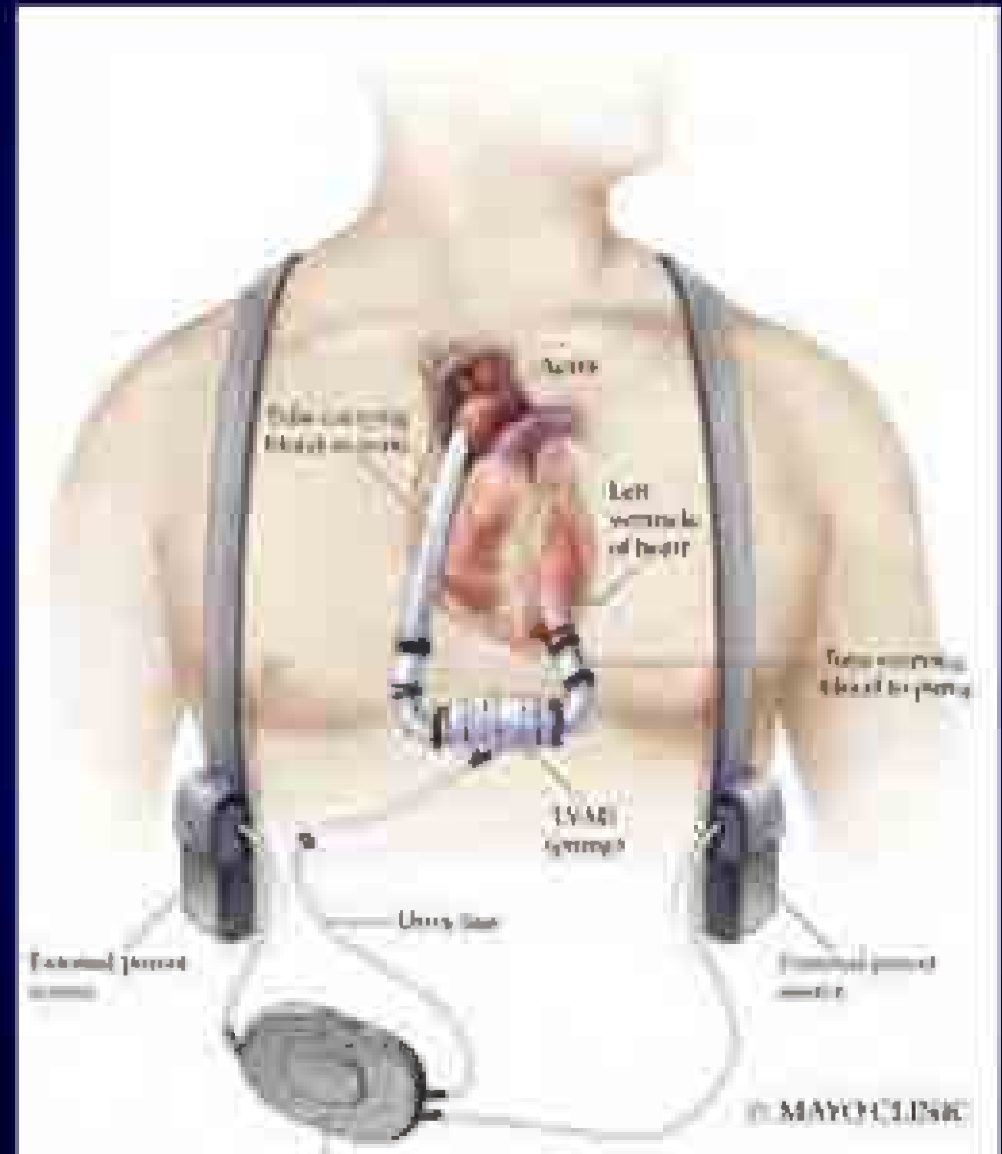






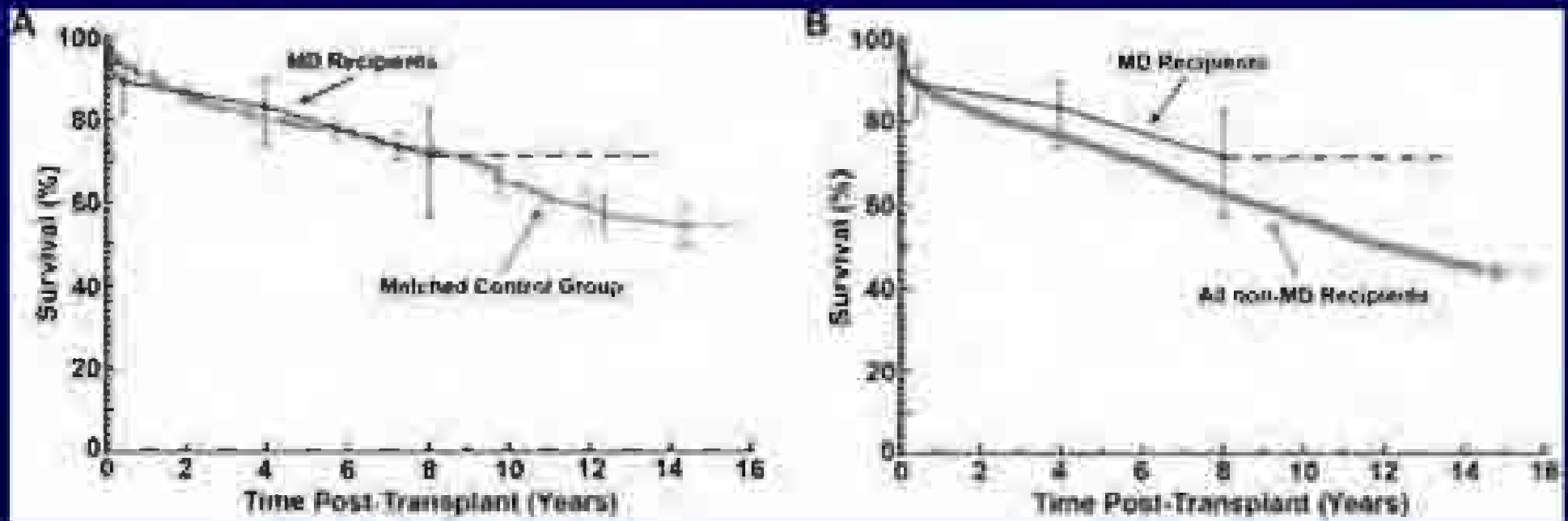
# Left Ventricular Assist Device

- Surgically implanted
- Continuous flow LV apex → aorta
- Electrically powered through percutaneous driveline
- Blood thinning with warfarin and aspirin
- Bridge to transplant (BTT) or destination therapy (DT)





# Survival Among Muscular Dystrophy Patients (Mostly BMD) after Heart Transplant



# Heart Failure

## Progression of Duchenne DCM

Clinical implication and therapeutic indication

Normal Heart



Early DCM



End Stage DCM



ACE Inhibitor (after 12 years old)  
Eplerenone

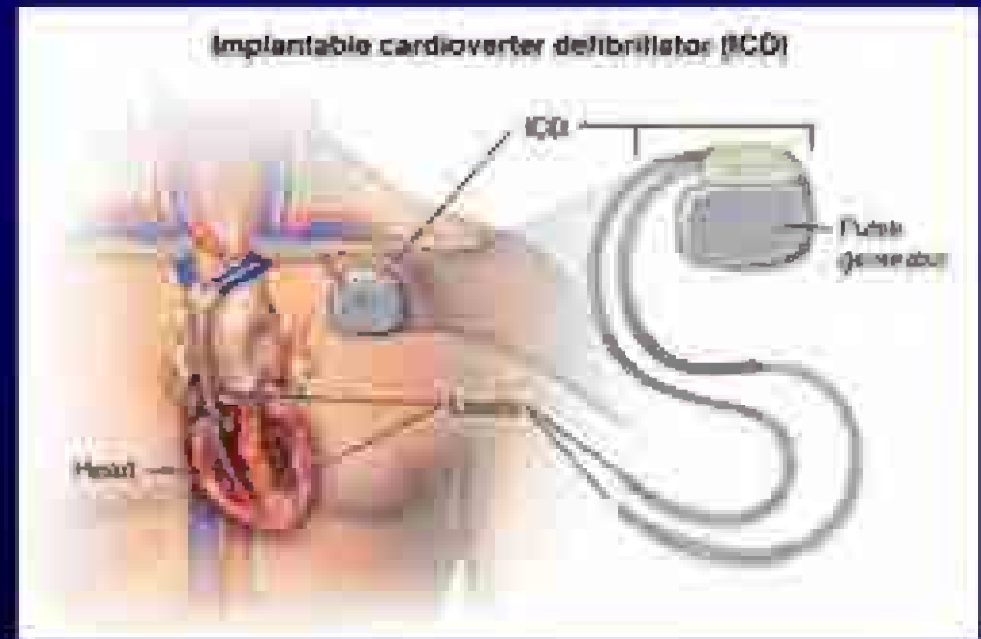
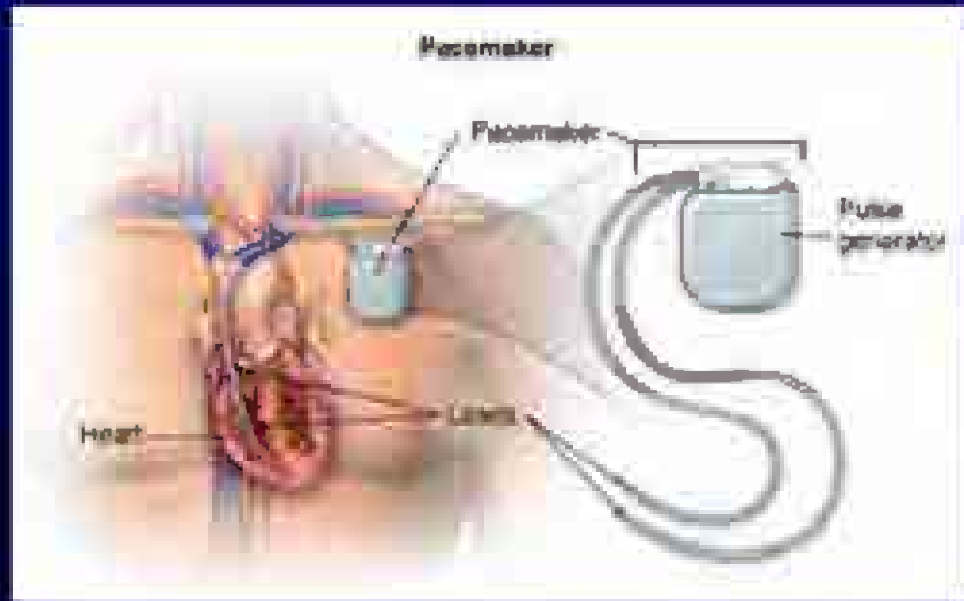
Antiremodelling therapy  
ACE Inhibitor (after 12 years old)  
Beta Blockers  
Eplerenone  
Ivabradine  
Sacubitril/Valsartan

ICD/CRT therapy

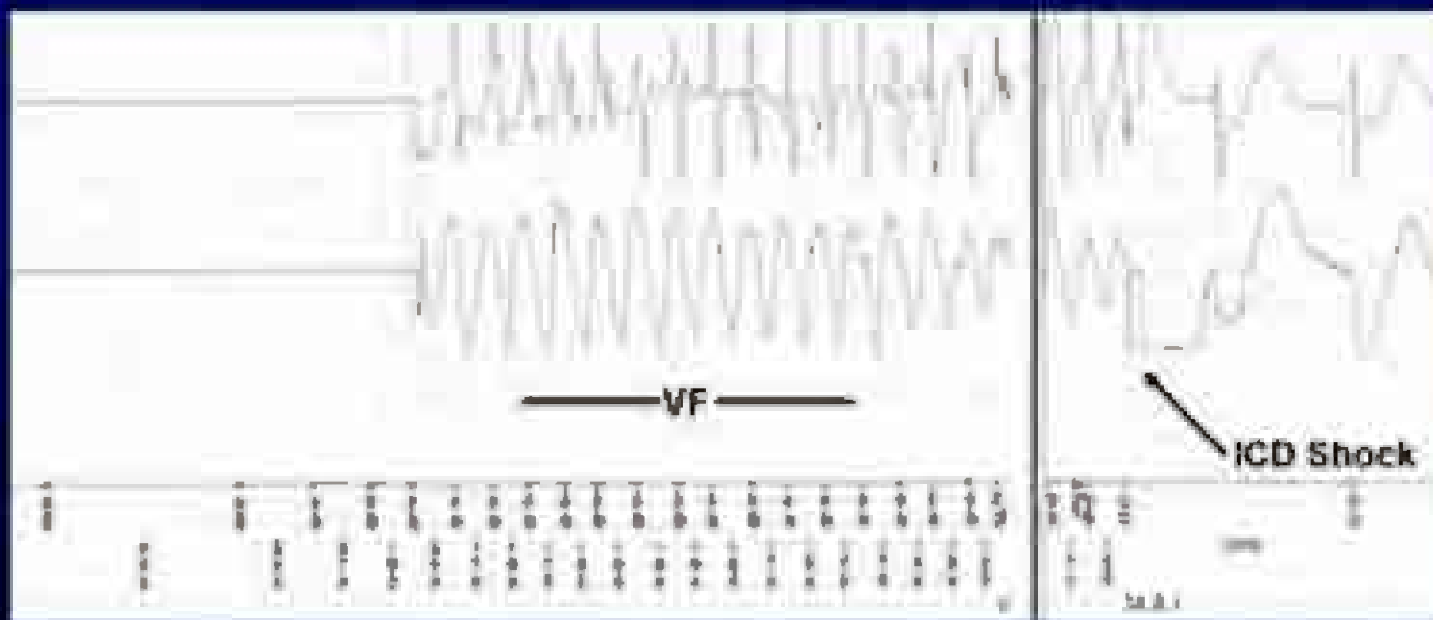
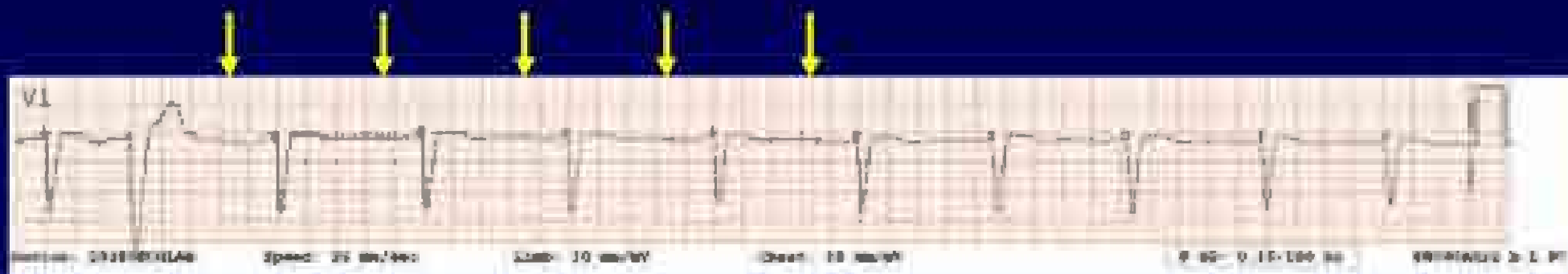
VAD as destination therapy

# Sudden Cardiac Death (SCD)

- Conduction block and low heart rate with fainting or near-fainting (generally uncommon)
- Pacemaker to mitigate risk as for patients without muscular dystrophy
- Ventricular tachycardia/fibrillation and excessively fast heart rate (more common, especially when LVEF  $\leq 35\%$ )
- ICD to mitigate risk
- ICD also works as a pacemaker



# Pacing versus ICD Shock

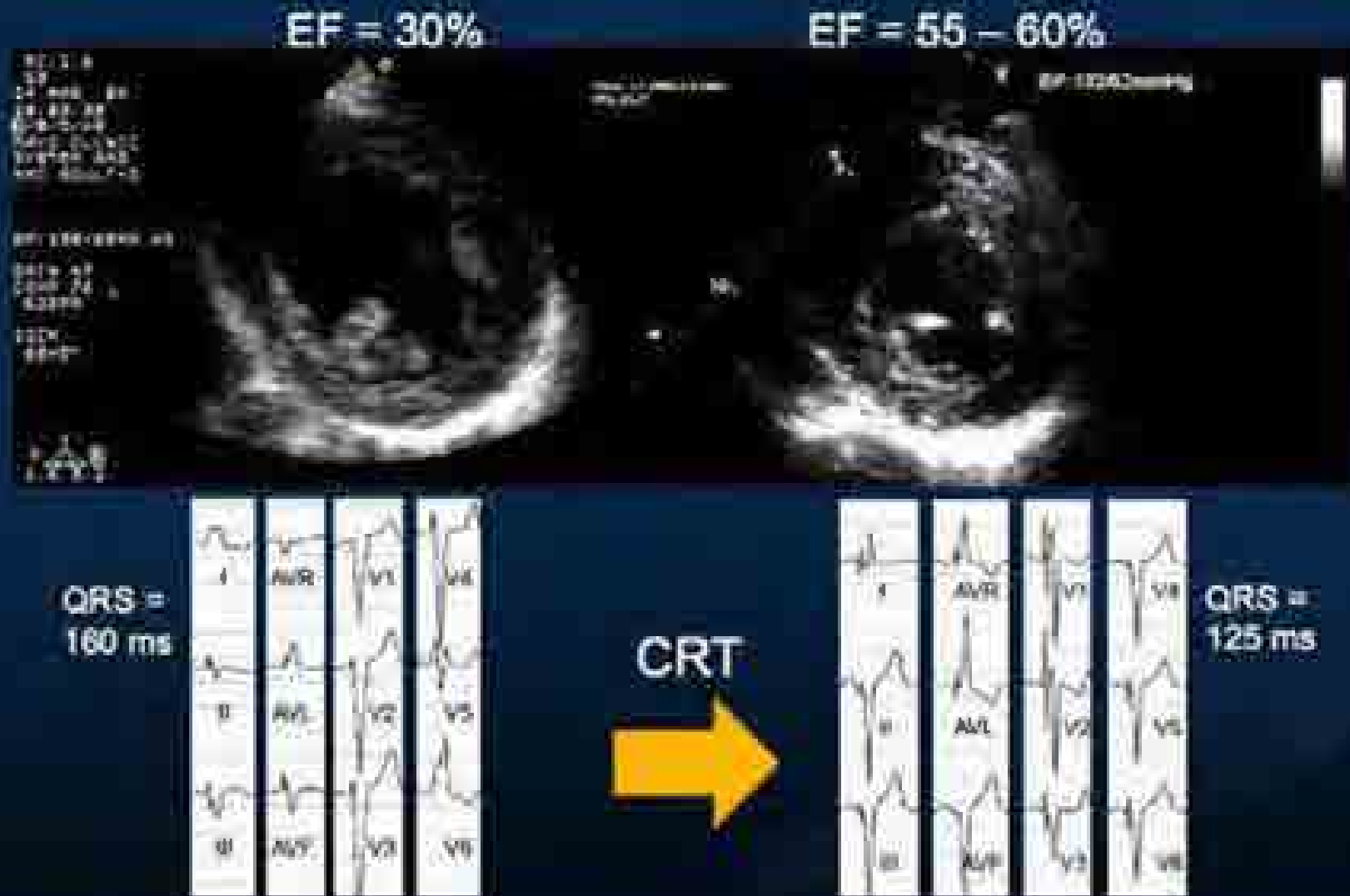


Baranchuk A  
et al. Cases  
Journal  
2008;1:373.

# **Recommendations for Implantable Cardioverter Defibrillator (ICD)**

- **Expected meaningful survival > 1 year**
- **Patients who have survived a sudden cardiac arrest or fainting episode from ventricular arrhythmia**
- **Patients with mild to moderate symptoms of heart failure and LVEF  $\leq$  35% despite medications**

# Cardiac Resynchronization Therapy (CRT)





# Atrial Fibrillation Treatments

- **Cardioversion (electrical or drug) to restore normal rhythm**
  - May need blood thinners or transesophageal echocardiogram first if atrial fibrillation has been ongoing for more than 48 hours
- **Antiarrhythmic medications to maintain normal rhythm**
- **If normal rhythm cannot be maintained: heart rate control and blood thinners to reduce the risk of stroke**

# Summary

- **Heart failure is a common complication of some of the more common dystroglycanopathies.**
- **Patients require close monitoring and early initiation of heart failure medications.**
- **Advanced heart failure therapies such as VADs and heart transplant can be considered in individual cases.**
- **Implantable cardioverter defibrillators (ICDs) may be considered in individual patients with documented ventricular arrhythmias or LVEF  $\leq$  35%.**





• X

# Graded Therapy for Heart Failure

