Treatment of Cardiac Disease in Propionic Acidemia

Kathryn Chatfield, MD, PhD

Instructor of Pediatrics, Division of Cardiology

University of Colorado School of Medicine

Children's Hospital Colorado

How can PA affect the heart?

1) Risk for developing cardiomyopathy (CM)

   CM is disease of the heart muscle- abnormal muscle contraction can mean the heart cannot generate enough force to deliver oxygen-containing blood to the body and the brain

2) Risk for developing prolonged QT interval

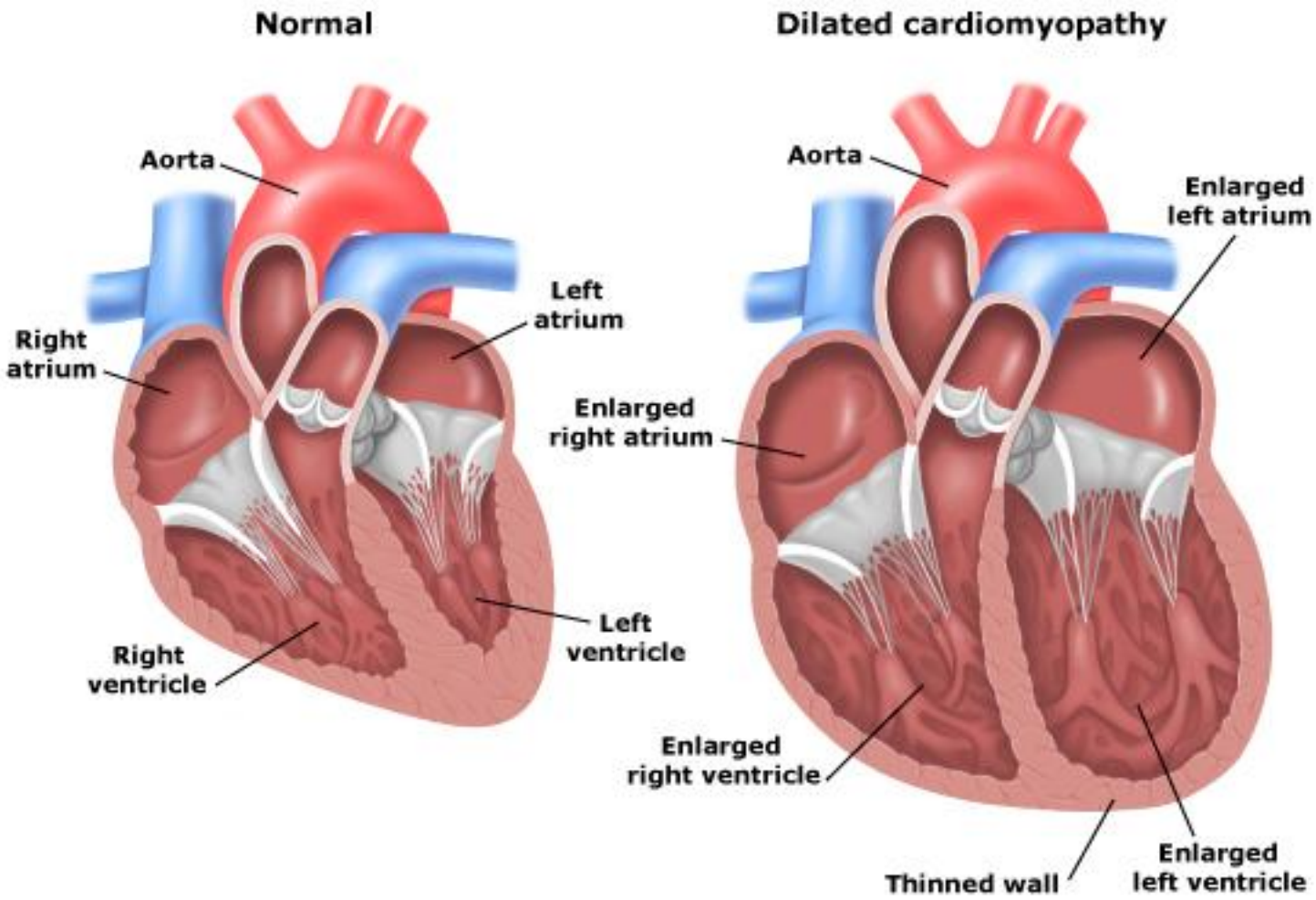
   Prolonged QT disease is an abnormality of the conduction system (the electrical system of the heart- these electrical signals tell the heart when to beat and allow this to happen in an organized way). A prolonged QT can mean a predisposition for developing an arrhythmia, or abnormal electrical conduction.

   The reason why individuals with PA develop heart muscle and conduction system abnormalities is not known.

What is Cardiomyopathy?

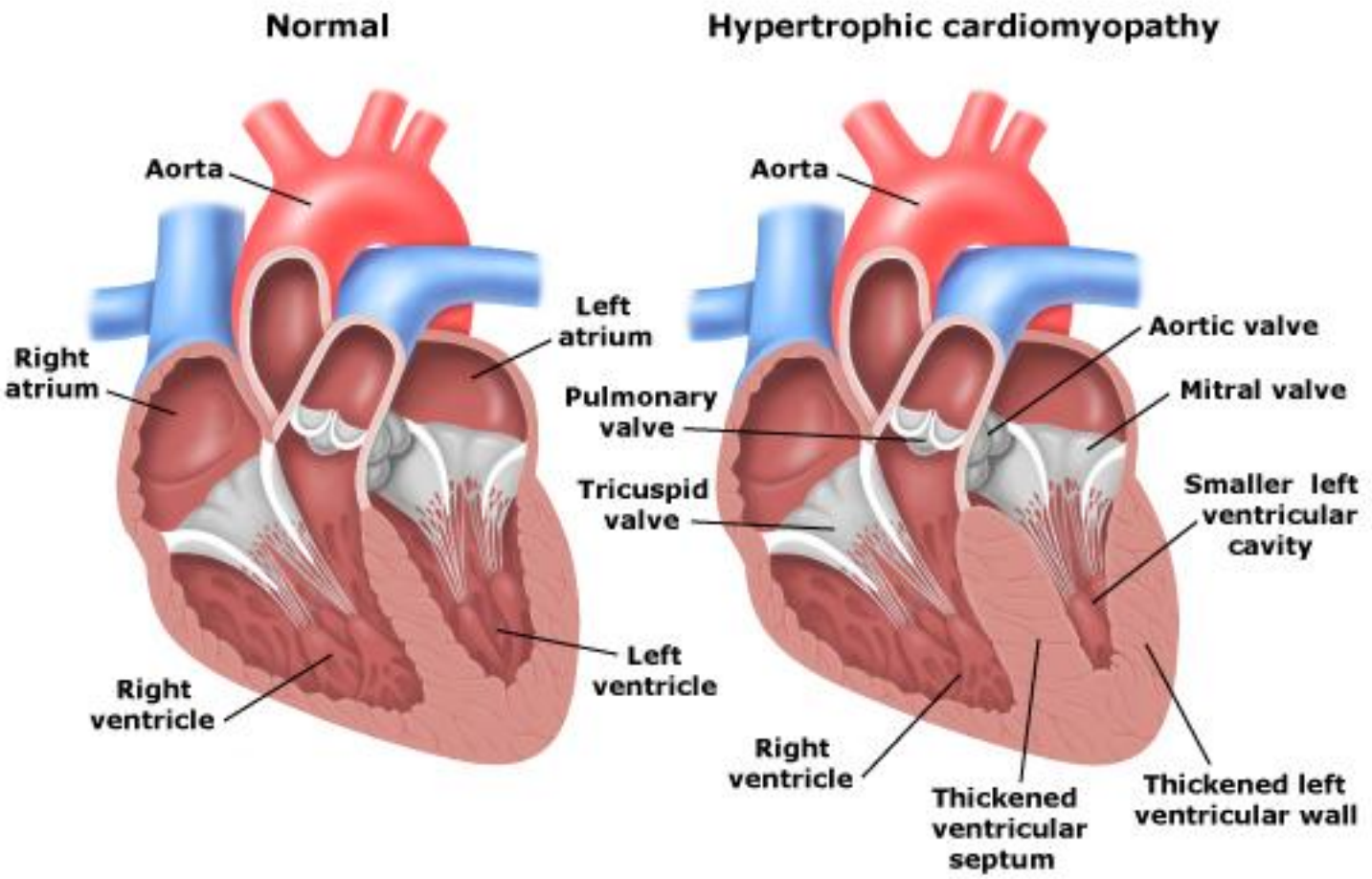
CM is a disease of the heart muscle and can come in two forms:

1) Dilated- DCM



What is Cardiomyopathy?

2) Hypertrophic- HCM



How do we diagnose cardiomyopathy?

-Echocardiography (ECHO) is the single best test to diagnose and follow CM

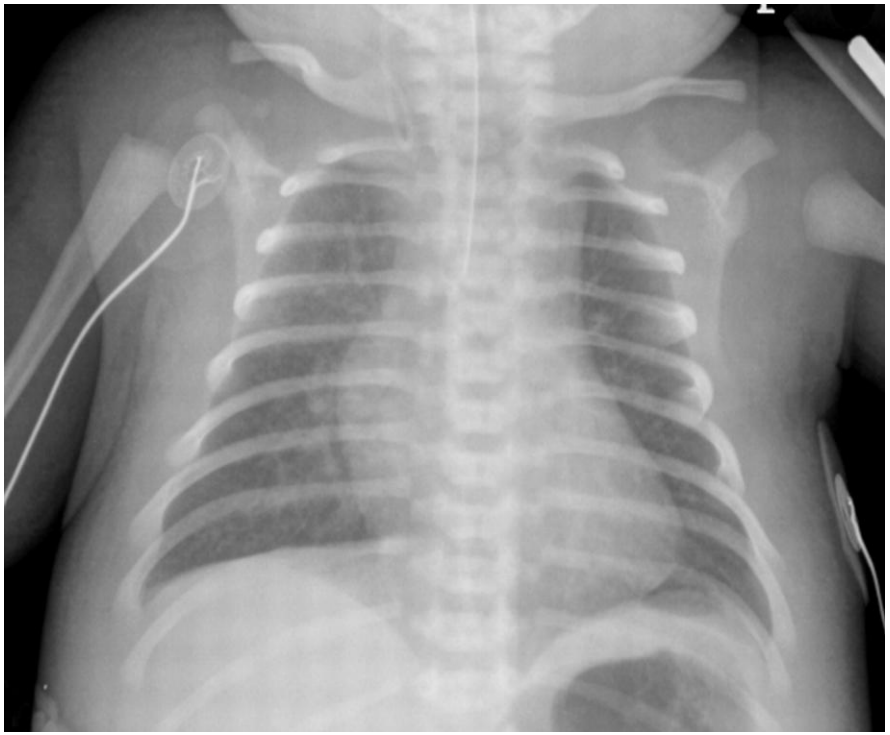
-Electrocardiography (ECG or EKG) can be helpful to screen for CM, but cannot diagnose CM

-Other tests can also be used (ex.- cardiac MRI) but are usually not necessary or practical

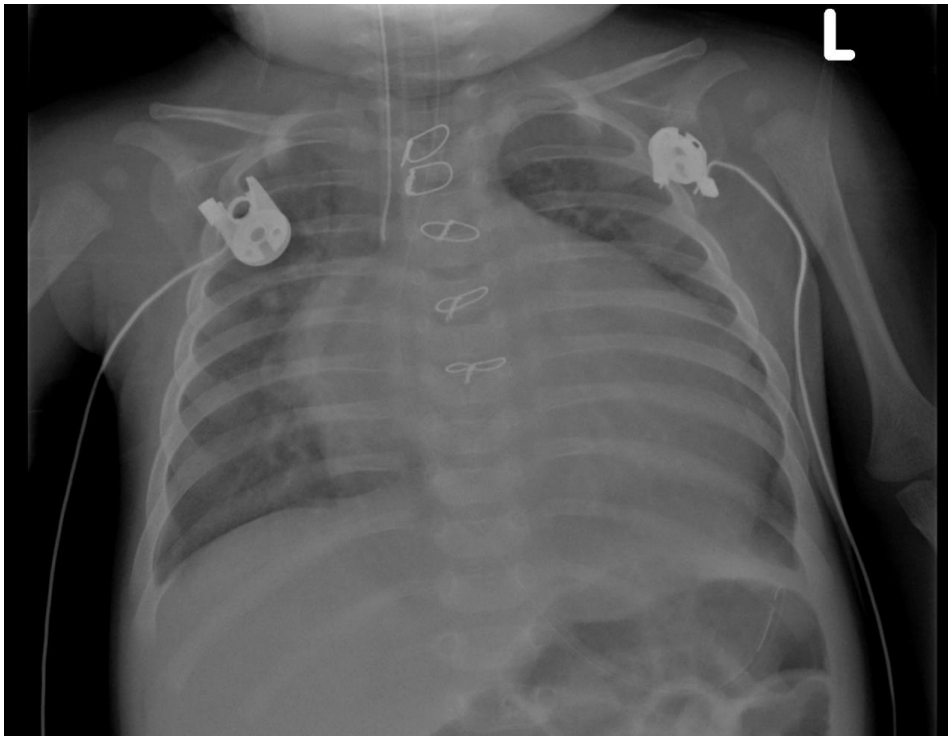
-Simple tests are also very useful- chest x-ray, some basic blood tests (if organs do not receive enough oxygenated blood they get sick)

CM can be detected by an x-ray:

Normal



Enlarged heart



How does EHCO help the cardiologist? How does it help a patient?

ECHO is very good for:

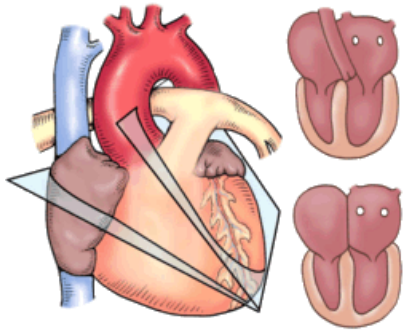
- Making a diagnosis
- Detecting subtle abnormalities early in disease
- Following changes over time
- Making objective measurements of heart function
  - (ejection fraction, shortening fraction)

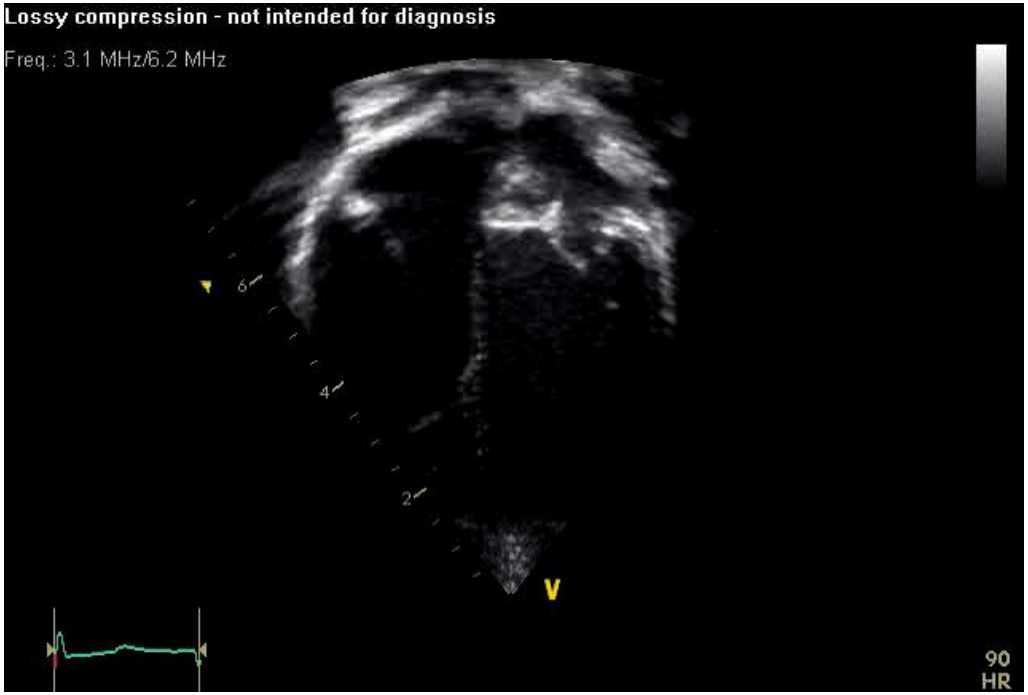
ECHO is not good for:

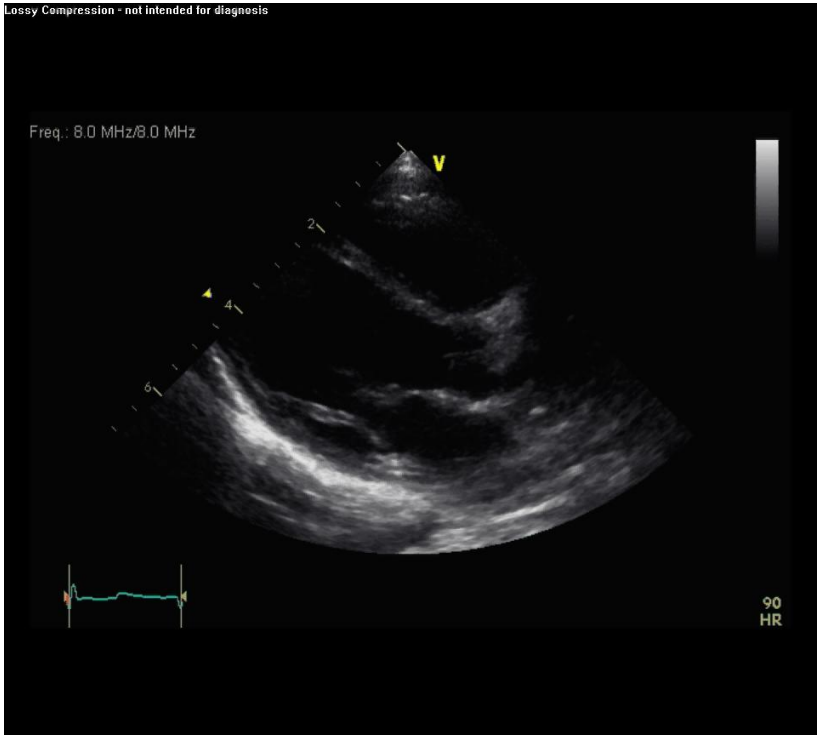
- Day-to-day management
- Detecting arrhythmias

What does an ECHO see?

What a normal heart looks like:

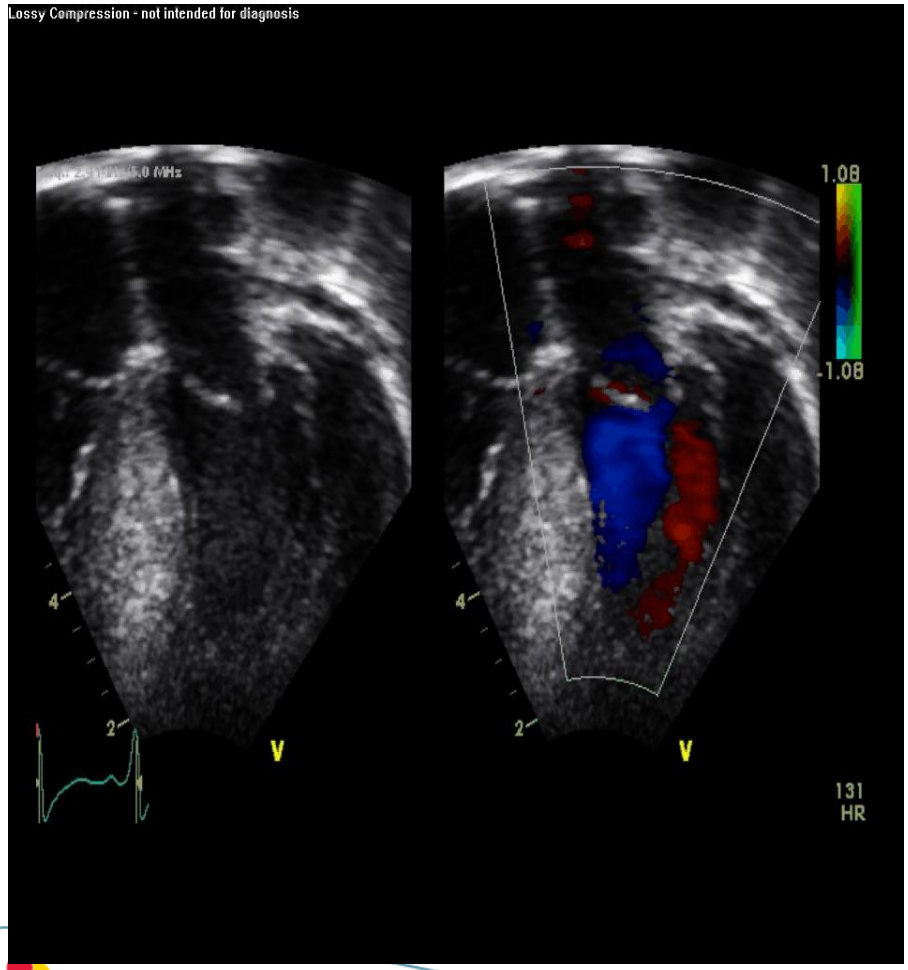


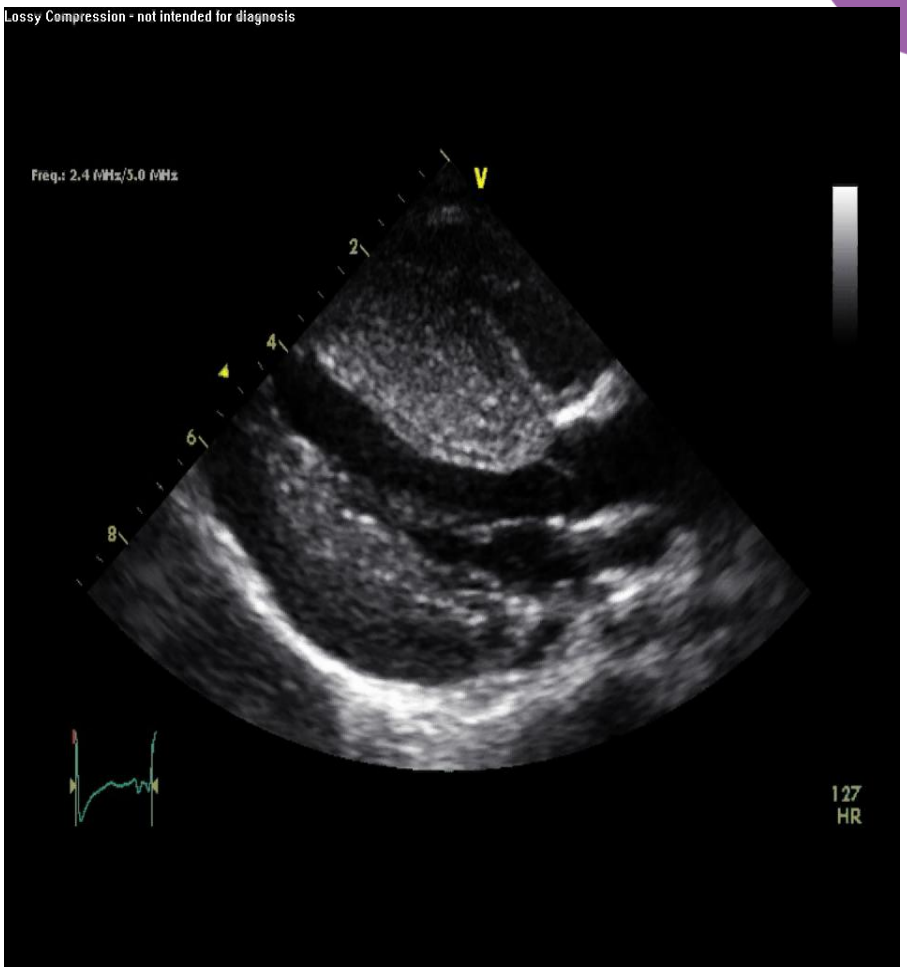




Dilated Cardiomyopathy: by ECHO

Hypertrophic cardiomyopathy: by ECHO





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Other ways that CM can be detected:

- SYMPTOMS: what parents may notice
  - Fatigue- inability to do the same activities, or tiring more quickly
  - Shortness of breath with activity
  - Weight loss
  - Nausea/vomiting, or early satiety
  - Swelling in face, abdomen, legs
  - Other symptoms may occur but are not typical: ex. chest pain, fainting
- SIGNS: what doctors will notice
  - Increase in heart rate
  - Extra heart sound (gallop, murmur)
  - Edema (swelling)
  - Liver enlargement
  - Signs of extra fluid in the lungs
- OTHER TESTS:
  - "BNP" is an indicator of heart muscle under stress
  - Other lab testing can show evidence of inadequate oxygen delivery to organs due to poor heart function

Cardiomyopathy in PA

- CM will be found in 1/4 to 1/3 of PA patients (based on 2 studies of ~20 patients each)
- DCM presents more commonly than HCM in PA
- *Both* Dilated and Hypertrophic CM have been seen
- Both dilated and hypertrophic CM can be seen in the *same patient at the same time*
- Sometimes HCM can turn into DCM

Cardiomyopathy in propionic acidaemia

Massoud AF, Leonard JV. **Eur J Pediatr. 1993 May;152(5):441-5**
Medical Unit, Institute of Child Health, London, United Kingdom

-19 patients

-5 or 6/19 had some evidence of CM

-3 died

-3 had resolution of findings

-Carnitine did not appear to have any affect

Cardiomyopathies in Propionic Aciduria are Reversible After Liver Transplantation

Stephane Romano, MD, Vassili Valayannopoulos, MD, Guy Touati, MD, Jean-Pierre Jais, MD, PhD, Daniel Rabier, MD, Yves de Keyzer, PhD, Damien Bonnet, MD, PhD, and Pascale de Lonlay, MD, PhD. **J Pediatr. 2010 Jan;156(1):128-34**
(Hopital Necker-Enfants Malades, Universite´ ParisDescartes, Paris, France)

- 20 patients total
- 6 developed cardiomyopathy
- 2 died of cardiac arrest
- 2 received *liver transplant* and cardiac function improved
- 2 not able to receive liver transplant due to cardiac disease

In PA patients diagnoses with Cardiomyopathy:

- Age at diagnosis: between 5-11 years in French cohort, but may occur as early as 10 months, or as late as adulthood
- CM does not correlate with PCC enzyme activity
- CM does not correlate with metabolic decompensation
- No evidence that Heart function responds to carnitine
- Cardiomyopathy has been treated with both liver and heart transplantation

What can we take from these studies?

- All children with PA should be screened for CM!

Health Supervision Guidelines: what the PA experts say

- Echocardiogram at presentation and every year to evaluate for CM
- Echo as needed to evaluate shortness of breath, tachycardia, or other signs/symptoms of heart failure

They also say:

- ECG annually to screen for long-QT
- Holter monitor annually (24 hour monitor)
- ECG and Holter if any syncope (fainting) or other symptoms concerning for arrythmia

Why should a PA patient see a cardiologist?

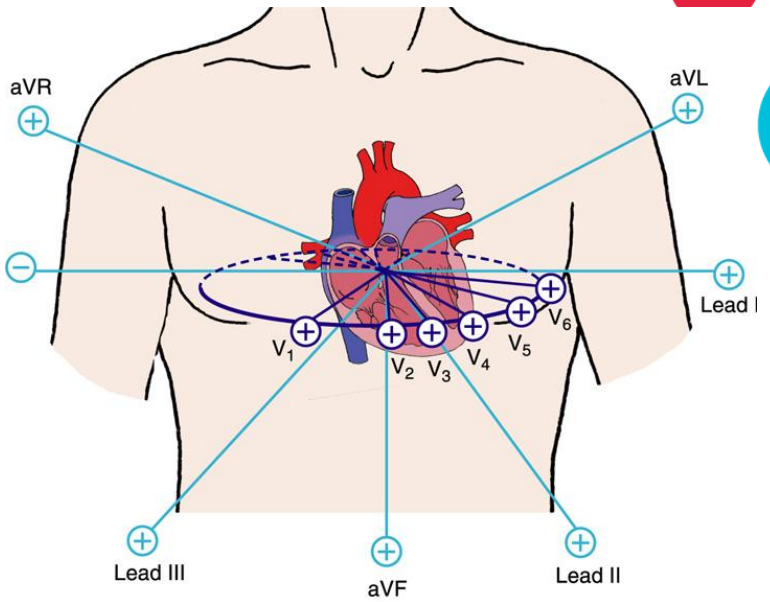
- ECHO can detect subtle abnormalities before symptoms are present
- There are medications that help slow the progression CM in children and help them feel better
- PA patients with severe CM may be candidates for organ transplantation

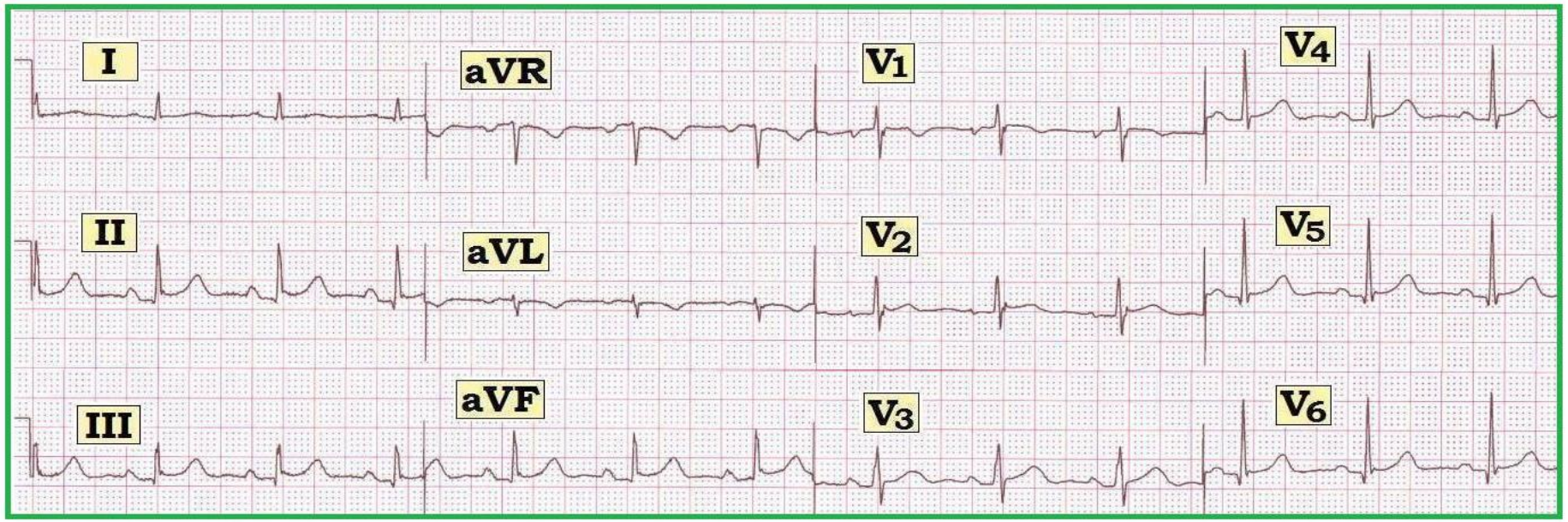
- A prolonged QT can also be treated (medications, devices)
- There are many medications that should be avoided in someone with a prolonged QT.

What is a QT??

- The QT is a time interval measured on an ECG (electrocardiogram)
- A QTc is a QT interval that is “corrected” for heart rate
- The QT can be thought of as the time the heart needs to “re-set” itself for the next heart beat.
- When the QTc is too long, dangerous arrhythmias can result leading to collapse and even death.

What an ECG looks like:





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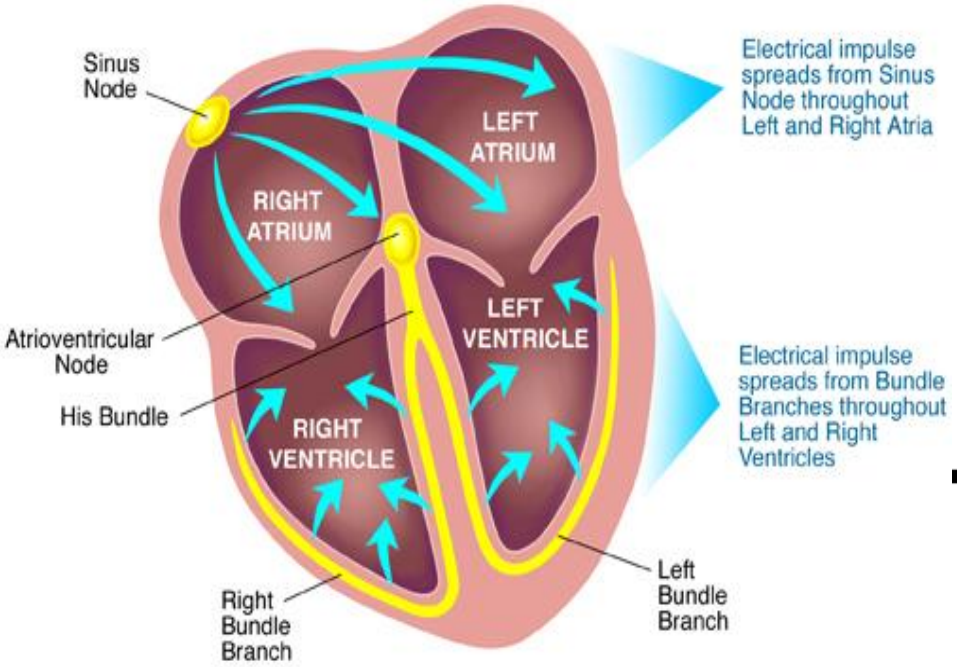
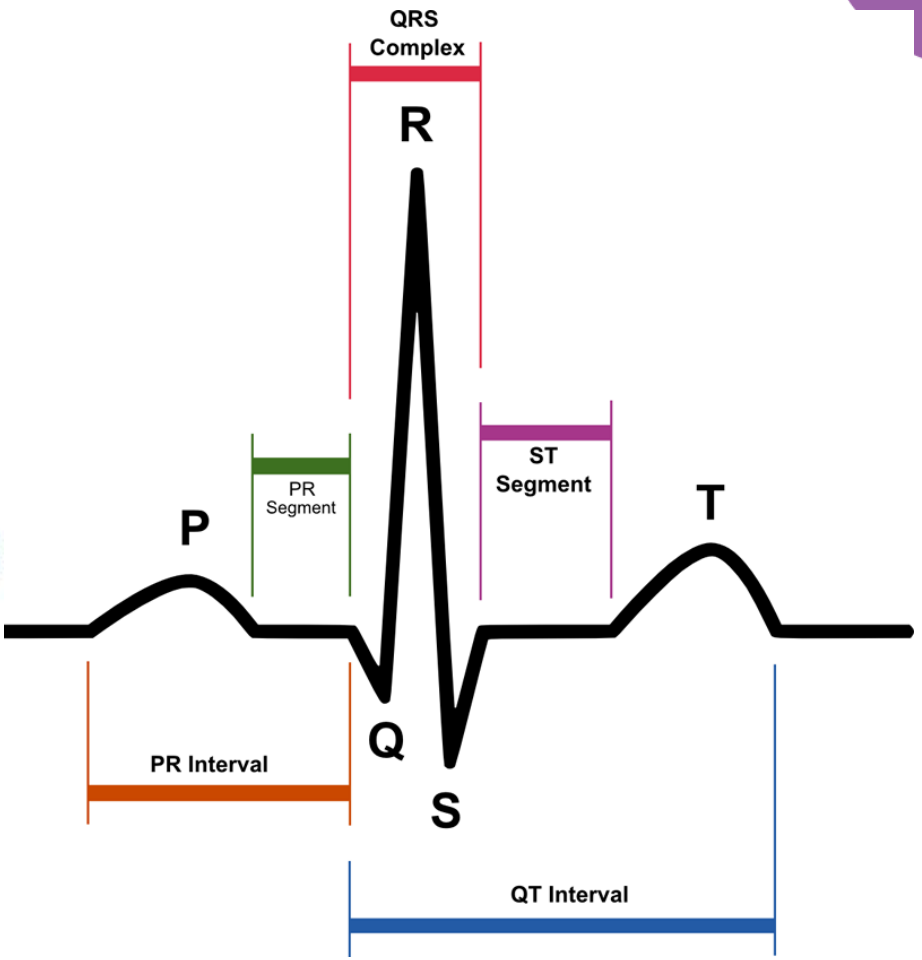
What an ECG tells you:





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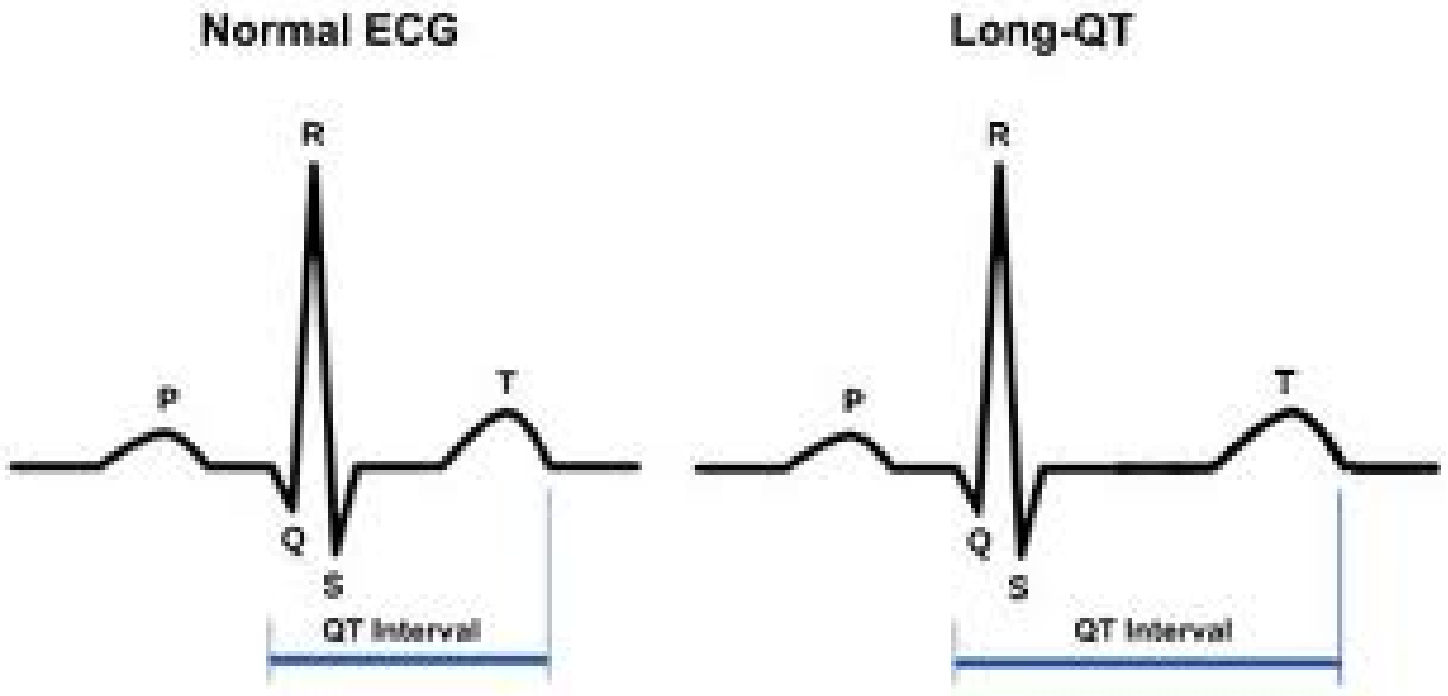
Compare normal to prolonged-QT



Prolonged QT in PA

- A study of 10 patients has shown that 70% of PA patients have a prolonged QTc (>440 msec)
- 60% have a QTc >460 msec (longer= more dangerous)
- 4 individuals underwent exercise testing, QTc was longer with exercise (this is very abnormal)
- There are case reports of PA patients having collapse (syncope) related to prolonged QTc
- No infants have been diagnosed with prolonged QTc
- The QTc may prolong with age

**Normal QTc is different for men and women

normal for male is <440, normal for female is <460

Summary: the heart of PA

- Cardiology follow-up every year is important
- Early detection of heart problems may help avoid serious illness and early death
- Most cardiologists do not know anything about PA, find a cardiomyopathy specialist in your area
- Educate your cardiologist about what your child or family member needs *every year*:
  - Screening for CM
  - Screening for prolonged QT

Pediatric cardiologist understand how to take care of these problems, find a doctor who is willing to work with your family!