Updates on Cardiomyopathy: Diagnosis and Management in FAOD

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Conflict of Interest Disclosures

Consulting

- Ultrageyx- discussing labeled use of Doljovi
- BioMarin
- Stealth

Funding

- NIH- NHLBI
- Doris Duke Charitable Foundation
- American Heart Association

A little about me

Training in Pediatric Cardiology and Clinical Genetics
Pediatric Heart Failure and Heart Transplant

Perspective based on

- Clinical interest in genetic and syndromic causes of heart disease in children
- Research in mechanisms of heart failure
- Secondary defects in energy metabolism in heart failure (pediatric)
- Mechanisms of heart failure in cardiomyopathy in FAOD and other metabolic cardiomyopathies

Overview: where are with treatment of cardiomyopathy (CM) in FAOD?

- Cases- examples to illustrate following topics
- Basic overview of Cardiomyopathy and how and the FAOD phenotype
- Mechanisms
- *Natural history of Cardiomyopathy in FAOD*
- Treatment of heart failure in FAOD- conventional approaches
- *FAOD-specific treatments – Triheptanoin (Doljovi)*
- *Cardiologist perspective on heart failure in FAOD*
- Future directions and new treatments

Case #1: Infant diagnosed with VLCADD by NBS

- Second child in the family, older brother who is healthy
- Concern for hypoglycemic seizure in newborn nursery, discharged home no other concerns
- Readmitted to NICU for jaundice- NBS on DOL#4 concerning for VLCADD
- Started on Enfaport with MCT
- Parents are distantly related
- ”Severe” mutation, truncating c.799_802delGTTA, p.Val267Glnfs*8
- Based on genetic testing, concern for early-onset cardiomyopathy type VLCADD
- ECHO screening frequently in first year of life
- No significant illness, few short hospitalizations

Case #2: Infant male diagnosed with LCHADD

- First child of this couple
- NBS screen most consistent with LCHADD, admitted to NICU at 7 days based on screen

- *HADHA* variants:
  - known LCHADD mutation c.1538G>C, p.E510Q
  - one variant of unknown significance in *HADHA* (p.G328R)

- Breast feeding and supplemented with Enfaport +MCT
- ECHO showed a small PDA, otherwise normal biventricular size and function

Review of Basics: Cardiomyopathy in FAOD

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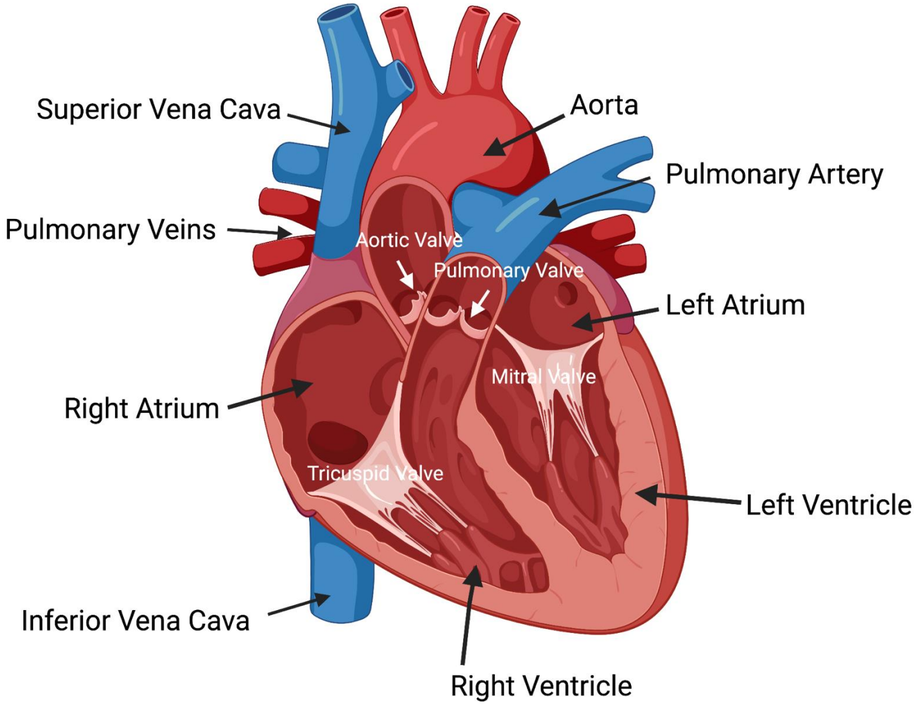
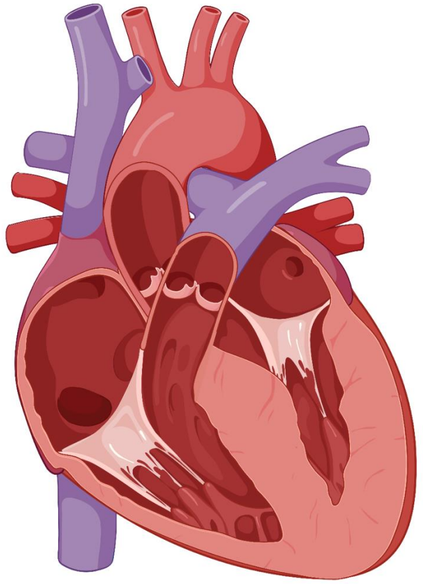
Cardiomyopathies- disease of the muscle

Normal Cardiac Anatomy

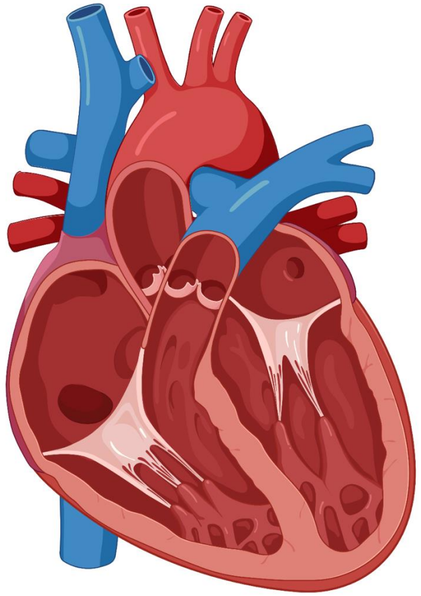


Disorder of diastolic function (relaxation/filling)



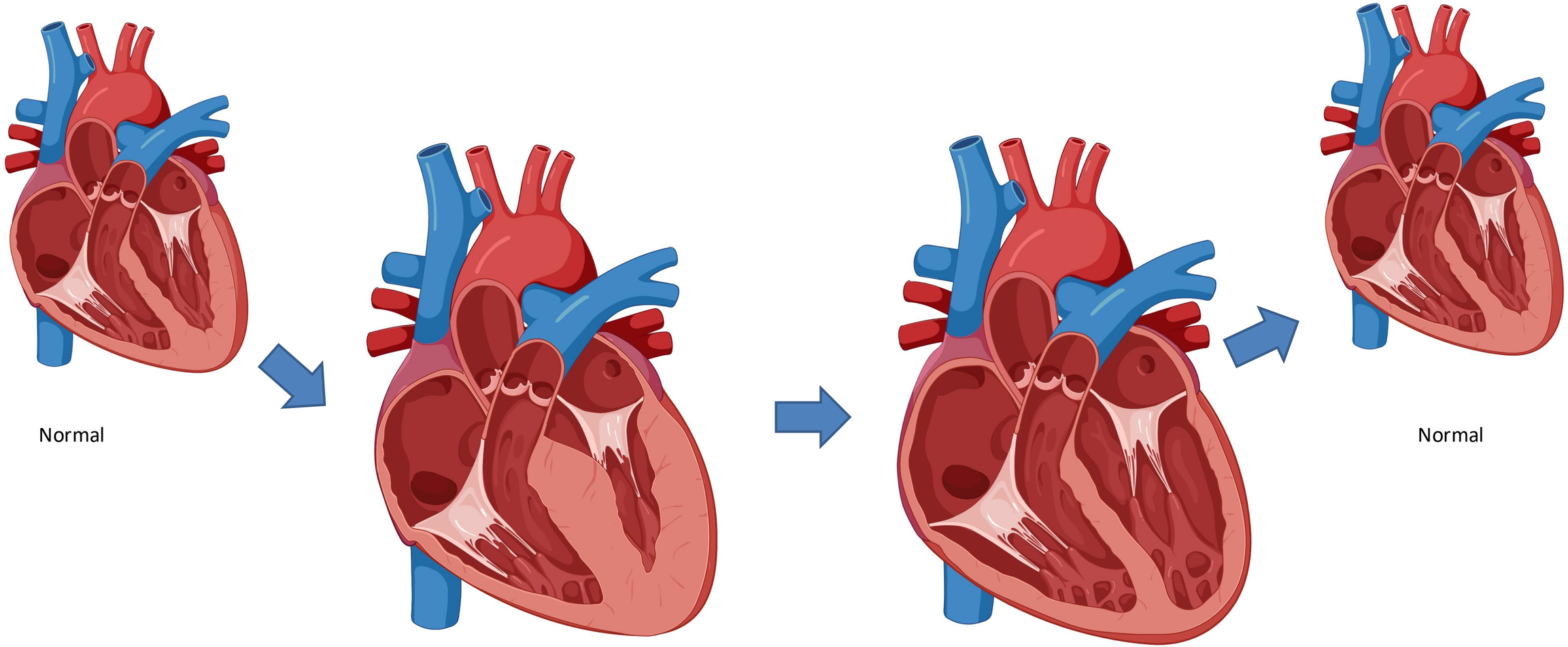
Hypertrophic Cardiomyopathy

Disorder of systolic function (squeeze/pumping)



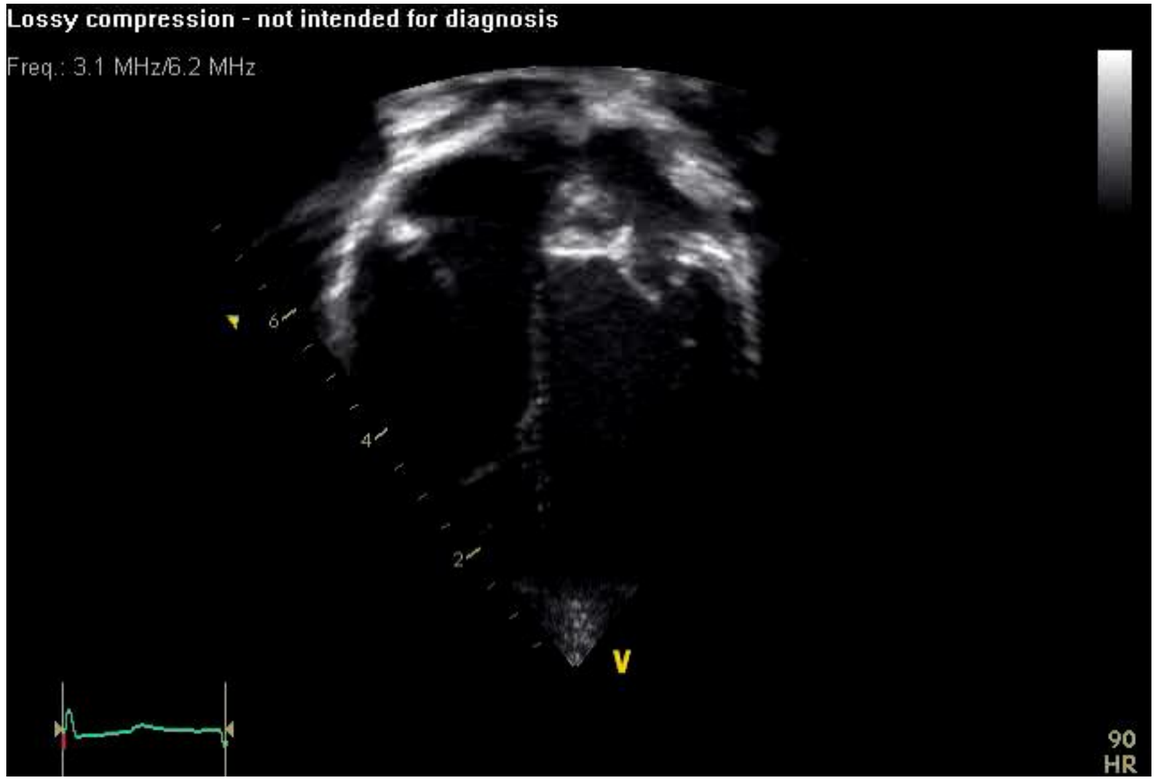
Dilated Cardiomyopathy

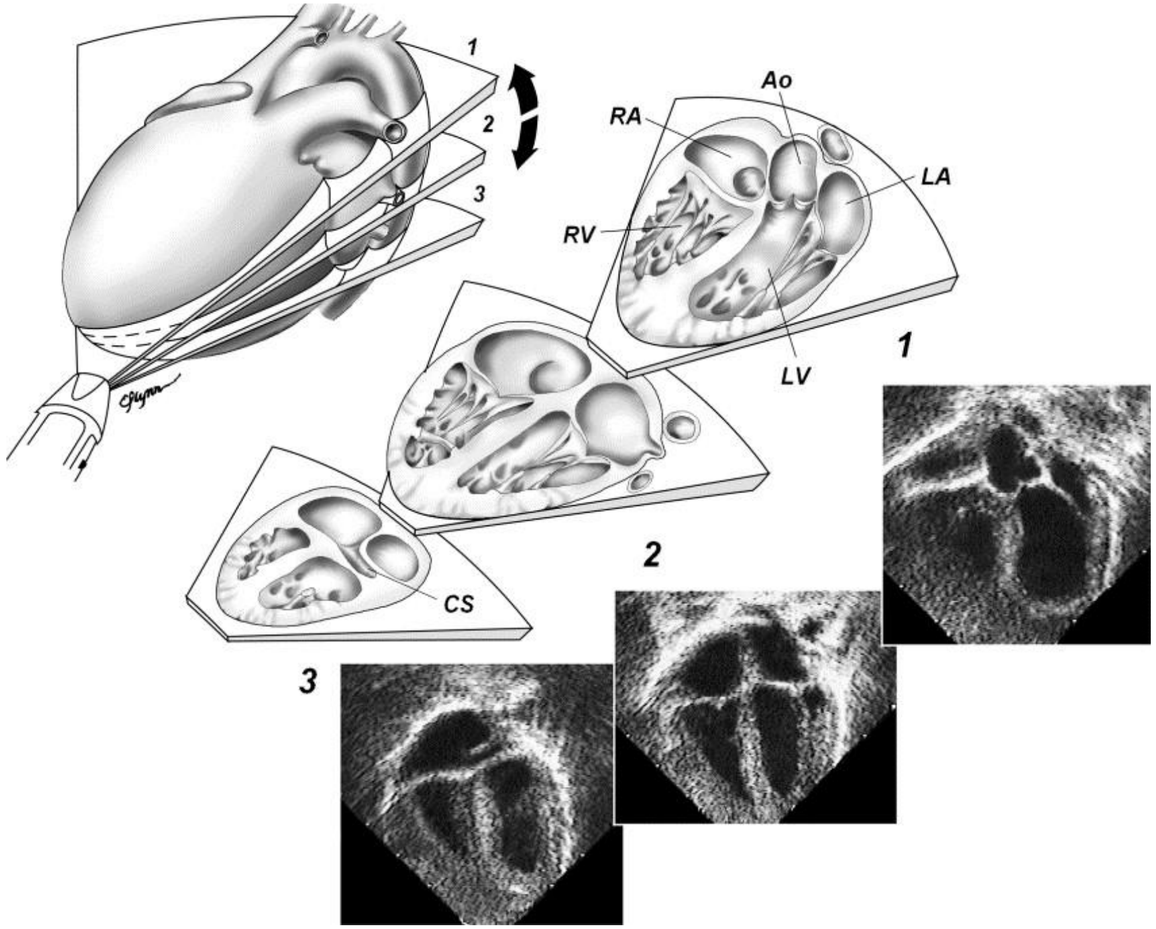
FAOD CM Phenotype:
Can look like hypertrophic, dilated CM or *both* *and* can reverse remodel



Making the diagnosis of CM: what normal looks like

- CXR, ECG (easy to do, inexpensive, but not best)
- ECHO (definitive)





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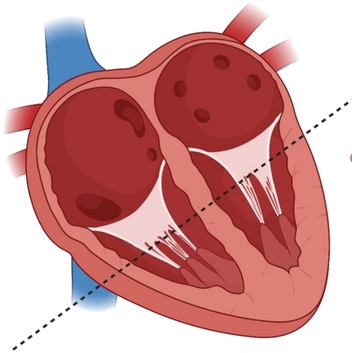
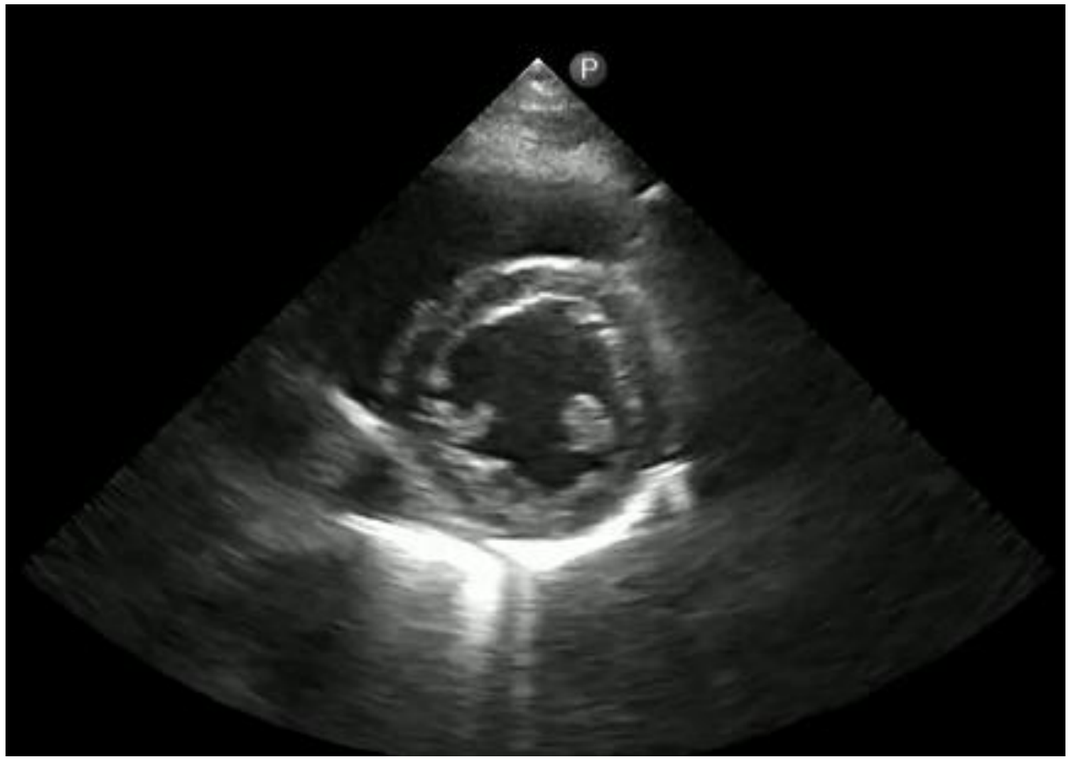
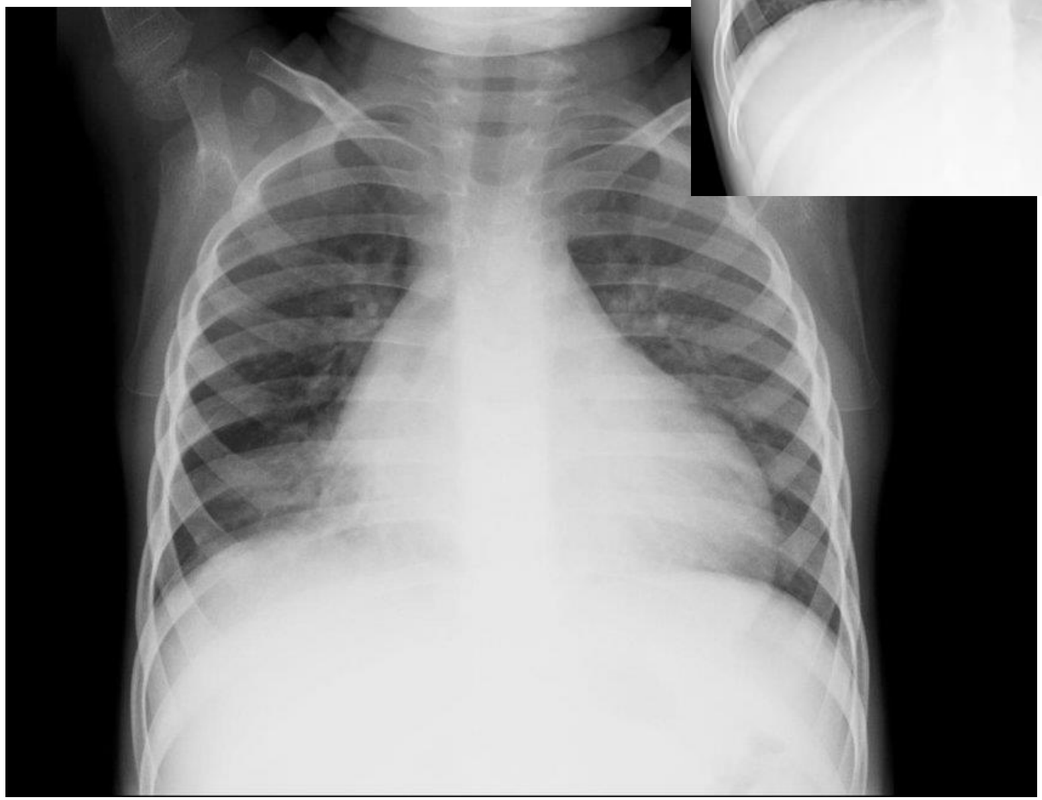
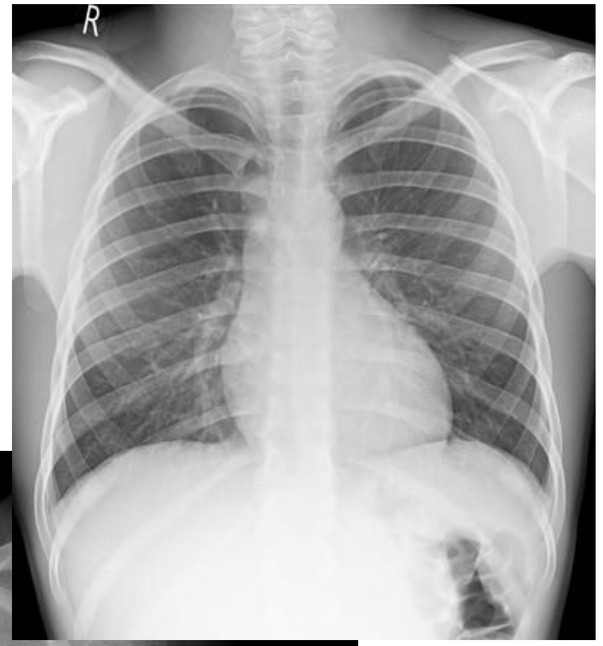


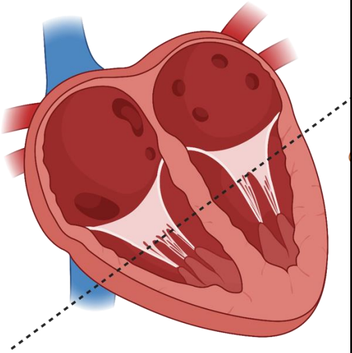


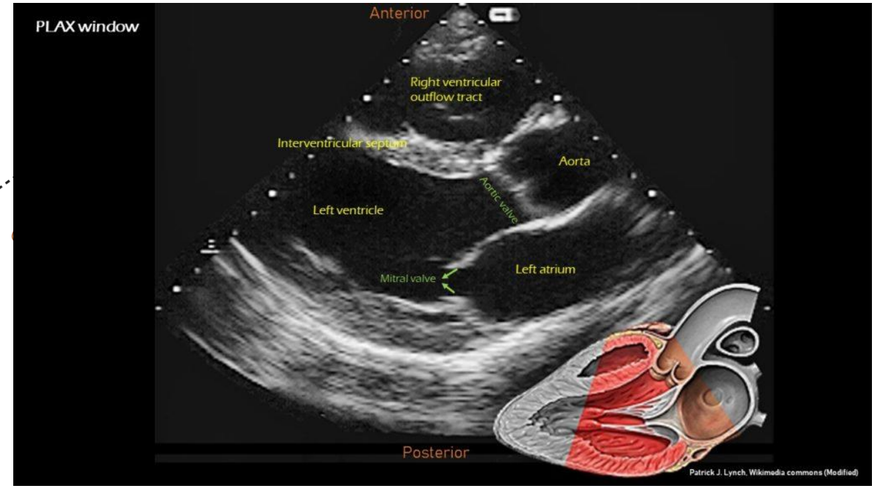


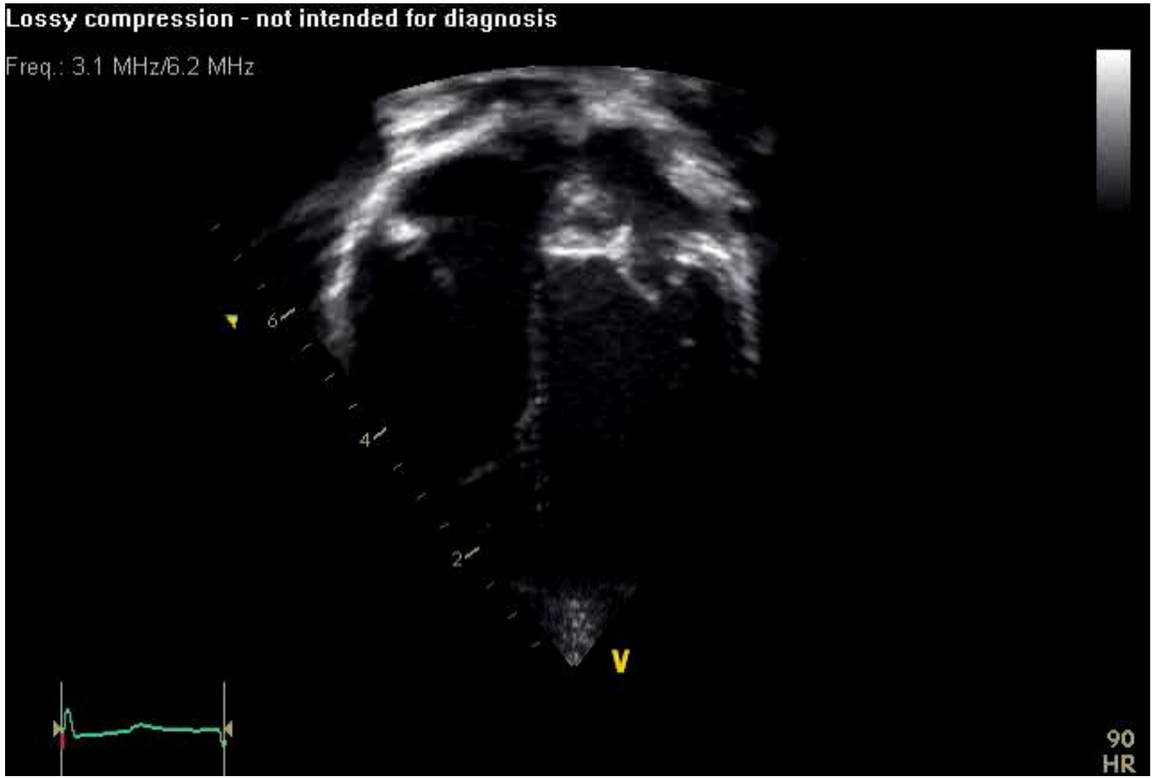


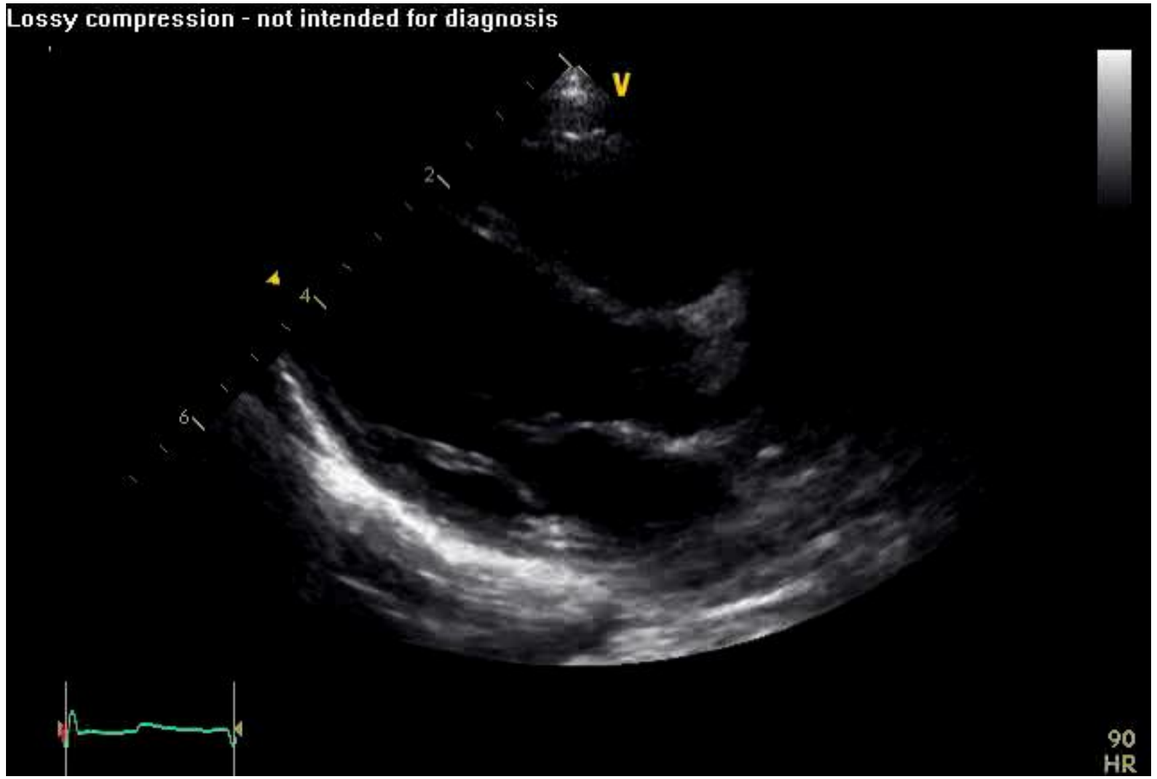
Case example:

- What a normal heart looks like:



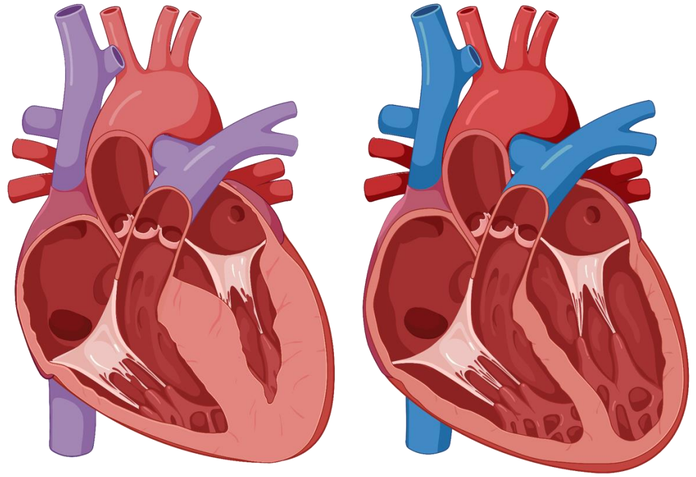


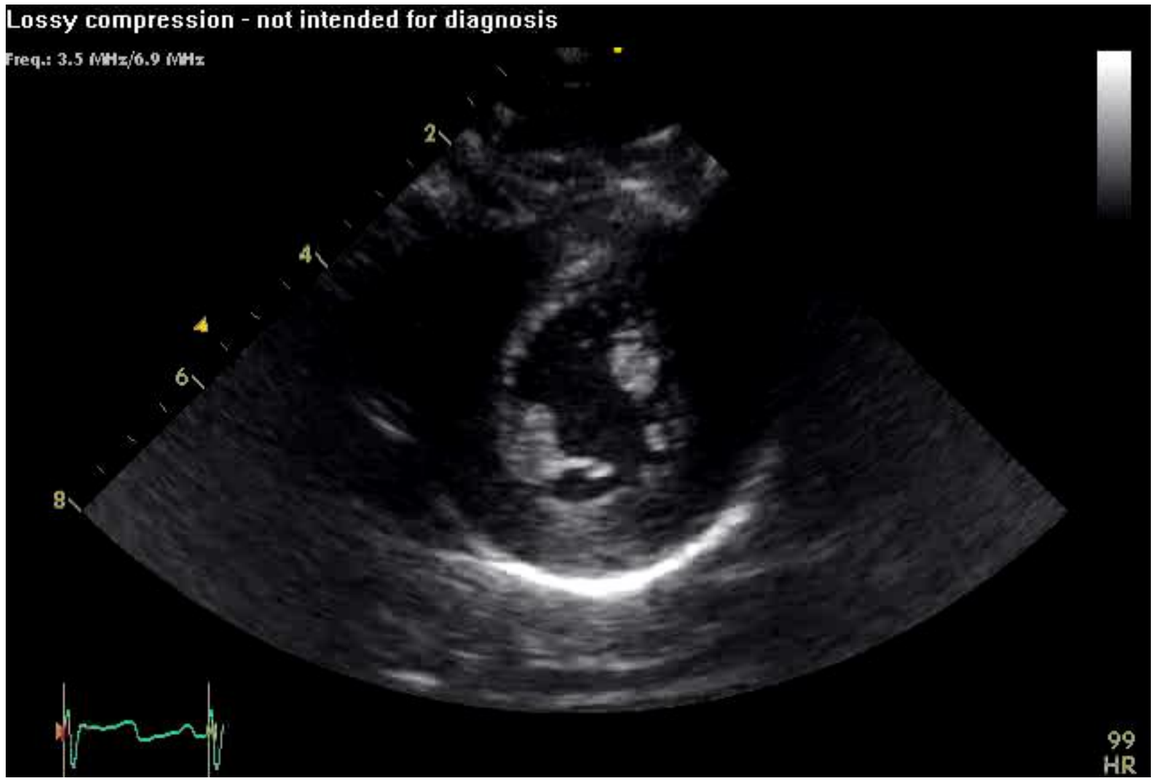


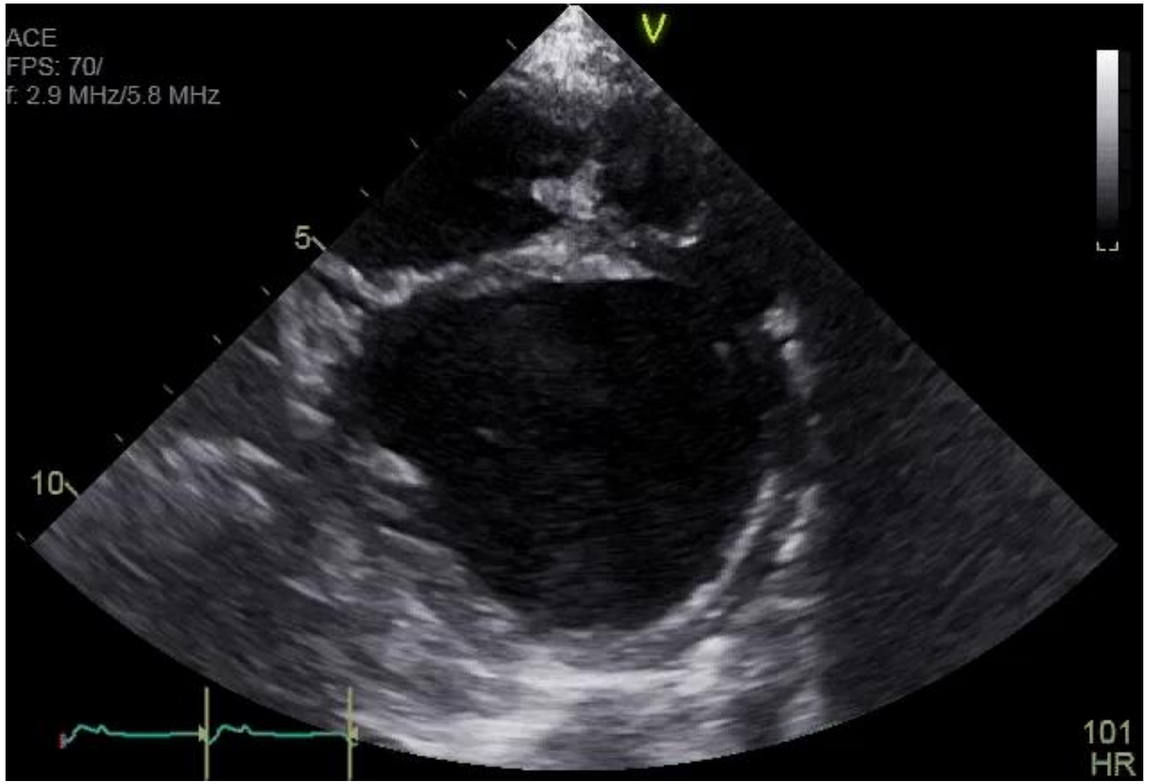


What Abnormal looks like: making the diagnosis of CM

- Other testing:
- NT proBNP or BNP, other labs- end organ function
- Cardiac- role in FAOD is area of research
  - Considerations: cost, time, sedation, safety







Children with Cardiomyopathy and Heart Failure

- Cardiomyopathy ≠ Heart Failure
- Heart Failure= measure of symptoms
- Sometimes signs/symptoms are subtle
- Slow changes are hard to recognize
- Can have moderate or severe dysfunction with no appreciated symptoms
- Kids compensate, until then don’t…
- Surveillance is intended to catch early signs/ changes

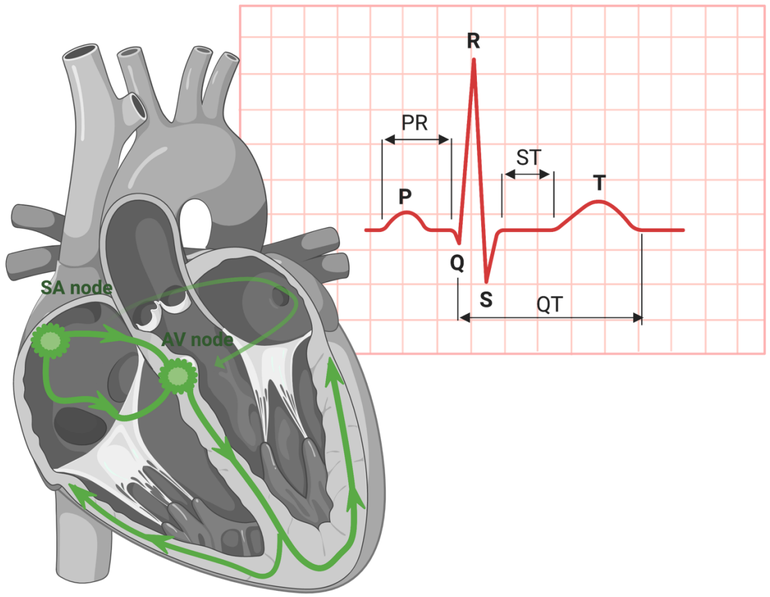
Cardiomyopathy phenotype in FAOD

- The CM phenotype in FAODs is similar across FAOD types/ genotypes
- Lumping FAODs together
- CM can be mixed type in the same patient or can change over time
- Variability between types of FAOD, and among patients with a specific FAOD
- Genotype not predictive (usually)

Gaps in knowledge

- *Predicting who will develop Cardiomyopathy and when*
- *Incidence of late-onset CM - unknown*

Arrythmia phenotype in FAOD: Often accompanies CM



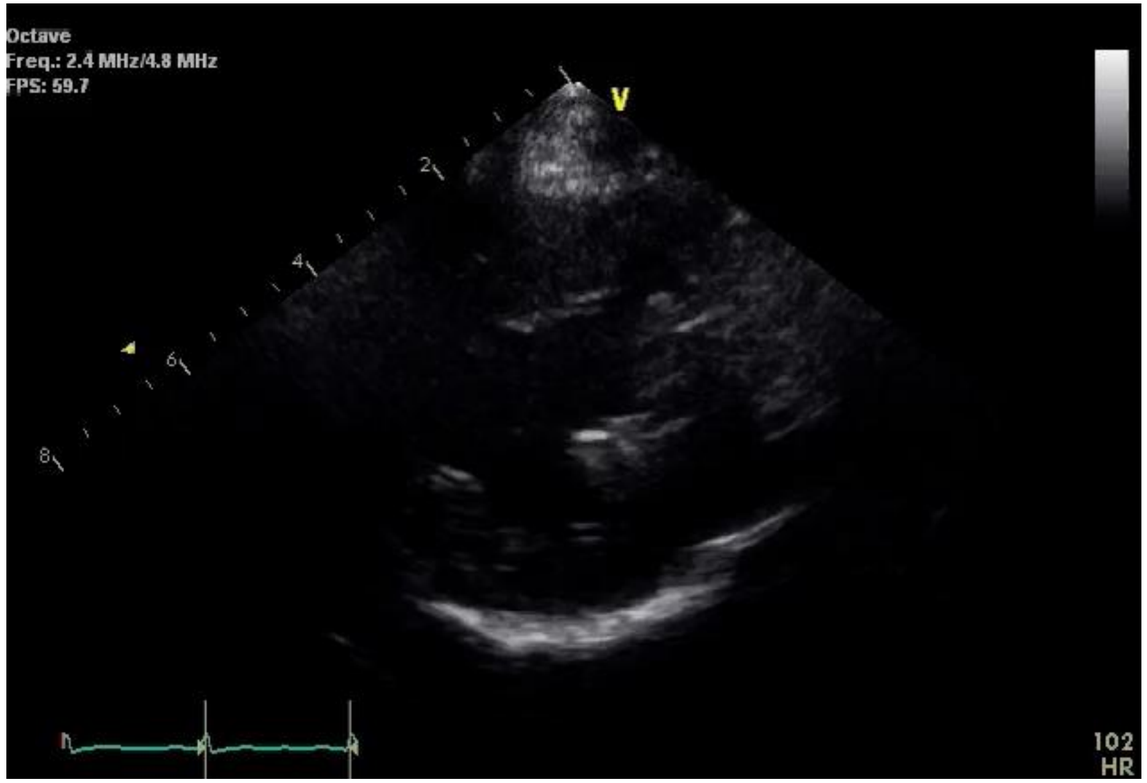
FAO defect	# patients	ECG abnl	Arrhythmia type	First symptom	CM (+/-)	Outcome
CPT-II	4	2/4	VT, VF	4/4	1/4	1 alive 4d- 17mo
CACT	6	5/6	SVT, VT/VF	6/6	0/6	1 alive 3d- 2mo
TFP	3	2/3	SVT, VT	3/3	3/3	11d-1mo
VLCAD	5	1/5	VT/VF	2/5	4/5	1 alive 3- 9mo
LCHAD	2	1/2	SVT, VT, VF	1/2	2/2	10mo- 18y
MADD	3	0/3	SVT, VT	2/3	0/3	7mo- 4y

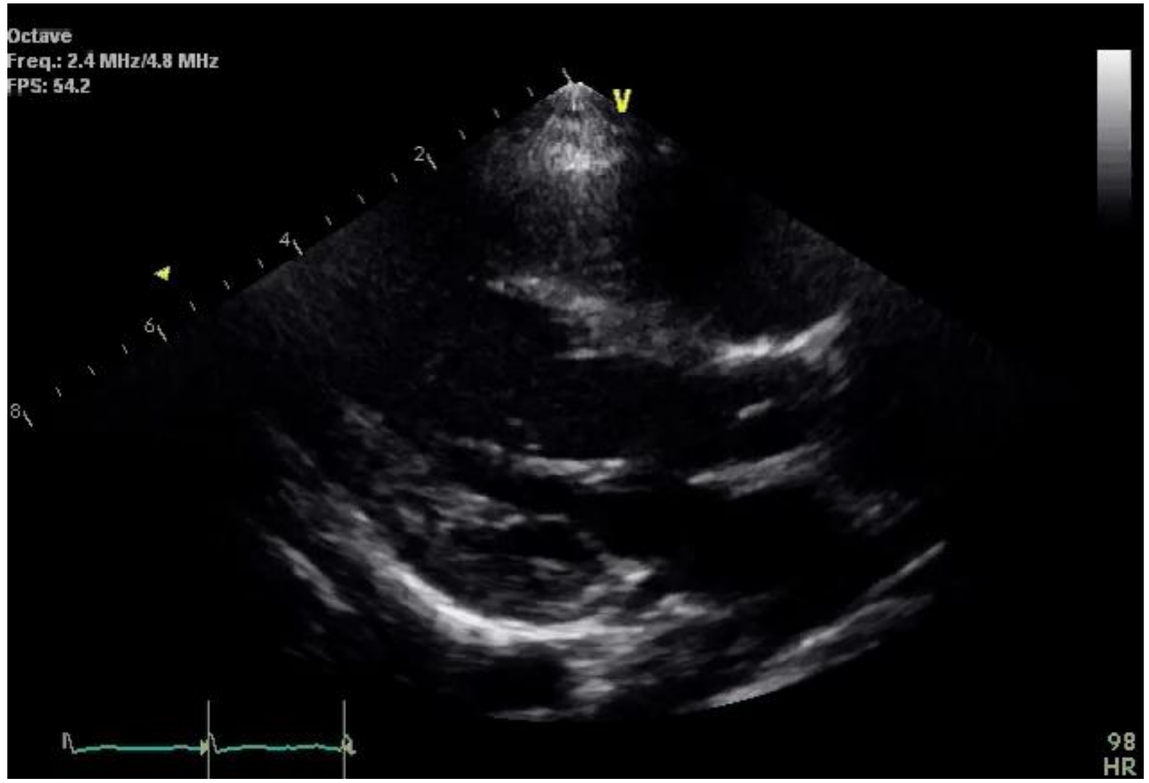
- Small groups of patients from 20+ years ago
- ~25% of patients in cohort had arrhythmia a presenting feature
- Some differences may exist between FAOD, association of CM
- Early presentation of arrhythmia may have implication on prognosis

Bonnet et al, Arrhythmias and Conduction Defects as Presenting Symptoms of Fatty Acid Oxidation Disorders in Children, Circ 1999.

Case #1: Young child with VLCADD: Early Signs of Cardiomyopathy

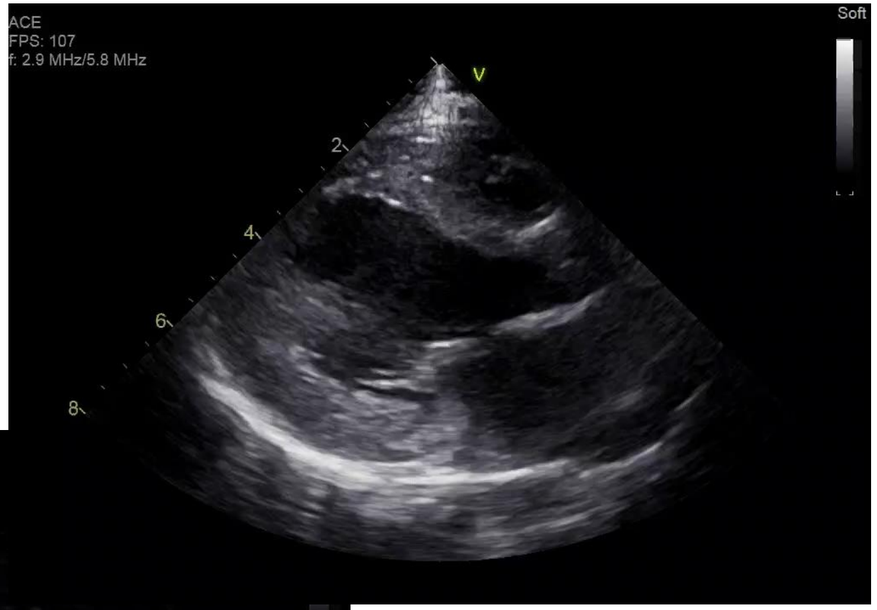
- Few hospitalizations in toddler years, no significant rhabdo or hypoglycemia
- Clues on echo suggest early cardiomyopathy

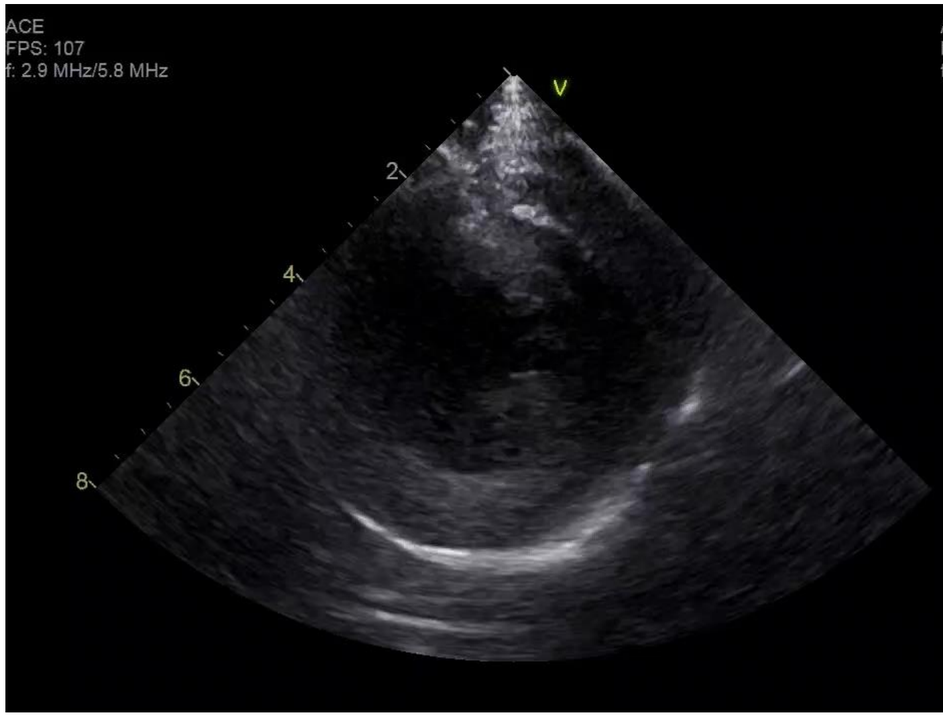


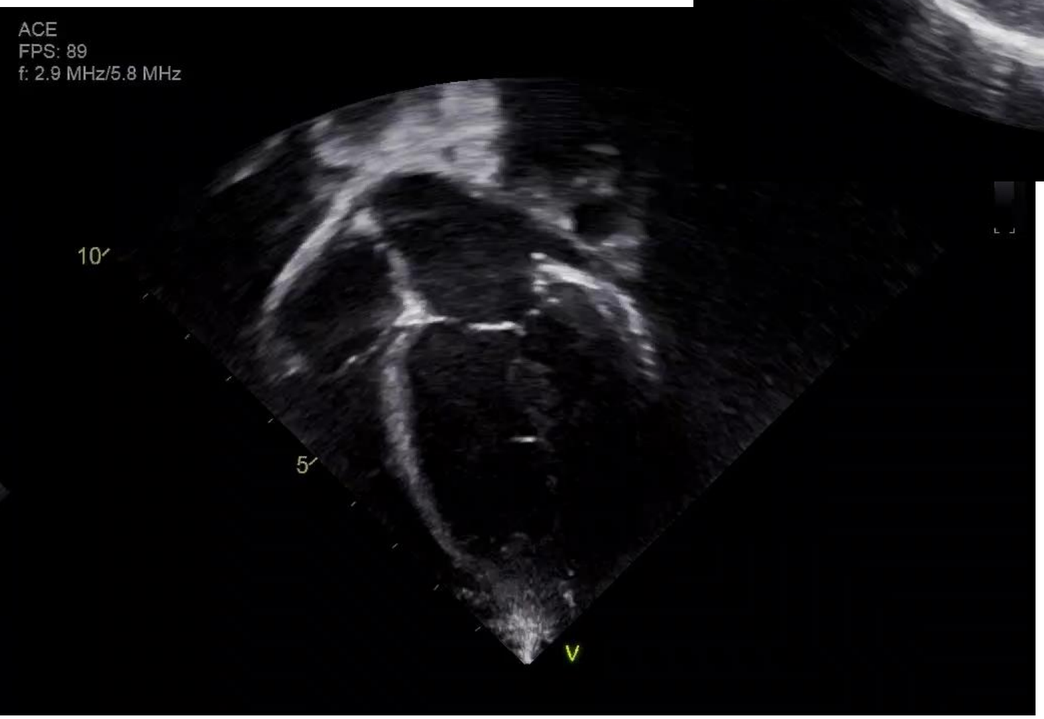


Case #1: Child with VLCADD: 3 years-old
Some worsening of heart function after winter URIs

- Sudden change observed by echo
- Guideline –directed medical therapy (GDMT) started (carvedilol)
- Continued work with metabolic RD to maximize daily calorie goals

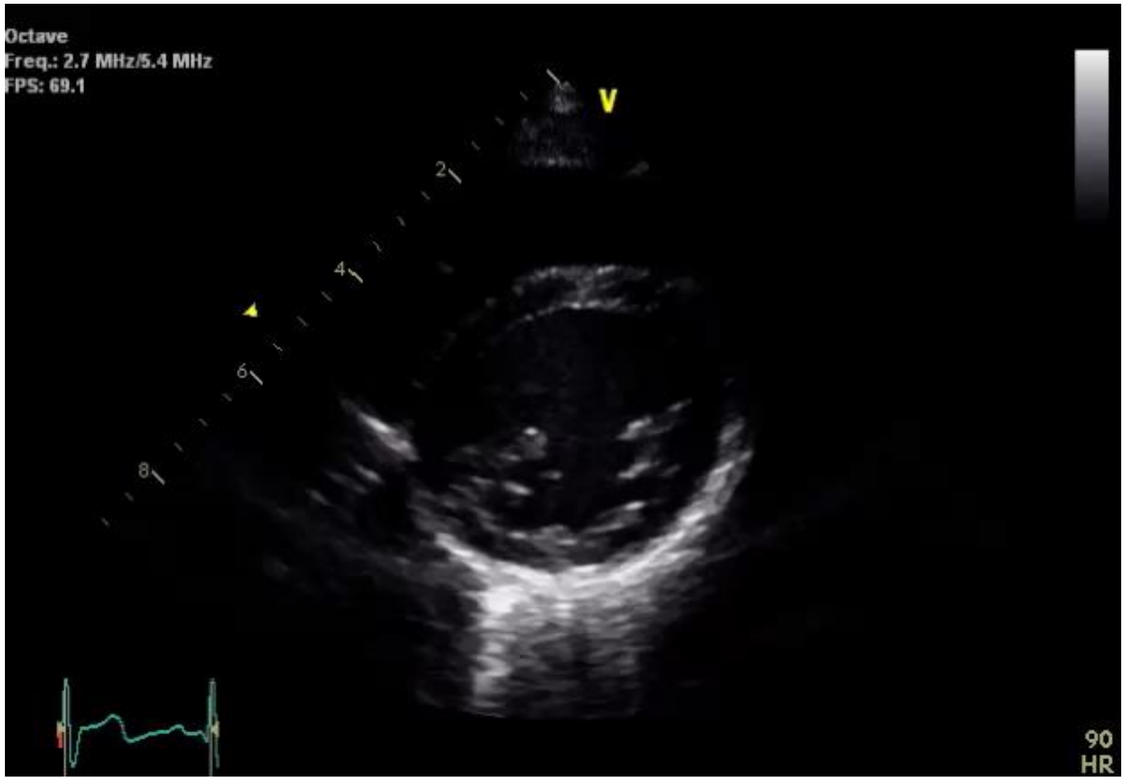


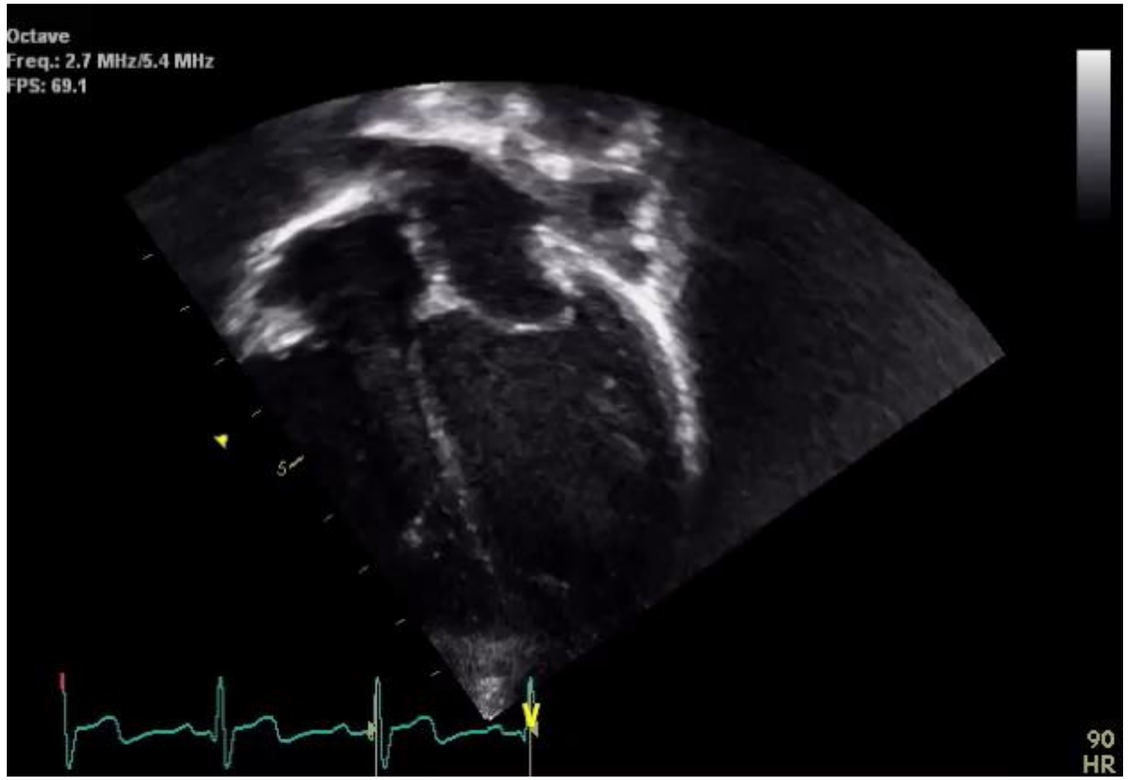




Case #2: Male diagnosed with LCHADD

- 5 hospitalizations- precautionary in first 10 years of life
- Very active and interested in sports: baseball, basketball and football
- Has some muscle symptom with mire intense exercise
- No evidence of cardiomyopathy, normal ECG



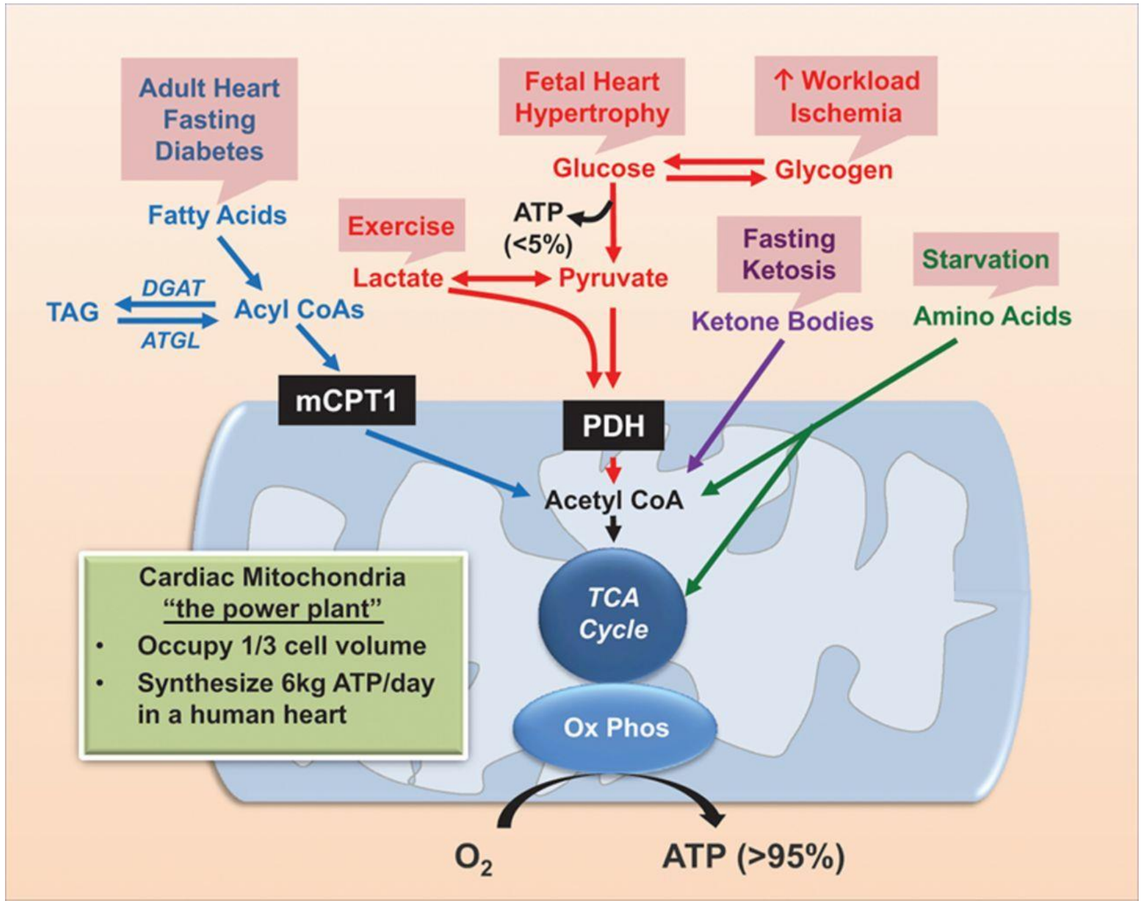


Mechanism of heart disease: mitochondria and metabolism

Why the heart is affected by FAOD

- Fuel (ATP) source needed constantly
- Heart uses fatty acids as a preferred fuel
- 95% of ATP generated in mitochondria
- Heart needs fuel for 2 major functions:
  - Muscle contraction (fueling the pump)
  - Conduction system (the electrical)

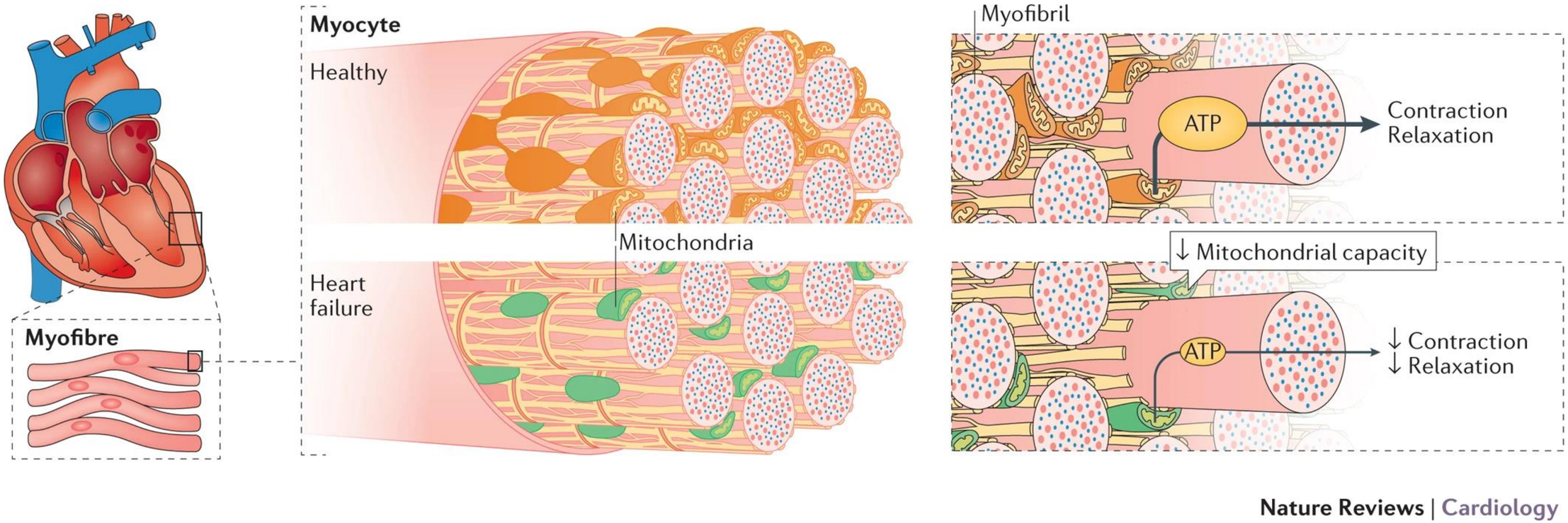
- Therapy should treat cardiac muscle and conduction problems



Kolwicz Jr et al, Cardiac Metabolism and its Interactions With Contraction, Growth, and Survival of Cardiomyocytes, Circ Res 2013

FAODs: Mechanism of Cardiac Disease

"Energetic failure" and toxic accumulation of fa-CoA

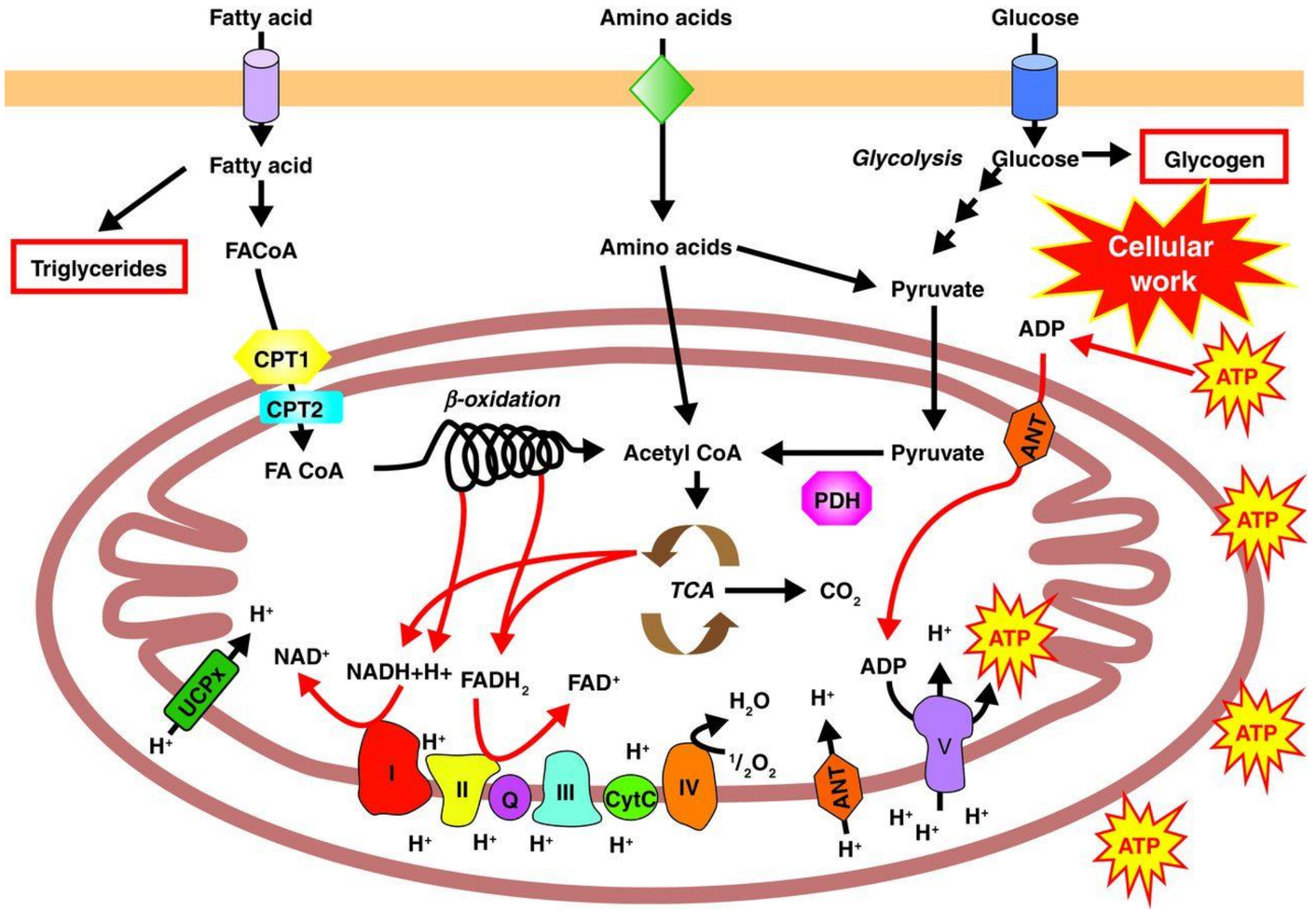


Brown, D et al, Mitochondrial function as a therapeutic target in Heart Failure, Nat Rev Cardiol 2016

Fatty Acid Oxidation Disorder: Mechanism of Cardiac Disease

Other possible mechanisms:

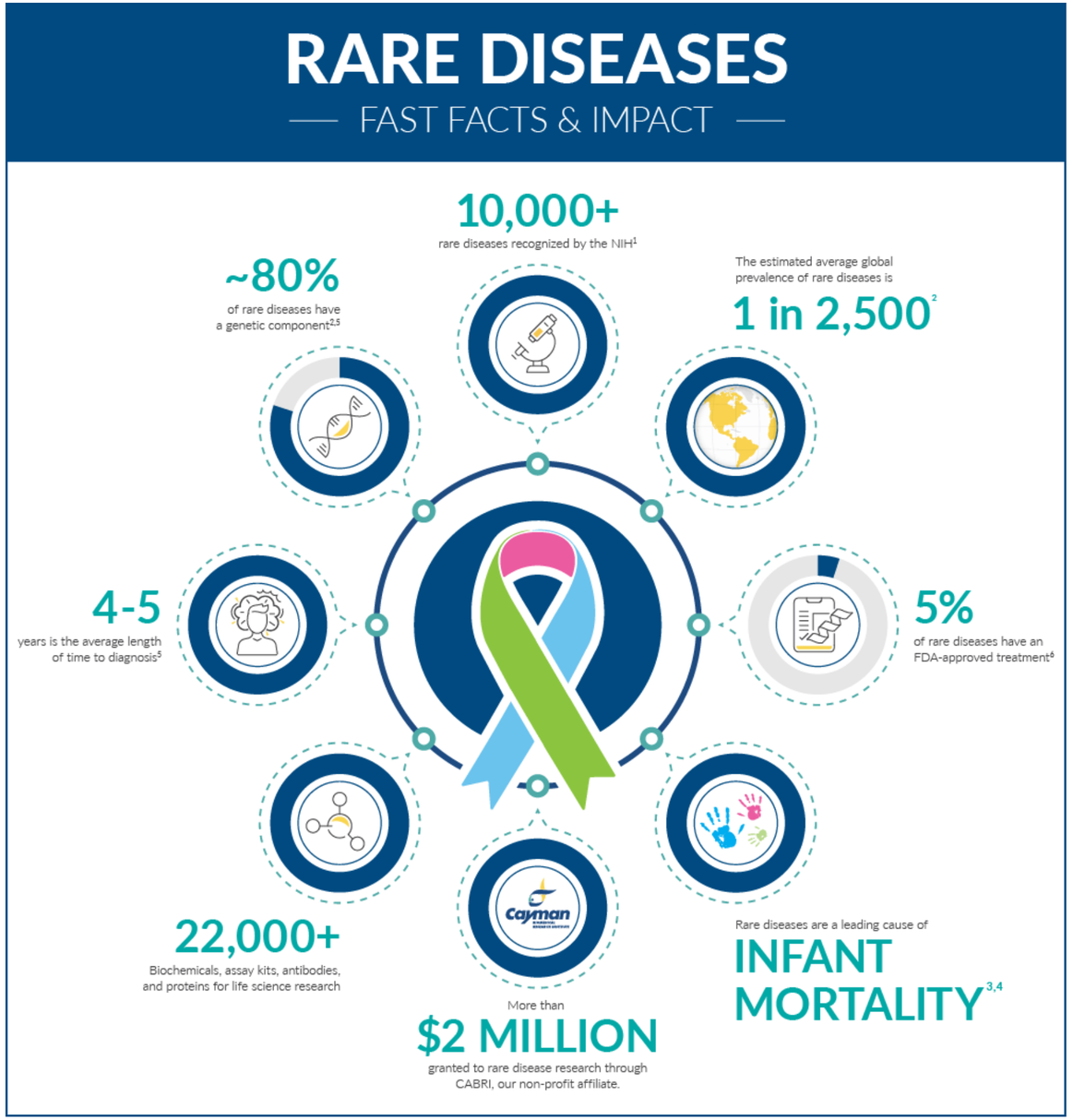
- Secondary respiratory chain dysfunction
- Decreased respiratory capacity
- Loss of metabolic “flexibility”
- Increased reactive oxygen species
- Altered mitochondrial phospholipid-Cardiolipin



Turner N et al, Fatty acid metabolism, energy expenditure and insulin resistance in muscle, Journal of Endocrinology Vol 220:T61, 2014

Some evidence of these concepts in mouse models

Several mechanisms of cardiac pathology
Lacking data specific to *heart* and in *humans*



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Resolution with GDMT

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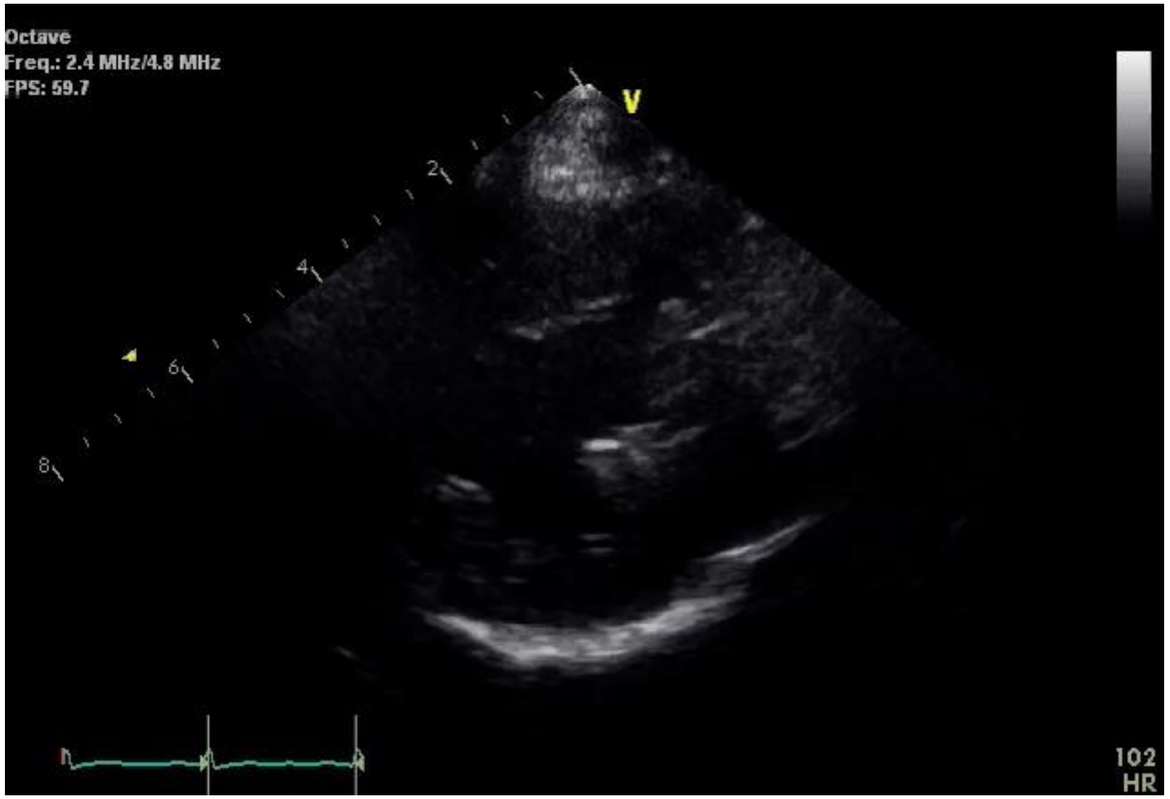
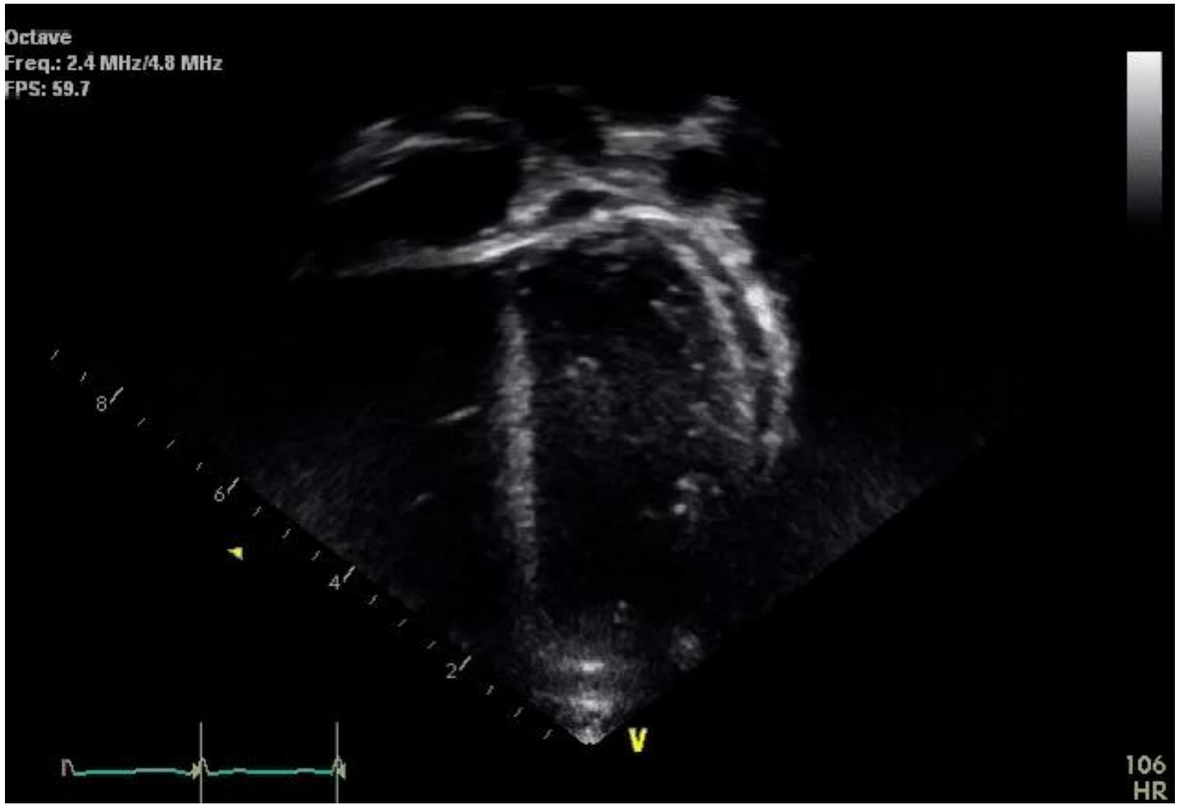
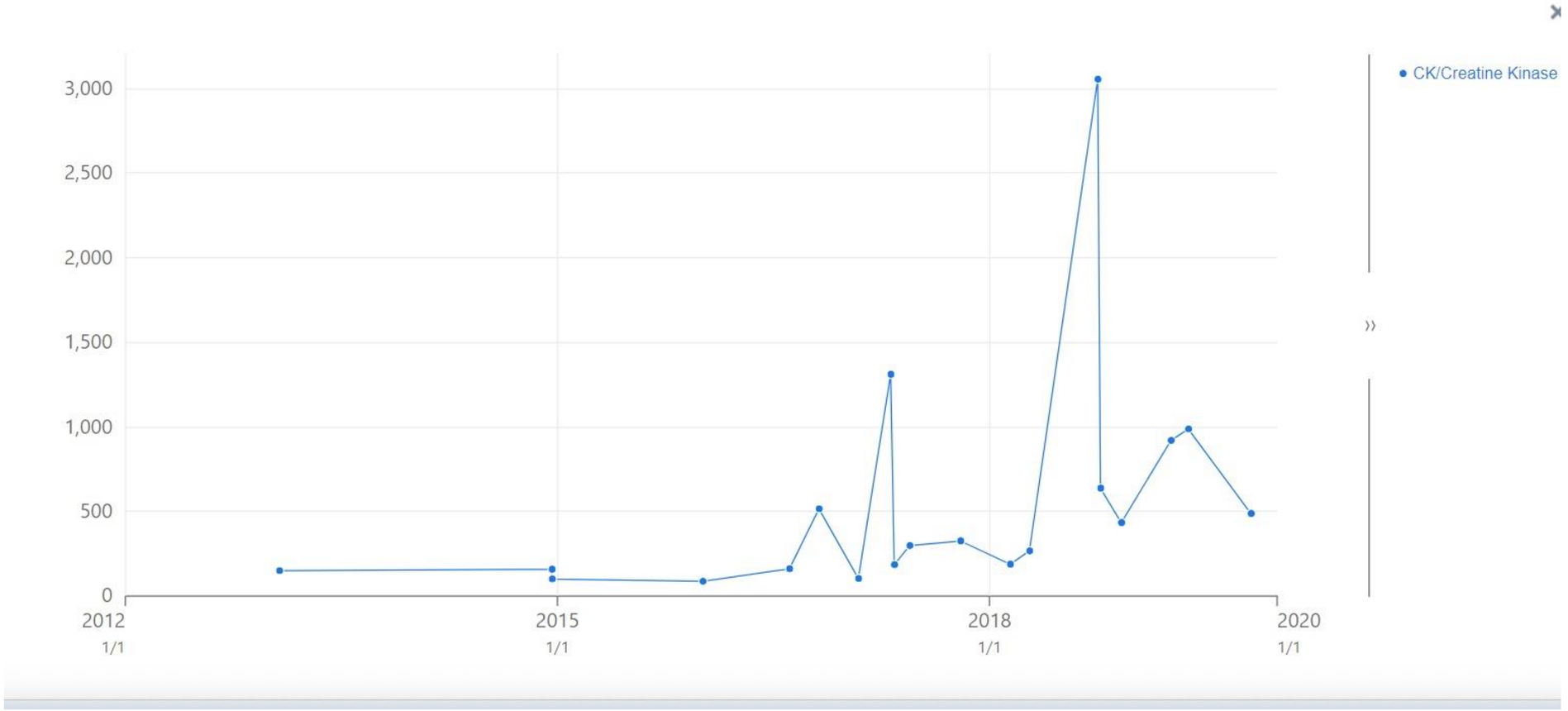
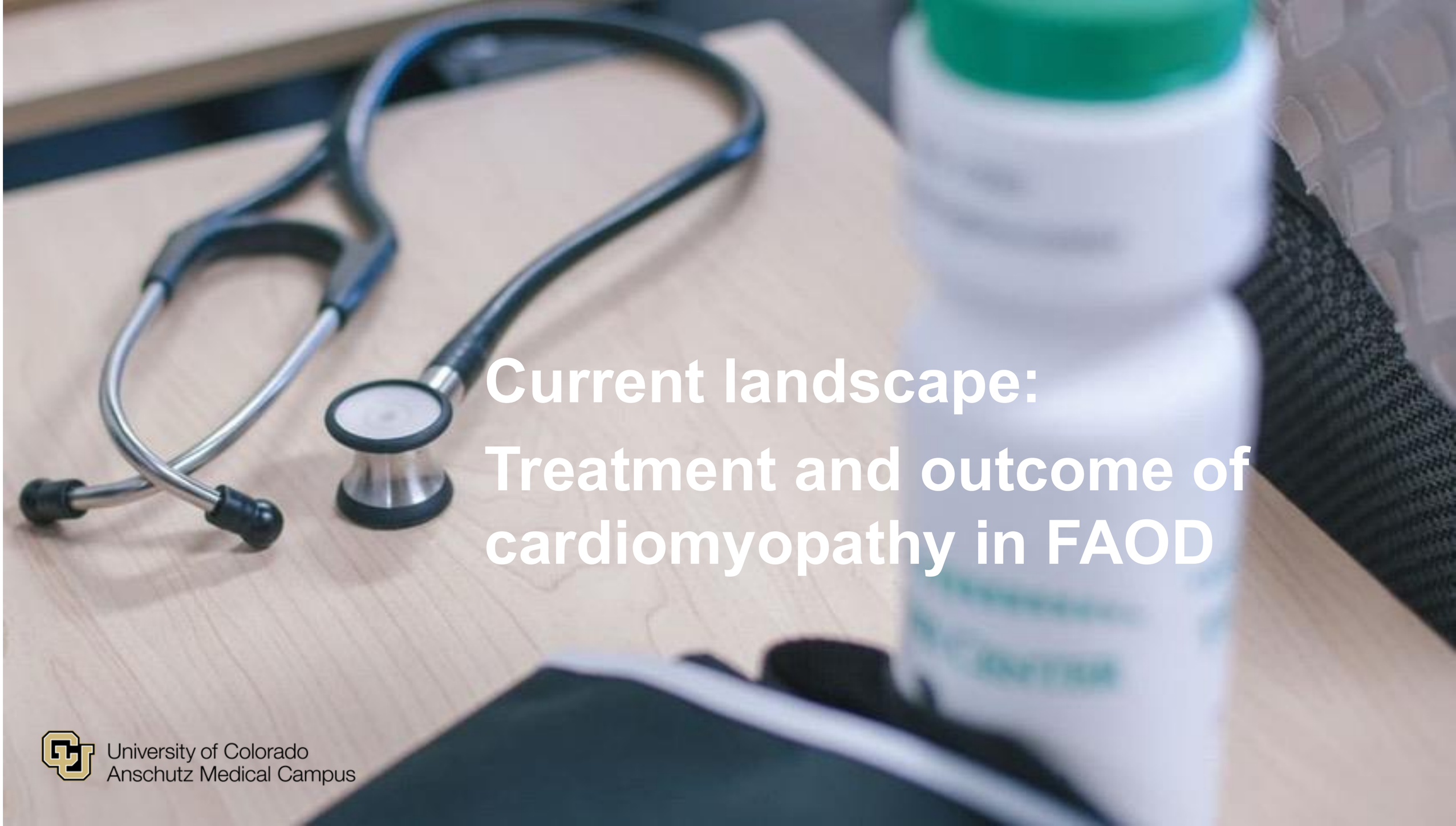




Case #2: Adolescent Male with “mild” LCHADD

- Continues to participate in sports, more bothersome muscle pain and elevations in CK with exercise.





Current landscape:

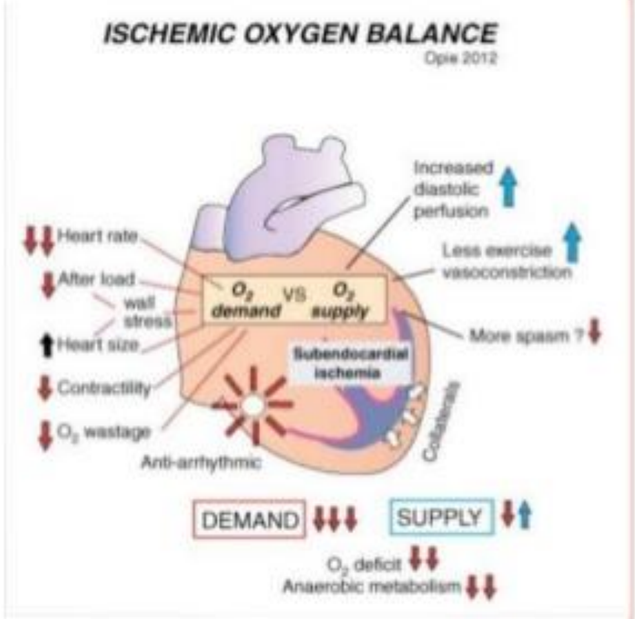
Treatment and outcome of cardiomyopathy in FAOD

University of Colorado
Anschutz Medical Campus

Influence of conventional therapies?
Mechanism of Beta blocker

PROTECTIVE EFFECTS OF BETA BLOCKERS

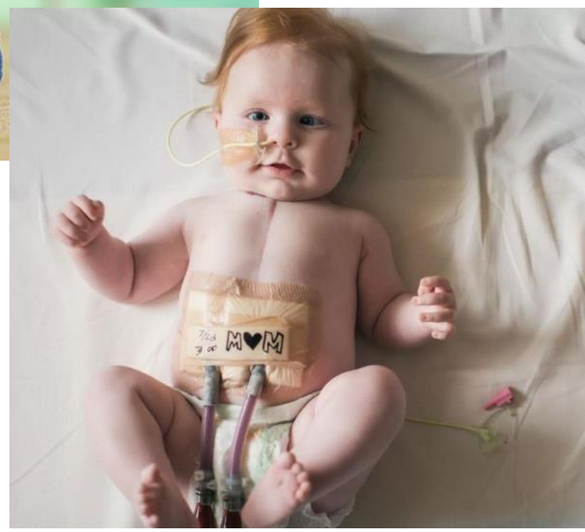
- ↓ HR and contractility
- ↓ VO_2
- ↓ apoptosis signalling
- Anti-ischemic and anti-arrhythmic effects - ↓ VF
- Anti-inflammatory
- Increase synthesis of myocardial proteins
- Shift from FFA to glucose metabolism
- Peripheral antioxidant effect
- Reduce catecholamine release

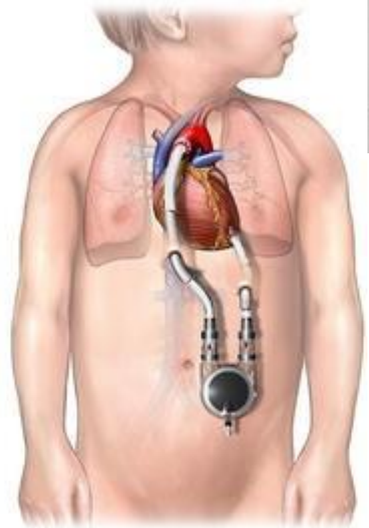


https://pt.slideshare.net/DrVivekBaliga1/beta-blockers-in-stemi/5

Cardiologist perspective on CM in FAOD

- Not all children respond to Doljovi
- In some cases severe disease may not be reversible
- In some cases delivery of compound may be a factor
- Conventional heart failure therapies are still employed/required for recover
- Heart transplant- when and when not?
- VAD- bridge to recovery vs. transplant





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J Inherit Metab Dis. 2017 November ; 40(6): 831–843. doi:10.1007/s10545-017-0085-8.

Triheptanoin versus trioctanoin for long-chain fatty acid oxidation disorders: a double blinded, randomized controlled trial

Melanie B. Gillingham[1], **Stephen B. Heitner**[2], **Julie Martin**[1], **Sarah Rose**[1,3], **Amy Goldstein**[4], **Areeg Hassan El-Gharbawy**[5], **Stephanie Deward**[5,6], **Michael R. Lasarev**[7], **Jim Pollaro**[8], **James P. DeLany**[9], **Luke J. Burchill**[2], **Bret Goodpaster**[9,10], **James Shoemaker**[11], **Dietrich Matern**[12], **Cary O. Harding**[1], and **Jerry Vockley**[5]

FDA approval of Doljovi

June 30, 2020

Therapy utilization

- Biochemical Geneticists /Genetics providers
- Dieticians
- Cardiology- slow acceptance of therapy

Gillingham: Study population

Diagnosis	Triheptanoin C7	MCT C8
CPT-2	(n=5) Age 21–64	(n=6) Age 8-43
VLCAD	(n=4) Age 7–38	(n=5) Age 23-42; 22-31
LCHAD/TFP	(n=7) Age 7–29	(n=5) Age 8–17
TOTAL:	n=16	n=16

Participant Characteristics	Triheptanoin C7	MCT C8
Age (years)	7–64	8–43
Males (n)	6	6
Females (n)	10	10
History of Cardiac Complications	4	0

Gillingham MB, et al. *J Inherit Metab Dis.* 2017;40(6):831-843.

Cardiac function in Study Population

Cardiac function

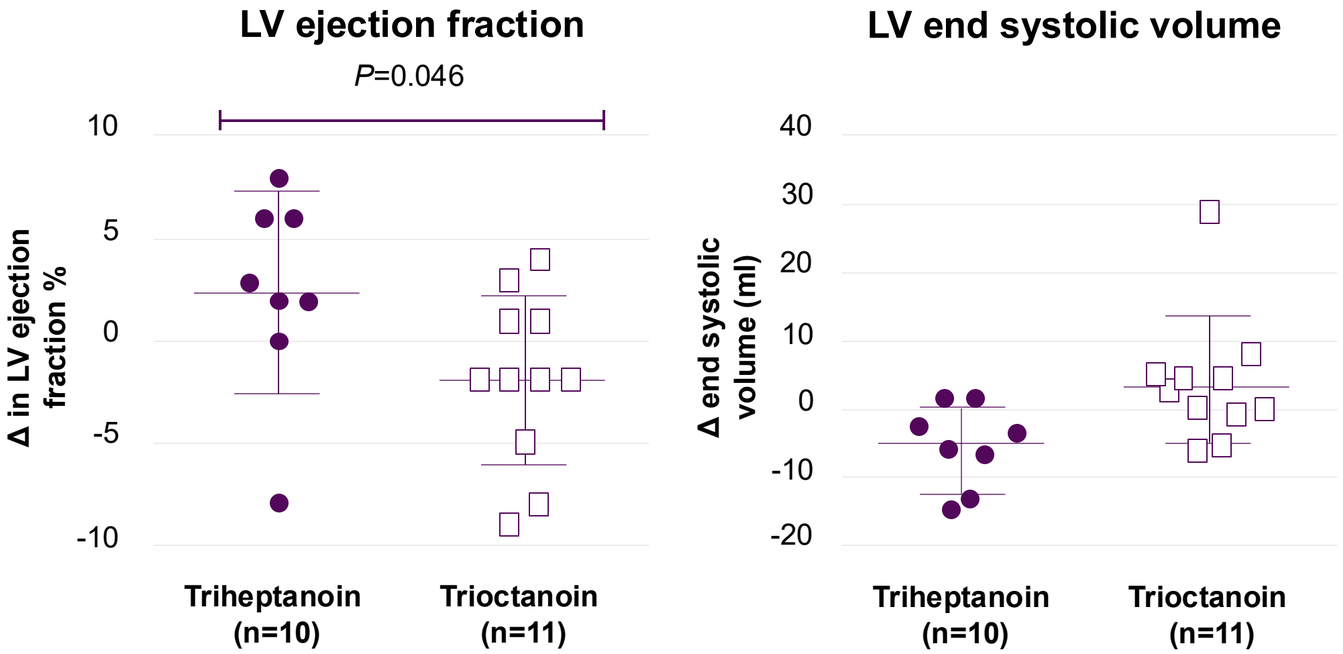
- LCHAD/TFP Patients
  - Three/12 had significant heart manifestations at the time of presentation that we resolved w diagnosis and treatment
  - 1 patient had a recent history of sudden cardiac arrest w/ resuscitation
  - **At the time of the study, all had normal cardiac function**
- VLCAD Patients
  - 1 patient presented in infancy w/ severe cardiac complications that resolved after diagnosis and treatment but cardiac function subsequently deteriorated and was **abnormal at the time of the study**
- CPT2 Patients
  - **None of the patients had a history of cardiac disease**

Gillingham MB, et al. *J Inherit Metab Dis.* 2017;40(6):831-843.

LV Ejection Fraction and LV End Systolic Volume

- Patients treated with triheptanoin had **7.4% greater relative left ventricular (LV) ejection fraction** compared with patients treated with trioctanoin (*P*=0.046)
- Patients treated with triheptanoin had a **7% decrease in LV end systolic volume** compared while those treated with trioctanoin experienced an increase (*P*=0.114) measure of dilation

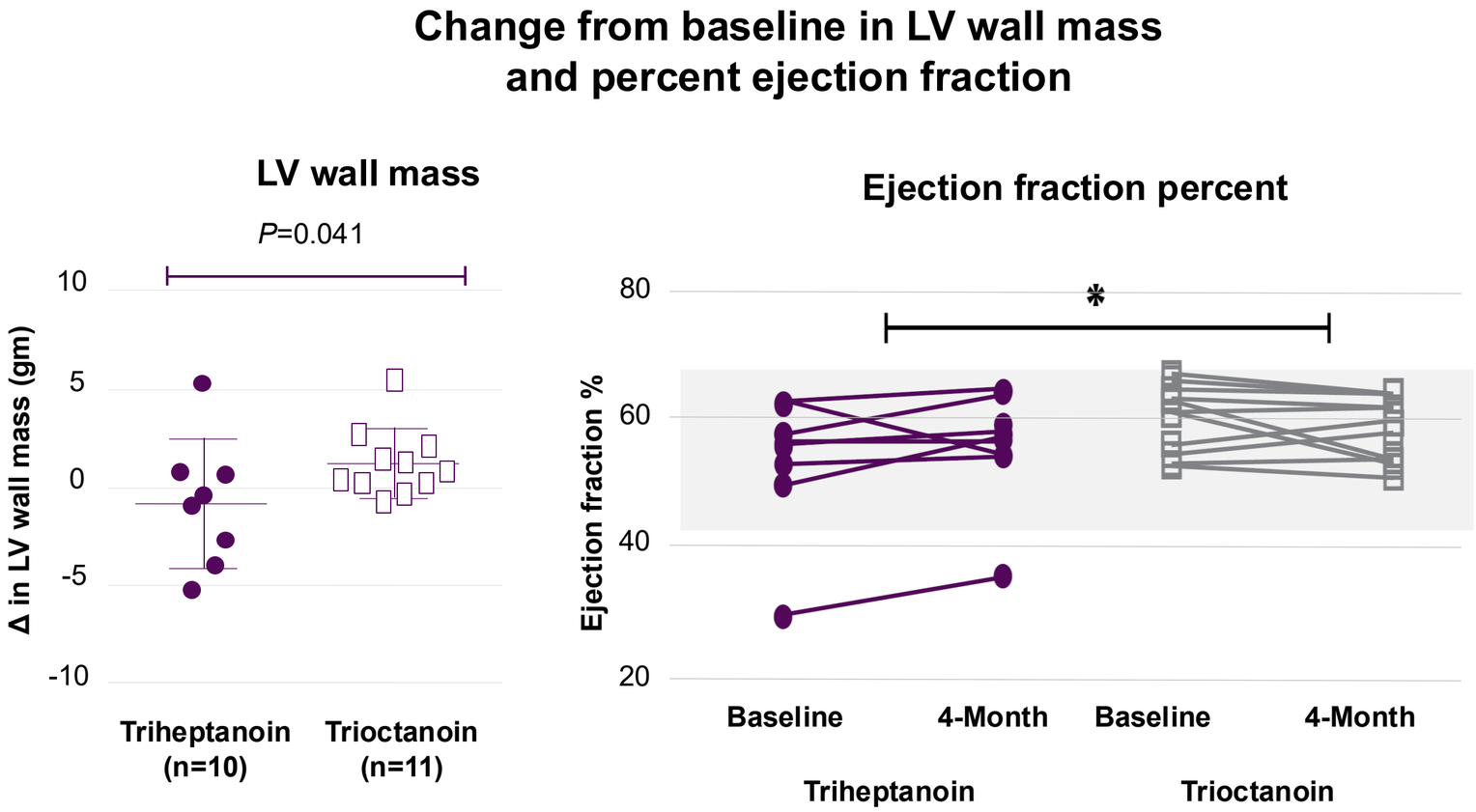
Change from baseline in LV ejection fraction and LV end systolic volume after 4 months of treatment



Gillingham MB, et al. *J Inherit Metab Dis.* 2017;40(6):831-843.

Gillingham: LV Wall Mass and Percent Ejection Fraction

- Patients treated with triheptanoin for 4 months experienced a **20% decrease in LV wall mass** compared with patients treated with trioctanoin for 4 months who experienced increased LV wall mass (*P*=0.041)
- All but 1 patient had a normal ejection fraction percent at baseline and most observed changes occurred within the normal range for LV ejection fraction.



Gillingham MB, et al. *J Inherit Metab Dis.* 2017;40(6):831-843.

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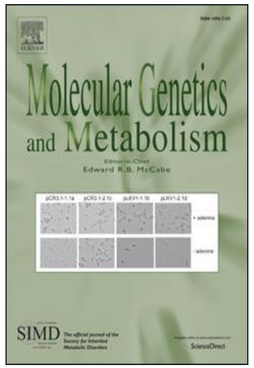

Triheptanoin treatment in patients with pediatric cardiomyopathy associated with long chain-fatty acid oxidation disorders

J. Vockley [a,*], J. Charrow [b], J. Ganesh [c], M. Eswara [d], G.A. Diaz [e], E. McCracken [a], R. Conway [f], G.M. Enns [g], J. Starr [h], R. Wang [h], J.E. Abdenur [h], J. Sanchez-de-Toledo [a], D.L. Marsden [i]

J. Vockley et al. *Triheptanoin treatment in patients with pediatric cardiomyopathy associated with long chain-fatty acid oxidation disorders.* Molecular Genetics and Metabolism 119 (2016) 223–231.

Patient characteristics- all with CM

- Case reports from 10 patients (8 infants) with moderate or severe cardiomyopathy associated with LC-FAOD
  - ➢VLCAD **(n=4);** CACT **(n=2)**; TFP **(2);** n=LCHAD **(n=2)**

- Moderately to severely impaired ejection fraction (EF) ranging from 12–45% at baseline

- All patients were managed with standard treatment, including medium chain triglyceride (MCT) oil
  - ➢While on this regimen, they presented with acute heart failure requiring hospitalization and cardiac support (ventilation, ECMO, vasopressors) and, in some cases, resuscitation

- The patients discontinued MCT oil and began treatment with triheptanoin (UX007)
  - – UX007 target dose was 25–35% of total calories, as tolerated, which is equivalent to approximately 2-4 g/kg in infants and young children, decreasing to 1-2 g/kg for older children and adolescents, and 1 g/kg for adults. (Range in these cases were 1-4 g/kg/day based on age and tolerability)

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Baseline Characteristics of LC-FAOD Patients

Case	Gender	LC-FAOD diagnosis	Genotype	Age at diagnosis	Initial presentation (Age/Symptoms)	Cardiomyopathy presentation (Age/Symptoms)	Age at trihep start	Prior MCT treatment
1	F	VLCAD	c.1678 + 3_1678 + 6 del AAGT	NBS	Neonatal hypoglycemia, metabolic acidosis	3 months; cardiac dysfunction	7 months	Y
2	M	VLCAD	Homozygous c.1807dupT (p.C603LfsX2)	NBS	Neonatal hypoglycemia, cardiac dysfunction	6 months; cardiac arrest, severe dilated CM	6 months	Y
3	F	TFP	c.1165 A > G c.1289 T > C	NBS	Neonatal hypoglycemia	8 months; significant left ventricular hypertrophy	8 months	Y
4	F	LCHAD	1528G > C 1528G > C	NBS	10 months; severe CM, heart failure	10 months; severe CM, heart failure	10 months	Y
5	F	CACT	c.84delT del + 3p21.31	NBS	Neonatal hypoglycemia, cardiac dysfunction	10 months; severe CM, heart failure, ascites	10 months	Y
6	F	TFP	Homozygous c.1678C > T	NBS	Neonatal hypoglycemia, mild biventricular dysfunction	1.5 months; heart failure	2.5 months	Y
7	F	VLCAD	c.1268C > T (p.S423 L)/c.1913C > T (p.S638F)	NBS	3 months; hypotensive, hypoglycemic, respiratory distress, hepatomegaly	3 months; cardiac failure	3 months	Y
8	F	VLCAD	c.887_888del c.1679- 6G > A	3.5 months	Neonatal hypoglycemia, hypothermia 3.5 months; acute CM w/biventricular hypertrophy, pericardial effusion, respiratory failure	3.5 months; acute CM with biventricular hypertrophy[1] 20 years; acute CM, cardiogenic shock, cardiac arrest	5 years 20 years	Y
9	M	LCHAD	homozygous 1528 G > C	NBS	Prior to age 8; rhabdomyolysis	8 years; bradyarrhythmia, cardiac arrest	8 years	Y
10	M	CACT	c.823C > T (p.R275X)/del E 5–9	<1 month	Hypothermia, altered consciousness, hyperammonemia	Day 11; cardiomegaly, mild LVH, decreased LV function	6 months	Y

CM = cardiomyopathy; LVH = left ventricular hypertrophy; MCT = medium chain triglyceride oil; NBS = newborn screening.

[1] Previously described in Roe et al. 2002.

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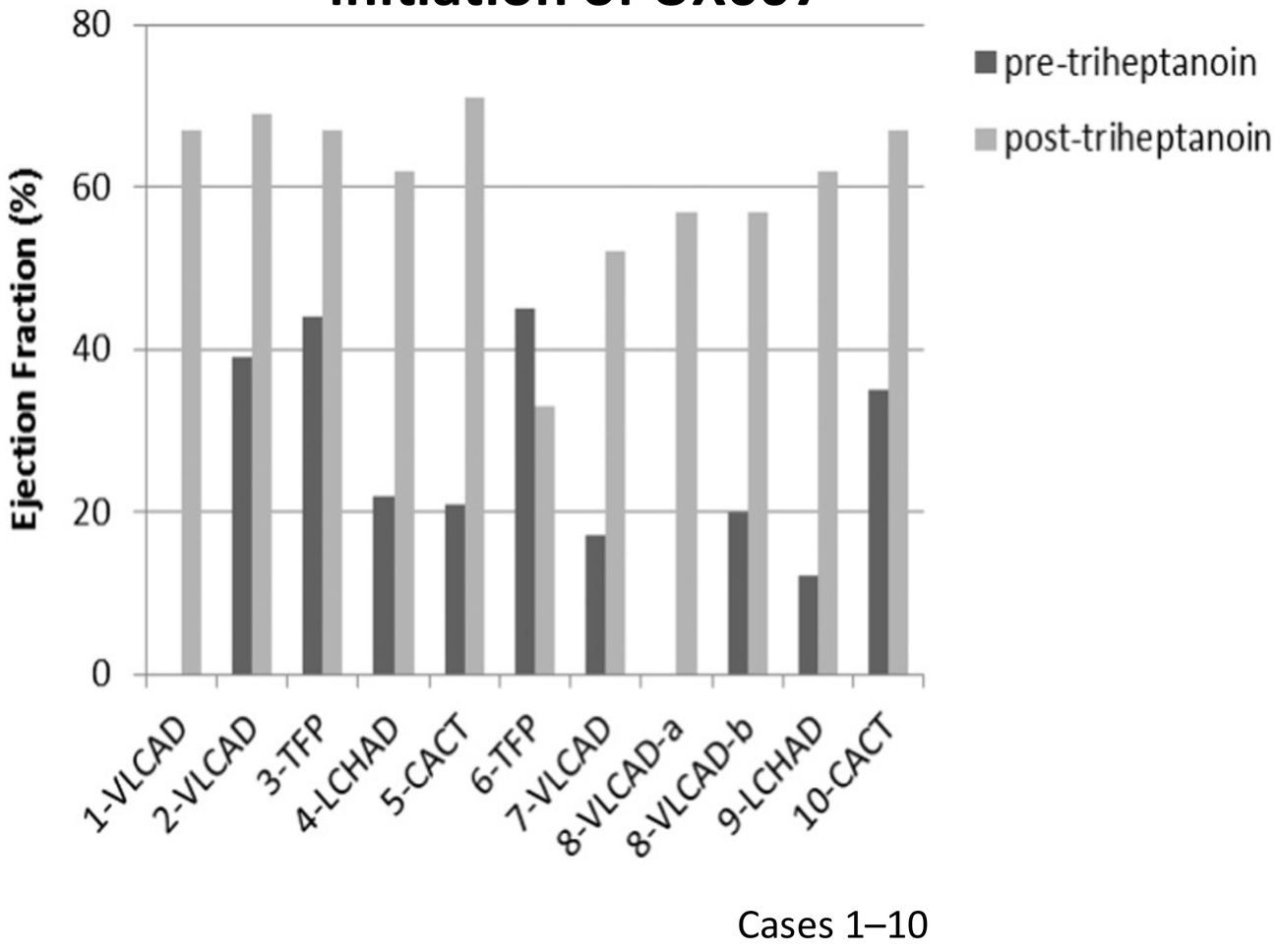
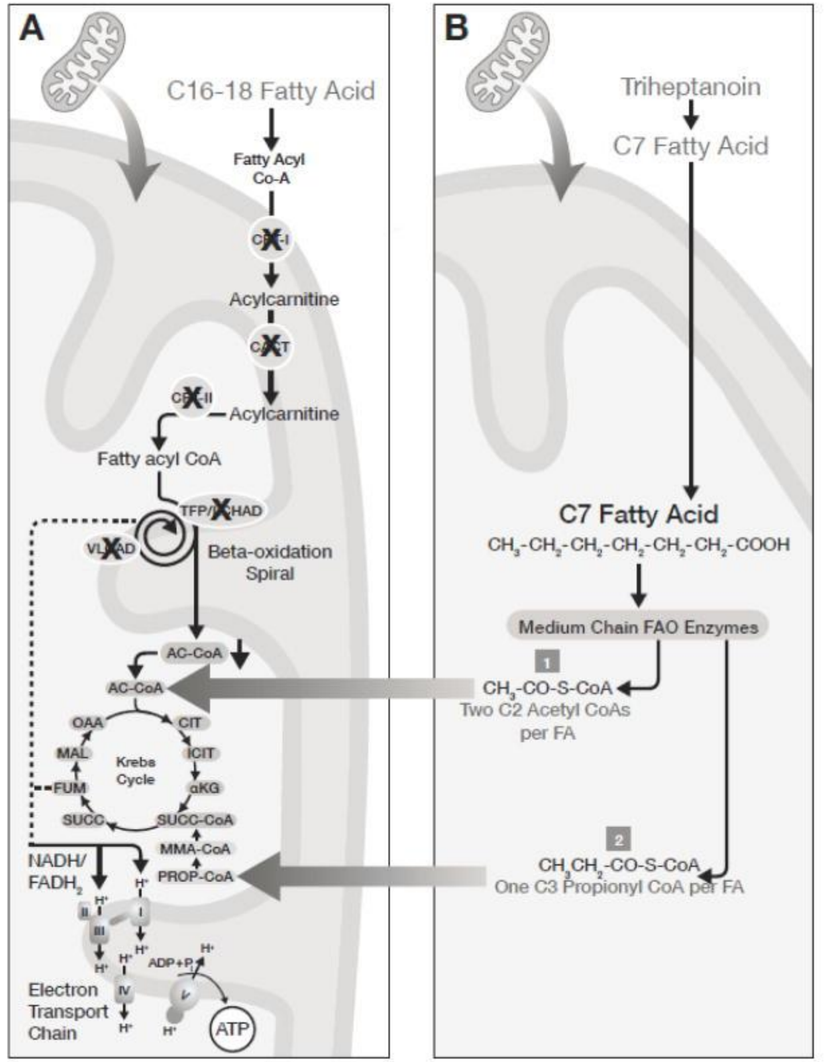
Changes in Peak Ejection Fraction

Peak ejection fraction (EF) improvements following initiation of UX007



Cases 1–10



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Safety and Tolerability

- The most common adverse event observed was gastrointestinal distress
- Ten patients:
  - 7 continued on treatment
  - 1 discontinued due to tolerability issues
  - 2 infants died during treatment though neither death was attributed to the administration of UX007 by the reporting physician, rather appearing related to underlying disease
    - One VLCAD female died at ~3.5 months of age of sepsis/necrotizing fasciitis (case 7)
    - One TFP female died at ~3.5 months of age (case 6) after metabolic and lactic acidosis and respiratory distress requiring ventilation, pericardial effusions requiring repeated draining, refractory cardiogenic shock with severe pulmonary hemorrhage

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Conclusions of triheptanoin studies

- Superior to MCT (non-inferior)
- Cardiomyopathy can resolve/normalize (reversibility)
- Not all severe cardiomyopathy patients have normalization, some still have poor outcome- death or heart transplant
- Triheptanoin does not replace conventional strategies to treat heart failure

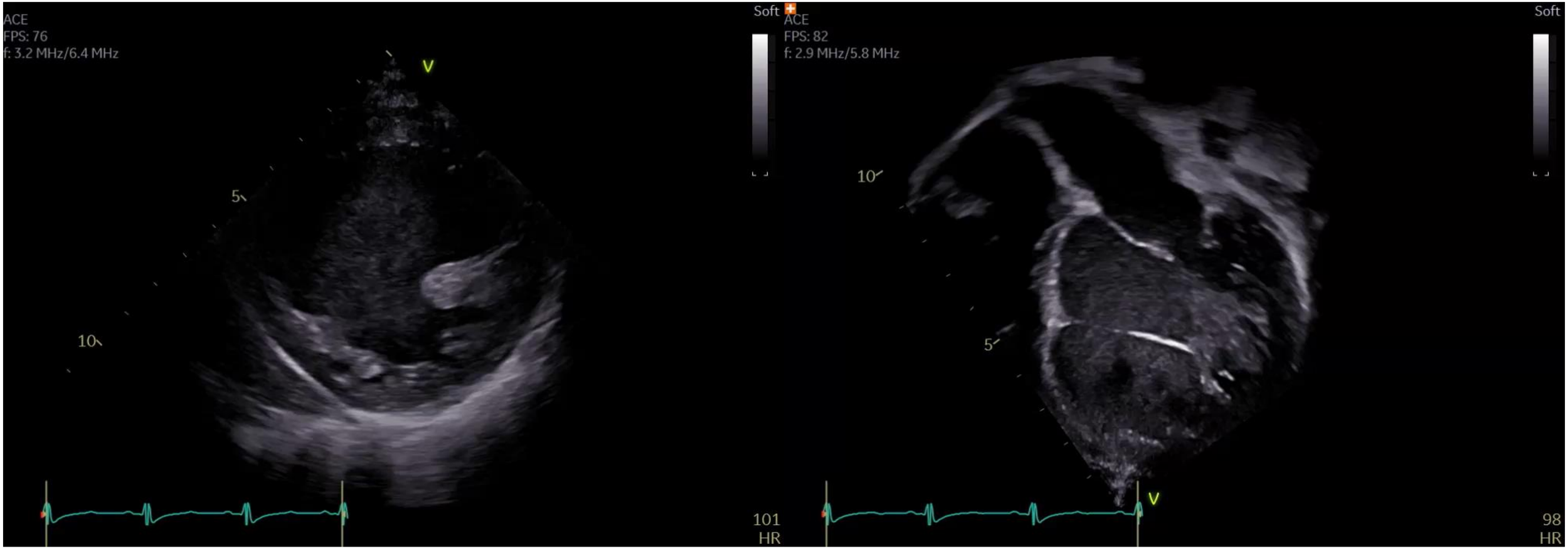
Case #1 VLCADD: ECHO trends over time

Trends in LVEF, FS and mass over time

DATE of EXAM	patient condition	LVEF%	FS%	LV mass g/Ht^2.7
1/24/22	Well- clinic	47.8	26.8	69.8
9/2/21	hosp f/u	48.9	27.8	58 (Dev)
8/23/21 after C7	Admit- URI	45.7	22.2	54.8
4/5/21	Well- clinic	47.7	27.2	55.8
7/6/20	Well- clinic	52.5	29	68.1
3/16/20	Admit- URI	51.7	24	73.9
12/23/19	Well- clinic	56.6	32.4	61.9
4/8/19 (Coreg stopped)	**Well- clinic**	**58.4**	32.8	ND
10/8/18	Well- clinic	53.8	33.2	56.6
7/23/18	Well- clinic	54.2	33	56.5
6/11/18	Well- clinic	51.7	26.7	77.6
5/23/18	Well- clinic	44.7	24.9	86.4
5/2/18	Well- clinic	44.2	25.3	104.1
4/2/18 (Coreg started)	Well- clinic	47.1	30	105.8
3/26/18	**Well- clinic after illness**	**40.1**	16.3	177
8/21/17	Well- clinic	ND	39.1	41.8
5/22/17	Well- clinic	65.5	37.8	44.8
4/23/17	Well- clinic	66.2	36.4	56.2

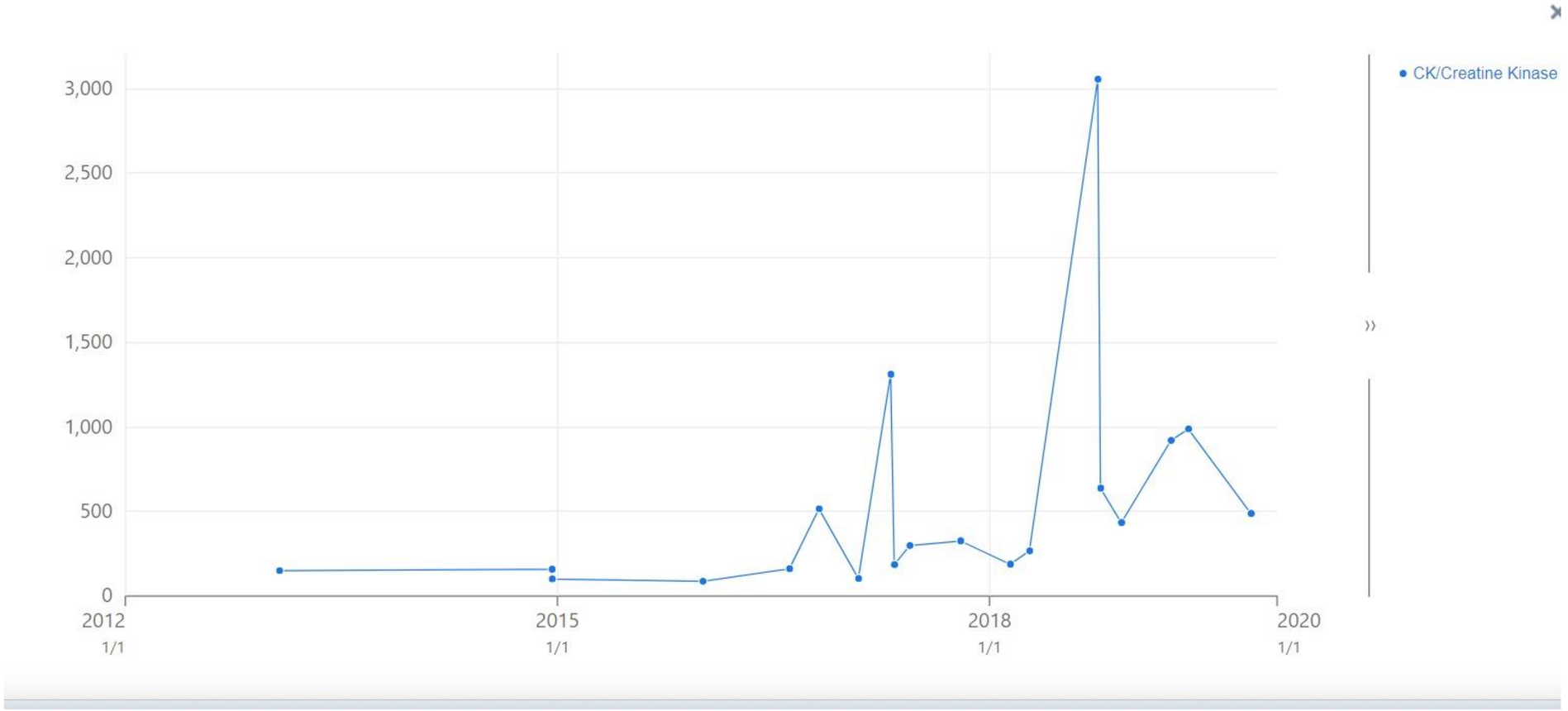
Case #1: VLCADD then things got worse again

- Slow decline becomes more rapid in spite of C7 and GDMT
- Admitted for NG feeding
- When stable enough for anesthesia, underwent G-tube placement

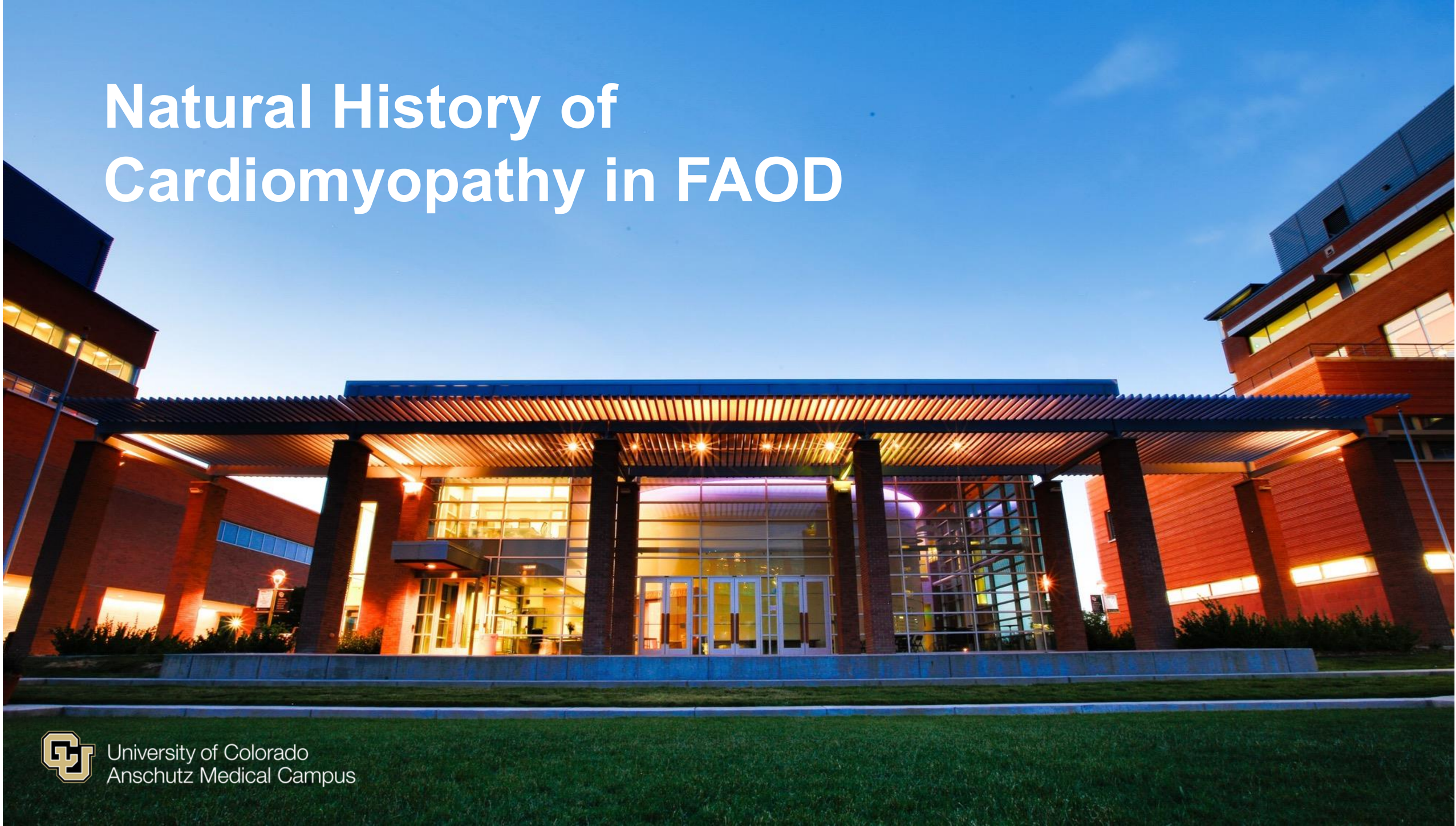


Case #2: Adolescent Male with “mild” LCHADD

- Continues to participate in sports, more bothersome muscle pain and elevations in CK with exercise.



Natural History of Cardiomyopathy in FAOD



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Presenting Signs and Symptoms in 50 LCHAD patients

Signs and Symptoms	11 Patients Presenting Without Acute Metabolic Derangement		39 Patients Presenting With Acute Metabolic Derangement	
	Number	Percentage	Number	Percentage
Hepatomegaly	6/10*	60%	28/36*	78%
Hepatic dysfunction	8/10*	80%	31/39*	79%
Cholestasis	3/10*	30%	6/34*	18%
Cardiomyopathy	**4/11***	**36%**	**17/35***	**49%**
Failure to thrive	8/11*	73%	14/35*	40%
Feeding difficulties	6/11*	55%	16/35*	46%
Vomiting	5/11*	45%	13/33*	39%
Hypotonia	7/11*	64%	22/36*	61%
Lethargy	3/10*	30%	10/35*	29%
Psychomotor retardation	3/11*	27%	9/36*	25%
Peripheral neuropathy	1/11*	9%	1/33*	3%
Microcephaly	3/11*	27%	2/33*	6%

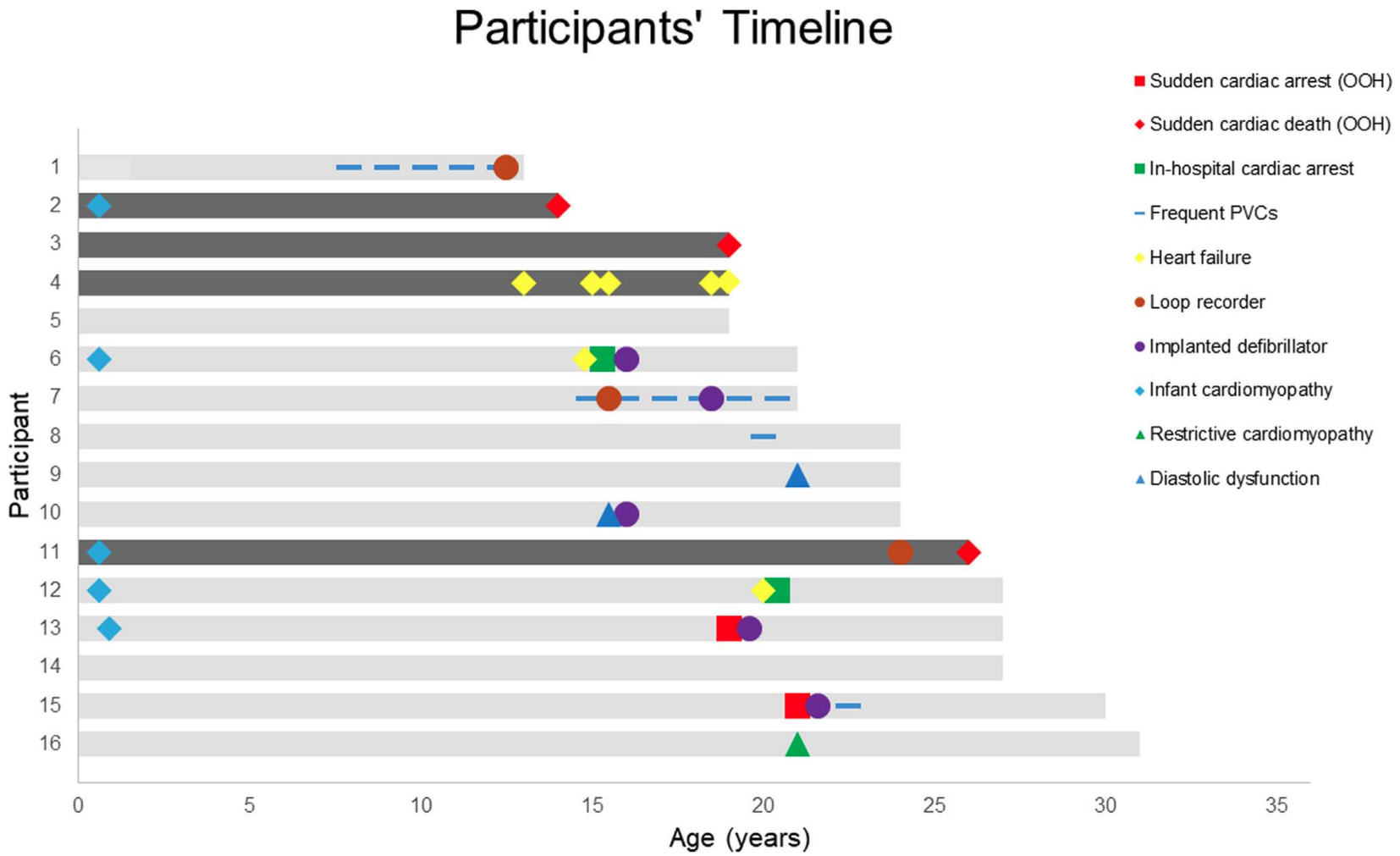
Den Boer, MEJ, et al, Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency: Clinical Presentation and Follow-Up of 50 Patients, Pediatrics 2002

Updated natural history of CM in FAOD: modern treatment

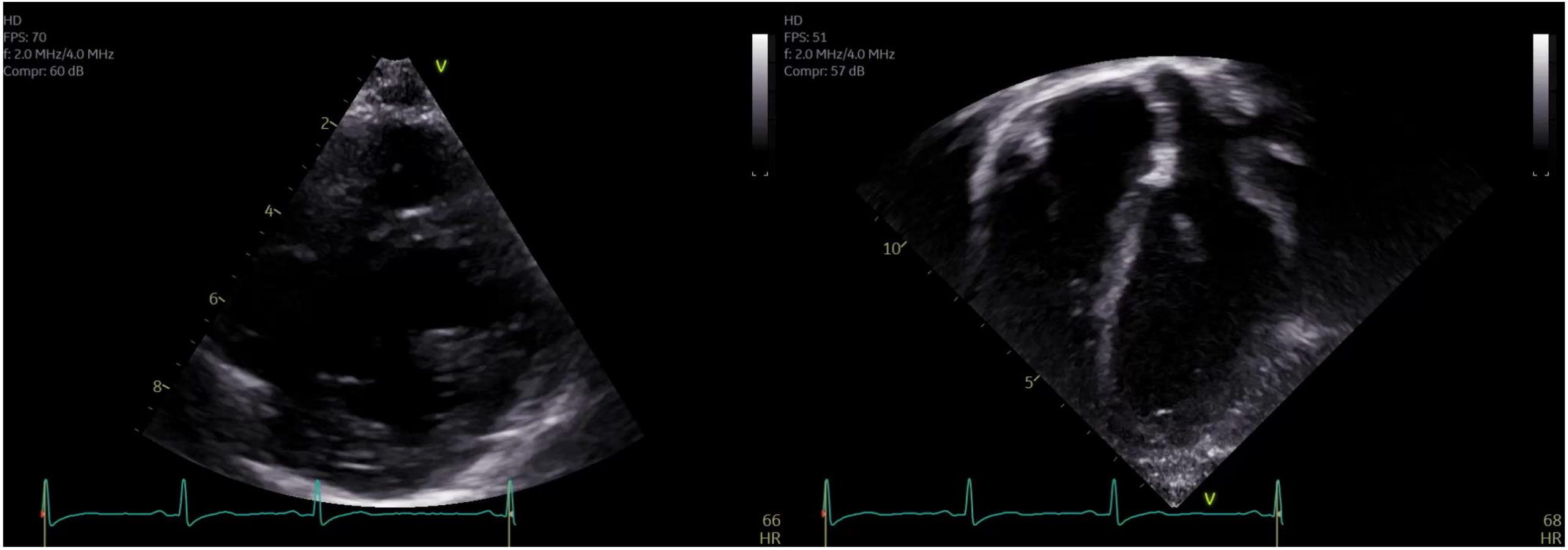
- Abstract/ poster- Gillingham et al, Disease characteristics in adult patients with FAOD
- What happens to the patients with CM?

Natural History of Cardiomyopathy in LCHADD

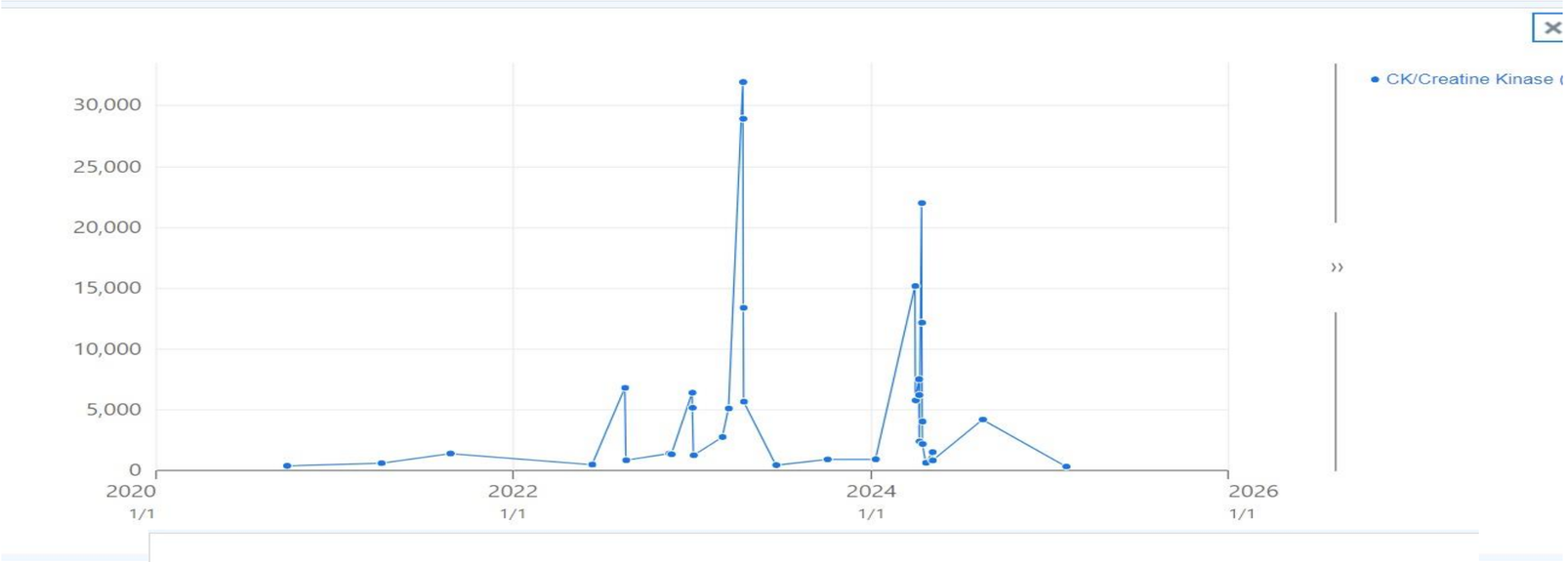
- Largely unknown, little long-term studies
- Many case reports/series- often skewed
- Important study by Gillingham group (Elizondo et al)

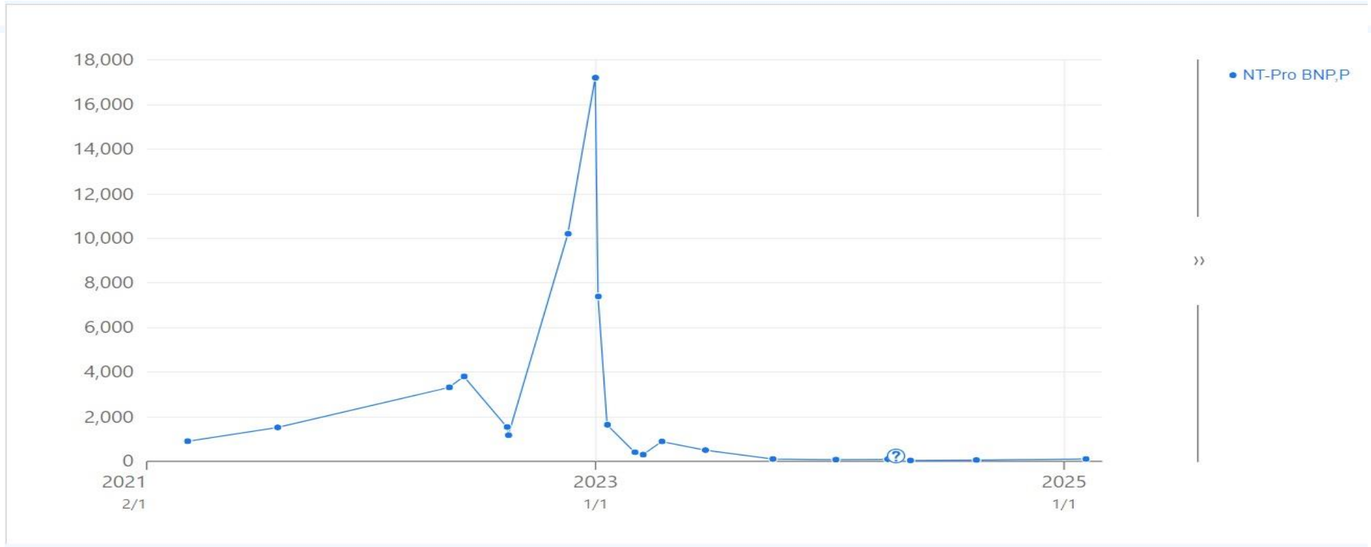


Case #1: VLCADD 2 years after G-tube



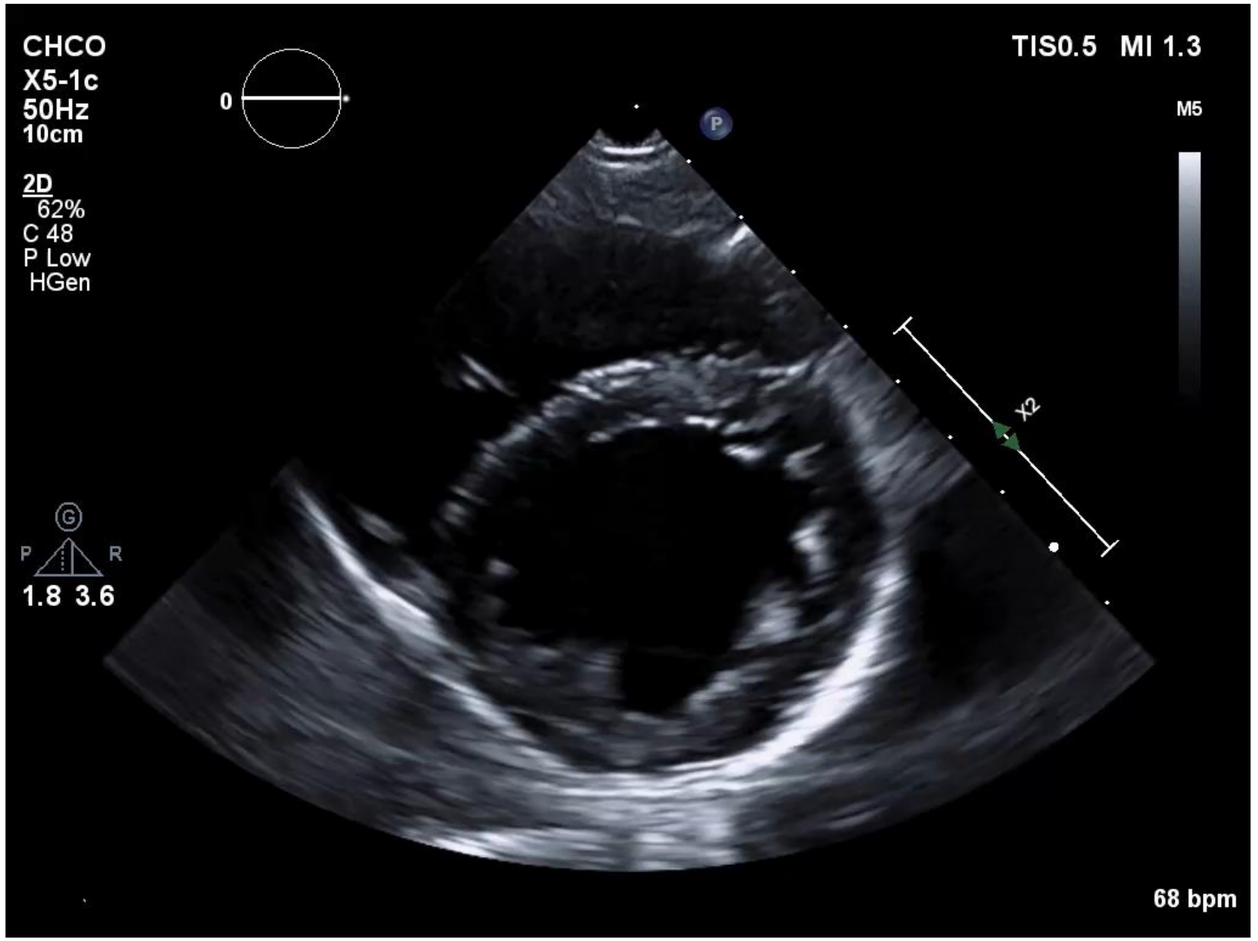
Case #1: VLCADD 2 years after G-tube

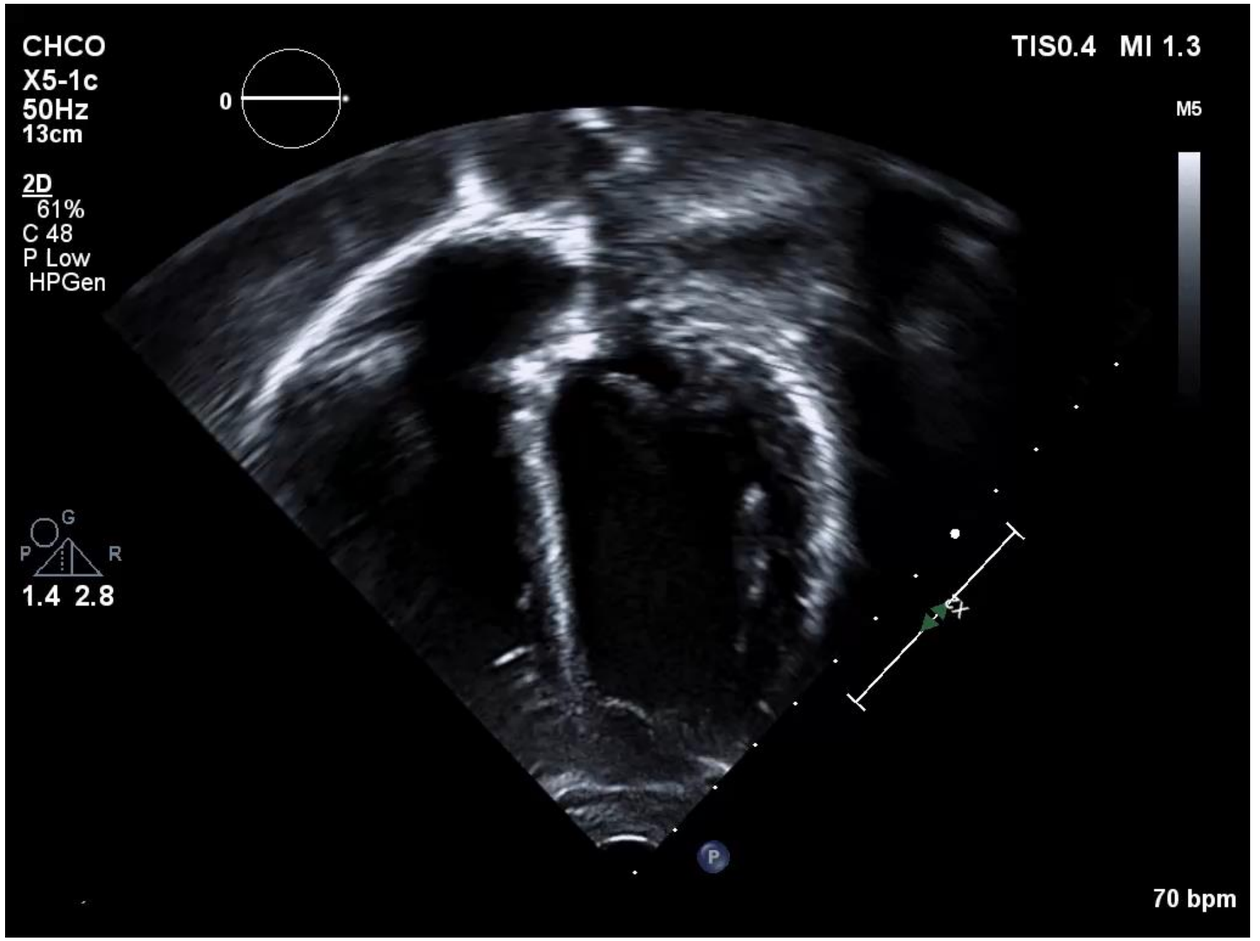




Case #2: Adolescent Male with “mild” LCHADD

- Continues to participate in sports, symptoms better with C7 therapy





Unanswered questions and future directions

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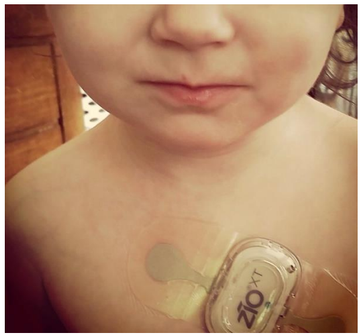
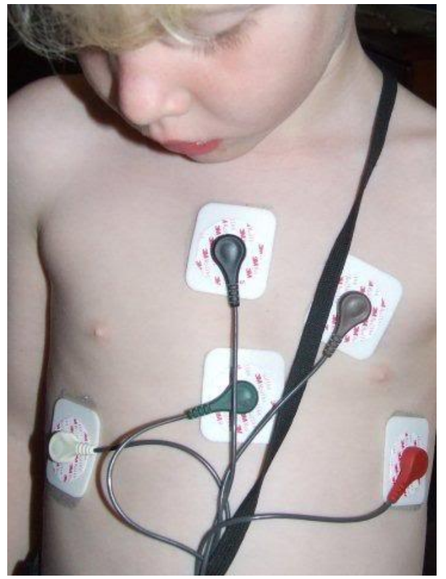
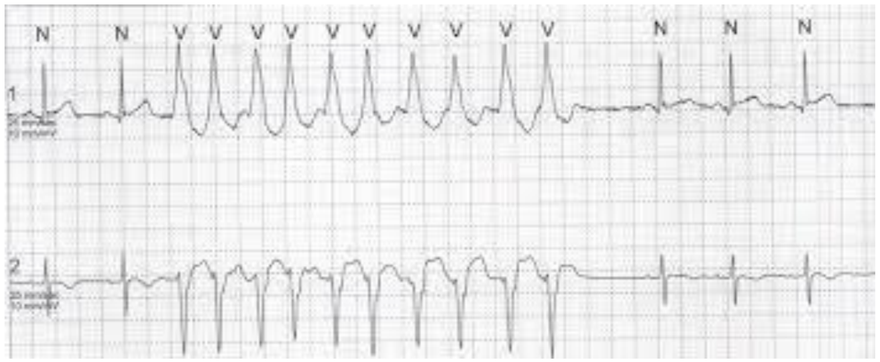
Health Supervision Guidelines: updates?

- 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
- ECG annually to screen for abnormalities
- Holter monitor every few years- annual (Zio monitor)
- Holter/Zio/Loop monitor if any syncope (fainting) or other symptoms (palpitations) concerning for arrhythmia
- *Consider cardiac MRI-especially if history of CM or repeat episodes of heart failure*







- **Individualized care for each patient**
  - **Based on genotype and phenotype**

Future Research and Therapy

- New diagnostic approach- cardiac MRI
- Data collection on recovery of CM (ACTION)
- Following outcomes with C7 therapy over longer periods of time
- Predicting the “non-responders”
- Exploring C7 as adjunct to conventional medical therapies (like beta blocker)
- New therapies- anapleurosis, ROS scavenging, alternative metabolism, pharmacology, mitochondrial-targeted, mito biogenesis
- Identification of biomarkers that can predict likelihood of developing cardiac disease
- Prevention vs. reversal- is one more important?

action

ADVANCED CARDIAC THERAPIES
IMPROVING OUTCOMES NETWORK

55 network care sites

1,100 network members

6 industry collaborators

16 ACTION manuscripts

60 network leaders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THANK YOU