
Minneapolis
Heart Institute
Foundation®
GRAND ROUNDS

Case Presentation

Jared Routh, MD
Cardiology Fellow

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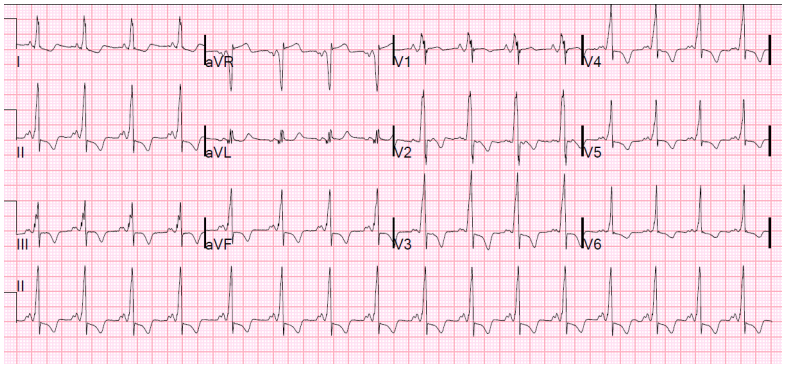
20 year old female with pre-excitation

- CC: Pre-excitation on EKG
- HPI:
  - 20 year old female who initially presented to the ED after smoking marijuana she suspected was laced.
  - She left without being seen.
  - EKG was obtained and showed pre-excitation and T wave abnormalities.



2

20 year old female with pre-excitation

- HPI con't:
  - In clinic, complained of rare palpitations.
  - Denies racing heart, lightheadedness/dizziness, syncope (ever).
  - Denies exertional symptoms (chest pain, dyspnea).
  - Denies orthopnea, paroxysmal nocturnal dyspnea, lower extremity edema.
- PMH, PSH – unremarkable.
- No medications.
- NKDA
- FH – paternal grandfather with stroke.
- Social history: Social alcohol use. Occasional marijuana use. Denies the use of other illicit drugs.

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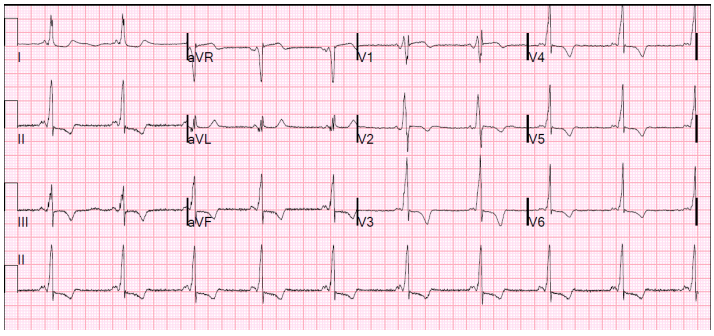
20 year old female with pre-excitation

- Physical examination:
  - Vital signs: HR 85, BP 115/75
  - CV examination: RRR without murmurs, rubs, gallops. No parasternal heave. No extra-systoles. JVP normal. Radial and dorsalis pedis pulses 2+. No lower extremity edema.
  - Remainder of the examination unremarkable.
- EKG performed in clinic showed pre-excitation.



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20 year old female with pre-excitation

- Plan:
  - 7 day Zio Patch
  - Treadmill exercise stress test to evaluate for resolution of delta wave at a higher heart rate
  - Transthoracic echocardiogram

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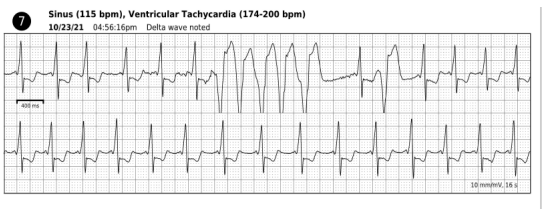
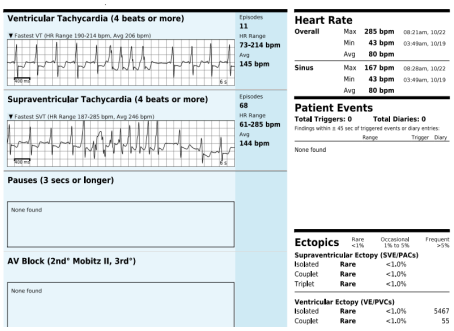
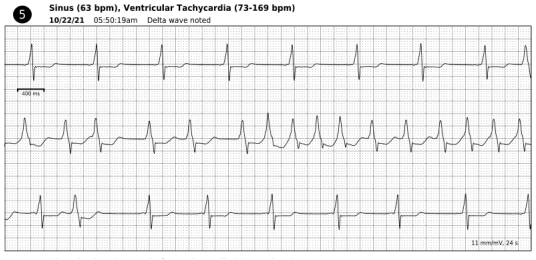
Zio Patch

- 11 runs of NSVT
  - Longest 17 beats
  - Fastest 214 bpm
- 68 SVT episodes
  - Fastest 285 bpm







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GXT

- Exercised for 9 min 16 sec and achieved 10.8 METS, peak HR 173 bpm
- Reason for stopping test: SOB
- Delta wave did not resolve at increased HR
- No exercise induced arrhythmias

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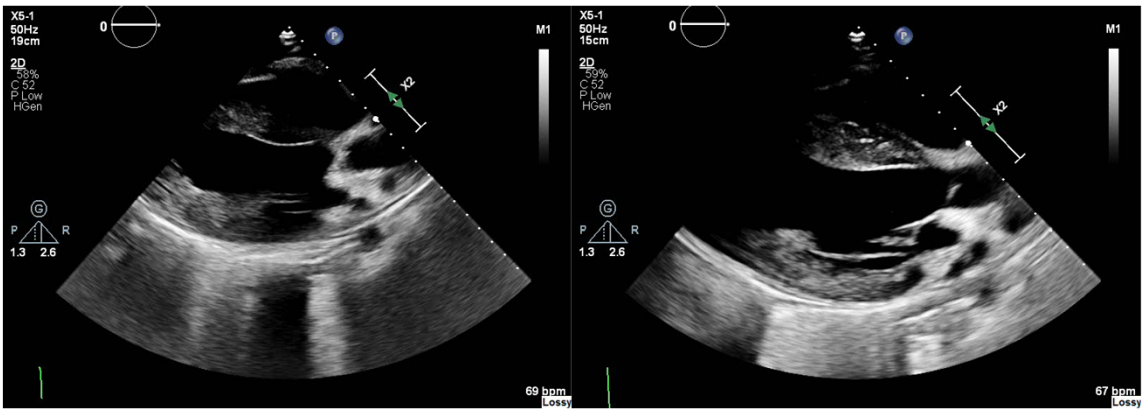
Transthoracic Echocardiogram



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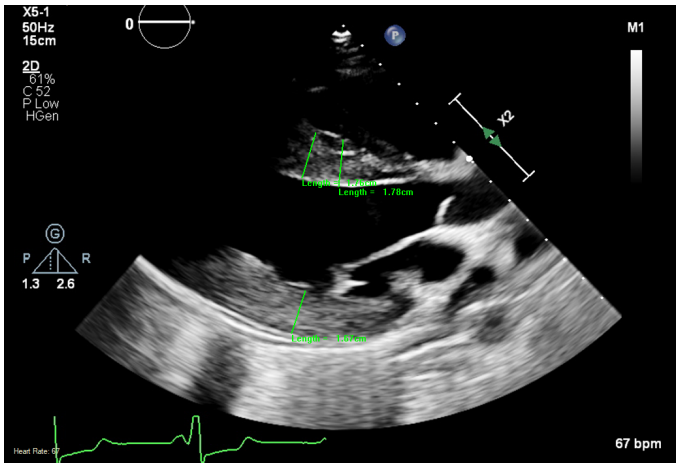
Transthoracic Echocardiogram



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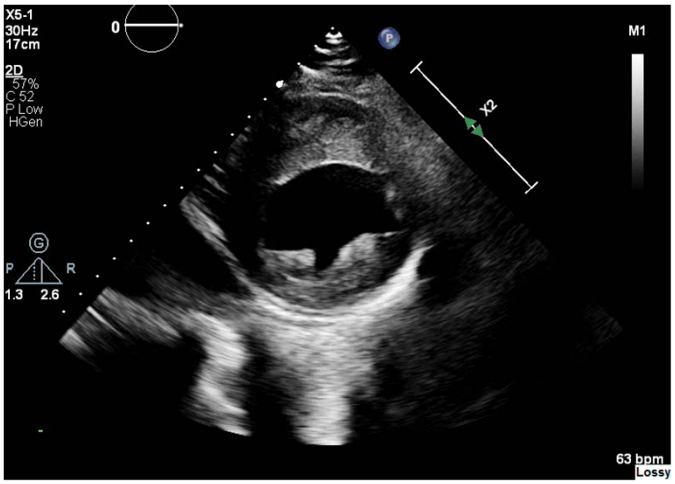
Transthoracic Echocardiogram



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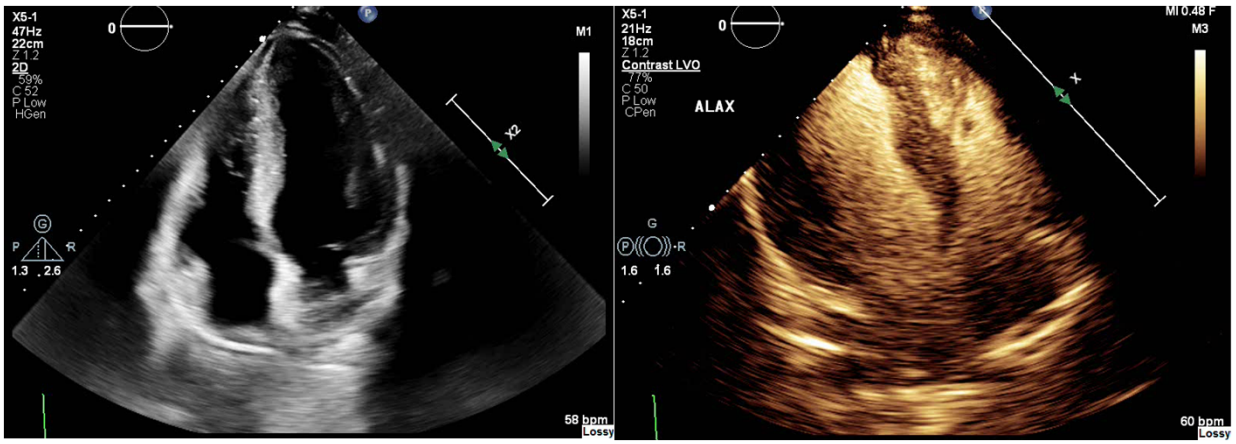
Transthoracic Echocardiogram



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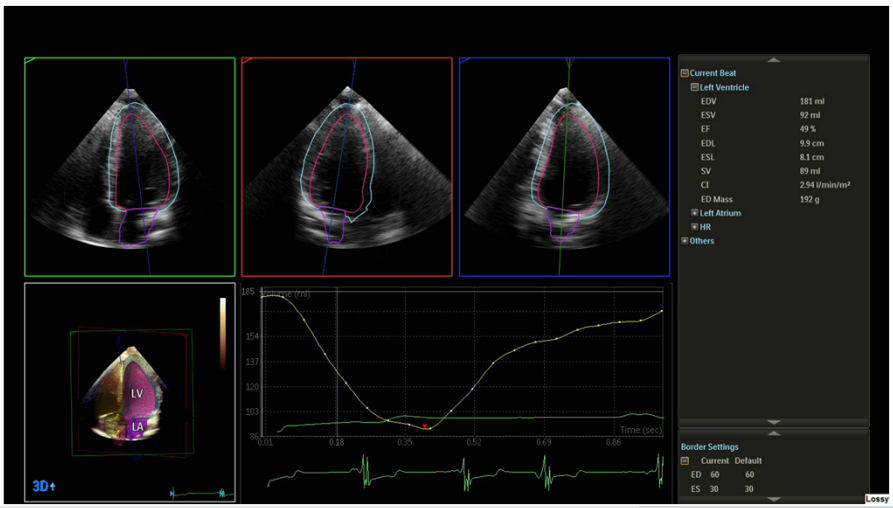
Transthoracic Echocardiogram



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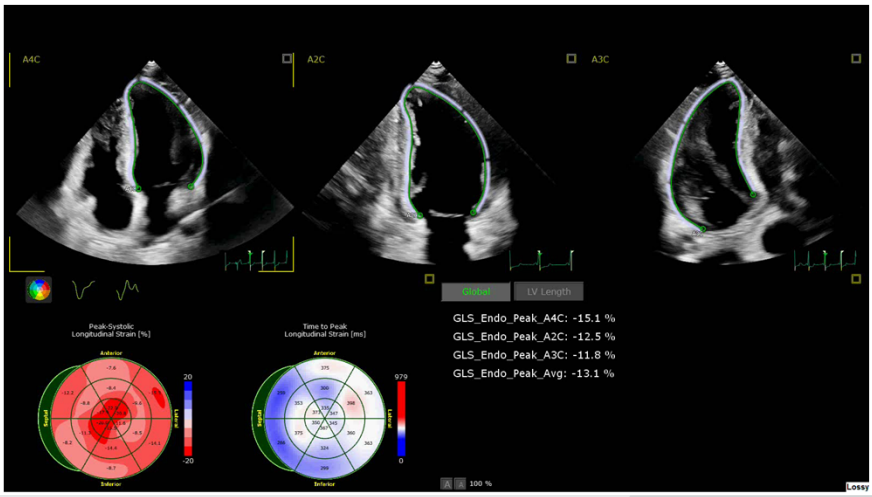
Transthoracic Echocardiogram



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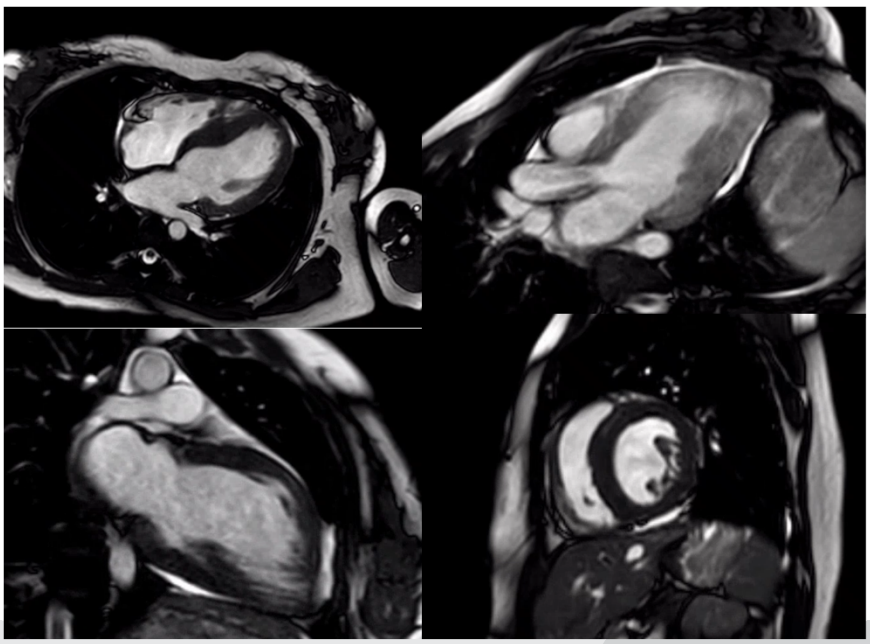

Cardiac MRI

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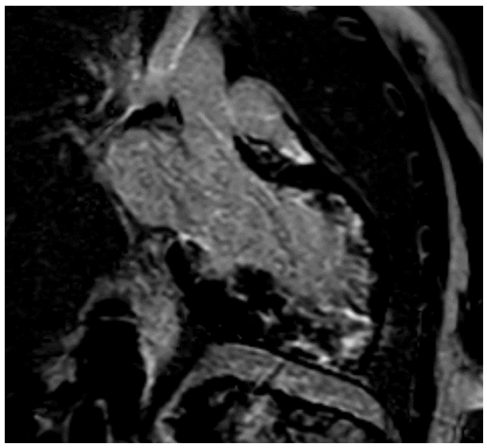

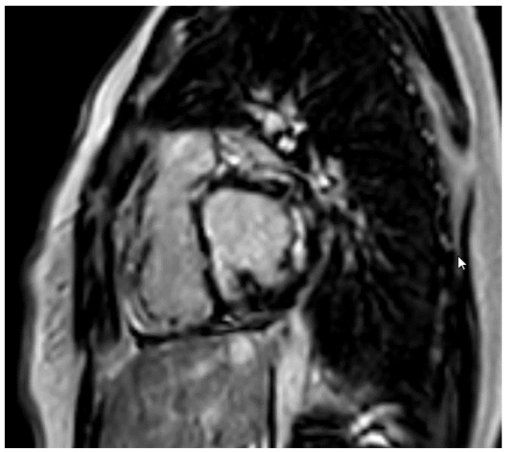

Cardiac MRI – LGE

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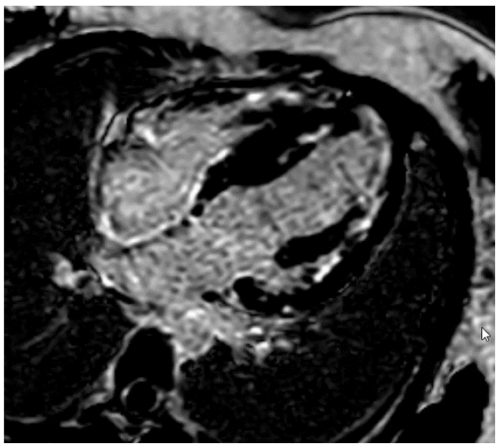

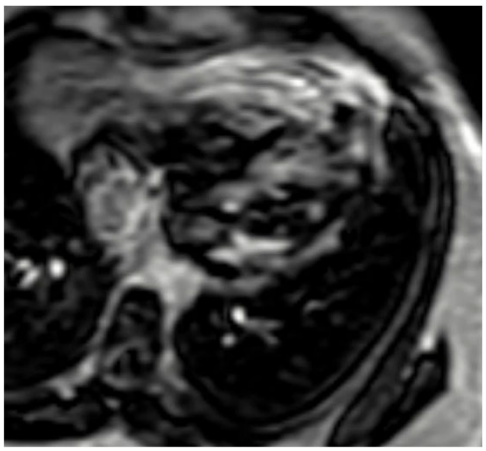

Cardiac MRI – LGE

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Invitae Genetic Testing

RESULT: POSITIVE

One Pathogenic variant identified in LAMP2. LAMP2 is associated with X-linked Danon disease.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
LAMP2	c.129T>A (p.Tyr43*)	heterozygous	PATHOGENIC
GATA5	c.682C>G (p.Arg228Gly)	heterozygous	Uncertain Significance
TTN	c.106994A>G (p.Lys35665Arg)	heterozygous	Uncertain Significance
GAA	c.2065G>A (p.Glu689Lys)	heterozygous	Benign (Pseudodeficiency allele)

About this test

This diagnostic test evaluates 100 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

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Danon Disease

NEUROLOGY (Ny) 31: 51-57, January 1981

Lysosomal glycogen storage disease with normal acid maltase

Moris J. Danon, M.D., Shin J. Oh, M.D., Salvatore DiMauro, M.D., Jose R. Manaligod, M.D., Ph.D., Abe Eastwood, Ph.D., Sakkubai Naidu, M.D., and Louis H. Schliselfeld, Ph.D.

Acid maltase (acid α-glucosidase) deficiency (AMD) occurs in infants, children, and adults.[1] In the infantile form (Pompe disease), glycogen accumulates in all tissues, especially heart, skeletal muscle, and central nervous system (CNS). Both the clinical course and the genetics of this type seem to be homogeneous. However, the childhood- and adult-onset forms vary in clinical presentation and seem to be genetically heterogeneous.[2] Light microscopy of AMD shows vacuolar myopathy with glycogen storage and histochemical reaction for acid phosphatase in the vacuoles.[1] Autophagic vacuoles, increased amounts of intermyofibrillar glycogen, and numerous membrane-bound "sacs" of glycogen are typical ultrastructural features in all three types.[1,3] Biochemical analysis shows increased glycogen content and absence or deficiency of acid maltase.[2] We studied two patients with pathologic changes in muscle that were typical of AMD; although biochemical studies showed increased glycogen content, acid maltase activity was normal in muscle and urine.

Case reports. Case 1. A 16-year-old boy presented in July 1976 with shortness of breath, fatigability, and generalized muscle weakness. This boy was born full-term after an uneventful pregnancy and delivery. He walked at about age 2, but by age 3 he had difficulty climbing stairs. Speech was delayed, and he later attended classes for the mentally retarded. At age 10, he suffered cardiac arrest after a fight and was resuscitated and defibrillated. Cardiologic studies, including cardiac catheterization, showed "hypertrophic nonobstructive cardiomyopathy," and he was treated with digoxin. Between ages 10 and 16, he was admitted several times for deteriorating cardiac condition and proximal muscle weakness. He was the fourth of six children. All his siblings and both parents, who were unrelated, were reported to be normal.

Examination at age 16 showed no gross dysmorphic features, but he was overtly mentally retarded. He seemed to be in respiratory distress. His pulse was 92 per minute. The liver was moderately enlarged (4 cm below the costal margin). There was no edema or cyanosis. A grade I-II systolic murmur was heard at the left lower sternal border. There was weakness and wasting of limb muscles, greater proximally, and neck flexion was weak. Tendon reflexes were present. Sensation was normal.

The following laboratory studies were normal: hemogram, urinalysis, glucose, and blood urea nitrogen. Alkaline phosphatase was 130 IU (normal, 20 to 124 IU). Serum glutamic-oxaloacetic transaminase (SGOT) was 424 IU (normal, 8 to 27 IU); pyruvic transaminase (SGPT), 458 IU (normal, 8 to 34 IU); lactate dehydrogenase (LDH), 854 IU (normal, 68 to 270 IU); and serum

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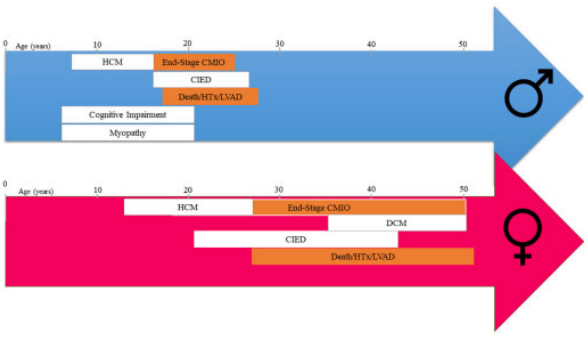
Danon Disease

- LAMP2 mutation
  - Lysosome associated membrane protein
  - Involved in autophagy and lisosomal protein degradation
  - Deposition of intracytoplasmic vacuoles
- X-linked dominant inheritance pattern
  - De novo mutations have been reported
  - Males are hemizygous for LAMP2



Boucek D et al. Genetics in Medicine 2011;13:563-568.
Nishino I et al. Nature 2000; 406:906-910.
D'souza R et al. Circ Heart Fail 2014;7:843-849.
Brambetti M. Int J of Card 2019;286:92-98.

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Clinical Manifestations

Table 3 Reported clinical characteristics

	Men (n = 26)	Women (n = 18)
Cardiac		
Symptomatic heart disease	88.5	77.7
Chest pain	41.6	37.5
Palpitations	76.5	68.8
Hypertrophic cardiomyopathy	88	33.3
Dilated cardiomyopathy	12	27.7
Conduction abnormality	86.4	80
Wolf-Parkinson-White	68.2	26.7
Cardiac ablation	53.3	30.8
Defibrillator implantation	41.2	31.3
Neurologic		
Learning and cognitive problems	100	46.6
Visual and retinal abnormalities	69.2	64.2
Symptomatic muscle disease	80	50
Muscle cramping	9.1	15.3
Neuropathy	9.1	38.5
Respiratory		
Symptomatic respiratory disease	50	16.7
Gastrointestinal		
Symptomatic GI disease	76.5	50
Other		
Hypertension	9.1	17.6
Hyperlipidemia	20	35.7
Laboratory values		
Creatine kinase (U/L)	943.7 (±326.8)	105.6 (±104.4)
Asparate aminotransferase (U/L)	290.4 (±108.7)	55.8 (±41.8)
Alanine aminotransferase (U/L)	234 (±101.6)	37 (±20.9)

The symptomatic data are presented as a percentage of affected individuals for whom data were available, and the laboratory values are presented as a mean (±standard deviation).

Boucek D et al. Genetics in Medicine 2011;13:563-568.
D'souza R et al. Circ Heart Fail 2014;7:843-849.

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Cardiac manifestations

Cardiac manifestations of study population.

	All		Males		Females		p value
	Patients with available data	Value	Patients with available data	Value	Patients with available data	Value	
Any cardiac abnormality	146	135 (92.5)	90	86 (95.6)	56	49 (87.5)	0.106
Cardiomyopathy classified	146	120 (82.2)	90	79 (87.8)	56	41 (73.2)	0.044
Hypertrophic cardiomyopathy at presentation	120	105 (87.5)	79	76 (96.2)	41	29 (70.7)	<0.001
LVOT obstruction	42	11 (26.2)	32	10 (31.2)	10	1 (10)	0.245
Concentric HCM	58	52 (89.7)	44	40 (90.9)	14	12 (85.7)	0.624
Age at time of HCM diagnosis, years old	76	14 (10.0–18.0)	52	13 (8.0–16.5)	24	16 (12.5–25.5)	**0.007**
HCM progression to end-stage cardiomyopathy	105	46 (43.8)	76	37 (48.7)	29	9 (31.0)	0.126
Age at end-stage cardiomyopathy, years old	38	21 (17.0–25.0)	29	20 (17.0–24.0)	9	28 (18.0–50.0)	0.153
Dilated cardiomyopathy at presentation	120	15 (12.5)	79	3 (3.8)	41	12 (29.3)	**<0.001**
Age at time of DCM diagnosis, years old	16	39 (26.0–48.5)	3	21.5 (18.0–22.0)	12	42.6 (35.5–50.0)	**0.004**
Diagnostic							
LVEF (%)-first reported value	77	50 (32.0–63.0)	47	50 (33.0–60.0)	30	58 (30.0–65.0)	0.430
LGE presence at CMR	26	21 (80.8)	13	12 (92.3)	13	9 (69.2)	0.322
Cardiac conduction abnormalities	146	84 (57.5)	90	52 (57.8)	56	32 (57.14)	1.000
WPW reported	146	61 (41.8)	90	43(47.8)	56	18 (32.1)	0.084
Atrial fibrillation, atrial flutter or other SVT reported	146	32 (21.9)	90	16 (17.8)	56	16 (28.6)	0.151
Sustained/non sustained VT reported	146	15 (10.3)	90	9 (10.0)	56	2 (3.6)	0.205
CIED reported	146	108 (74.0)	90	70 (77.8)	56	38 (67.9)	0.840
ICD	108	40 (37.0)	70	26 (37.1)	38	14(36.8)	1.000
CRT	108	5 (4.7)	70	3 (4.3)	38	2 (5.3)	1.000
Pacemaker	108	10 (9.1)	70	7 (10.0.)	38	3 (7.7)	1.000
Age at CIED, years old	50	25 (17.0–28.0)	35	21.3 (16.0–25.0)	15	33.5 (21.0–43.0)	**<0.001**
Age at first outcome, years old (combined outcome: HTx, VAD, death)	51	23 (19.0–32.0)	33	21 (17.0–25.0)	18	38 (28.0–52.0)	**<0.001**

Values are median (Q1–Q3), or n (%). HCM, Hypertrophic Cardiomyopathy; DCM, Dilated Cardiomyopathy; LVOT, left ventricle outflow tract; WPW, Wolff-Parkinson-White; SVT, supraventricular Tachycardia; CIED, cardiac implantable electronic devices, ICD, implantable cardioverter defibrillator, CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement; CMR: cardiac magnetic resonance; HTx, heart transplant, LVAD, left ventricular assist device.
Bold values indicates significance at p-value <005

Brambetti M. Int J of Card 2019;286:92-98.

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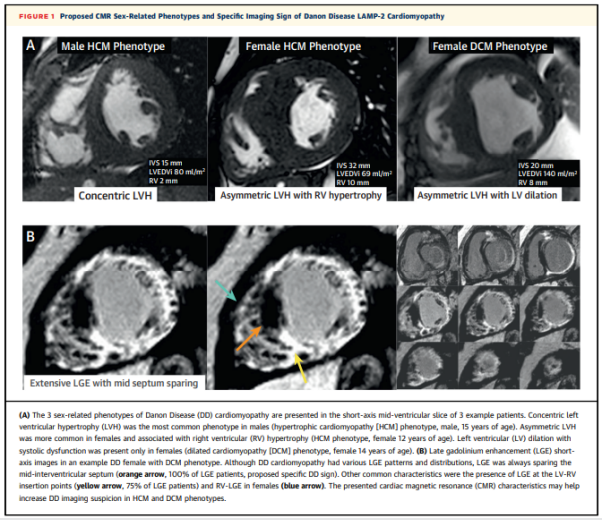
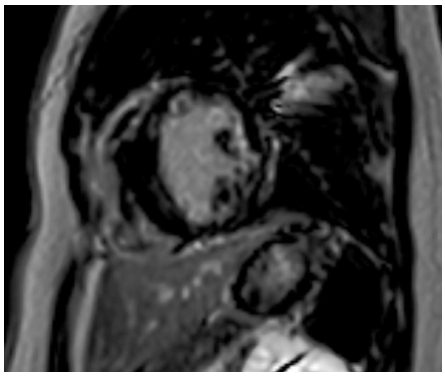
CMR in Danon Disease





Rigolli M et al. JACC CV Imaging 2021;14:514-516.

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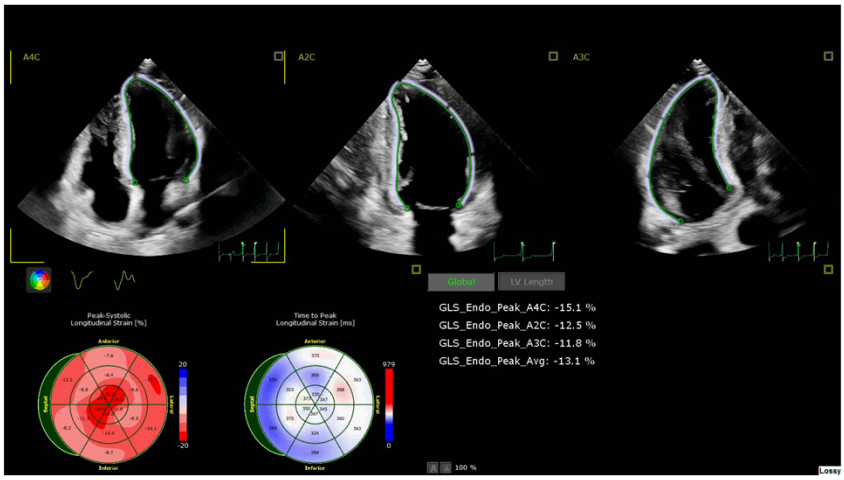
Strain imaging in Danon Disease



Bui Q et al. J Am Heart Assoc 2021;10:1-10.
Changsheng M. Eur Heart J Case Rep 2021;12.

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Clinical Outcome and Phenotypic Expression in *LAMP2* Cardiomyopathy

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METABOLIC MYOCARDIAL storage diseases that mimic the clinical and phenotypic expression of hypertrophic cardiomyopathy (HCM) have recently been reported in young patients,[1] including those diseases due to mutations in the X-linked lysosome-associated membrane protein gene (*LAMP2*; OMIM 309060; Danon disease).[1-7] The morphologic expression and the clinical course experienced by patients with this newly identified cardiomyopathy[2-7] are incompletely resolved. Therefore, it is informative to report our experience with an assessment of the natural his-

Context Mutations in X-linked lysosome-associated membrane protein gene (*LAMP2*; Danon disease) produce a cardiomyopathy in young patients that clinically mimics severe hypertrophic cardiomyopathy (HCM) due to sarcomere protein mutations. However, the natural history and phenotypic expression of this newly recognized disease is incompletely resolved and its identification may have important clinical implications.

Objectives To determine the clinical consequences, outcome, and phenotypic expression of *LAMP2* cardiomyopathy associated with diagnostic and management strategies.

Design, Setting, and Patients Clinical course and outcome were assessed prospectively in 7 young patients (6 boys) with defined *LAMP2* mutations from the time of diagnosis (age 7-17 years; median, 14 years) to October 2008. Phenotypic expression of this disease was assessed both clinically and at autopsy.

Main Outcome Measures Progressive heart failure, cardiac death, and transplant.

Results Over a mean (SD) follow-up of 8.6 (2.6) years, and by age 14 to 24 years, the study patients developed left ventricular systolic dysfunction (mean [SD] ejection fraction, 25% [7%]) and cavity enlargement, as well as particularly adverse clinical consequences, including progressive refractory heart failure and death (n=4), sudden death (n=1), aborted cardiac arrest (n=1), or heart transplantation (n=1). Left ventricular hypertrophy was particularly marked (maximum thickness, 29-65 mm; mean [SD], 44 [15] mm), including 2 patients with massive ventricular septal thickness of 60 mm and 65 mm at ages 23 and 14 years, respectively. In 6 patients, a ventricular preexcitation pattern at study entry was associated with markedly increased voltages of R-wave or S-wave (15-145 mm; mean [SD], 69 [39] mm), and deeply inverted T-waves. Autopsy findings included a combination of histopathologic features that were consistent with a lysosomal storage disease (ie, clusters of vacuolated myocytes) but also typical of HCM due to sarcomere protein mutations (ie, myocyte disarray, small vessel disease, myocardial scarring).

Conclusions *LAMP2* cardiomyopathy is a profound disease process characterized by progressive clinical deterioration leading rapidly to cardiac death in young patients (<25 years). These observations underscore the importance of timely molecular diagnosis for predicting prognosis and early consideration of heart transplantation.

JAMA. 2009;301(12):1253-1259 www.jama.com

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Table. Clinical, Demographic, and Pathologic Findings in 7 Patients With *LAMP2* Cardiomyopathy[a]

	Patient (Sex)						
	1 (M)	2 (M)	3 (F)	4 (M)	5 (M)	6 (M)	7 (M)
Age at cardiac diagnosis, y	8	14	11	15	17	7	15
Age at last evaluation/death, y	14	23	22	21	24	20	23
Follow-up duration, y	6	9	11	6	7	13	8
Presentation	Heart murmur (sports examination)	Syncope	Heart murmur	Family history	Abnormal ECG	Chest pain	AF
NYHA functional class							
Initial	I	I	I	I	I	I	I
Most recent	I	IV	I	III	IV	III	III
Paroxysmal AF/flutter	Yes	No	Yes	Yes (3 episodes)	Yes	Yes	Yes
Medical treatment[b]	Atenolol, verapamil, amiodarone, warfarin	Sotalol, amiodarone, warfarin, spironolactone	Metoprolol	Atenolol	Spironolactone, metoprolol, lisinopril, digoxin, diuretics, warfarin	Sotalol, atenolol, diuretics	Atenolol, sotalol, warfarin, diuretics, amiodarone
Family history of CM	0	Brother: WPW/LVH; aunt: WPW	0	Mother: dilated CM/transplant	0	0	0
Electrocardiogram (initial)							
WPW	Yes[c]	Yes	Yes	Yes	0	Yes	Yes[c]
Maximum voltage, mm	145	80	75	55	15	55	56
PR interval, ms	105	80	125	80	154	80	110
Other	T-inversion (11 mm), inferior Qs	T-inversion (30 mm), IVCD	T-inversion (25 mm)	T-inversion (22 mm)	LAD, absent R (V1-V3)	T-inversion (15 mm)	T-inversion (10 mm), LBBB
LV outflow gradient (rest), mm Hg[d]	65	0 (mild SAM)	0	0	0	65	0
Maximum LV wall thickness, mm[d]	65[e]	60	30	37[f]	35	52[g]	29
Ejection fraction, %							
Initial	70	Normal	64	70	75	66	68
Most recent	36	25	35	20	22	15	23
LV cavity end diastole, mm							
Initial	25	42	37	40	37	54	55
Most recent	43	70	53	60	49	NA	68
Left atrium (initial), mm	35	39	32	38	41	36	30
Mitral regurgitation (initial)	Moderate	Mild	Mild	Mild	Mild	0	0
24-Hour ambulatory Holter ECG	633 PVBs, 8 couplets	NA	3 PVBs, 1 couplet	Sinus bradycardia	NSVT	NSVT	127 PVBs, 1 couplet
Complications	End-stage[h]	End-stage,[h] embolic stroke	End-stage[h]	End-stage[h]	End-stage,[h] acute cardiac/renal failure, syncope	End-stage,[h] pulmonary hypertension, ICD shock for VT	End-stage[h]

Maron BJ. JAMA 2009;301:1253-1259.

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Table. Clinical, Demographic, and Pathologic Findings in 7 Patients With *LAMP2* Cardiomyopathy[a] (continued)

	Patient (Sex)						
	1 (M)	2 (M)	3 (F)	4 (M)	5 (M)	6 (M)	7 (M)
Clinical status (most recent)	Sudden death (found dead in bed)	Acute HF death	Alive (ICD shock for VT [222/min])	Acute HF death	Sudden/HF death	Progressive HF death, liver/multisystem failure, pneumonia	Alive, transplant
ICD	Yes	Yes	Yes	Yes	Yes	Yes	0
Serum enzymes elevated[i]	Yes	Yes	0	Yes	Yes	Yes	0
Cognitive issues	0	0	0	ADHD	0	BI	0
Genetic transmission	Sporadic	Maternal	Sporadic	Maternal	Maternal	Sporadic	Sporadic
Mutation	Y109ter (truncates protein at residue 109)	IVS6 + 1_4 del GTGA (in-frame deletion of exon 6 + 41aa)	IVS6-2A→G (frameshift after 22aa; no RNA)	928G→A (missense V310I + deletion of exon 7)	IVS1 + 1G→T (deletes 21aa)	IVS1-2A→G (deletes exon 2 + frameshift)	928G→AI (missense V310I + deletion of exon 7)

Maron BJ. JAMA 2009;301:1253-1259.

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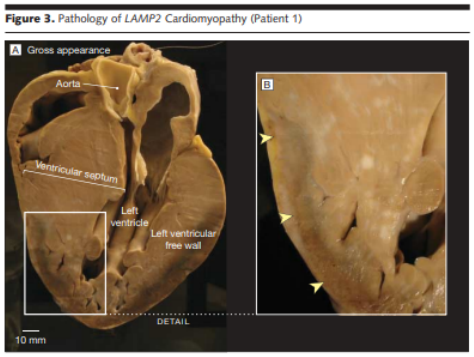

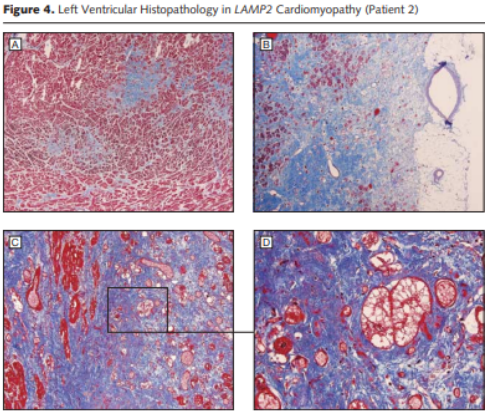

Maron BJ. JAMA 2009;301:1253-1259.

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Therapy

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Trial record **2 of 2** for: danon

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Gene Therapy for Male Patients With Danon Disease (DD) Using RP-A501; AAV9.LAMP2B

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03882437

Recruitment Status : Recruiting
First Posted : March 20, 2019
Last Update Posted : August 30, 2021
See Contacts and Locations

Study Description Go to

Brief Summary:
This is a non-randomized open-label Phase 1 study to evaluate the safety and toxicity of gene therapy using a recombinant adeno-associated virus serotype 9 (AAV9) containing the human lysosome-associated membrane protein 2 isoform B (LAMP2B) transgene (investigational product (IP), RP-A501) in male patients with Danon Disease (DD).

Condition or disease	Intervention/treatment	Phase
Danon Disease	Biological: RP-A501	Phase 1

Detailed Description:
The study is a non-randomized open-label Phase I clinical trial to characterize the safety and toxicity associated with infusion of a recombinant adeno-associated serotype 9 (rAAV9) capsid containing the human lysosome-associated membrane protein 2 isoform B (LAMP2B) transgene (investigational product (IP), RP-A501) in male patients with Danon Disease (DD).

During the course of the study, approximately 7-10 male subjects age 8 and over will receive a single intravenous (IV) infusion of the IP. Prior to infusion of IP, rituximab and sirolimus will be administered prophylactically.

All patients are planned to be followed for 36 months after investigational product administration. After the end of the follow-up period, patients will enter a Long-Term Follow-Up (LTFU) study enabling follow-up for an additional 2 to 5 years post-IP administration.

The study will also enable an initial evaluation of whether or not the IP results in cardiomyocyte and skeletal muscle transduction and gene expression and preliminary assessment of the extent of cardiomyocyte and histologic correction. Additionally, a preliminary evaluation of clinical stabilization following infusion will also be made.

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Take home points

- Danon disease is also mistaken for HCM (or other HCM mimics).
- Diagnosis requires clinical suspicion especially in young patients with LVH and WPW.
  - Avoid misdiagnosis and delays in care
- Genetic testing should be considered in patients with undifferentiated cardiomyopathy

TABLE 5 Clinical Features in Patients With "HCM Phenocopies (Mimics)"

Typical Presentation Age	Systemic Features	Possible Etiology	Diagnostic Approach
Infants (0-12 mo) and toddlers	Dysmorphic features, failure to thrive, metabolic acidosis	▪ RASopathies ▪ Glycogen storage diseases, other metabolic or mitochondrial diseases ▪ Infant of a mother with diabetes	▪ Geneticist assessment ▪ Newborn metabolic screening ▪ Specific metabolic assays ▪ Genetic testing
Early childhood	Delayed or abnormal cognitive development, visual or hearing impairment	▪ RASopathies ▪ Mitochondrial diseases	▪ Biochemical screening ▪ Genetic testing
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HCM indicates hypertrophic cardiomyopathy.

2020 ACC/AHA HCM Guidelines.

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Clinical manifestations

Males

- Cardiomyopathy – nearly all
- Skeletal muscle weakness 80-90%
- Cognitive impairment 70-100%
- Conduction abn 86-100%
  - WPW 69%
- Myopathy 80-90%
- Retinal involvement 69%

Females

- Cardiomyopathy – nearly all
  - *Equal rates of dilated and hypertrophic*
- Skeletal muscle weakness 33-50%
- Cognitive impairment 6-47%%
- Conduction abn 80-100%
  - WPW 27%
- Myopathy – much less involvement
- Retinal involvement 64%

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Table 1 Danon disease population

	Men (n = 43)[a]	Women (n = 39)
Symptomatic clinical disease	37 (94.9)	31 (91.2)
Clinical diagnosis[b]	39 (100)	32 (94.1)
Cardiac transplant	13 (33.3)	6 (17.6)
Living	23 (59.0)	23 (67.6)
Mean age (yr)		
First symptom	11.7 (±6.4)	26.8 (±14.2)
Diagnosis[b]	13.1 (±7.0)	30.9 (±15.2)
Cardiac transplant	20.8 (±6.7)	32.3 (±14.5)
Death	20.1 (±5.2)	40.2 (±12.6)

[a]Subject numbers reflect subjects where complete data were available (percentages or standard deviations are given in parentheses).
[b]Diagnosis of cardiac or skeletal myopathy, cardiac preexcitation, or confirmed Danon disease (whichever came first). In two male and one female cases, cardiac abnormalities were detected by screening before the onset of symptomatic clinical disease.

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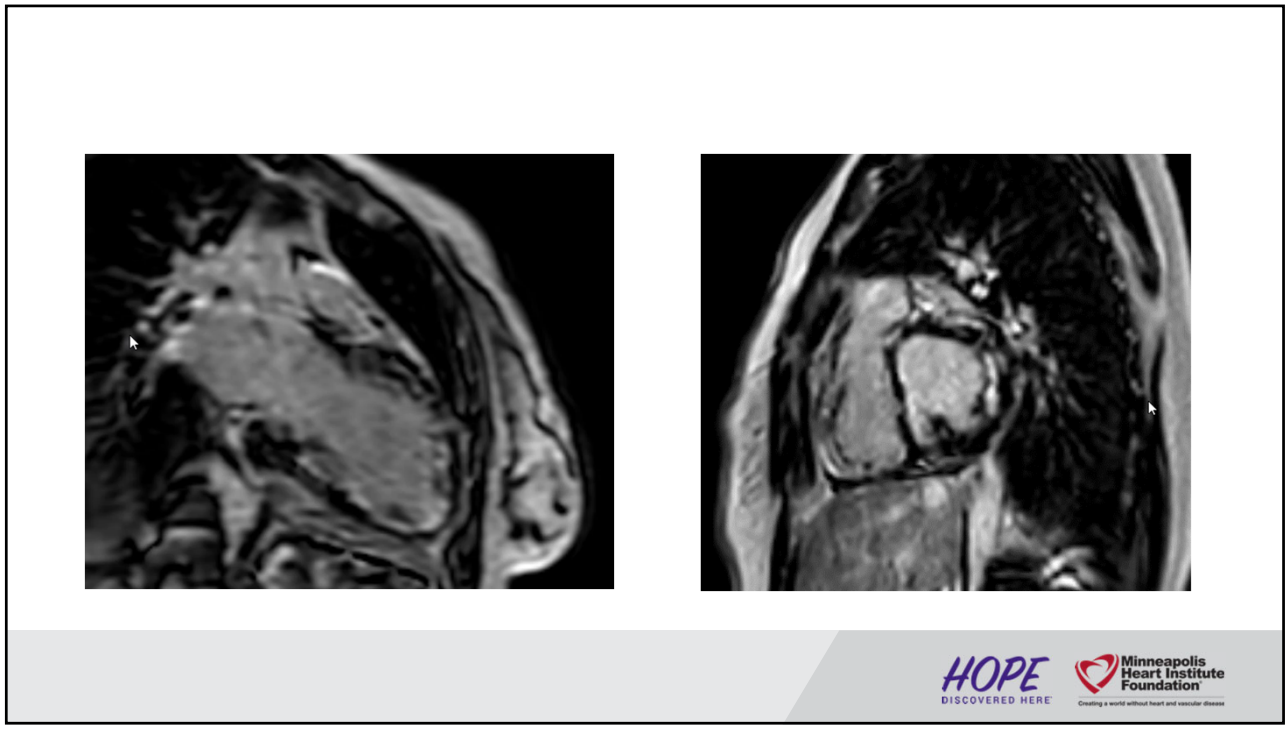
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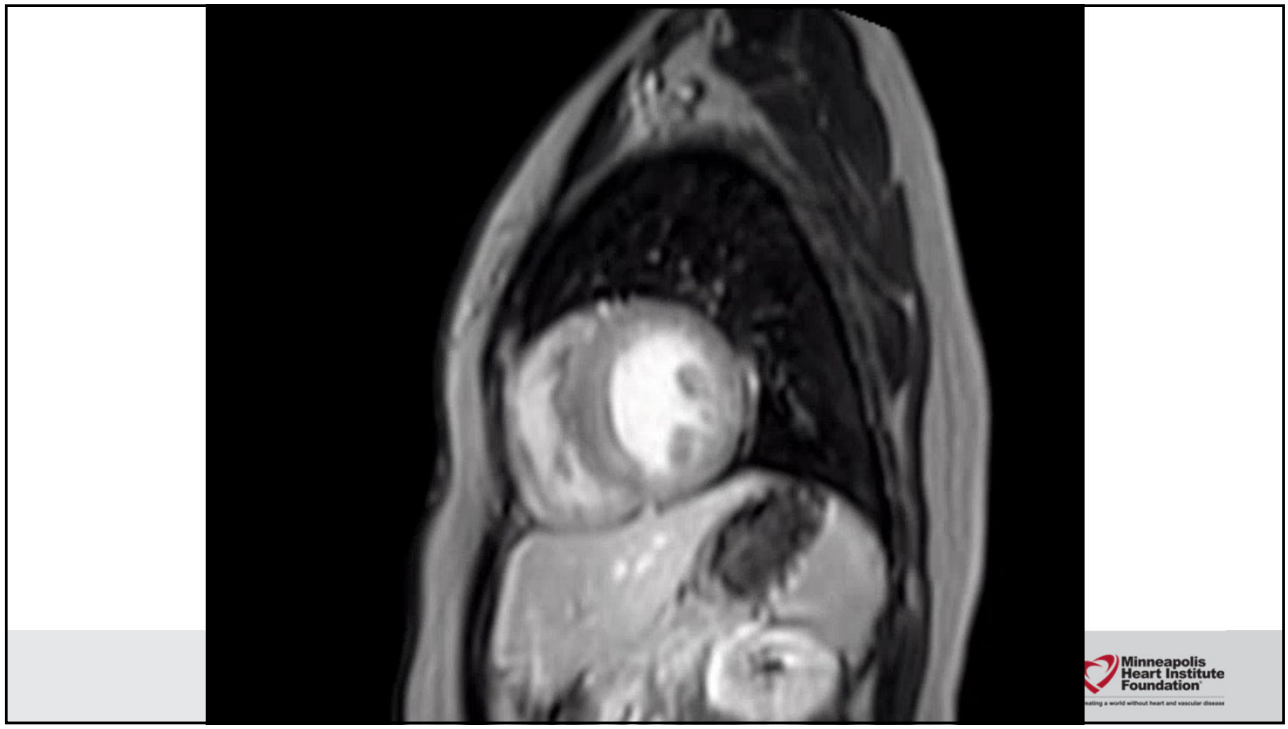
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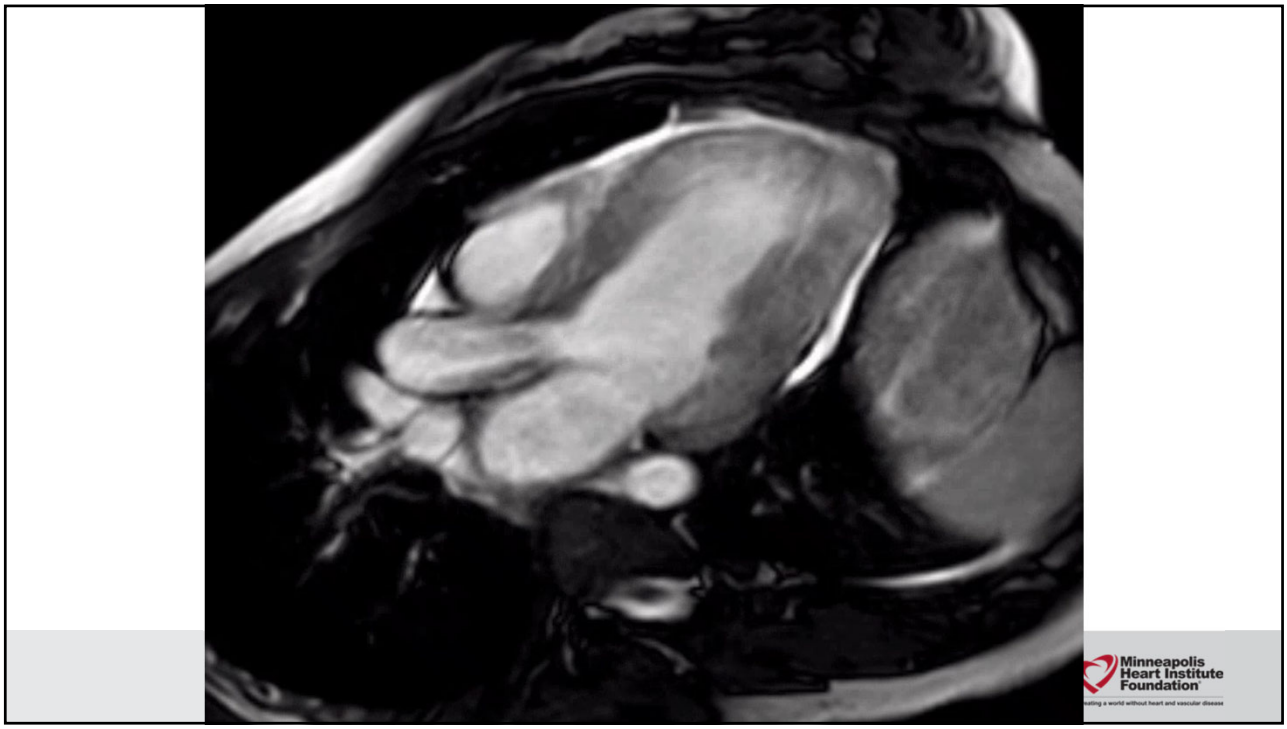
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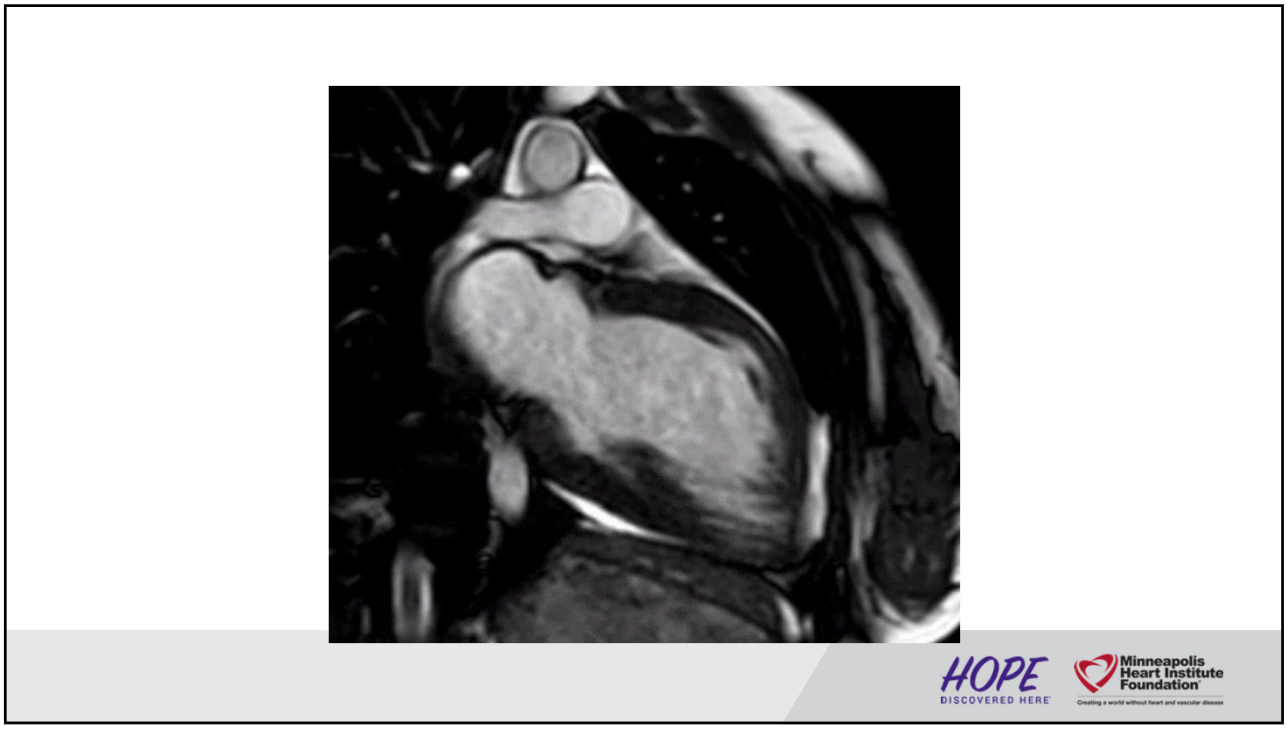
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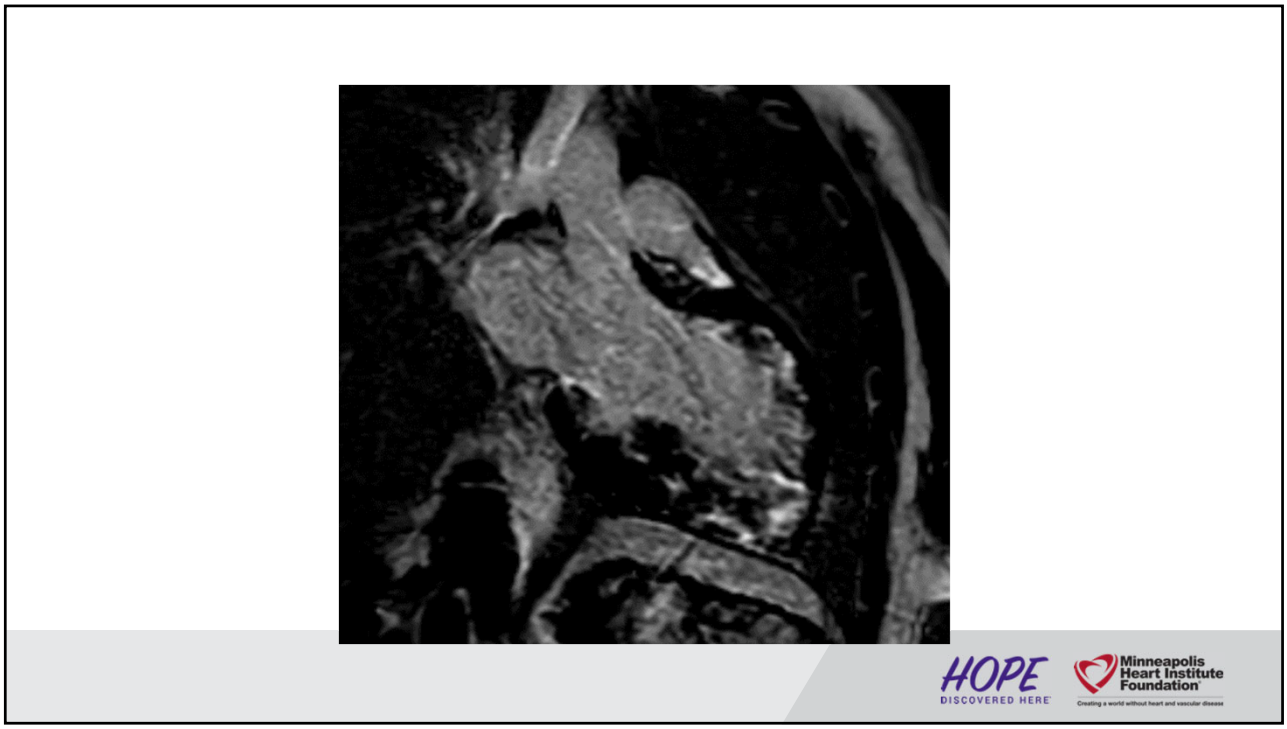
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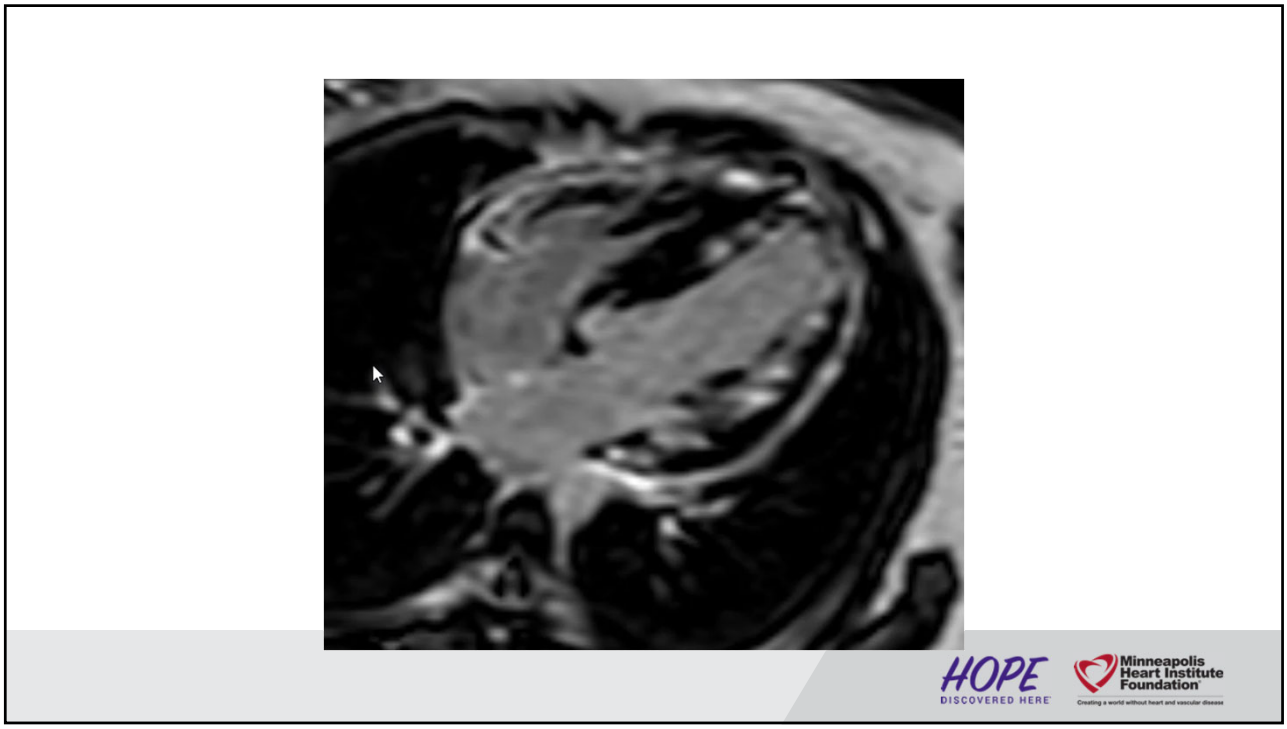
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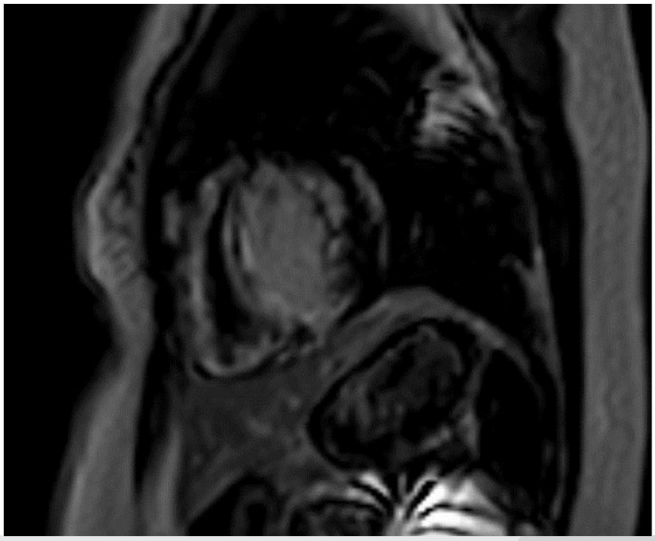

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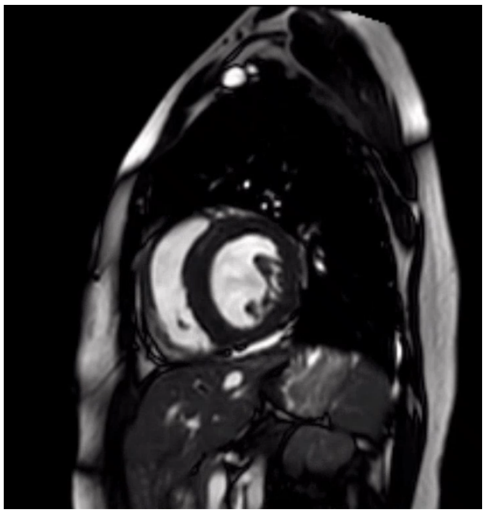
Cardiac MRI



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HCM Mimics

TABLE 5 Clinical Features in Patients With "HCM Phenocopies (Mimics)"

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HCM indicates hypertrophic cardiomyopathy.

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(Not) Just another mitral stenosis case

2/14/2022

Iulia Tulai MD, Cardiology Fellow
Minneapolis Heart Institute

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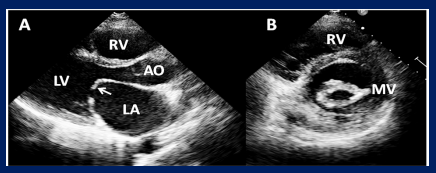
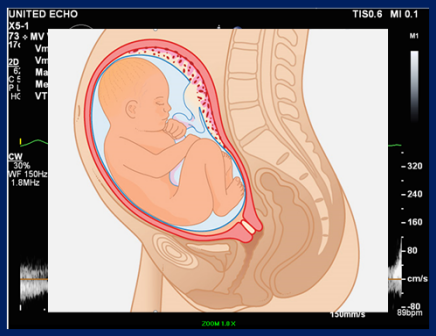
Case presentation

- **35 y.o. female – cardio-obstetric clinic**



- **PMH:**
  - ***Symptomatic*** **rheumatic mitral stenosis**
    - Diagnosed 5 months ago
      - Stress echo mitral gradient 8 → 28 mmHg
    - Scheduled for balloon valvuloplasty
    - Cancelled – 6 weeks pregnant



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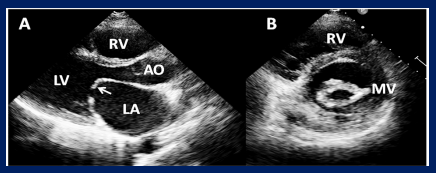
Case presentation…

- **History:**
  - **35 y.o. female – cardio-obstetric clinic visit**
  - ***Symptomatic*** **rheumatic mitral stenosis**
  - 17 weeks pregnant
    - ❑ SOB walking 100 feet
    - ❑ Intermittent palpitations
    - ❑ No syncope
    - ❑ BP 90s/60s, HR ~70s
    - ❑ Already on Toprolol 12.5 mg daily



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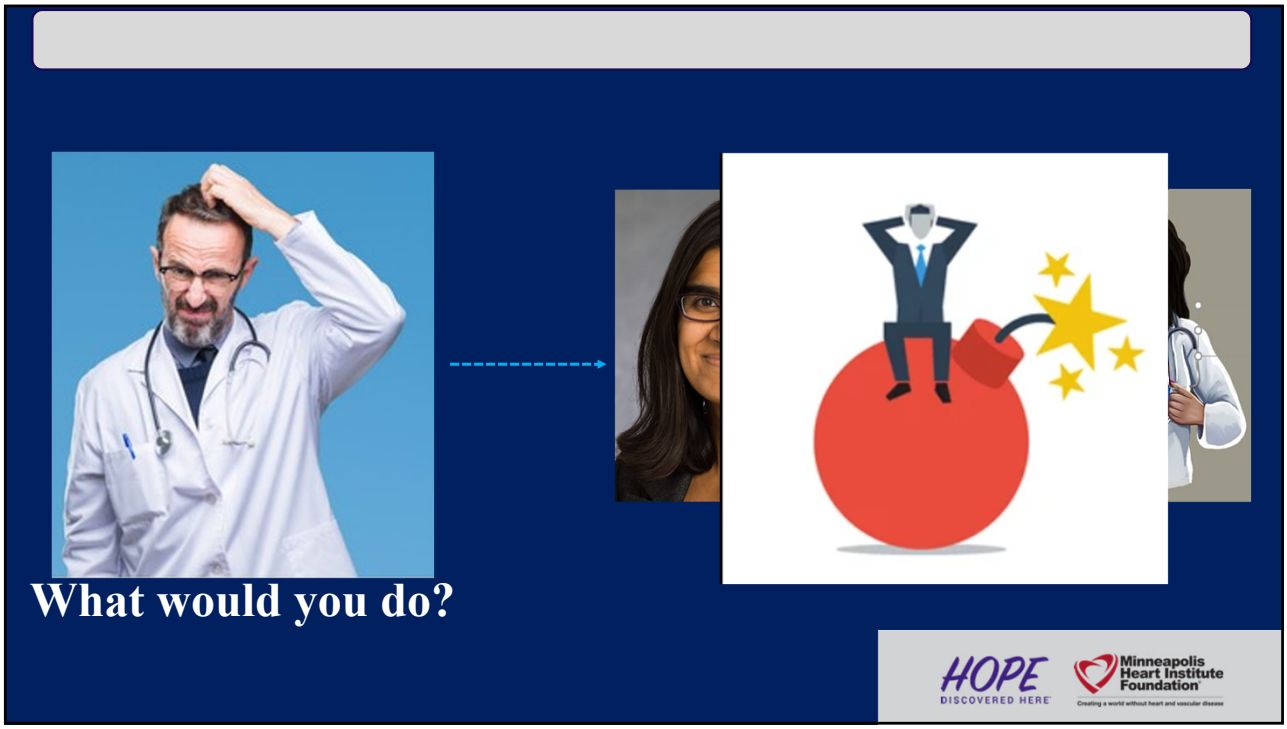
What would you do?
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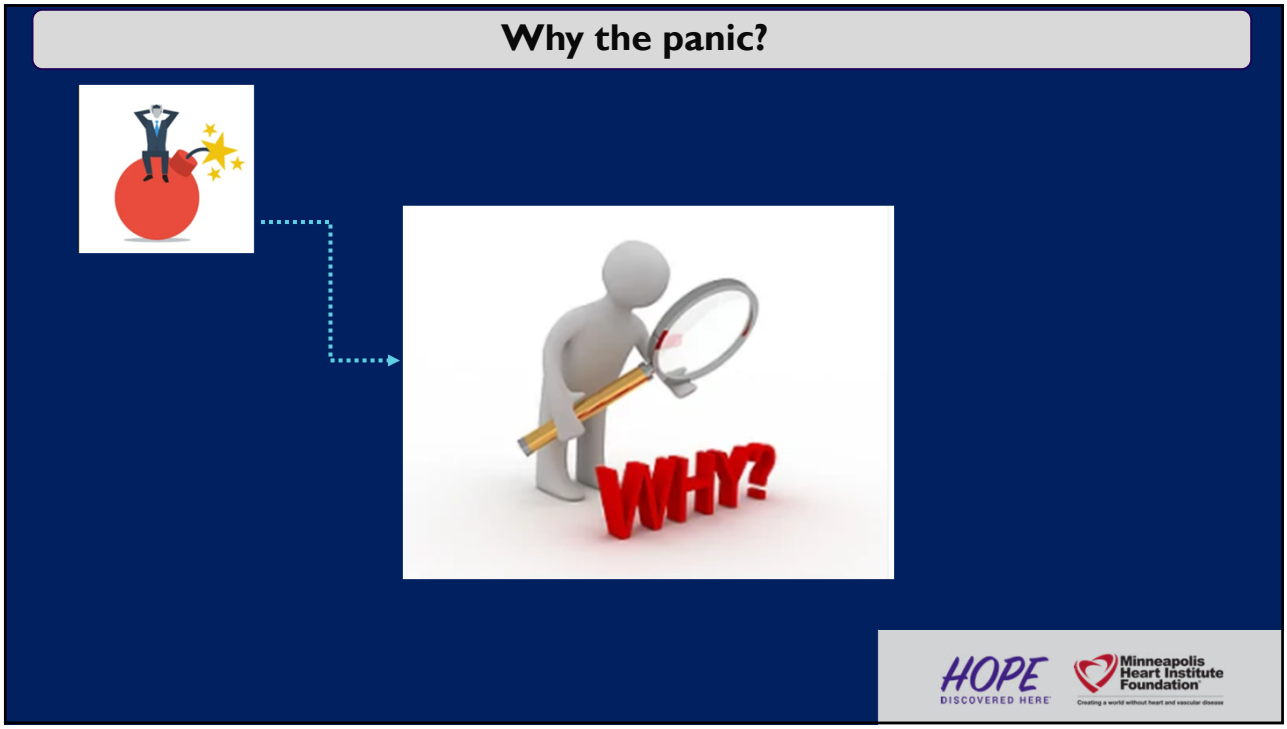
Why the panic?
WHY?
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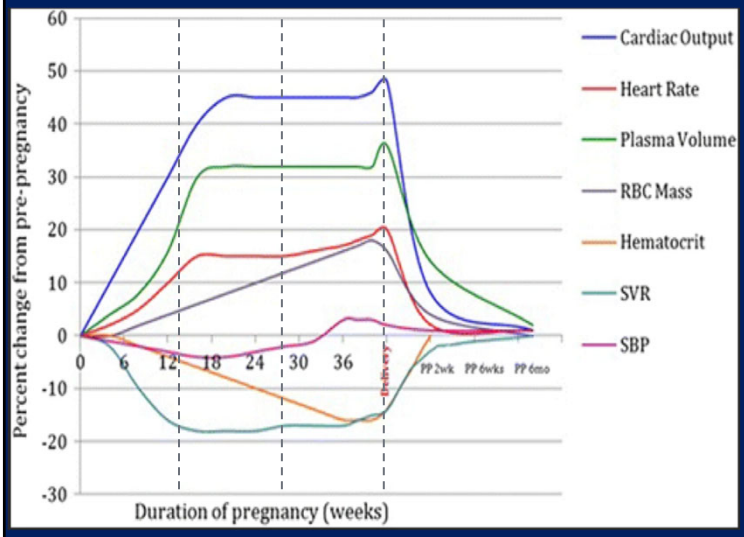
Hemodynamics of pregnancy



MV Ordonez et al, Pregnancy in the FONTAN palliation: physiology, management and new insights from bioengineering. Journal of Congenital Cardiology

1. ↑ Blood volume ~50% increase

- Estrogen-mediated stimulation of RAAS
- plasma >> RBC mass → "anemia"
- 20-100% increase, average ~50% increase

2. ↑ CO {↑ SV, ↑ HR} ~30-50% above baseline

- ↑ preload (increased blood volume)
- ↓ SVR (relaxin, elastase)
- ↑ HR by ~10-15 BPM

3. ↓ BP and ↓ SVR

- DBP>> SBP → wider pulse pressure
- Begins in 1st trimester
- Nadir ~ 10 mmHg below baseline at the end of 2nd trimester

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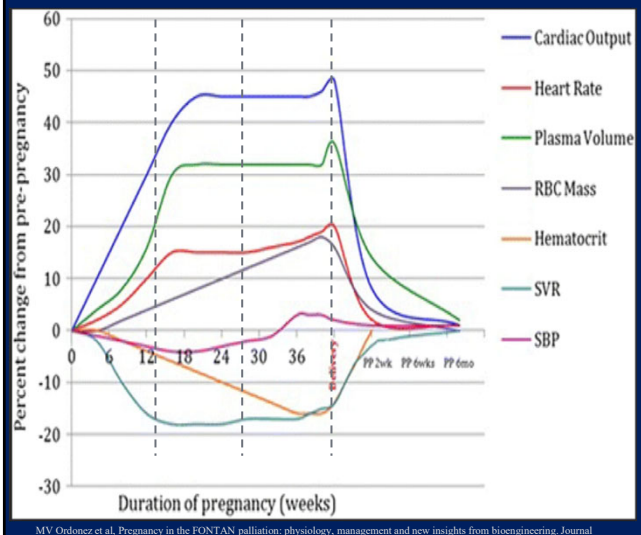
Hemodynamics of pregnancy



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4. During labor & delivery → 75% ↑CO (contractions)

- ↑ SV: ⟸ *autotransfusion* = 300-500 ml blood displaced into the maternal circ. / each uterine contr.
- ↑ HR

5. Postpartum – rapid volume shift

- blood loss: 300-500 ml (vaginal) / 500-800 ml (C-section)
- temporary ↑ venous return:
  - autotransfusion
  - relief of caval compression
- ⟹ ↑ SV, ↑ CO ⟹ ↑ renal blood flow ⟹ brisk diuresis

6. Hypercoagulability

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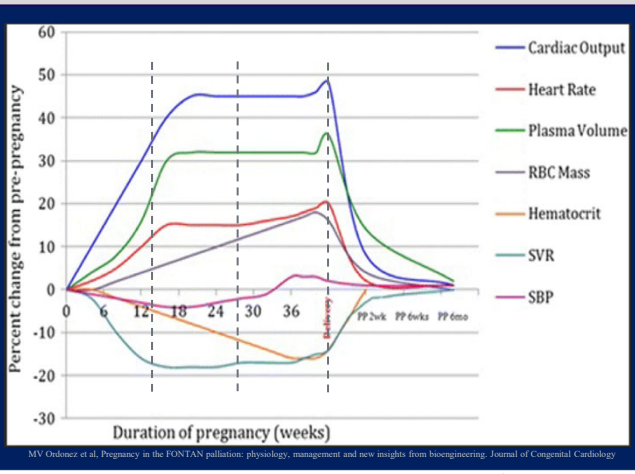
Mitral stenosis in pregnancy

- **Mild MS** – *usually* well tolerated
- **Severe MS:**
  - **≤ 1.5 cm²** – 30% of patients will develop HF [2nd trimester]
  - **≤ 1.0 cm²** – 50% of patients will develop HF [2nd trimester]
- **0-3% mortality** in *developed* countries



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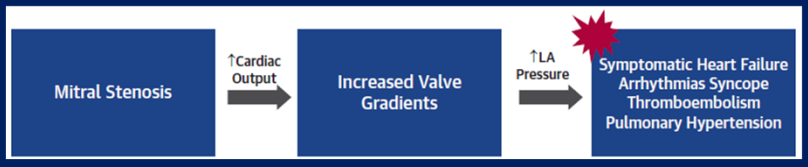

Park *et. al.* Cardio-Obstetrics Part 3/5, JACC 77/14, 2021: 1799-812

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How can we help such patients?

1. Prevention = Preconception planning / visit
   - Risk stratification tools: CarPreg II, ZAHARA, mWHO
2. Medical treatment / optimization
3. Valve intervention

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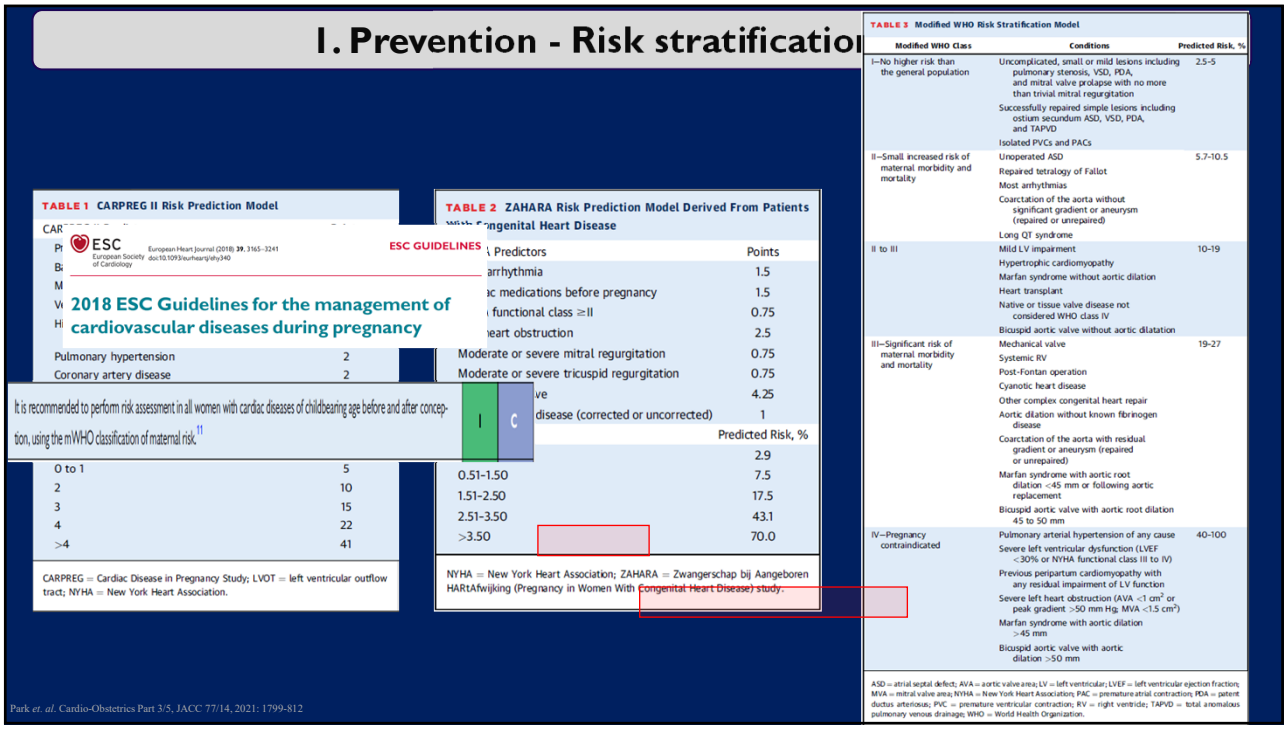

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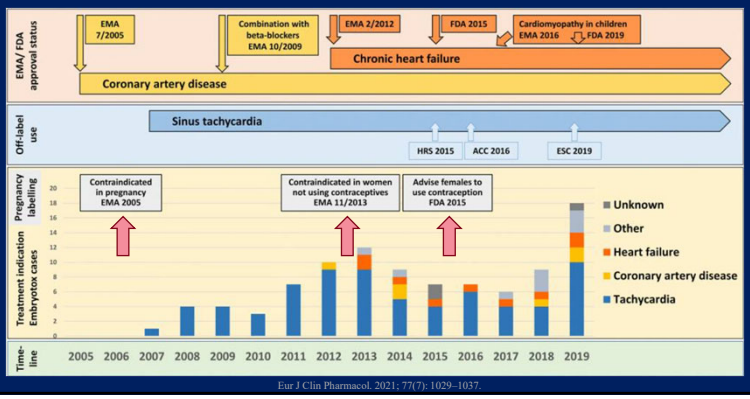
Medical optimization

1. **Decrease transmitral gradient - betablockers**
   - Low BP; can't uptitrate her betablocker
   - ~~Ivabradine~~ – not approved in pregnancy
     - animal studies: embryofetal toxicity, teratogenicity and increased post-implantation loss



Eur J Clin Pharmacol. 2021; 77(7): 1029–1037.

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Medical optimization

2. **Prevent CHF; maintain euvolemia**
   - Check serial BNPs
     - Differentiate pregnancy Sx vs CHF Sx
     - Should remain normal throughout pregnancy
3. **Identify tachyarrhythmia**
   - If Afib+:
     - needs anticoagulation
     - maintain sinus rhythm?

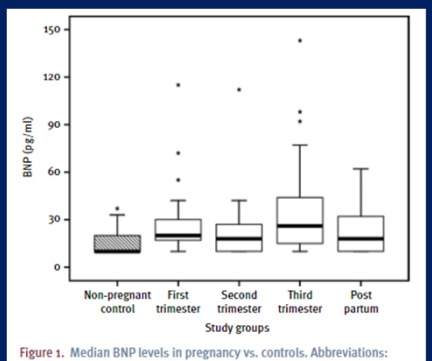

Figure 1. Median BNP levels in pregnancy vs. controls. Abbreviations: BNP, B-type natriuretic peptide.

Clin. Cardiol. 32, 8, E60–E62 (2009)A. B. Hameed et al.: Longitudinal changes in BNP levels in pregnancy and postpartum

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How can we help such patients?

1. Prevention = Preconception planning / visit
   - Risk stratification tools: CarPreg, ZAHARA, mWHO
2. Medical treatment / optimization
3. Valve intervention - When?

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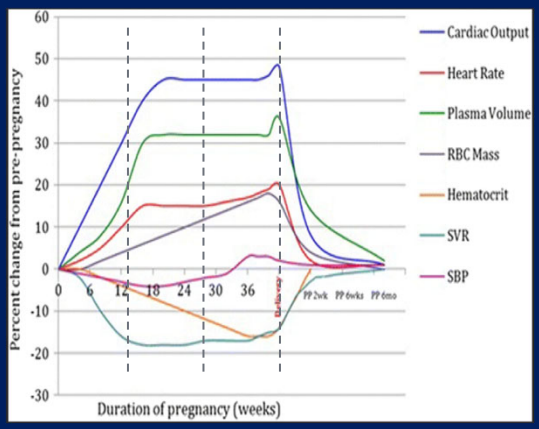
When to intervene in pregnancy?



Developmental Period	EGA	Age of Conceptus	Estimated Threshold Dose	Main Effect
Any	Any	Any	5 cGy (5 rads)	Noncancer health effects not detected below threshold
Developmental Effects				
Preconception	1-2 weeks	n/a	n/a	Mother has not yet ovulated
Preimplantation period	3-4 weeks	<2 weeks	10 cGy (10 rads)	Main risk: Pregnancy loss (baseline population risk below threshold)
Organogenesis	4-10 weeks	2-8 weeks	10-20 cGy (10-20 rads)	Greatest risk for major malformations; lesser risk for growth restriction (baseline population risk below threshold)
Fetal period	8-17 weeks[a]	6 (8)-15 weeks[a]	For severe mental retardation: 10 cGy (10 rads)[b]	Greatest risk for growth restriction, microcephaly, and mental retardation (baseline population risk below threshold)
	18-27 weeks	16-25 weeks	For reduction in IQ :10 cGy (10 rads)[c]	Main risk: Cognitive impairment, growth restriction, death (baseline population risk below threshold)
	28 weeks to term	26 weeks to term	50 cGy (50 rads)	Main risk: Cognitive impairment, growth restriction, death (baseline population risk below threshold)

Note. Gray (Gy) is the International System unit for the radiation absorbed dose rad, which is the old but still frequently used unit (1 Gy = 100 rads; 1 cGy = 1 rad). Radiographic exposure from a single diagnostic procedure to less than 5 cGy (5 rads) has not been associated with an increase in fetal abnormalities or pregnancy loss. Although concerns about exposure in the range from 5 to 10 cGy (5-10 rads) have been raised, serious developmental risk to the fetus is not known until the absorbed dose reaches 10 cGy (10 rads).
[a]Overlap observed in main effects during late organogenesis/early fetogenesis.
[b]Available data suggest that the risk of severe mental retardation is approximately 40% per 100 cGy (100 rads) of exposure above 10 cGy (10 rads).
[c]Available data suggest that the risk of severe mental retardation is approximately 9% per 100 cGy (100 rads) of exposure above 10 cGy (10 rads). Risk of reduction in IQ is estimated at 13 to 21 points per 100 cGy (100 rads) of exposure.

Procedure	Fetal Exposure cGy (rad)
Chest x-ray (2 views)	$2\text{-}7 \times 10^{-5}$
Mammogram (4 views)	0.01-0.04
Abdominal x-ray (1 view)	0.1-0.3
Pelvic x-ray (1 view)	0.2-0.35
Ventilation–perfusion scan	0.01-0.04
Helical CT chest	$1\text{-}10 \times 10^{-3}$
CT abdomen	1.7-3.5
CT pelvis	1.0-4.6

- Delay Rx procedures at least 12 weeks from LMP
  - Organogenesis is complete
- Best time – after 4th month of 2nd trimester:
  - Organogenesis is complete
  - Fetal thyroid is inactive
  - Small uterine volume

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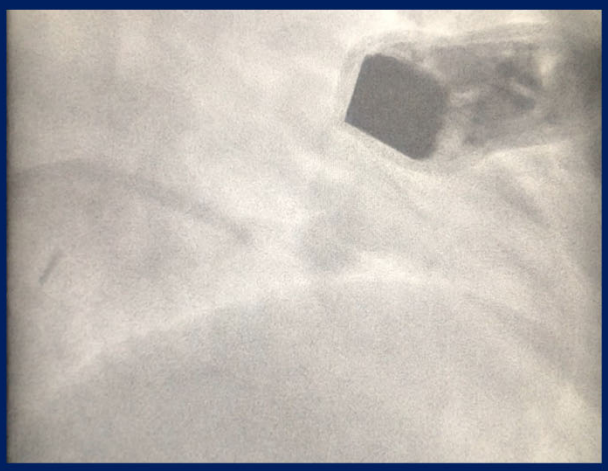
Balloon valvuloplasty



- PBMV – 19 weeks gestation
- Guidance:
  - Fluoroscopic
  - transthoracic
  - intracardiac guidance
  - 491 mGy *to the mother*
  - Fetus – difficult to calculate, but… low
    - If fetus in the direction of the radiation bean, radiation ~ 0.15 x mother's entrance skin dose
- Inoue 26 mm balloon used
- 3 total balloon inflations
- Post procedure MG ~ 5mmHg (from 8mmHg)
- Further dilatations not done (MR risk)

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Now…

- 27 weeks gestation
- Medications:
  - Metoprolol XL 12.5 every evening
  - ASA 81 mg daily (gestational diabetes, risk of pre-eclampsia)
  - No anticoagulation (no Afib)
- Repeat TTE last week MVA ~ 1.8 cm2
- Cardiology visit last week: symptoms NYHA II-III
- She WILL need surgical MVR/R

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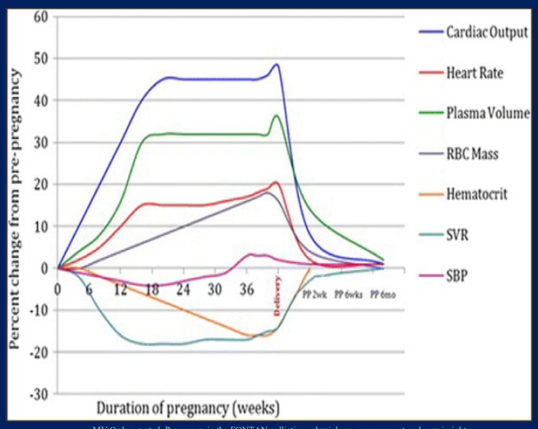
Take home messages

1. Remember the hemodynamics of pregnancy
2. Remember to use mWHO for young women at any childbearing age – estimates mom's risk
3. If a condition is in mWHO class IV
   - ❑ recommend *against* immediate pregnancy
4. Recommend contraception! {estrogen-free}
5. Safest window for ionizing radiation-therapies
   - ❑ At least 12 weeks after LMP
   - ❑ Safest – after 4th month of 2nd trimester
   - ❑ <10-20 cGy



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Resources

JACC FOCUS SEMINAR: CARDIO-OBSTETRICS

JACC FOCUS SEMINAR

Team-Based Care of Women With Cardiovascular Disease From Pre-Conception Through Pregnancy and Postpartum

JACC Focus Seminar 1/5

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2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy

The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC)

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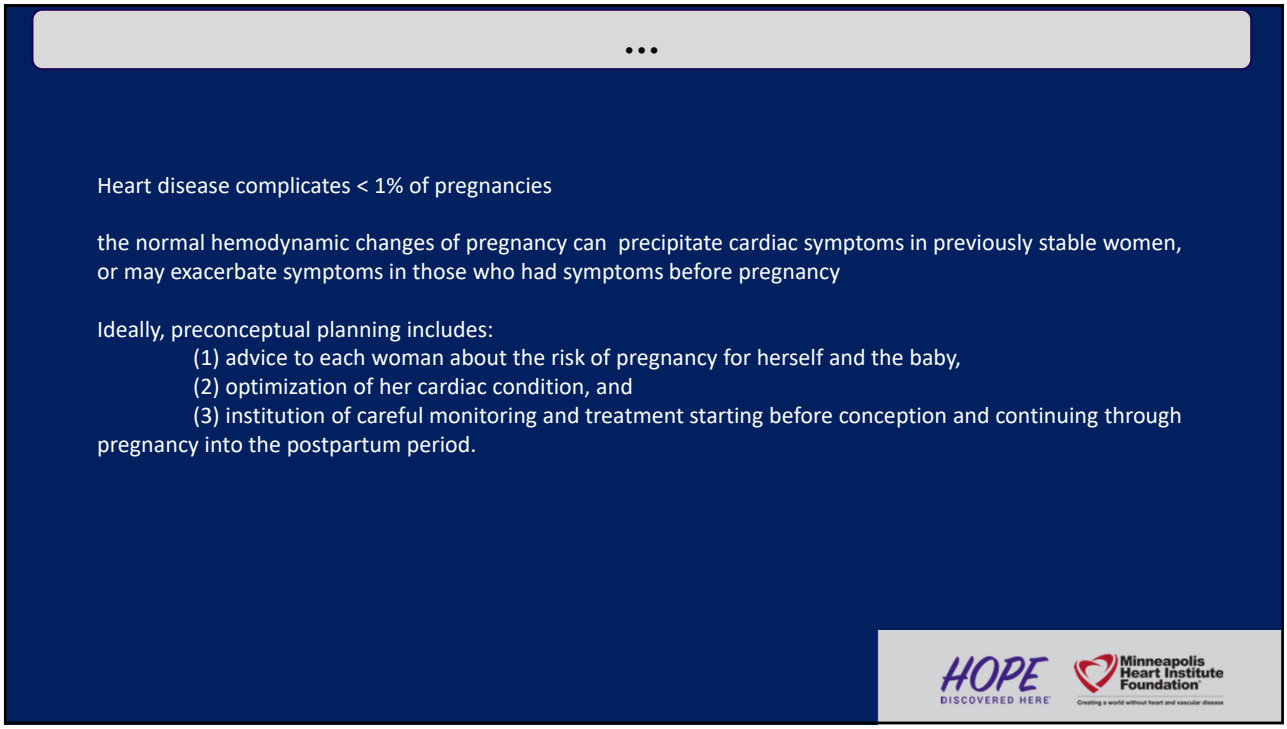
...
Heart disease complicates < 1% of pregnancies
the normal hemodynamic changes of pregnancy can precipitate cardiac symptoms in previously stable women, or may exacerbate symptoms in those who had symptoms before pregnancy
Ideally, preconceptual planning includes:
(1) advice to each woman about the risk of pregnancy for herself and the baby,
(2) optimization of her cardiac condition, and
(3) institution of careful monitoring and treatment starting before conception and continuing through pregnancy into the postpartum period.
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Box 2 Cardiac findings in a normal pregnancy

- Normal history
  - Fatigue
  - Decreased exercise tolerance
  - Palpitations
  - Lower extremity oedema
  - Orthopnoea
- Normal examination
  - Midsystolic murmur at left base (pulmonic flow murmur)
  - Continuous murmur (mammary souffle)
  - Split S1
  - Distended neck veins with prominent a and v waves
  - Lower extremity oedema

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Imaging considerations…

- Compression of the IVC decreases CO by up to 30% when supine (3rd trimester) → imaging and flows can be affected
- TEE: >18 weeks pregnant woman's fasting status = "full stomach"
  - High progesterone
    - → decreased gastric motility
    - → increased relaxation of the lower esophageal sphincter
    - + increased intra-abdom pressure
      - → high risk of emesis and aspiration
      - → endotracheal intubation is frequently recommended with TEE >1st trimester

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Treatment considerations

- Knowledge of safety and efficacy
- 1) Safety: FDA (A,B,C, D and X) → summaries w risks and benefits
  - LacMed – for lactating women
- 2) Efficacy:
- Increased hepatic clearance
- Increased renal clearance
- Decreased albumin and plasma binding proteins
- → pharmacokinetics are altered in pregnant state
- → effective dose of a drug may be HIGHER or LOWER than in nonpregnant state
- → effective dose may change throughout pregnancy

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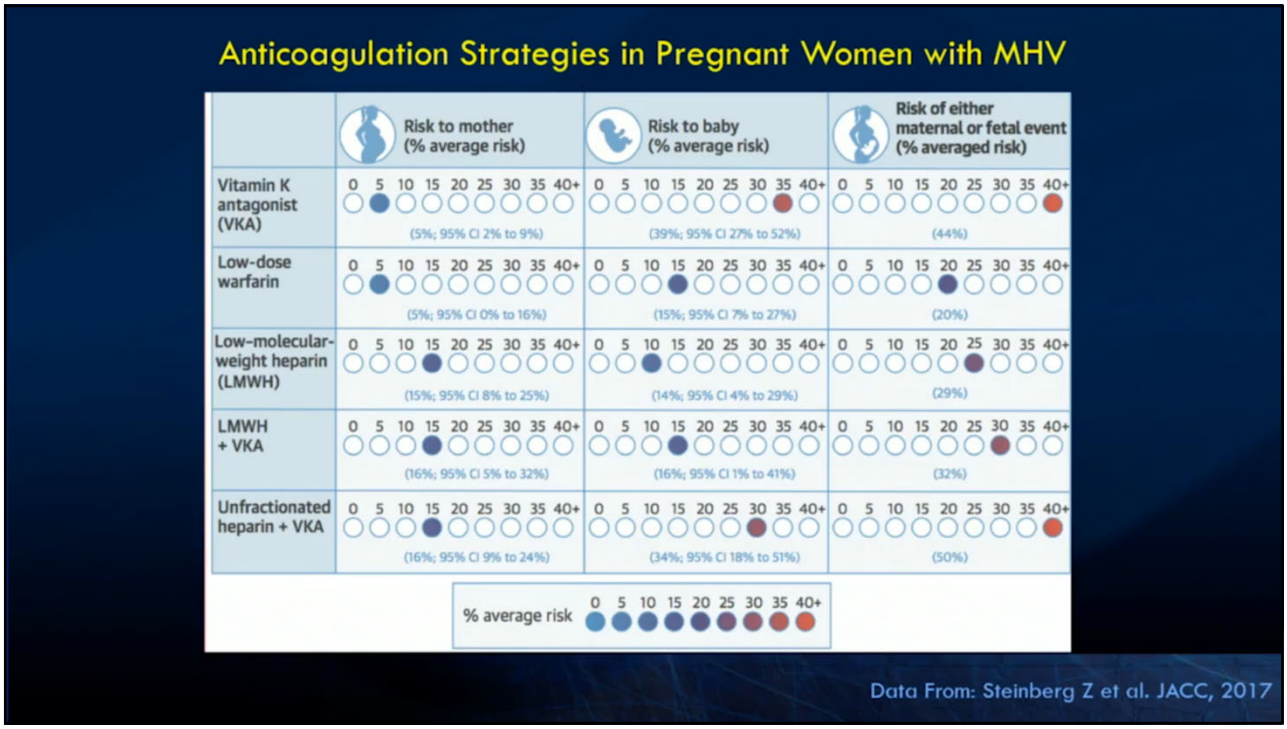
Anticoagulation Strategies in Pregnant Women with MHV
Risk to mother (% average risk)
Risk to baby (% average risk)
Risk of either maternal or fetal event (% averaged risk)
Vitamin K antagonist (VKA)
(5%; 95% CI 2% to 9%)
(39%; 95% CI 27% to 52%)
(44%)
Low-dose warfarin
(5%; 95% CI 0% to 16%)
(15%; 95% CI 7% to 27%)
(20%)
Low-molecular-weight heparin (LMWH)
(15%; 95% CI 8% to 25%)
(14%; 95% CI 4% to 29%)
(29%)
LMWH + VKA
(16%; 95% CI 5% to 32%)
(16%; 95% CI 1% to 41%)
(32%)
Unfractionated heparin + VKA
(16%; 95% CI 9% to 24%)
(34%; 95% CI 18% to 51%)
(50%)
% average risk
0 5 10 15 20 25 30 35 40+
Data From: Steinberg Z et al. JACC, 2017

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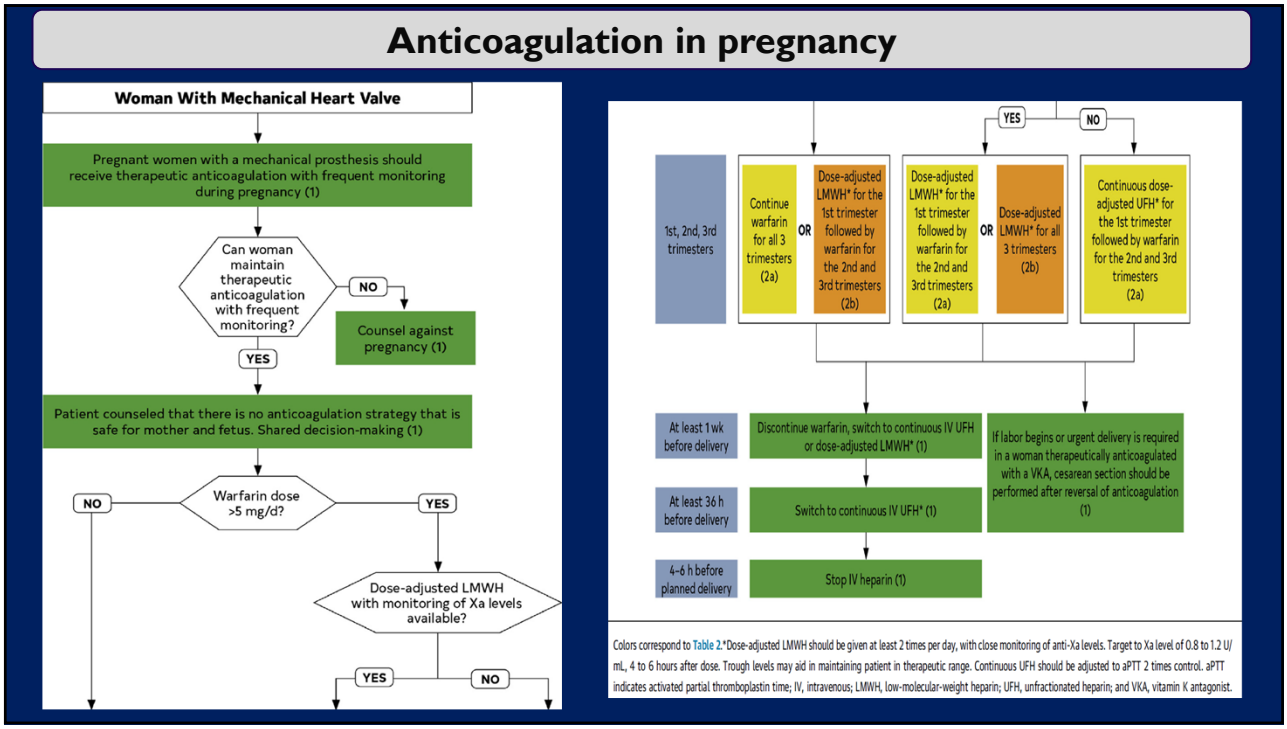
Anticoagulation in pregnancy
Woman With Mechanical Heart Valve
Pregnant women with a mechanical prosthesis should receive therapeutic anticoagulation with frequent monitoring during pregnancy (1)
Can woman maintain therapeutic anticoagulation with frequent monitoring?
NO
Counsel against pregnancy (1)
YES
Patient counseled that there is no anticoagulation strategy that is safe for mother and fetus. Shared decision-making (1)
Warfarin dose >5 mg/d?
NO
YES
Dose-adjusted LMWH with monitoring of Xa levels available?
YES
NO
YES
NO
1st, 2nd, 3rd trimesters
Continue warfarin for all 3 trimesters (2a)
OR
Dose-adjusted LMWH* for the 1st trimester followed by warfarin for the 2nd and 3rd trimesters (2b)
Dose-adjusted LMWH* for the 1st trimester followed by warfarin for the 2nd and 3rd trimesters (2a)
OR
Dose-adjusted LMWH* for all 3 trimesters (2b)
Continuous dose-adjusted UFH* for the 1st trimester followed by warfarin for the 2nd and 3rd trimesters (2a)
At least 1 wk before delivery
Discontinue warfarin, switch to continuous IV UFH or dose-adjusted LMWH* (1)
If labor begins or urgent delivery is required in a woman therapeutically anticoagulated with a VKA, cesarean section should be performed after reversal of anticoagulation (1)
At least 36 h before delivery
Switch to continuous IV UFH* (1)
4-6 h before planned delivery
Stop IV heparin (1)
Colors correspond to Table 2.*Dose-adjusted LMWH should be given at least 2 times per day, with close monitoring of anti-Xa levels. Target to Xa level of 0.8 to 1.2 U/mL, 4 to 6 hours after dose. Trough levels may aid in maintaining patient in therapeutic range. Continuous UFH should be adjusted to aPTT 2 times control. aPTT indicates activated partial thromboplastin time; IV, intravenous; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; and VKA, vitamin K antagonist.

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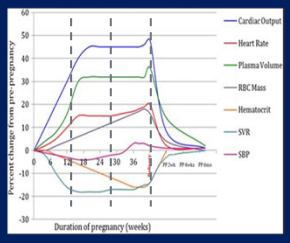
Why the panic?

- What would you do?



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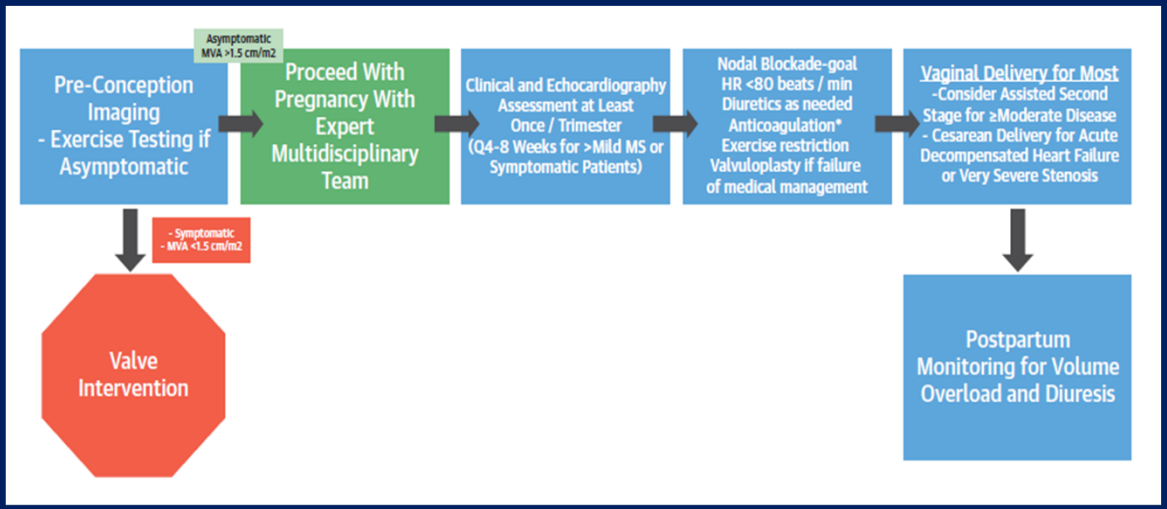
Mitral stenosis in pregnancy



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APRIL 13, 2021:1763–77

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Terminology…

Preconception visit:

1. Establish the level of ***maternal and fetal risk***
   - risk stratification tools: CarPreg, ZAHARA, mWHO
2. ***Optimization*** of mom's cardiac condition
   - Optimize CV condition & optimize medications
3. Institute careful ***monitoring and treatment plan***

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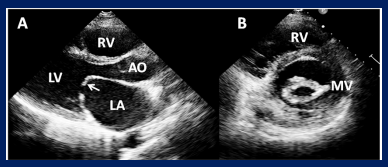
Rheumatic MS - timeline of diagnosis

➢ **TTE** (5 months prior):

- MG 8 mmHg @ 89 BPM
- PHT ~148-150 msec, MVA ~ 1.5 cm^2
- Ø PASP



➢ **Stress echo with bicycle ergometry** (5 months prior – on metoprolol):

- **Rest** (HR=86, BP 96/70 mmHg):
  - MG 8 mmHg
  - PASP ~ 30 mmHg
- **Stress** (HR=133 [73% APMHR], BP 122/74, 5.8 METS)
  - MG 28 mmHg
  - Ø PASP

➢ **TEE** (4 months prior):

- Favorable mitral valve anatomy / Wilkins score for balloon valvuloplasty

➢ **Recommended balloon valvuloplasty**

- Cancelled – 6 weeks pregnant

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Preconception planning

1. 1) Risk stratification tools

ESC European Society of Cardiology — European Heart Journal (2018) 39, 3165–3241 doi:10.1093/eurheartj/ehy340 — ESC GUIDELINES

2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy

It is recommended to perform risk assessment in all women with cardiac diseases of childbearing age before and after conception, using the mWHO classification of maternal risk.[11] | I | C

TABLE 3 Modified WHO Risk Stratification Model

Modified WHO Class	Conditions	Predicted Risk, %
I—No higher risk than the general population	Uncomplicated, small or mild lesions including pulmonary stenosis, VSD, PDA, and mitral valve prolapse with no more than trivial mitral regurgitation	2.5-5
	Successfully repaired simple lesions including ostium secundum ASD, VSD, PDA, and TAPVD	
	Isolated PVCs and PACs	
II—Small increased risk of maternal morbidity and mortality	Unoperated ASD	5.7-10.5
	Repaired tetralogy of Fallot	
	Most arrhythmias	
	Coarctation of the aorta without significant gradient or aneurysm (repaired or unrepaired)	
	Long QT syndrome	
II to III	Mild LV impairment	10-19
	Hypertrophic cardiomyopathy	
	Marfan syndrome without aortic dilation	
	Heart transplant	
	Native or tissue valve disease not considered WHO class IV	
	Bicuspid aortic valve without aortic dilatation	
III—Significant risk of maternal morbidity and mortality	Mechanical valve	19-27
	Systemic RV	
	Post-Fontan operation	
	Cyanotic heart disease	
	Other complex congenital heart repair	
	Aortic dilation without known fibrinogen disease	
	Coarctation of the aorta with residual gradient or aneurysm (repaired or unrepaired)	
	Marfan syndrome with aortic root dilation <45 mm or following aortic replacement	
	Bicuspid aortic valve with aortic root dilation 45 to 50 mm	
IV—Pregnancy contraindicated	Pulmonary arterial hypertension of any cause	40-100
	Severe left ventricular dysfunction (LVEF <30% or NYHA functional class III to IV)	
	Previous peripartum cardiomyopathy with any residual impairment of LV function	
	Severe left heart obstruction (AVA <1 cm² or peak gradient >50 mm Hg; MVA <1.5 cm²)	
	Marfan syndrome with aortic dilation >45 mm	
	Bicuspid aortic valve with aortic dilation >50 mm	

ASD = atrial septal defect; AVA = aortic valve area; LV = left ventricular; LVEF = left ventricular ejection fraction; MVA = mitral valve area; NYHA = New York Heart Association; PAC = premature atrial contraction; PDA = patent ductus arteriosus; PVC = premature ventricular contraction; RV = right ventricle; TAPVD = total anomalous pulmonary venous drainage; WHO = World Health Organization.

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Heart in Flames:
A Case of the Not-so-Sweethearts

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Disclosure

- None

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Case

- 47 M with no significant PMH
  - 7/2020 -> developed worsening cough and fever, hospitalized with multifocal pneumonia
    - Started on treatment for CAP and clinically improved over 3 days
    - Slow progress at home
    - Started having intermittent pleuritic chest pain and developed LLE pain (behind left knee, travels down calf into ankle/foot)
  - 8/2020 -> ANW
    - LE u/s: normal
    - CXR: stable/slight improvement of b/l upper lobe opacities
    - EKG: no current of injury
    - CTPE negative for PE
      - RUL consolidation with evolution of central cavitation - ?necrotizing PNA vs granulomatous infection
    - Troponin 5.7
      - Cardiology consulted

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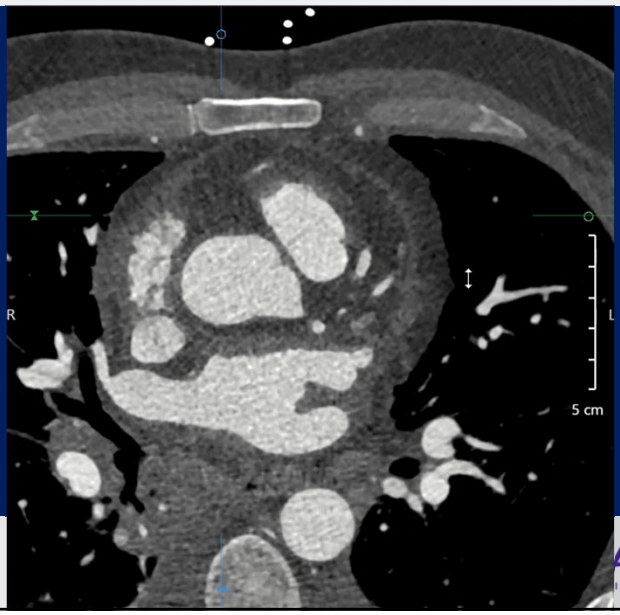
Coronary CTA



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Cardiology Impression

- Presumed acute myopericarditis in setting of multifocal PNA vs pulmonary vasculitis
  - ID, Pulmonology following
  - ANA, ANCA testing pending; HIV and COVID negative
  - Bronchoscopy planned

  - TTE with LVEF 55%, abnl mid anterior septum and septum
  - → CMR

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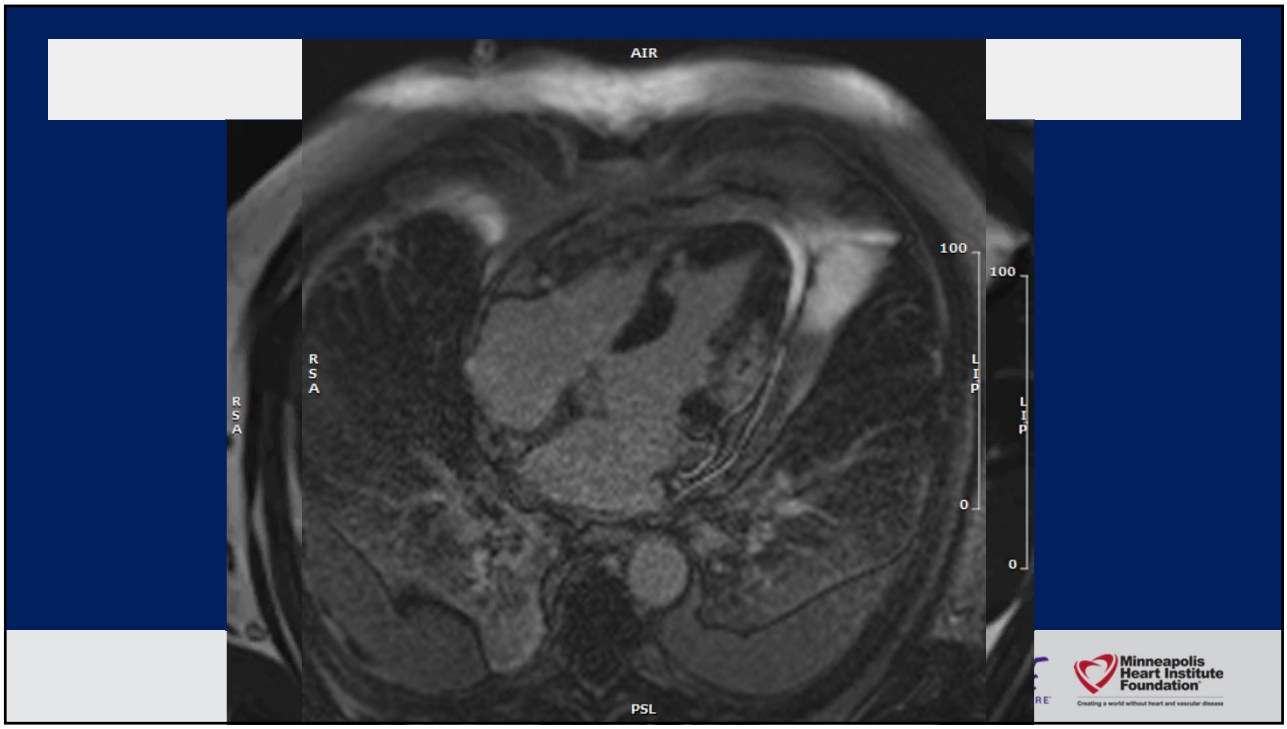

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CMR

- Two discrete myocardial infarctions with evidence of MVO and edema in different coronary distributions
  - Consistent with multivessel embolism vs possible coronary vasculitis
  - Consider invasive angiography, if needed for diagnostic purposes (pending pulmonary evaluation)
- Markedly inflamed pericardium on CMR c/w acute pericarditis
  - Continued on colchicine

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Laboratory Evaluation

Normal Creatinine, + microscopic hematuria

INFLAMMATORY MARKERS		
C-REACTIVE PROTEIN...	9.13 ▲	
SEDIMENTATION RATE...		113 ▲
ANA		
ANTINUCLEAR ANTIBO...		Negative *
ANCA		
ANCA		C-ANCA Positive * !
ANCA TITER		>=1:1280 !
MYELOPEROXIDASE ABY		<3.2
MYELOPEROXIDASE AB...		Negative *
PROTEINASE 3, ABY,...		1,156.7 ▲
PROTEINASE 3, INTERP		Positive * !

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ANCA-Associated Vasculitis

- Diagonsed with granulomatosis with polyangiitis (Wegner's)
  - Supported by +ANCA and anti-proteinase 3 titers
  - Pulmonary disease, neuropathy, coronary arteritis
  - Lung bx for confirmation → no granulomas
    - Rheumatology thought GPA most likely dx and started on prednisone

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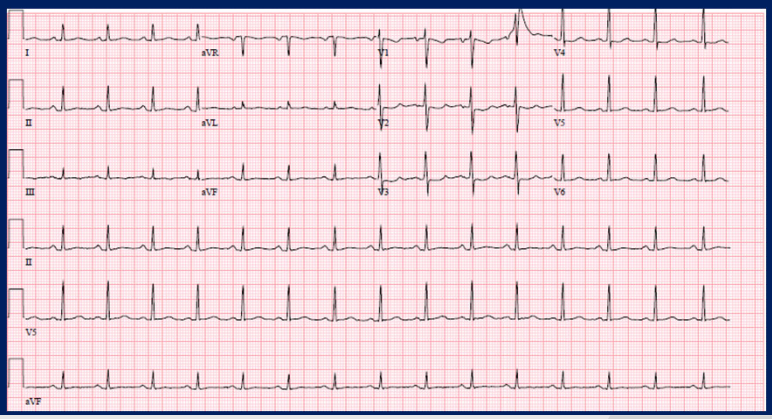
New Chest Pain

- Acute onset of substernal chest pressure (not pleuritic)



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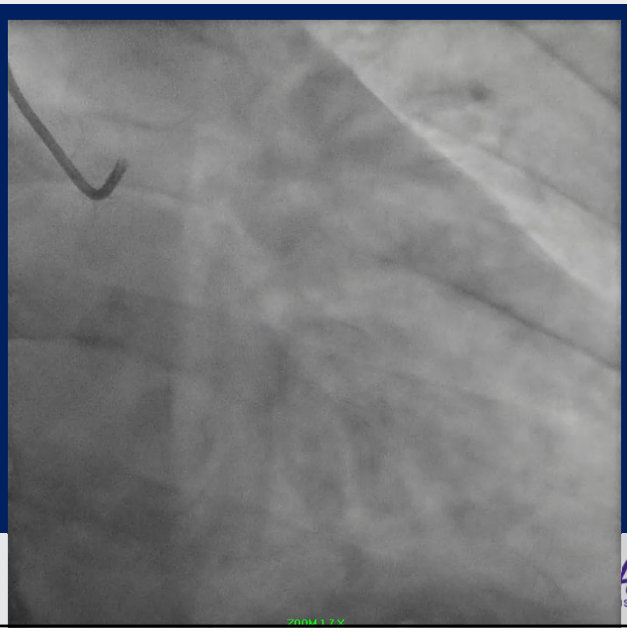
Invasive Coronary Angiogram



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Invasive Coronary Angiogram

SUMMARY OF FINDINGS:

1. Angiography confirming MRI findings of a discrete myocardial infarction in 2 territories consistent with a cardioembolic occurrence.
2. Occluded intermediate and occluded LAD diagonal, both relatively terminal.
3. Vasculitic changes noted in the distal first obtuse marginal branch with eating of the small vessel consistent with vasculitis.
4. Recommendation to proceed with treatment of underlying vasculitis. No complications encountered.

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Case Follow-up

- Medically managed infarct of the intermediate artery
  - Hemodynamically stable and ?benefit of revascularization in setting of vasculitis
- Continued on high dose prednisone and started on IV rituximab
- Following with outpatient rheumatology and cardiology
  - Resolution of chest symptoms
  - Leg/foot pain persist, though slowly improving
  - ANCA negative as of 3/2021 (recurrence less likely)

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Coronary Artery Vasculitis

- Cardiac manifestations in systemic vasculitis are variable
  - Myocarditis, pericarditis, valvular disease > coronary artery vasculitis
  - Generally rare, portend poor prognosis
  - CAV most commonly described in PAN, KD, TA, and GCA
- High index of suspicion for CAV in setting of unexplained ACS
  - Especially in young pts with known vasculitis
- RR of CHD-related mortality in pts with AAV 2-4x higher than controls
  - Accelerated CAD vs active inflammation

Cohen Tervaert JW. Cardiovascular disease due to accelerated atherosclerosis in systematic vasculitides. Best Pract Res Clin Rheumatol 2013;27:33-44.

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Cardiac Involvement in GPA

- Heterogeneous clinical presentation of GPA
  - Upper/lower RT and kidney involvement are typical
  - Cardiac involvement is rare (and variable)
    - European Vasculitis Study group: 5.7% of pts with newly dx ANCA-associated vasculitis had cardiac involvement of any type
      - Independent risk factor for relapse
- No difference in demographics / clinical features in patients with or without cardiac involvement in GPA

J Rheumatol. 2015 Jul; 42(7): 1209–1212.

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Multimodality Imaging

- Invasive angiography
  - Characteristic features of CAV, though limited ability to differentiate
  - Benefit of IVUS
- CTA or MRA
  - Recommended to evaluate for other vascular involvement
  - Additional benefit with MRI for evaluation of myocarditis/pericarditis
- PET
  - Helpful in evaluating hypermetabolism of aorta and first order branches
  - Poor sensitivity for medium and small-vessel vasculitis (incl. coronaries)
- Perfusion studies
  - Helpful for determining viability, though cannot differentiate vasculitic from atherosclerotic processes

Hashimoto Y, Numano F, Maruyama Y, et al. Thallium-201 stress scintigraphy in Takayasu arteritis. Am J Cardiol 1991;67:879-82.

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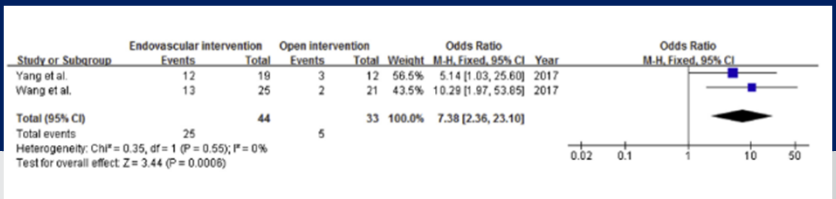
Revascularization

- Limited data, regardless of etiology (case reports, retrospective cohort studies)
  - No prospective RCT re optimal timing or method of revascularization
  - Observational data suggest surgery should be avoided during active stage of inflammation
  - Regardless of revascularization strategy, management of underlying vasculitis is essential
- Meta-analysis comparing outcomes of endovascular vs open surgical intervention in TA pts
  - 770 patients - 389 endovascular, 420 surgical
    - Subgroup analysis based on lesion location
    - Coronary restenosis occurs more often with PCI than with CABG



Jung JH, Lee YH, Song GG, Jeong HS, Kim JH, Choi SJ. Endovascular versus open surgical intervention in patients with Takayasu's arteritis: a meta-analysis. Eur J Vasc Endovasc Surg 2018;55:888-99.

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Coronary Artery Vasculitis

Table 1 – Highlighted Conditions With Arteritis or Periarteritis of the Coronaries

Condition	Size Artery Involved	Estimated Annual Incidence	Common Clinical Characteristics	Common Laboratory Abnormalities	Frequency Coronary Involvement	Suggestive Coronary Angiographic Features	Suggestive Extra-Coronary Angiographic Features	Treatment
Takayasu's arteritis	Large (++) Medium (+)	1-2 per million	Onset < 40 yrs Limb claudication Arterial bruit Asymmetric pulse/BP	↑ ESR, CRP	10-30%	Ostial/proximal stenosis Skip lesions	Thickening ± narrowing/occlusion of large arteries (aorta or primary branches)	GC MTX TNF-inhibitor
Giant cell arteritis	Large (++) Medium (+)	10-30 / 100,000*	Onset ≥ 50 yrs Cranial symptoms (Headache, jaw claudication, double vision, vision loss)	↑ ESR, CRP	Rare	Tapered smooth narrowing Skip lesions	If large vessels involved: similar to Takayasu but aorta and subclavians > carotid, other	GC TCZ
Polyarteritis nodosa	Medium (++) Small (+)	4-10 per million	Skin nodules, livedo Abdominal pain Testicular pain (men) Mononeuritis multiplex	Hepatitis serologies (-) ANCA	10-50%	Aneurysm or alternating aneurysm/narrowing (beaded pattern)	-Visceral infarcts -Aneurysms (micro or saccular) -Alternating aneurysm/narrowing (beaded pattern)	GC CYC MTX
ANCA vasculitis	Medium (+) Small (++)	1-3 / 100,000	Recurrent sinusitis Pulmonary nodules Hemoptysis Glomerulonephritis Leukocytoclastic vasculitis	(+) p-ANCA/MPO or (+) c-ANCA/PR3 (+) Hematuria ↑ Creatinine	Rare	Non-specific	N/A	Induction: GC + (RTX or CYC) Maintenance RTX or AZA, MTX

Koster MJ, Warrington KJ. Vasculitis of the coronary arteries. Am Coll Cardiol. 2019.

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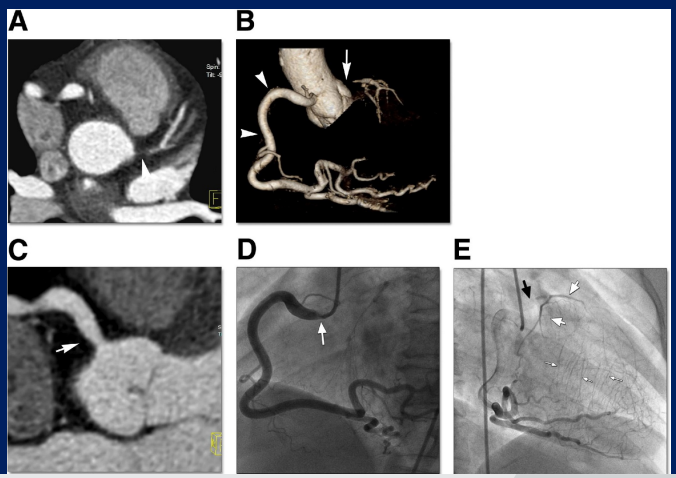
Takayasu Arteritis



JACC Cardiovasc Imaging. 2011 Sep;4(9):958-66. doi: 10.1016/j.jcmg.2011.04.019.

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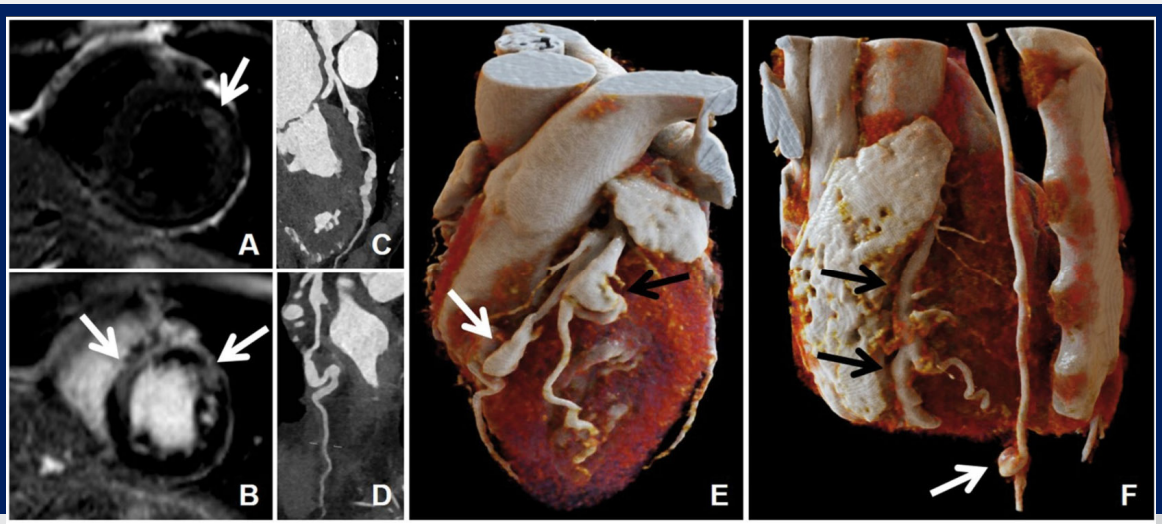
Polyarteritis Nodosa



Eur Heart J, Volume 39, Issue 27, 14 July 2018, Page 2603, https://doi.org/10.1093/eurheartj/ehy090

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