Heart Disease in Barth Syndrome: Diagnosis and Management

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Cardiac Findings in Barth Syndrome

- Brief preliminary communication in 1981 by Barth et al. described new X-linked syndrome[1]
  - Heart muscle
  - Skeletal muscle
  - Neutrophil leukocytes
- Further reported in 1983 with report of a large pedigree[2]
  - The untreated patients, all boys, died in infancy or early childhood from speticemia or cardiac decompensation

[1]Barth et al.In: *Mitochondrial and Muscular Disorders*.1981:161-164.

[2]Barth et al. *J Neurol Sci*. 1983;62:327-355.

Cardiac Findings in Barth Syndrome

- Clinical cardiac features in BS may include:
- Left ventricular (LV) myopathic changes with varying degrees of dysfunction:
  - Hypertrophy
  - Dilation
  - Noncompaction
- Arrhythmia
- Sudden cardiac death (SCD)

Cardiac Findings in Barth Syndrome

- Multicenter review of pediatric patients with confirmed Barth Syndrome
- 34 subjects identified (Age:1.2-22.6 yrs)
- All underwent comprehensive cardiac examination including:
  - Echocardiography
  - Electrocardiography (including SAECG)
  - Microvolt T wave alternans testing
  - Biochemical and hematologic laboratories
  - Physical therapy evaluation

Soencer et al. *Pediatrics* 2006;118:e337-346.

Cardiac Findings in Barth Syndrome

- Family history positive for suspected or confirmed BS in 63%
- 90% had evidence cardiomyopathy
- 53% had increased trabeculations or left ventricular noncompaction (LVNC)
- Substantial number of documented ventricular arrhythmias

Soencer et al. *Pediatrics* 2006;118:e337-346.

Cardiomyopathies

- *Dilated Cardiomyopathy (DCM)*
- *Hypertrophic Cardiomyopathy (HCM)*
- Restrictive Cardiomyopathy (RCM)
- Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)
- *Left Ventricular Noncompaction (LVNC)*

Left Ventricular Noncompaction

- Left ventricular noncompaction (LVNC) was first described in 1984[1]
- Since that time, only limited reports have been published
- These are small, single center series in both adults and children

[1]Engberding R , Bender F. *Am J Cardiol* 1984;53:133-4.

Left Ventricular Noncompaction

- LVNC has been classified as a primary cardiomyopathy with a genetic origin
- Morpholigically characterized by a severely thickened, 2-layered myocardium, numerous prominent trabeculations, and deep intertrabecular recesses
- Clinically and genetically a very heterogeneous disorder
- Symptomatic versus asymptomatic at presentation may be predictive of outcome

Maron et al. *Circulation*. 2006;113:1807-1816.

Oechslin et al. *J Am Coll Cardiol*. 2000;36:493-500.

Left Ventricular Noncompaction

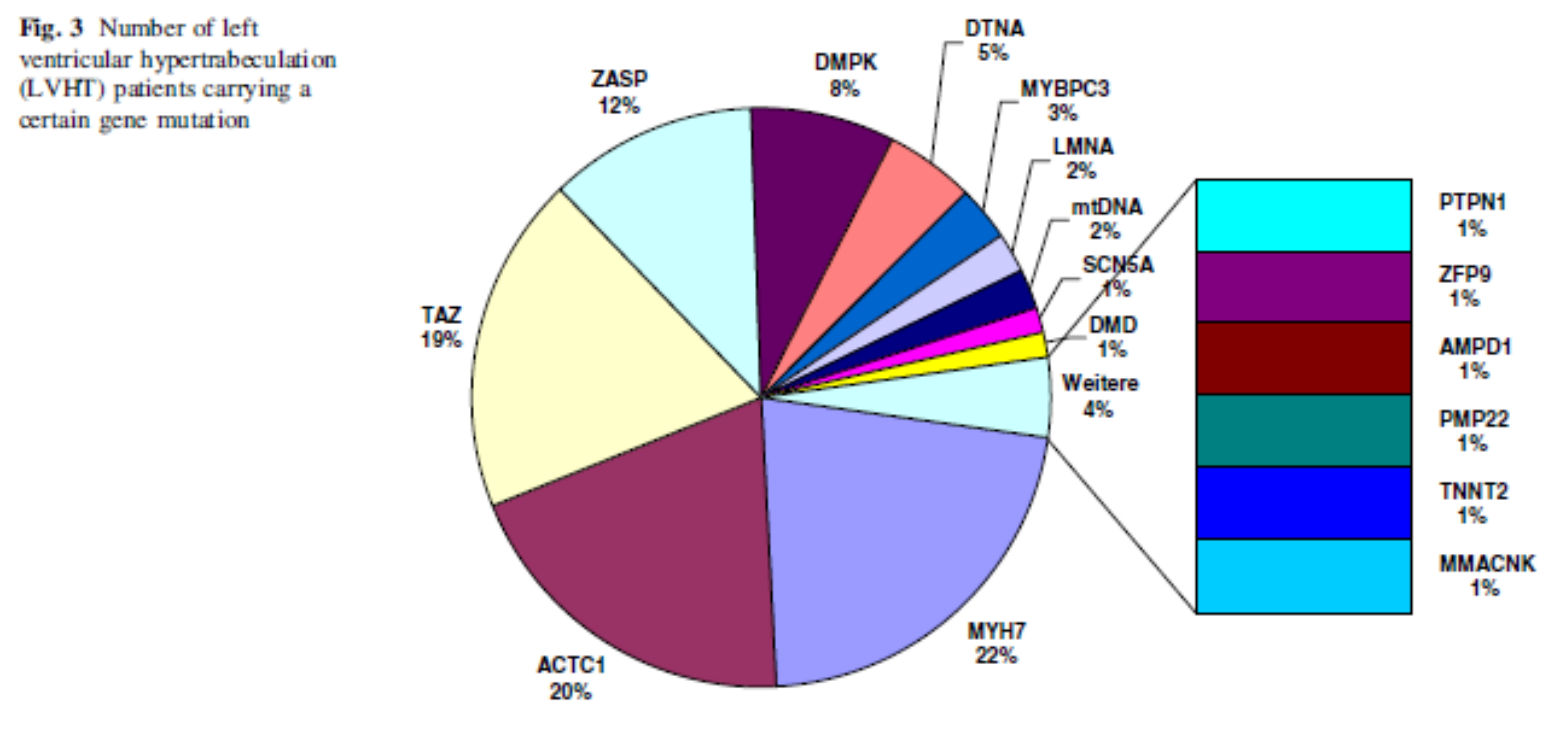


Fig. 3 Number of left ventricular hypertrabeculation (LVHT) patients carrying a certain gene mutation

Finsterer J. *Pediatr Cardiol.* 2009;Jan 29 online.

Left Ventricular Noncompaction

- LVNC has a heterogeneous clinical presentation and course
  - Normal size and function
  - Dilated +/- dysfunction
  - Hypertrophic
  - Mixed
- ECG abnormalities, arrhythmias, and sudden death are frequently described in association with LVNC, but the phenotype has not been well defined

Left Ventricular Noncompaction

- During cardiac development, myocardium initially trabeculated
  - Period before coronary development
- Adaptation to provide coronary blood flow to the developing myocardium
- Development of the coronary vasculature associated temporally with the loss of LV trabeculations
- Between gestational weeks 5-8, trabeculae regress and myocardium “compacts”

Left Ventricular Noncompaction

Table 1 Genetic disorders attributable to a distinct mutation associated with left ventricular hypertrabeculation (LVHT)

Disorder	Gene	Protein	NOP	References
Mitochondrial disorders	mtDNA, nDNA genes	Respiratory chain subunits, tRNAs	40	[23, 35, 37–39, 45, 50, 58, 107, 117]
Barth syndrome	G4.5, TAZ	Taffazin	30	[12, 20, 73, 107, 126, 148–150]
Hypertrophic/dilated CMP	MHY7	Beta-myosin heavy-chain 7	1, 8, 9, 12	[18, 57, 69, 77]
Hypertrophic cardiomyopathy	ACTC	Cardiac alpha-actin	27	[56, 77, 93]
Zaspopathy	CypherZASP/LDB3	LIM domain-binding protein	15	[107, 140, 148]
Zaspopathy/Barth syndrome	TAZ/ZASP	Compound heterozygote	1	[87]
Myotonic dystrophy type 1	DMPK	Protein-kinase	11	[43, 48, 113]
Dystrobrevinopathy	DTNA	α-Dystrobrevin	6, 1	[62, 148]
Hypertrophic/dilated CMP	MYBPC3	Myosin-binding protein C	4	[57, 71, 145]
Dystrophinopathy	DMD	Dystrophin	3	[36, 44, 83, 131]
Emery-Dreifuss muscular dystrophy	LMNA	Laminin	2 + 1 carrier	[56, 109]
Sick-sinus, long-QT syndrome	SCN5A	Sodium channel type V-alpha	2 families	[84]
Melnick Fraser syndrome	FLNA	Filamin A	2	[32, 147]
Noonan syndrome	PTPN11, SHP2	Tyrosine phosphorylase	2	[4, 96]
MLS (MIDAS syndrome)	HCCS	Mt holocytochrome c-type synthase	2	[55, 75]
Myotonic dystrophy type 2	ZNF9	Zink-finger protein 9	1	[142]
MADA deficiency	GAA	MADA	1	[41]
CMT1A	PMP22	PMP22	1	[22]
Hypertrophic/dilative CMP	TNNT2	Cardiac troponin T	1	[77]
Beals-Hecht syndrome	FBN2	Fibrillin 2	1	[88]
Leopard syndrome	PTPN11	Tyrosine phosphatase SHP2	1	[82]
Cobalamin C-deficiency	MMACHC	Methylmalonic aciduria cblC type	1	[135]
Nail patella syndrome	LMX1B	Transcription factor	1	[40]
Congenital adrenal hypolplasia	NR0B1 (DAX–1)q	Dosagesensitive sex-reversal adrenal hypoplasia congenital critical region on the X-chromosome, gene 1	1	[107]

Finsterer J. *Pediatr Cardiol.* 2009;Jan 29 online.

Left Ventricular Noncompaction

- Isolated LVNC defined as occurring in the absence of other structural cardiac malformations
- Nonsyndromic LVNC refers to the absence of other extracardiac developmental discorders

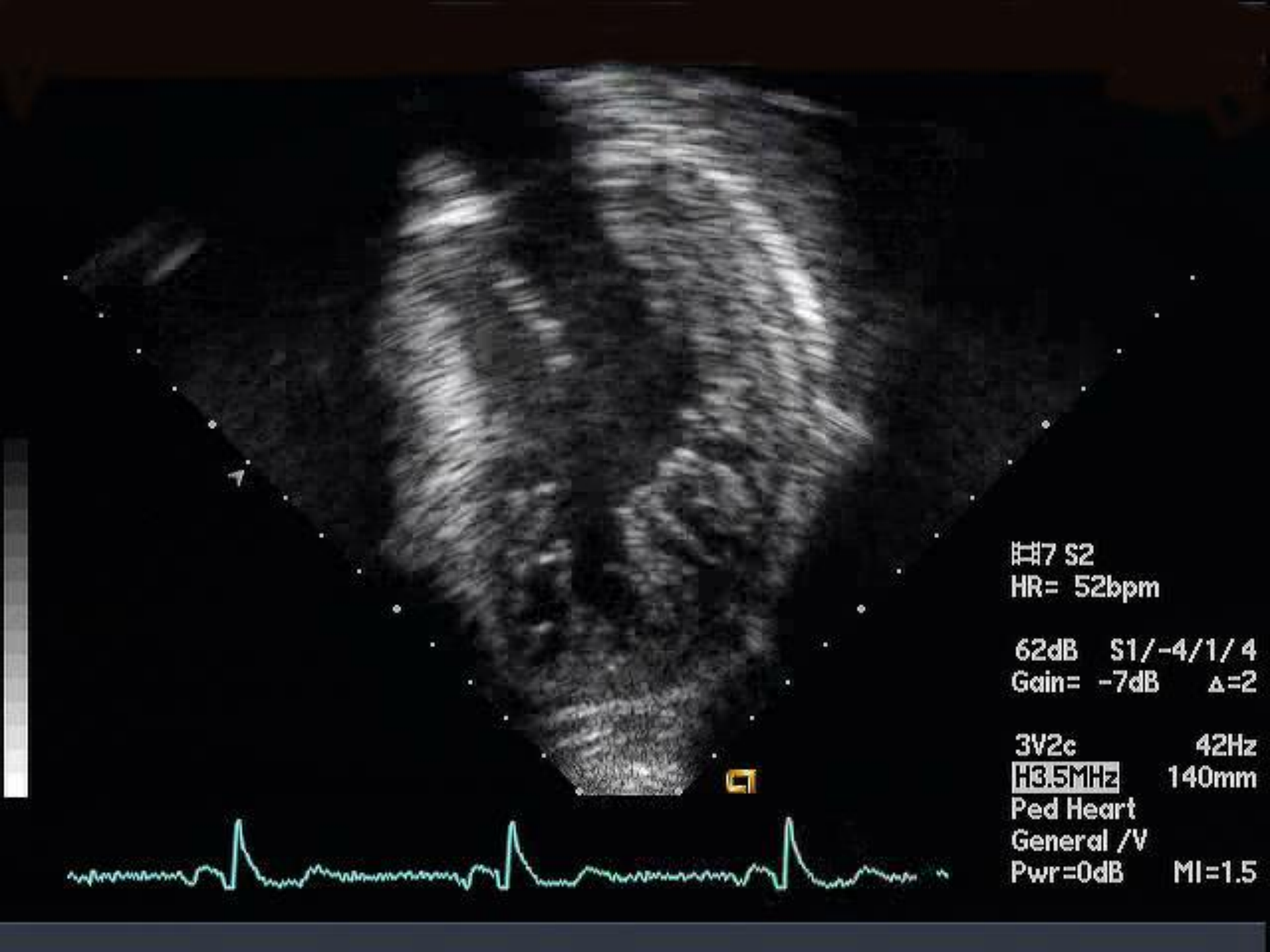
Left Ventricular Noncompaction

- Echocardiography mainstay for diagnosis
- Jenni et al proposed diagnostic criteria
  - Lack of coexisting cardiovascular abnormalities
  - Segmental LV wall thickening with a thin compacted epicardial layer and a thicker noncompacted endocardial layer
  - End-diastolic noncompacted-to-compacted myocardial ratio of >2.0 (>1.3-1.5 in infants)
  - Presence of color Doppler flow within the recesses

Jenni et al. *Heart*.2001;86:666-671.

Left Ventricular Noncompaction

- Location of noncompacted segments also important
  - Usually located in the apical, mid-lateral, and mid-inferior LV segments
- Noncompacted segments often hypercontractile
- Other echocardiographic findigns may include decreased LV EF, diastolic dysfunction, abnormal LV papillary muscle architecture, and LV thrombi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HR= 52bpm
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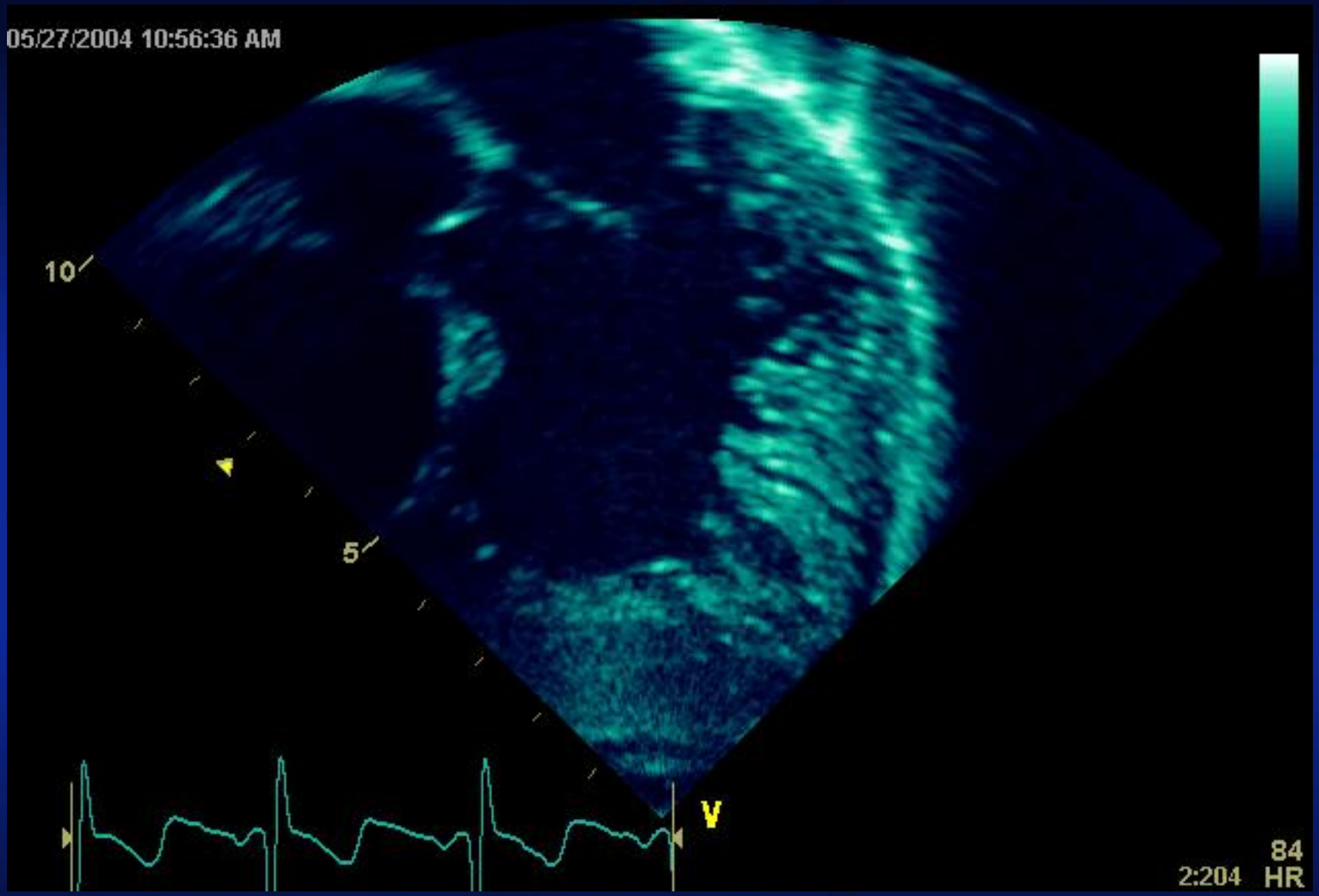
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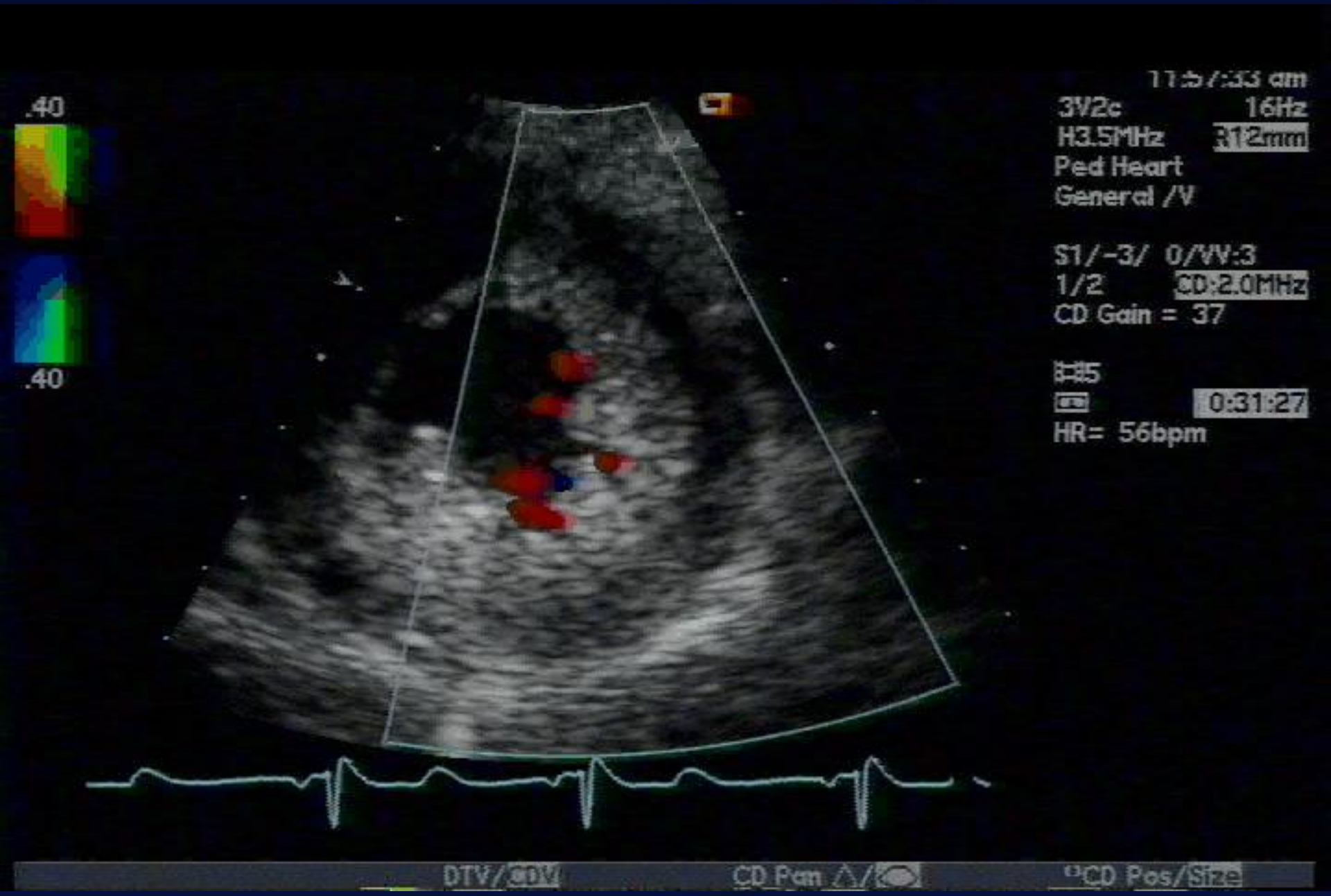
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.40
3V2c
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Ped Heart
General /V
S1/-3/ 0/VV:3
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DTV/CDV
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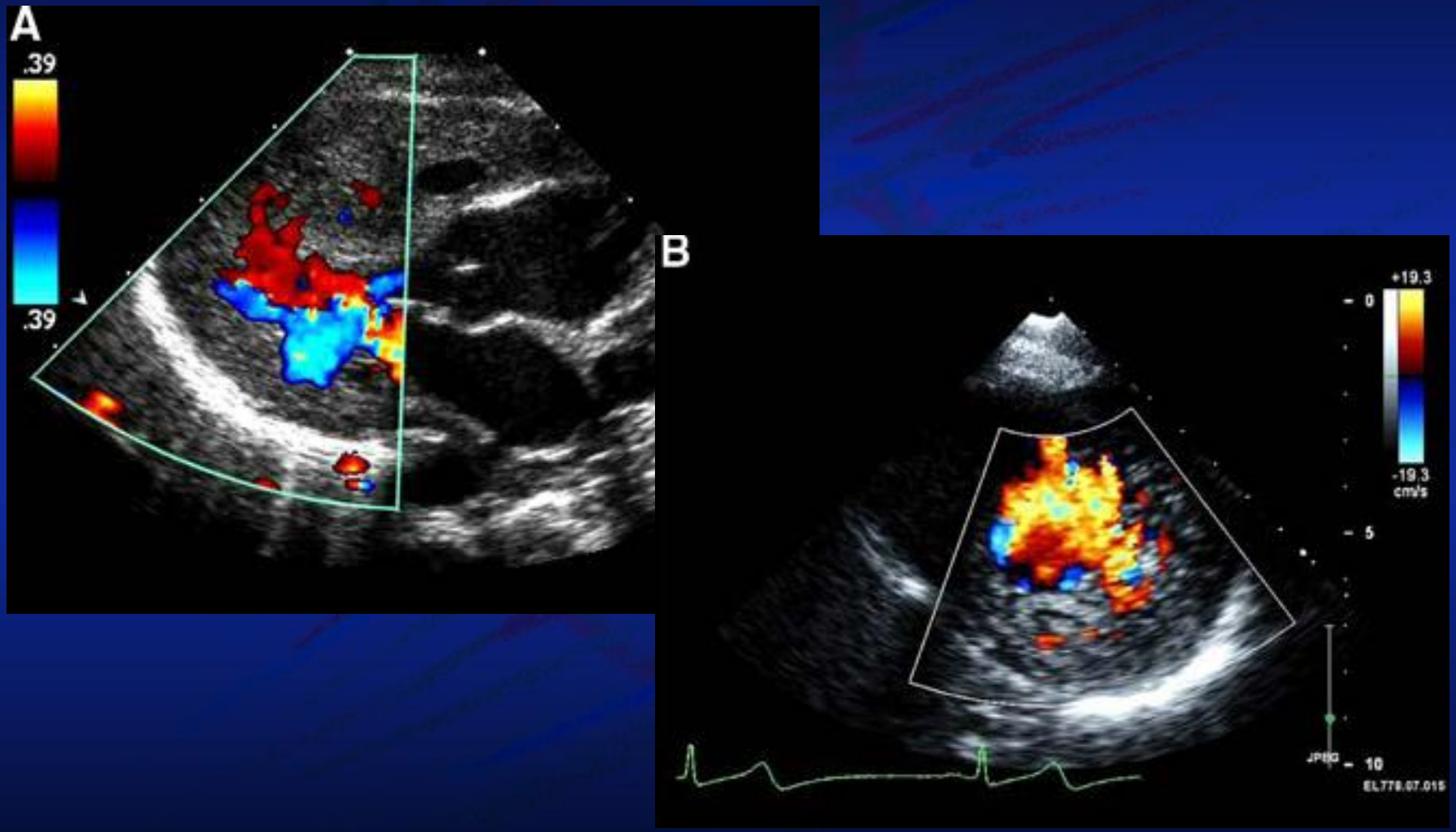
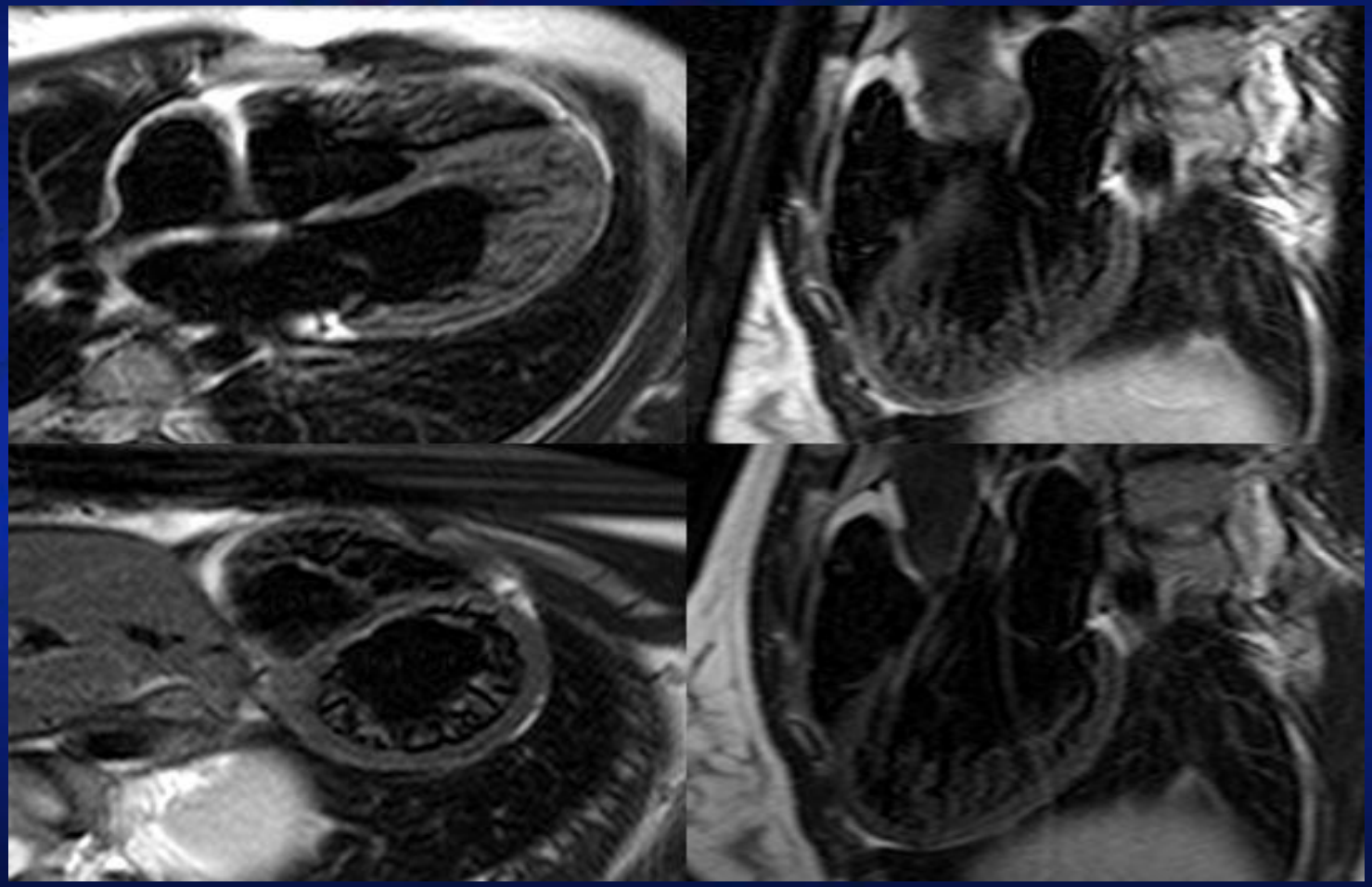
CD Pos/Size

Left Ventricular Noncompaction

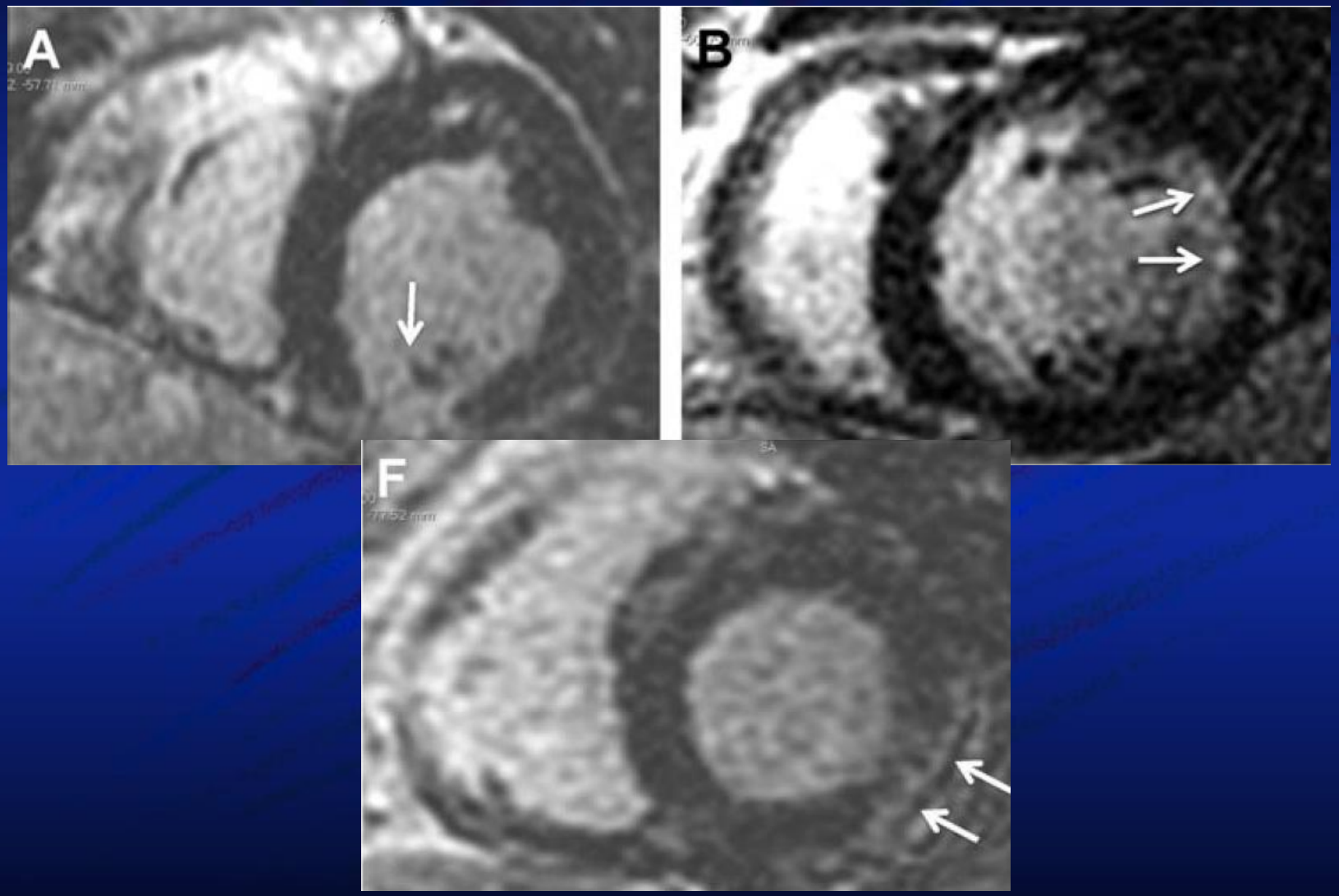


Eidem BW. 2009. *Pediatr Cardiol*. Online first

Left Ventricular Noncompaction



Myocardial Fibrosis in Left Ventricular Noncompaction



Nucifora et al. *Eur J Heart Fail* 2011;13:170-6.

Scar in the Heart Muscle

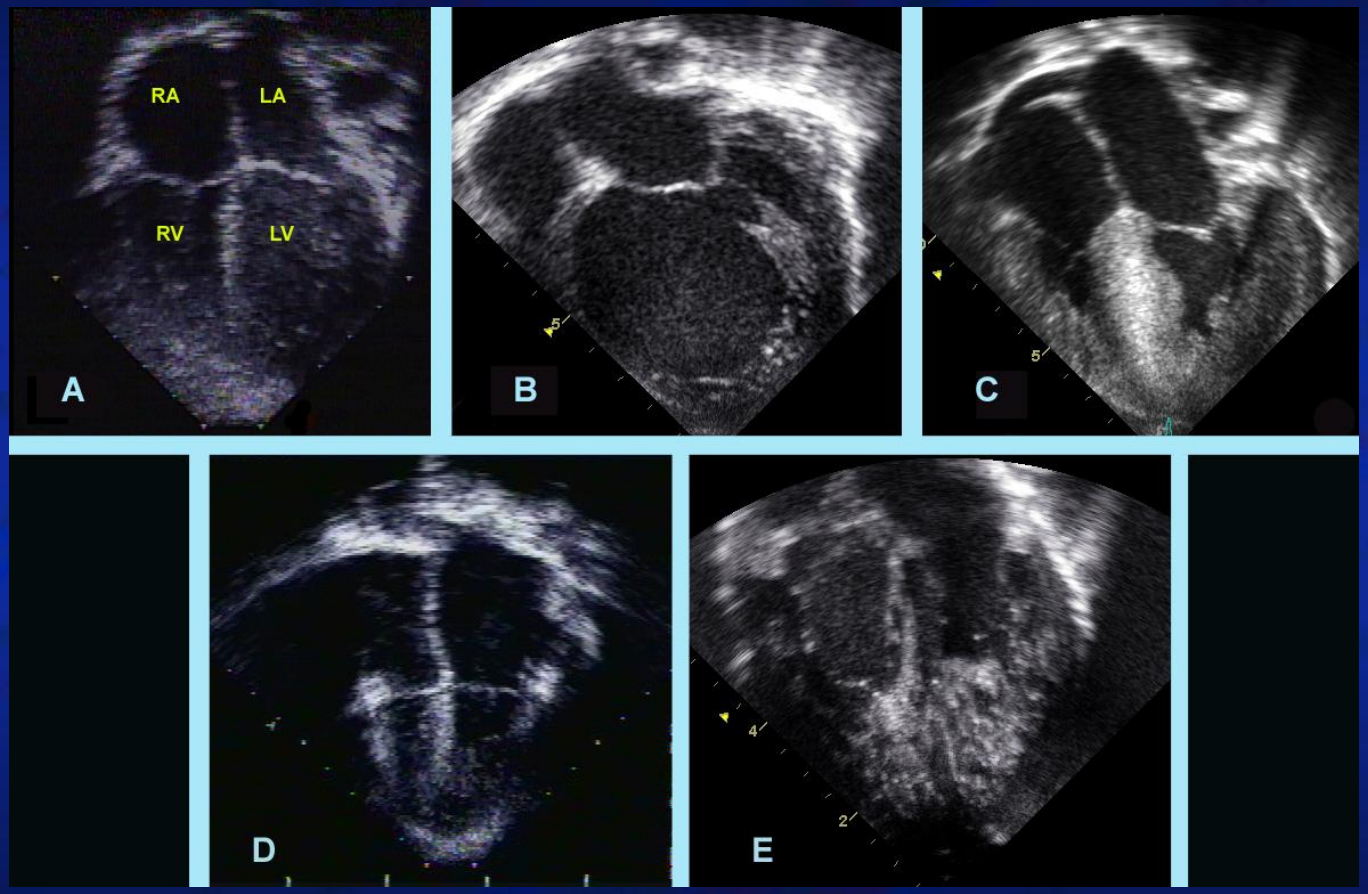
Table 2 Univariate and multivariate regression analyses to determine the independent correlates of left ventricular ejection fraction in isolated left ventricular non-compaction

	Univariate		Multivariate			
			Model 1		Model 2	
	β	*P*-value	β	*P*-value	β	*P*-value
Age	−0.32	0.038	−0.17	0.13	−0.14	0.036
Male	−0.13	0.43	—	—	—	—
LV mass index	−0.40	0.009	−0.098	0.41	−0.18	0.12
Number of LV non-compacted segments	−0.012	0.94	—	—	—	—
Maximal non-compacted/compacted myocardium ratio	−0.29	0.059	−0.10	0.36	−0.001	0.99
Presence of LV LGE	−0.73	<0.001	−0.63	<0.001	—	—
%LV LGE	−0.68	<0.001	—	—	−0.62	<0.001

For multivariate analysis, two different models were computed, including either presence of LV LGE (Model 1) or %LV LGE (Model 2). Abbreviations as in *Table 2*.

Nucifora et al. *Eur J Heart Fail* 2011;13:170-6.

Associated Phenotypes with Left Ventricular Noncompaction



Left Ventricular Noncompaction

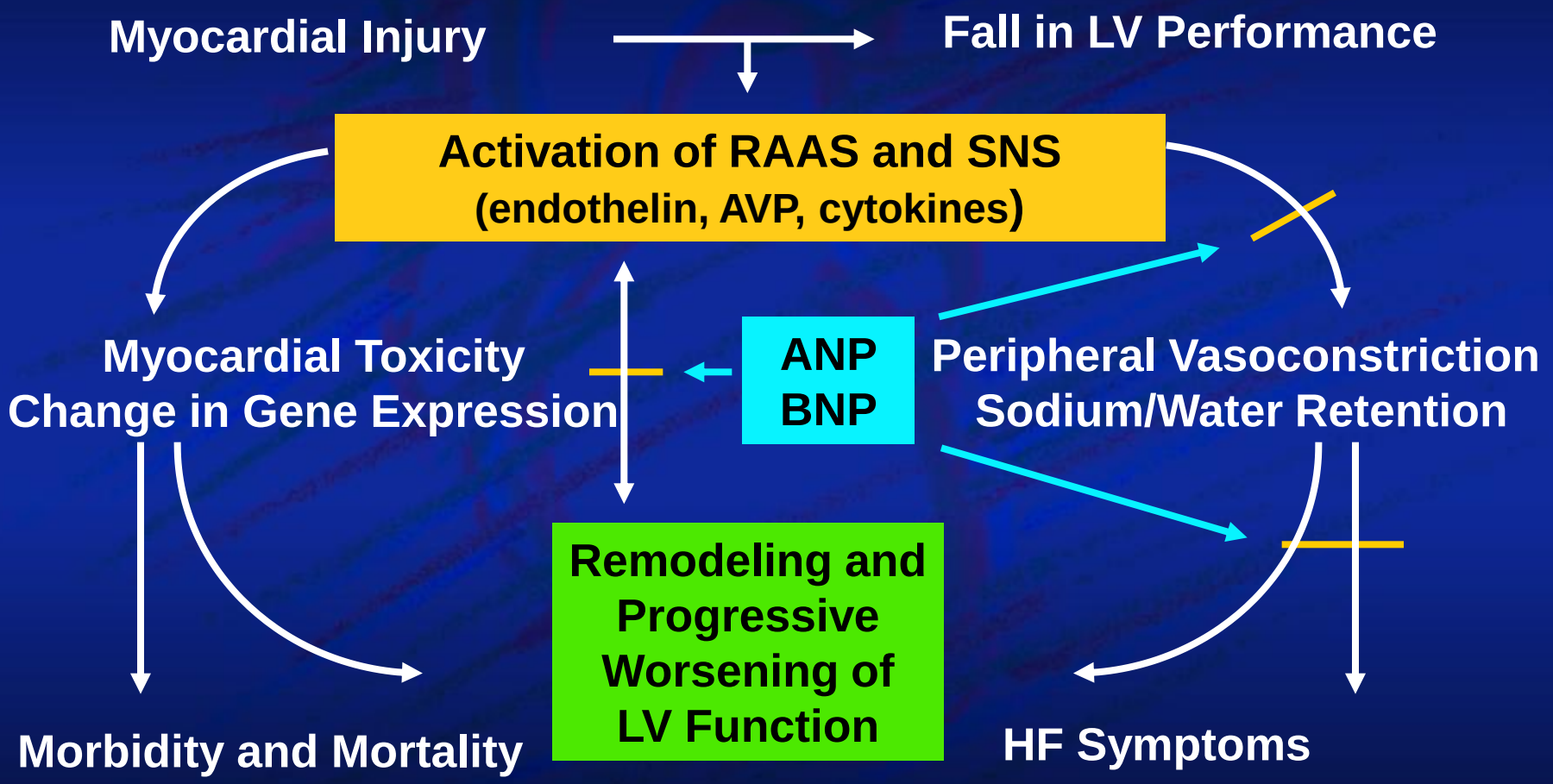
- Clinical manifestations
  - Heart failure
  - Embolic events
  - Arrhythmias
  - Sudden cardiac death

Heart Failure Defined

"Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood."

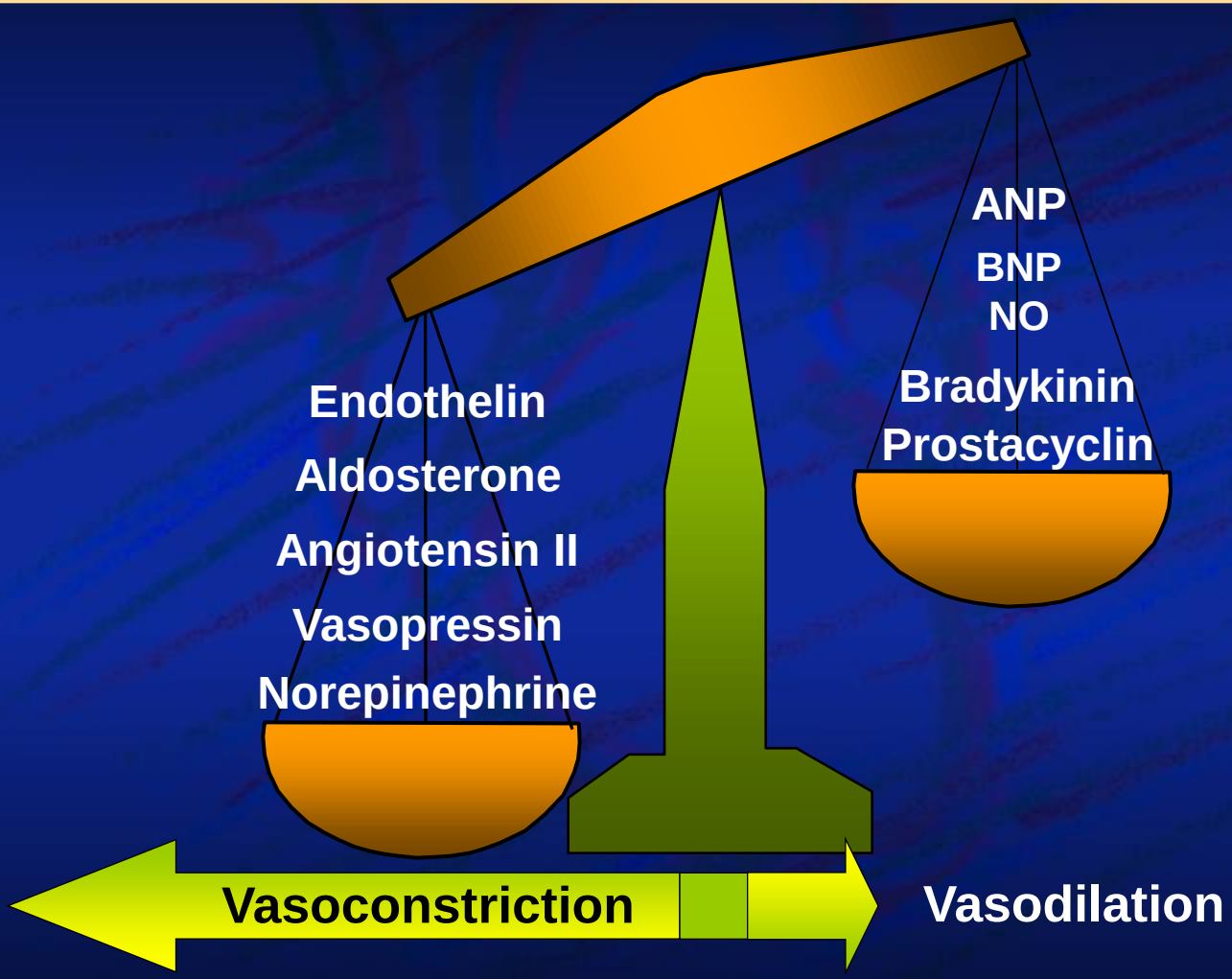
Hunt SA et al. *Circulation*. 2001;104:2996

The Heart Failure Syndrome



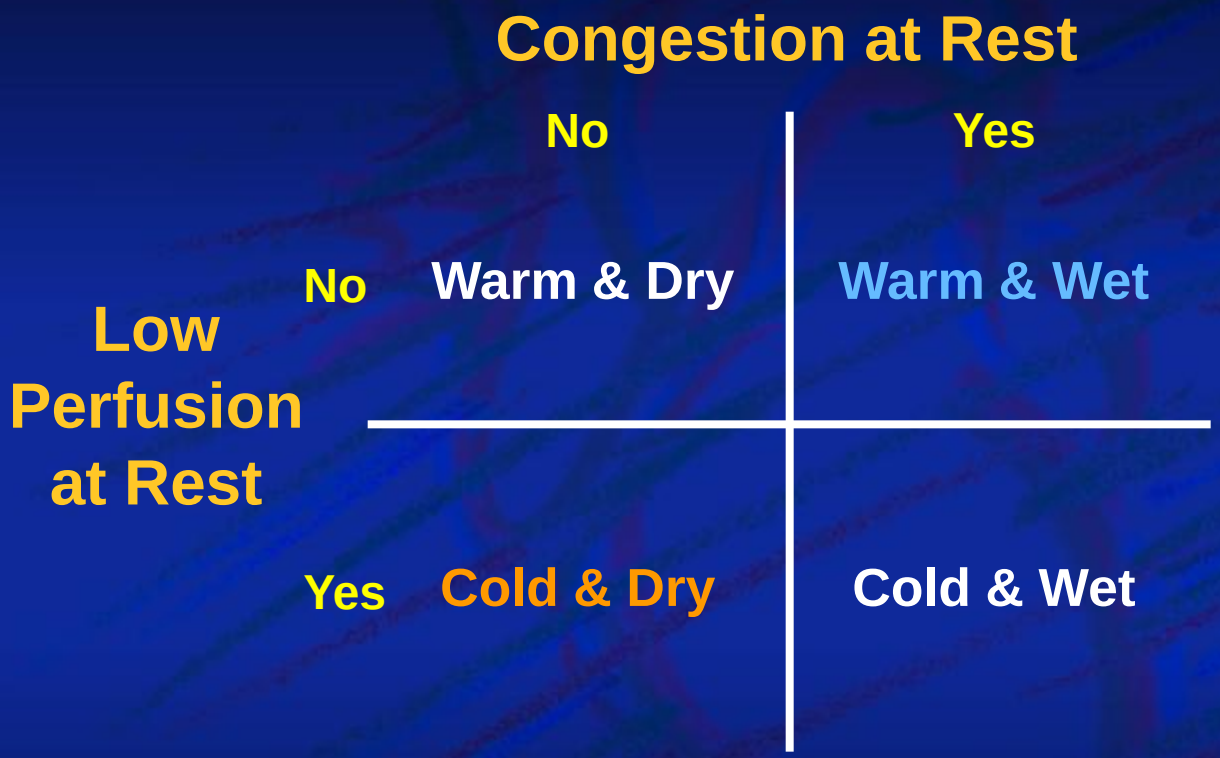
Shah M et al. *Rev Cardiovasc Med.* 2001;2(suppl 2):S2

Pharmacologies in Heart Failure Management



Shah M et al. *Rev Cardiovasc Med.* 2001;2(suppl 2):S2

Hemodynamic Profile Assessment



Signs/symptoms of congestion

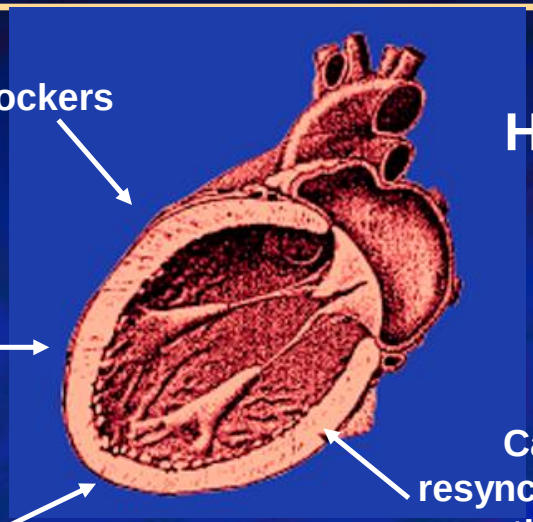
- Orthopnea/PND
- JVD
- Ascites
- Edema
- Rales (rare in HF)

Possible evidence of low perfusion

- Narrow pulse pressure
- Sleepy/obtunded
- Low serum sodium
- Cool extremities
- Hypotension with ACE inhibitor
- Renal dysfunction (one cause)

Stevenson LW. *Eur J Heart Fail.* 1999;1:251

Sites of Action for HF Therapies



Heart

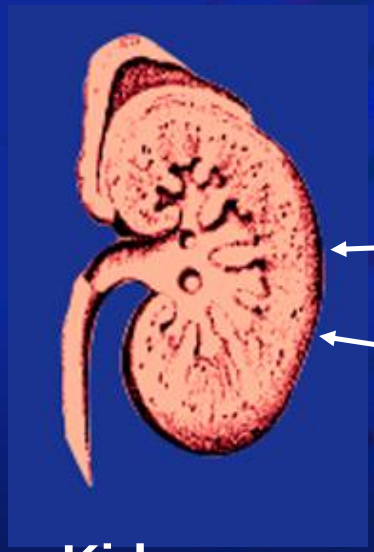
Beta blockers

Digoxin, inotropes

Cardiac-resynchronization therapy

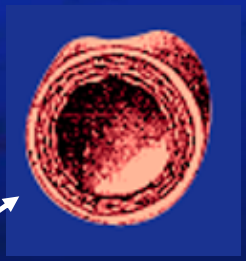
ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists

Diuretics, aldosterone antagonists, nesiritide



Kidney

Peripheral Arteries

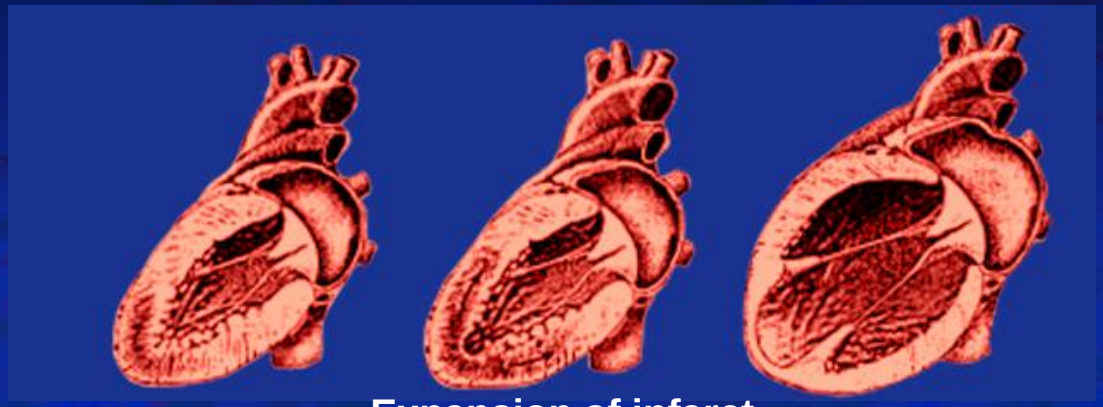


ACE inhibitors, angiotensin receptor blockers, vasodilators, alpha blockade, nesiritide, exercise

Jessup M, Brozena S. *N Engl J Med.* 2003;348:2007

Ventricular Remodeling

Ventricular Remodeling After Acute Infarction



Initial infarct

Global remodeling
(days to months)

Expansion of infarct
(hours to days)

Ventricular Remodeling in Diastolic and Systolic HF

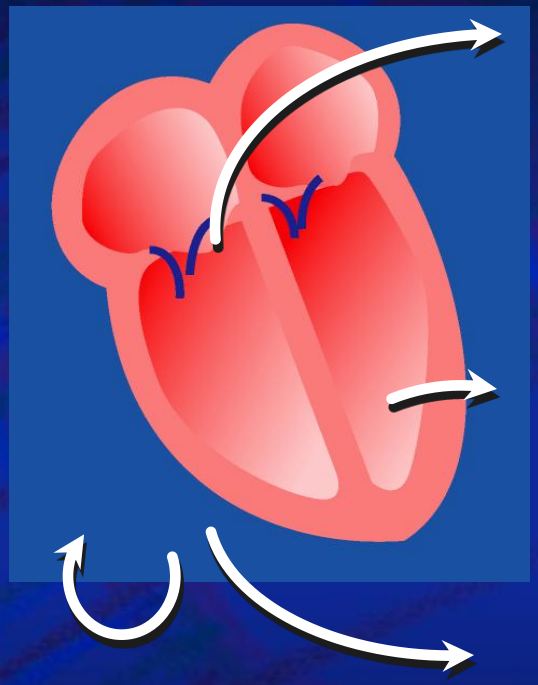
Normal heart

Dilated heart
(systolic HF)

Hypertrophied heart
(diastolic HF)

Jessup M et al. *N Engl J Med.* 2003;348:2007

Pharmacologies in Heart Failure Management



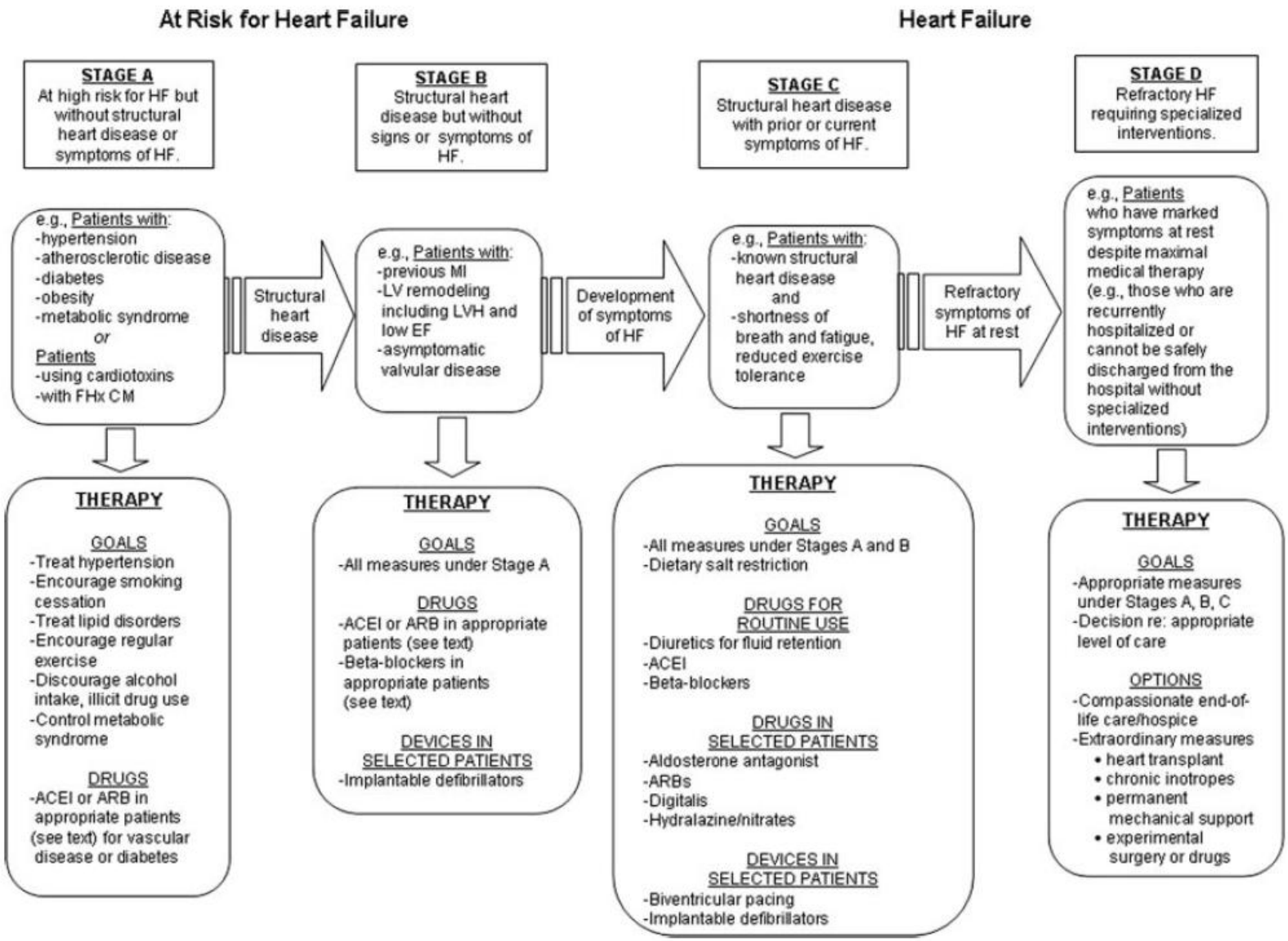
Cardiac
- Lusitropic
- Antifibrotic
- Antiremodeling

Hemodynamic (balanced vasodilation)
- Veins
- Arteries
- Coronary arteries

Neurohormonal
- ↓ aldosterone
- ↓ endothelin
- ↓ norepinephrine

Renal
- ↑ sodium and water excretion

Abraham WT et al. *J Card Fail*. 1998;4:37
Clemens LE et al. *J Pharmacol Exp Ther.* 1998;287:67
Marcus LS et al. *Circulation.* 1996;94:3184
Tamura N et al. *Proc Natl Acad Sci U S A.* 2000;97:4239
Zellner C et al. *Am J Physiol.* 1999;276(3 pt 2):H1049



Jessup et al. *Circulation* 2009;119:1977-2016.

Heart Failure in Children

- Heart failure in childhood may present in the first days of life or anytime thereafter
- Signs and symptoms of heart failure in children may include:
  - Breathlessness
  - Tachypnea or tachycardia
  - Diaphoresis
  - Failure to thrive

Cardiac Findings in Barth Syndrome

TABLE 3 Evaluation in Cases of Documented Arrhythmia

Patient	Arrhythmia	EPS	ECG[a]	QTc, msec[a]	TWA[a]	SA-ECG[a]
1	Cardiac arrest (VF)	NA	NA	413 before arrest	NA	NA
2	Cardiac arrest (VF)	+VT	LVH, ST-T wave changes	450	Negative	Normal
3	VT (Holter)	+VT/VF	RBBB	NA	Positive	Abnormal
4	VT (Holter)	+VT	Low voltage, flat T waves	427	Negative	Normal
5	VT (Holter)	NA	LVH, abnormal T waves	480	Positive	Borderline
6	None demonstrated	+VT	LAD, T wave flattening	407	Negative	Borderline
7	VT (Holter)	NA	LVH with strain	353	Negative	Normal

EPS indicates electrophysiology study; VF, ventricular fibrillation; NA, not applicable; VT, ventricular tachycardia; LVH, LV hypertrophy; RBBB, right bundle branch block; LAD, left axis deviation.
[a] Study results from current evaluation.

TABLE 4 Characteristics of Those With and Without Documented VA

Measure	Arrhythmia Group, Mean (*n*)	No-Arrhythmia Group, Mean (*n*)	*P*
Age, y	18.1 (6)	9.2 (25)	.002
EF, %	47 (6)	51 (24)	.20
SF *z* score	−2.7 (6)	−2.6 (20)	.81
LVIDd *z* score	2.3 (6)	1.7 (20)	.24
LVEDV *z* score	1.8 (6)	1.9 (24)	.52
BNP, pg/mL	399 (5)	342 (18)	.74
QTc, msec	423 (5)	439 (25)	.52

LVEDV indicates LV end-diastolic volume.

Soencer et al. *Pediatrics* 2006;118:e337-346.

EKG Abnormalities in LVNC

- Steffel et al. recently reviewed 78 patients with isolated LVNC
- Most common findings were intraventricular conduction delay, voltage evidence of LVH, and repolarization abnormalities
- No ECG findings or patterns specific for LVNC at the first presentation were found

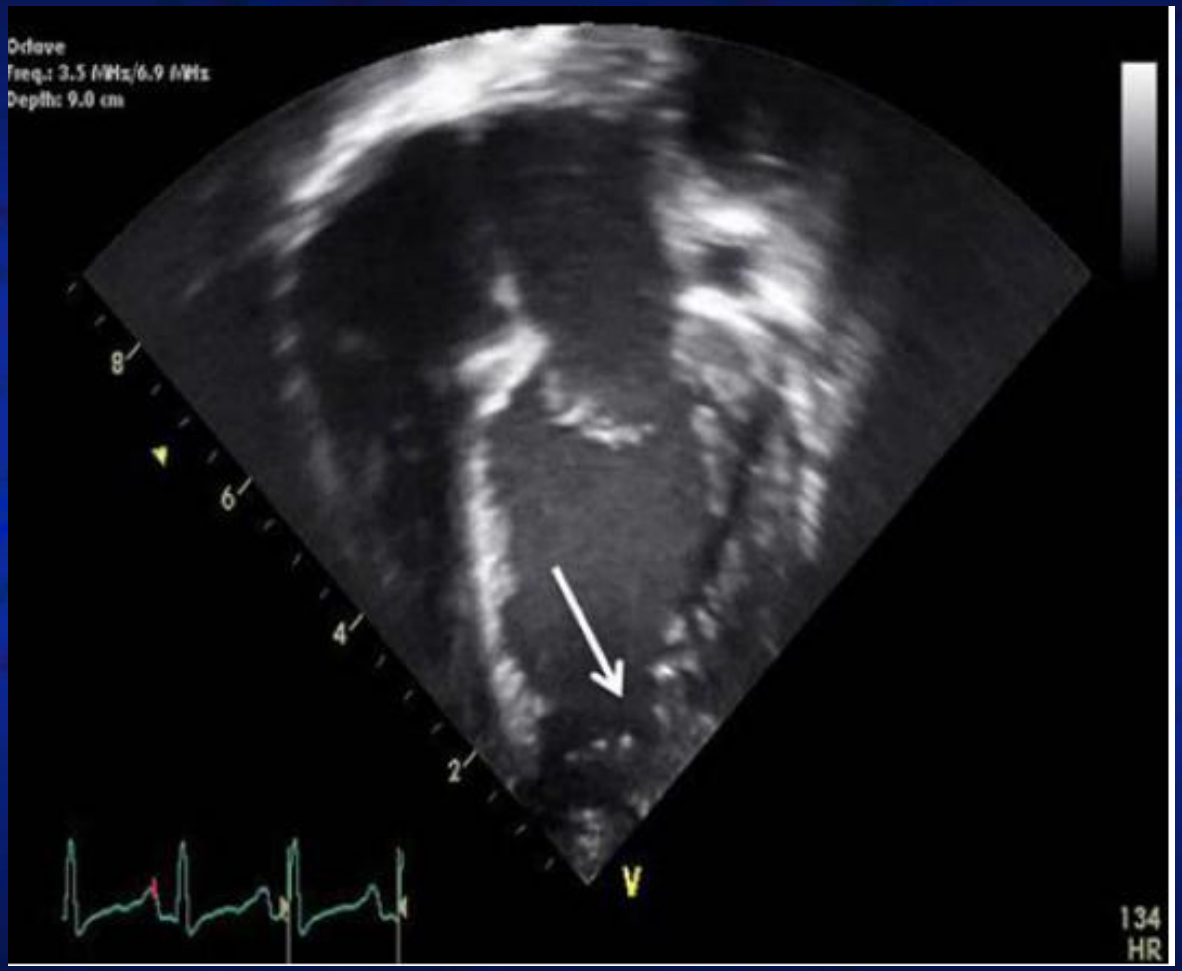
Steffel et al. *Am J Cardiol* 2009;104:984-989

Full Spectrum of Advanced Heart Failure Management

- Male infant presented at 3 days of life in cardiogenic shock
- Echocardiogram revealed LVH, severely depressed biventricular systolic function, and LVNC
- Genetic testing revealed deletion of exons 1-5 of TAZ

Hanke et al. *Pediatr Cardiol* 2012; March 17:epub ahead of print.

Left Ventricular Noncompaction in Barth Syndrome



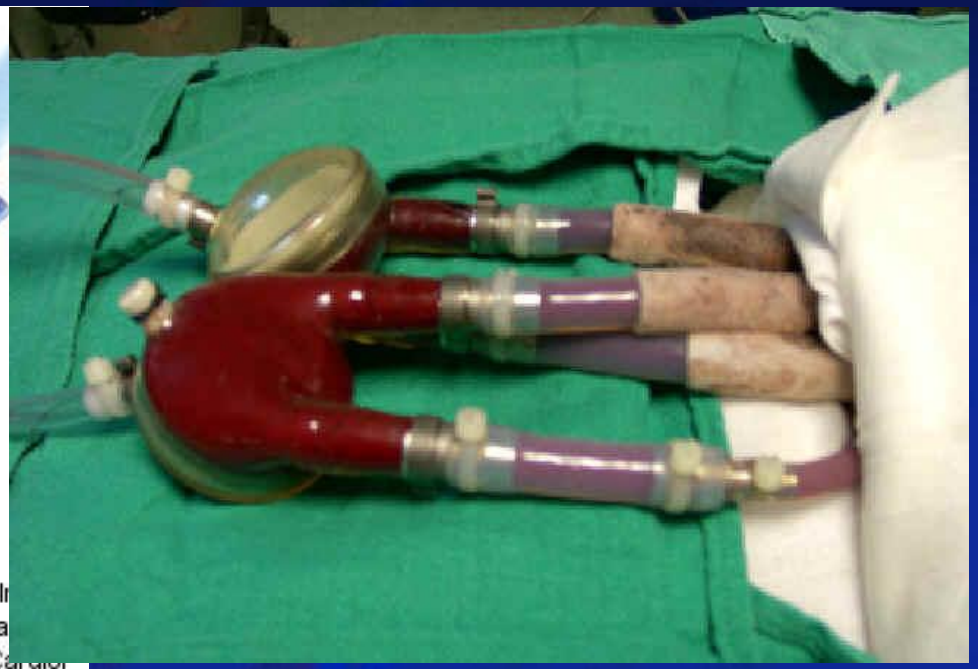
Hanke et al. *Pediatr Cardiol* 2012; March 17:epub ahead of print.

Full Spectrum of Advanced Heart Failure Management

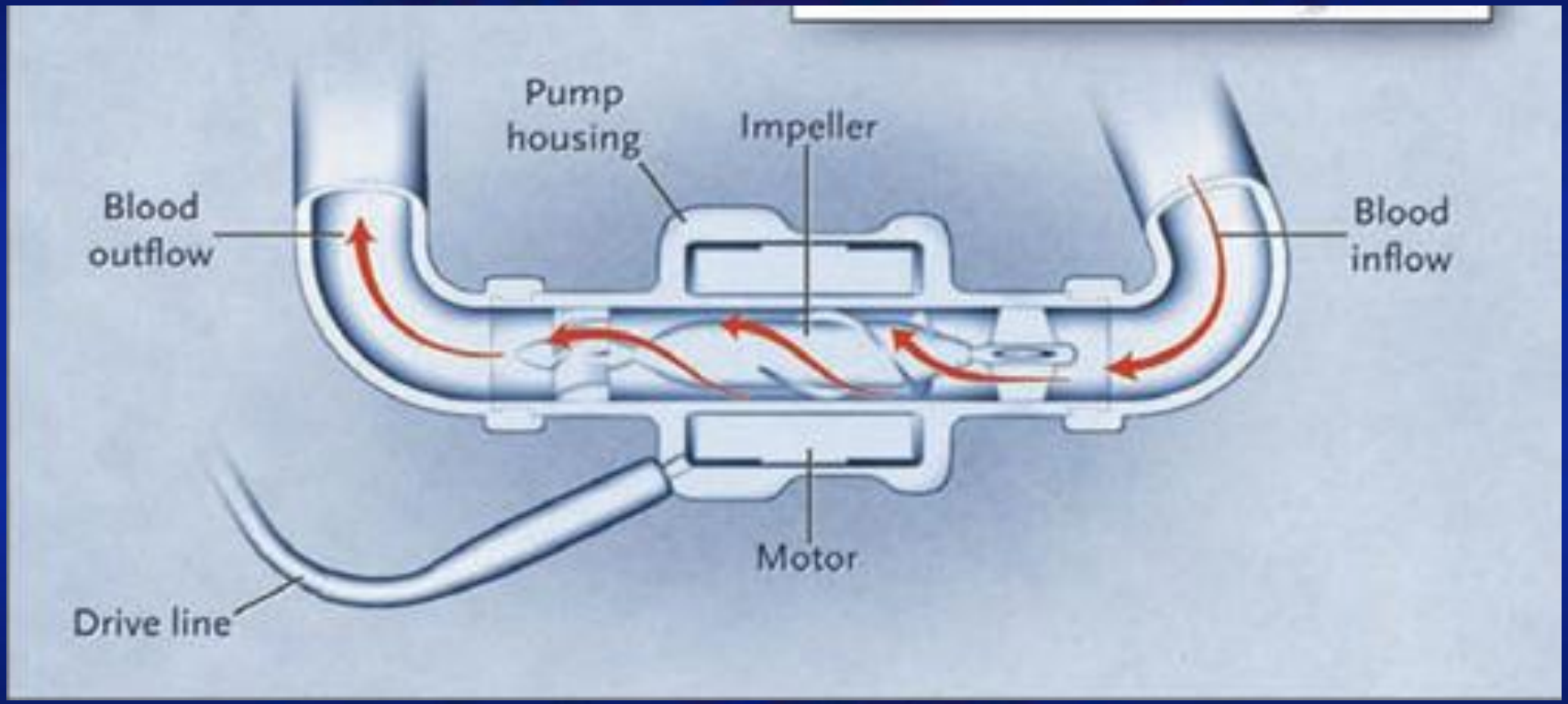
- Clinical course was progressive
- Eventually had worsening myocardial function requiring intravenous medical support
- Ultimately required advanced therapy in the form of mechanical circulatory support
  - Sent for scheduled implantation of Berlin EXCOR LVAD

Hanke et al. *Pediatr Cardiol* 2012; March 17:epub ahead of print.

Mechanical Assist Devices
Berlin Heart

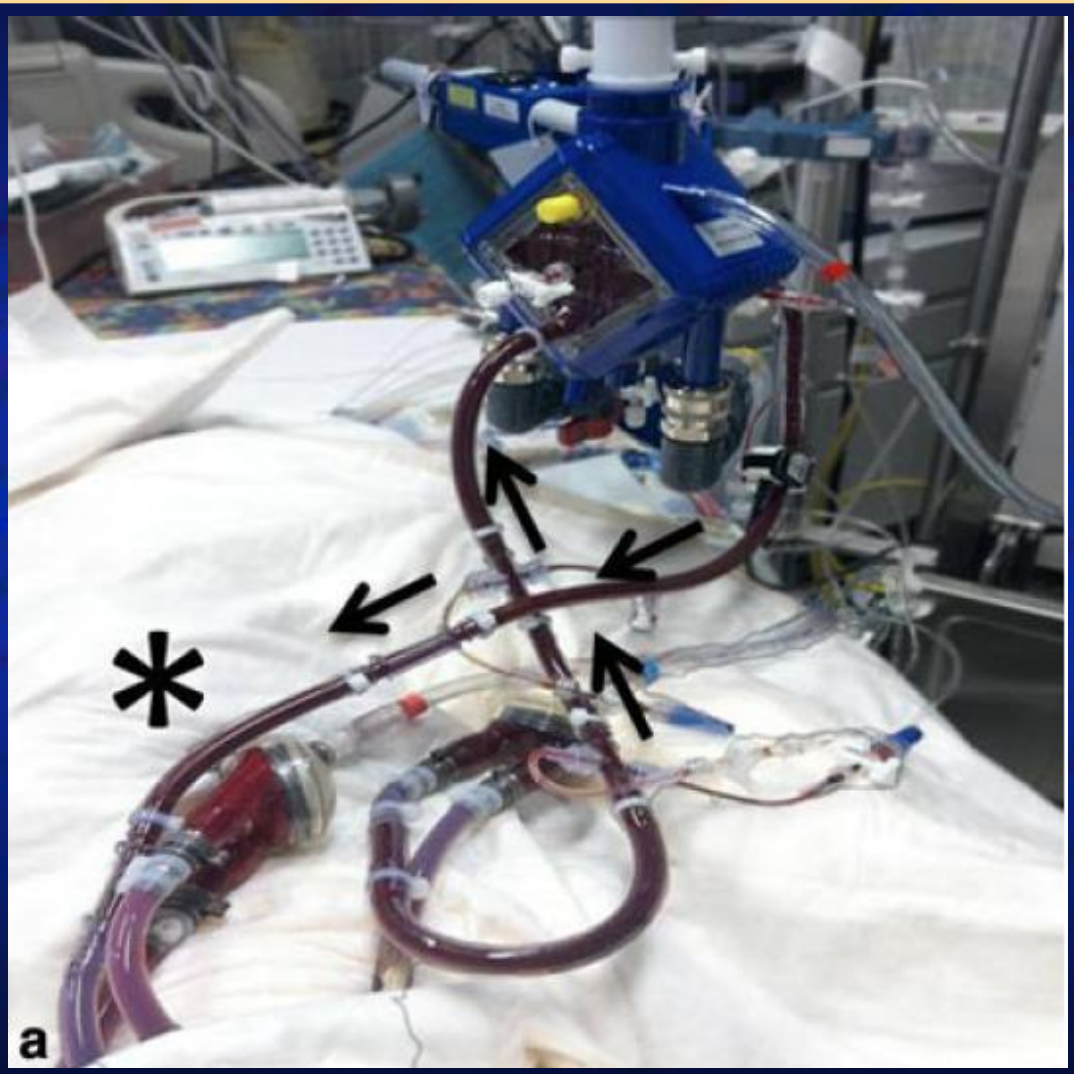


Axial-Flow Pumps



Baughman et al. *NEJM* 2007;357:846-849.

Novel Approach to Mechanical Circulatory Support



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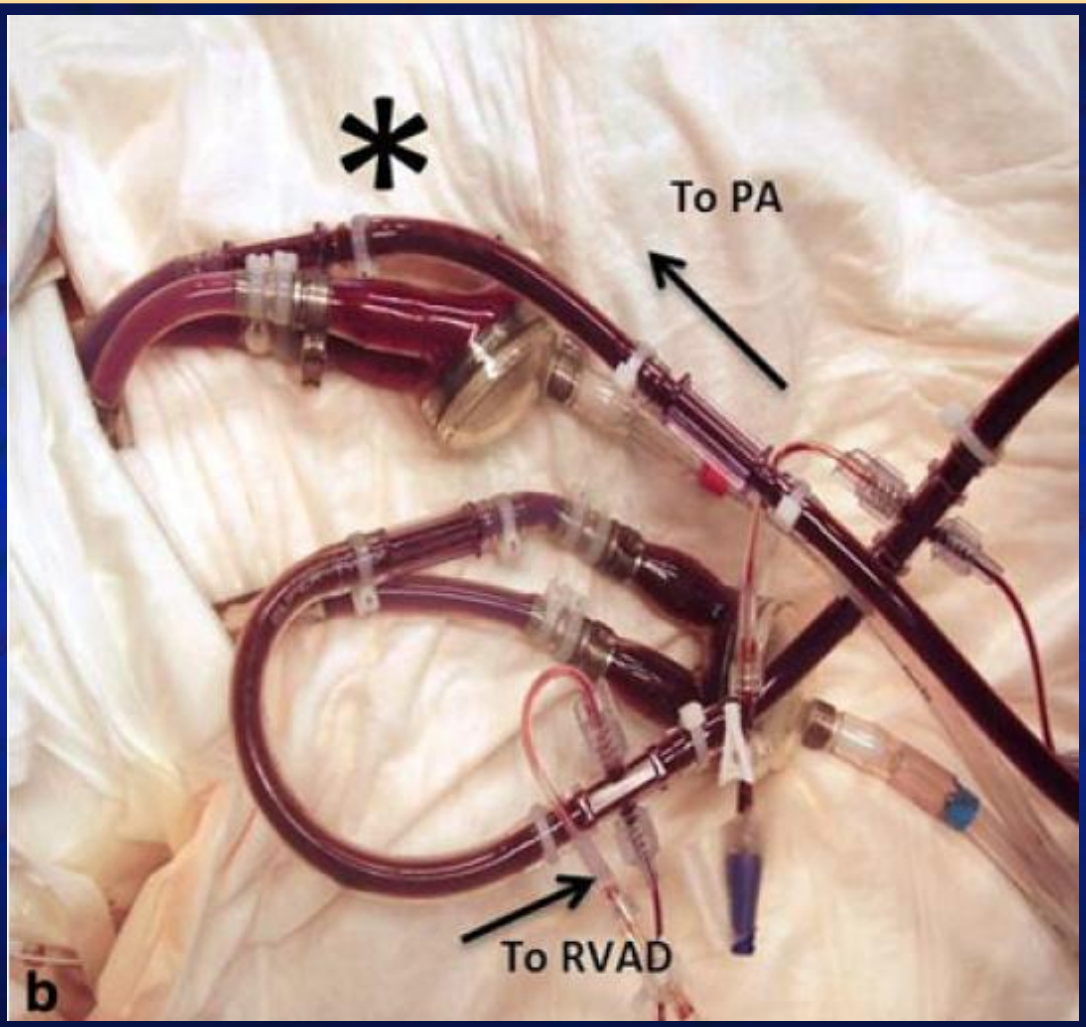
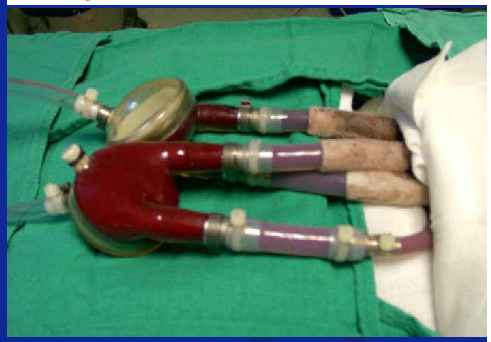
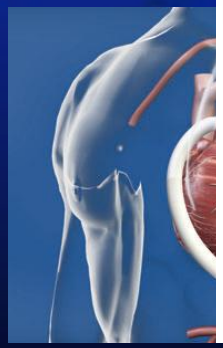
Novel Approach to Mechanical Circulatory Support

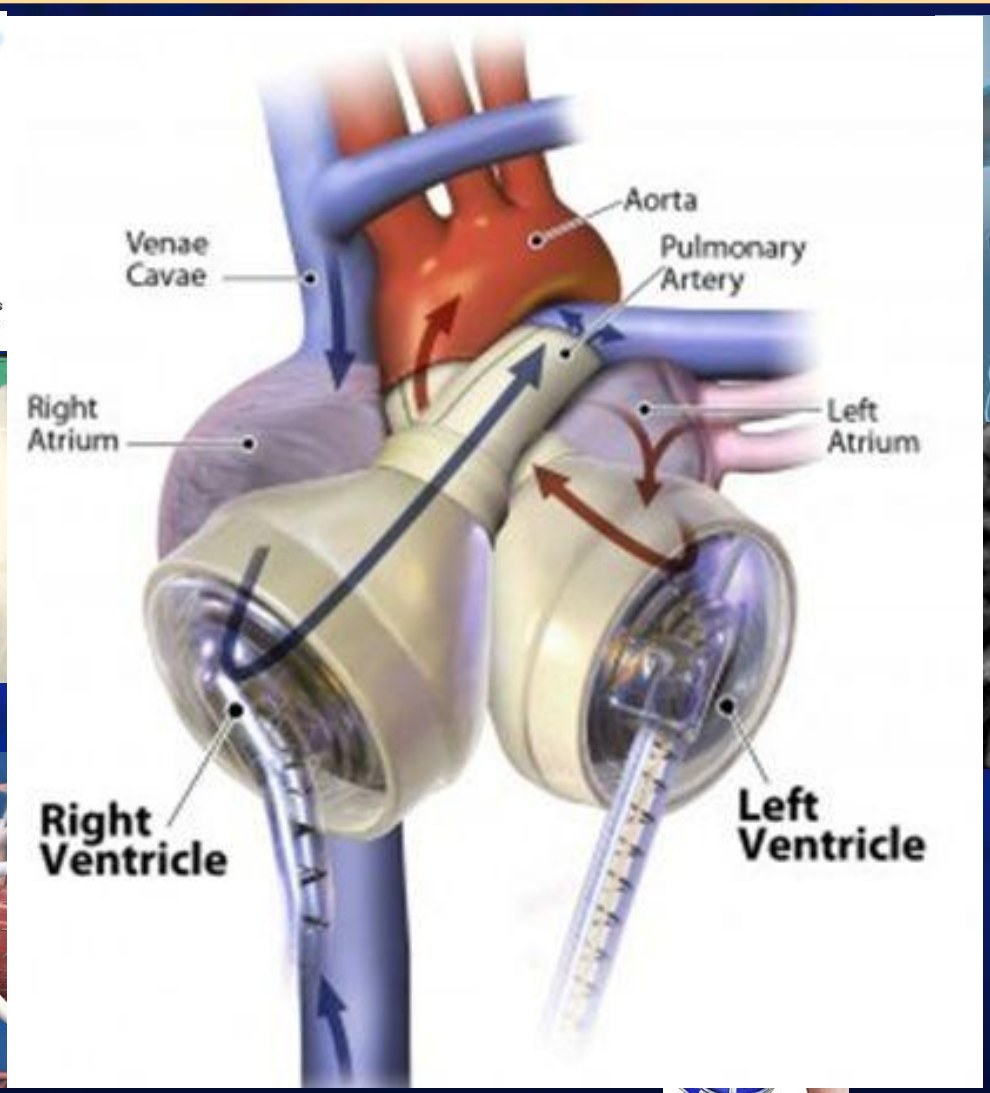


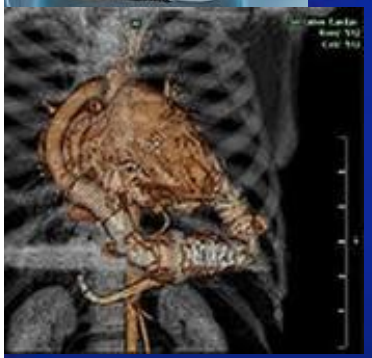
Hanke et al. *Pediatr Cardiol* 2012; March 17:epub ahead of print.

Ventricular Assist Devices
The Next Frontier









Cardiac Recommendations for LVNC

- Children with LVNC should be screened and have continued monitoring for ECG changes, arrhythmias, and cardiac dysfunction (ECG, Holter, echo yearly)
- Children with cardiac dysfunction or arrhythmias should be restricted from competitive athletics
- Children with LVNC and normal cardiac size and function without arrhythmias should not be formally restricted but must undergo rigorous prospective surveillance

Cardiac Recommendations for LVNC

- Newer imaging strategies can assist in diagnosis and treatment
- Management of myocardial dysfunction guided by associated findings
  - Function, thickness, valvular disease, scar
- Consideration of anticoagulation
- Heart thickness and function can change over time

Cardiac Recommendations for LVNC

- Advanced therapies such as mechanical circulatory support and cardiac transplant may be necessary and should be considered
- Each patient must be given individualized approach with careful consideration of comorbidities and most appropriate interventions