Heart Disease in Barth Syndrome: Diagnosis and Management

John Lynn Jefferies, MD, MPH, FAAP, FACC
Director, Cardiomyopathy and Advanced Heart Failure
Co-Director, Cardiovascular Genetics
Associate Director, Heart Institute Research Core
Associate Professor, Pediatric Cardiology and Adult Cardiovascular Diseases
The Heart Institute
Cincinnati Children’s Hospital
Cardiac Findings in Barth Syndrome

- Brief preliminary communication in 1981 by Barth et al. described new X-linked syndrome¹
  - Heart muscle
  - Skeletal muscle
  - Neutrophil leukocytes
- Further reported in 1983 with report of a large pedigree²
  - The untreated patients, all boys, died in infancy or early childhood from septicemia or cardiac decompensation

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

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

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\textsuperscript{1}
- Since that time, only limited reports have been published
- These are small, single center series in both adults and children

\textsuperscript{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
- Morphologically 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

Left Ventricular Noncompaction

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

- ZASP 12%
- DMPK 8%
- MYBPC3 3%
- LMNA 2%
- mtDNA 2%
- SCN5A 1%
- DMD 1%
- Weitere 4%
- ACTC1 20%
- MYH7 22%
- TAZ 19%

- PTPN1 1%
- ZFP9 1%
- AMPD1 1%
- PMP22 1%
- TNNT2 1%
- MMACNK 1%
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
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>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
<th>Protein</th>
<th>NOP</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondrial disorders</td>
<td>mtDNA, nDNA genes</td>
<td>Respiratory chain subunits, tRNAs</td>
<td>40</td>
<td>[23, 35, 37–39, 45, 50, 58, 107, 117]</td>
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<tr>
<td>Barth syndrome</td>
<td>G4.5, TAZ</td>
<td>Taffazin</td>
<td>30</td>
<td>[12, 20, 73, 107, 126, 148–150]</td>
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<tr>
<td>Hypertrophic/dilated CMP</td>
<td>MYH7</td>
<td>Beta-myosin heavy-chain 7</td>
<td>1, 8, 9, 12</td>
<td>[18, 57, 69, 77]</td>
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<td>Hypertrophic cardiomyopathy</td>
<td>ACTC</td>
<td>Cardiac alpha-actin</td>
<td>27</td>
<td>[56, 77, 93]</td>
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<tr>
<td>Zasopathy</td>
<td>CypherZASP/LDB3</td>
<td>LIM domain-binding protein</td>
<td>15</td>
<td>[107, 140, 148]</td>
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<td>Zasopathy/Barth syndrome</td>
<td>TAIZZASP</td>
<td>Compound heterozygote</td>
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<td>[87]</td>
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<tr>
<td>Myotonic dystrophy type 1</td>
<td>DMPK</td>
<td>Protein-kinase</td>
<td>11</td>
<td>[43, 48, 113]</td>
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<td>Dystrobrevinopathy</td>
<td>DTNA</td>
<td>α-Dystrobrevin</td>
<td>6, 1</td>
<td>[62, 148]</td>
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<td>MYBPC3</td>
<td>Myosin-binding protein C</td>
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<td>[57, 71, 145]</td>
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<td>Dystrophin</td>
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<td>Emery-Dreifuss muscular dystrophy</td>
<td>LMNA</td>
<td>Laminin</td>
<td>2 + 1 carrier</td>
<td>[56, 109]</td>
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<td>Sick-sinus, long-QT syndrome</td>
<td>SCN5A</td>
<td>Sodium channel type V-alpha</td>
<td>2 families</td>
<td>[84]</td>
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<td>Melnick Fraser syndrome</td>
<td>FLNA</td>
<td>Filamin A</td>
<td>2</td>
<td>[32, 147]</td>
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<tr>
<td>Noonan syndrome</td>
<td>PTPN11, SHP2</td>
<td>Tyrosine phosphorylase</td>
<td>2</td>
<td>[4, 96]</td>
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<td>MLS (MIDAS syndrome)</td>
<td>HCCS</td>
<td>Mt holocytchrome c-type synthase</td>
<td>2</td>
<td>[55, 75]</td>
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<td>ZNF9</td>
<td>Zink-finger protein 9</td>
<td>1</td>
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<tr>
<td>MADA deficiency</td>
<td>GAA</td>
<td>MADA</td>
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<td>[41]</td>
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<td>CMT1A</td>
<td>PMP22</td>
<td>PMP22</td>
<td>1</td>
<td>[22]</td>
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<tr>
<td>Hypertrophic/dilative CMP</td>
<td>TNNT2</td>
<td>Cardiac tropomin T</td>
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<td>[77]</td>
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<td>Beals-Hecht syndrome</td>
<td>FBN2</td>
<td>Fibrillin 2</td>
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<tr>
<td>Leopard syndrome</td>
<td>PTPN11</td>
<td>Tyrosine phosphatase SHP2</td>
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<tr>
<td>Cobalamin C-deficiency</td>
<td>MMAHC1</td>
<td>Methylmalonic aciduria cbIC type</td>
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<td>[135]</td>
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<td>Nail patella syndrome</td>
<td>LMX1B</td>
<td>Transcription factor</td>
<td>1</td>
<td>[40]</td>
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<tr>
<td>Congenital adrenal hypoplasia</td>
<td>NR0B1 (DAX–1)q</td>
<td>Dosagesensitive sex-reversal</td>
<td>1</td>
<td>[107]</td>
</tr>
</tbody>
</table>

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 disorders
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

Location of noncompacted segments also important
  - Usually located in the apical, mid-lateral, and mid-inferior LV segments

Noncompacted segments often hypercontractile

Other echocardiographic findings may include decreased LV EF, diastolic dysfunction, abnormal LV papillary muscle architecture, and LV thrombi
Left Ventricular Noncompaction
Left Ventricular Noncompaction
Myocardial Fibrosis in Left Ventricular Noncompaction
### Table 2 Univariate and multivariate regression analyses to determine the independent correlates of left ventricular ejection fraction in isolated left ventricular non-compaction

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th></th>
<th>Multivariate</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>β</td>
<td>P-value</td>
<td>β</td>
<td>P-value</td>
<td>β</td>
<td>P-value</td>
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<tr>
<td>Age</td>
<td>−0.32</td>
<td>0.038</td>
<td>−0.17</td>
<td>0.13</td>
<td>−0.14</td>
<td>0.036</td>
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<tr>
<td>Male</td>
<td>−0.13</td>
<td>0.43</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LV mass index</td>
<td>−0.40</td>
<td>0.009</td>
<td>−0.098</td>
<td>0.41</td>
<td>−0.18</td>
<td>0.12</td>
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<tr>
<td>Number of LV non-compacted segments</td>
<td>−0.012</td>
<td>0.94</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Maximal non-compacted/compacted myocardium ratio</td>
<td>−0.29</td>
<td>0.059</td>
<td>−0.10</td>
<td>0.36</td>
<td>−0.001</td>
<td>0.99</td>
</tr>
<tr>
<td>Presence of LV LGE</td>
<td>−0.73</td>
<td>&lt;0.001</td>
<td>−0.63</td>
<td>&lt;0.001</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>%LV LGE</td>
<td>−0.68</td>
<td>&lt;0.001</td>
<td>—</td>
<td>—</td>
<td>−0.62</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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.
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

Myocardial Injury

Fall in LV Performance

Activation of RAAS and SNS
(endothelin, AVP, cytokines)

Myocardial Toxicity

Change in Gene Expression

Peripheral Vasoconstriction

Sodium/Water Retention

Remodeling and Progressive Worsening of LV Function

Morbidity and Mortality

HF Symptoms

Pharmacologies in Heart Failure Management

- ANP
- BNP
- Prostacyclin
- Bradykinin
- NO

- Endothelin
- Aldosterone
- Angiotensin II
- Vasopressin
- Norepinephrine

- Vasoconstriction
- Vasodilation
Hemodynamic Profile Assessment

Congestion at Rest

<table>
<thead>
<tr>
<th>Low Perfusion at Rest</th>
<th>No</th>
<th>Warm &amp; Dry</th>
<th>Warm &amp; Wet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Cold &amp; Dry</td>
<td>Cold &amp; Wet</td>
</tr>
</tbody>
</table>

Signs/symptoms of congestion
- Orthopnea/PND
- JVD
- Ascites
- Edema
- Rales (rare in HF)

Possible evidence of low perfusion
- Narrow pulse pressure
- Cool extremities
- Sleepy/obtunded
- Hypotension with ACE inhibitor
- Low serum sodium
- 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
- ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists, nesiritide

Peripheral Arteries
- ACE inhibitors, angiotensin receptor blockers, vasodilators, alpha blockade, nesiritide, exercise

Ventricular Remodeling

Ventricular Remodeling After Acute Infarction

Initial infarct
Expansion of infarct (hours to days)
Global remodeling (days to months)

Ventricular Remodeling in Diastolic and Systolic HF

Normal heart
Hypertrophied heart (diastolic HF)
Dilated heart (systolic HF)

Pharmacologies in Heart Failure Management

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

Neurohormonal
- ↓ aldosterone
- ↓ endothelin
- ↓ norepinephrine

Renal
- ↑ sodium and water excretion

Cardiac
- Lusitropic
- Antifibrotic
- Antiremodeling

Clemens LE et al. J Pharmacol Exp Ther. 1998;287:67
At Risk for Heart Failure

**STAGE A**
At high risk for HF but without structural heart disease or symptoms of HF.
- Patients with:
  - Hypertension
  - Atherosclerotic disease
  - Diabetes
  - Obesity
  - Metabolic syndrome
  - Using cardiotoxins
  - With FHECM

**THERAPY**
- **GOALS**
  - Treat hypertension
  - Encourage smoking cessation
  - Treat lipid disorders
  - Encourage regular exercise
  - Discourage alcohol intake, illicit drug use
  - Control metabolic syndrome
- **DRUGS**
  - ACEI or ARB in appropriate patients (see text)
  - Beta-blockers in appropriate patients (see text)
  - Devices in selected patients
  - Implantable defibrillators

**STAGE B**
Structural heart disease but without signs or symptoms of HF.
- Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

**THERAPY**
- **GOALS**
  - All measures under Stage A
  - Dietary salt restriction
- **DRUGS**
  - ACEI or ARB in appropriate patients (see text)
  - Beta-blockers in appropriate patients (see text)
  - Diuretics for fluid retention
  - ACEI
  - Beta-blockers
  - Aldosterone antagonist
  - ARBs
  - Digitalis
  - Hydralazine/nitrates
  - Biventricular pacing
  - Implantable defibrillators

Development of symptoms of HF

**STAGE C**
Structural heart disease with prior or current symptoms of HF.
- Patients with:
  - Known structural heart disease
  - Shortness of breath and fatigue
  - Reduced exercise tolerance

**THERAPY**
- **GOALS**
  - All measures under Stages A and B
  - Dietary salt restriction
  - Diuretics for fluid retention
  - ACEI
  - Beta-blockers
  - Aldosterone antagonist
  - ARBs
  - Digitalis
  - Hydralazine/nitrates
  - Biventricular pacing
  - Implantable defibrillators

Heart Failure

**STAGE D**
Refractory HF requiring specialized interventions.
- Patients who have marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)

**THERAPY**
- **GOALS**
  - Appropriate measures under Stages A, B, C
  - Decision re: appropriate level of care
- **OPTIONS**
  - Compassionate end-of-life care/hospice
  - Extraordinary measures
    - Heart transplant
    - Chronic inotropes
    - Permanent mechanical support
    - Experimental surgery or drugs

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

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

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. *Study results from current evaluation.

### TABLE 4: Characteristics of Those With and Without Documented VA

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

LVEDV indicates LV end-diastolic volume.

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.

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
Left Ventricular Noncompaction in Barth Syndrome

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

Mechanical Assist Devices
Berlin Heart
Axial-Flow Pumps

Novel Approach to Mechanical Circulatory Support

Novel Approach to Mechanical Circulatory Support

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.