Biomarkers, Course, and Surrogate Endpoints in Pediatric Cardiomyopathy

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Preventive Strategies: Progressively less effective as the number increases. Primary prevention is possible at number 1. Secondary prevention is possible at numbers 2, 3, and 4.

Treatment Strategies: Greater impact with higher numbers but longer effects with lower numbers. Treatment is possible at numbers 4 and 5 to reduce sequelae.

Biomarkers/Surrogate Endpoints: Potentially more useful with lower numbers for alteration of course with interventions. Potentially more useful with higher numbers for decisions about transplantation.
Criteria for Biomarkers Concerning Cardiac Status

• Association of biomarkers with structural parameters

• Variation of biomarkers parallel to variation in other parameters reflecting cardiac disease

• Good specificity and sensitivity

• Measurement of the biomarker should be
  • Accurate
  • Reproducible
  • Cheap
  • Easy accessible for clinicians

• Addition of new information next to existing tests

• Improvement of patient management in clinics
Initial incidence & mortality peak in early childhood; then all measures increase up to at least age 80 years

Wilkinson, Lipshultz, et al., Prog Pediatric Cardiol 2011
NHLBI/CCF PCMR: Functional Status in Pediatric Cardiomyopathy

CHQ Parent Report Domain Z-scores (N=303)

* p<0.05

PF = Physical Functioning
RE = Role/Social Limits - Emotional
RP = Role/Social Limits - Physical
PAIN = Bodily Pain
BEH = Behavior
MH = Mental Health
SE = Self-Esteem
GH = General Health Perception
PE = Parental Impact - Emotional
PT = Parental Impact - Time

Sleeper, Lipshultz, et al., Circulation 2004; 5th World Cong of Paed Card and Card Surg 2009
PCMR Organizational Structure

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**Participating Clinical Centers**
≈ 100 in the U.S. & Canada
PCMR Overview

- 10 different inclusion criteria—based on echocardiographic measurements and patterns

- 16 different exclusion criteria—due to age, toxic exposures, any diseases/syndromes/defects known to cause cardiomyopathies, etc.

- Enrolled a total of 3,549 subjects across 98 clinical centers

- Follow-up per patient is mean 3.4±3.6 years (median= 2 yrs, range= 0-20 yrs)

- The grand total of follow-up time in the registry is 14,149 years, representing over 36,265 data collection forms completed
Primary cause of 61 cases of HCM and 77 cases of DCM diagnosed in 1996, 1997, 1998, and 1999. The primary causes of the remaining cases were unknown at diagnosis.

Lipshultz et al., N Engl J Med 2003
The Cause of DCM is an Independent Predictor of the Outcome of Death

Towbin, Lipshultz, et al., JAMA 2006
Poorer Outcomes in Children with Idiopathic DCM Compared to Myocarditis

Biopsy Positive

Clinically-Diagnosed Myocarditis (CDM) Group

Idiopathic Dilated Cardiomyopathy Group

Foerster, Lipshultz, et al., Circ Heart Fail 2010
Competing Risks in Pediatric DCM

• Donor hearts for transplantation should be matched to children with the highest mortality risk.

• For idiopathic DCM, increased LVEDD was associated with increased transplantation risk but not mortality.

• Short stature was significantly related to death but not transplantation; this might present an opportunity to improve the selection algorithm.

Alvarez, Lipshultz, et al., Circulation 2011
Competing Risk Estimates of Death, Transplant, and Survival for Children with Idiopathic DCM

n = 1192

Alive, No Tx

Cardiac Tx

Death, Pre-Tx

At Risk: 1192 616 453 359 272 223 162 110 82 59 44 28 18 13 6 4 1

Alvarez, Lipshultz, et al., Circulation 2011
Newborn boy with CHF, HCM (thick LV walls), and DCM (reduced LV FS and LV dilation).

Father has clinically unsuspected HCM on screening.

Successful inpatient response to anticongestive therapy.

D/C to home on Day 10.

Mild non-progressive CHF on anticongestive therapy at home with slow weight gain.

URI symptoms at 2 months of age.

Sudden death at home two days after onset of URI symptoms.
Time to Death from Diagnosis in Pure HCM Cases by Age at Diagnosis

Log-rank p<0.001

<1 year (n=328)
1 to <6 years (n=114)
6 to <12 years (n=169)
12 to <18 years (n=244)
Death or Transplant-Free Survival by HCM Subgroup

Lipshultz et al., Circulation 2008
Death or Transplant-Free Survival by HCM Subgroup

Lipshultz et al., Circulation 2008
### Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>CHF</th>
<th>Female</th>
<th>CHF</th>
<th>↓ Age</th>
<th>CHF</th>
<th>↓ Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>(by etiology)</td>
<td>↓ BSA</td>
<td>↓ LV FS</td>
<td>Black</td>
<td>Black</td>
<td>↓ Age</td>
<td>+ Fam Hx of Heart Dz</td>
</tr>
</tbody>
</table>

### NHLBI PCMR: Effect of Risk Factors Combinations on Outcome of Children with Hypertrophic Cardiomyopathy

S. Lipshultz et al., Circulation 2008
Multimarker strategy to improve diagnostic performance as illustrated by receiver operating characteristic curves

G. de Couto, et al., Nature Reviews Cardiology 2010
Mechanism of Doxorubicin Cardiotoxicity

Free Radicals
- Quinone-Semiquinone Recycling
- Dox-Iron Complex
↓ Antioxidant enzymes
↓ Thiol Groups
↑ Oxidative stress

Subcellular Changes

Cardiomyopathy
Congestive heart failure

Doxorubicin

DNA Intercalation
DNA-Topo II – Dox Complex

Impairs DNA replication

Anti-tumor Effects
NCI-POG >6,000 Survivors: Relative Risk of Early Cardiotoxicity as a Function of the Cumulative Number of Risk Factors Present

Risk Factors:
1) Cumulative dose of anthracycline ≥550 mg/m² (RR 5.2)
2) Maximal dose of 50 mg/m² (RR 2.8)
3) Female sex (RR 1.9)
4) Black race (RR 1.7)
5) Trisomy 21 (RR 3.4)
6) Exposure to amsacrine (RR 2.6)

NCI DFCI Childhood ALL Cohort: LV Contractility (Health of Heart Muscle Cells)

Long-Term Follow-Up is Essential to See if an Early Doxorubicin “Hit” Results in Late Cardiotoxicity Associated with Progressive Cardiovascular Morbidity and Mortality

- >12 million US cancer survivors
- >50% anthracycline exposed
- **20-year Survivors**
  - >8-fold increased CV mortality
  - >4-fold increased sudden death
  - 10-fold increased atherosclerosis
  - 5-fold increased myocardial infarction
  - ↑ CV mortality from 15 to 25 yrs after Dox
- **30-year Survivors**
  - >3-fold increased anthracycline – associated CV mortality
  - 15-fold higher rates of heart failure
  - 10-fold higher rate of other CV disease
  - 9-fold higher rate of stroke

Dashed lines are the upper and lower 95% CI from the predicted mean ± 2 SE of the mean.

Lipshultz et al., JCO 2010
Tukenova et al., JCO 2010
Armstrong et al., JCO 2009
Mertens et al., JCO 2001
Moller et al., JCO 2001
Mulrooney, BMJ 2009
Lipshultz et al., NEJM 2004
Lipshultz et al., JCO 2005
Lipshultz et al., NEJM 1991
Lipshultz et al., NEJM 1995
Oeffinger et al., NEJM 2006
4,122 5-yr Childhood Cancer Survivors with 86,453 pt-yrs of Follow-up from France and UK, 27-year average F/U

Tukenova et al., JCO 2010


Tukenova et al., JCO 2010
Estimates of (A) cumulative cardiovascular and (B) cardiac mortality in the French-British cohort and expected in the general population in France and Great Britain

Tuksenova et al., JCO 2010
NCI DFCI Cardiotoxicity 8 Years After Anthracycline Treatment of Childhood Cancer

LV Fractional Shortening (Heart Function)

Contractility (Health of Heart Muscle)

Female Sex

Cumul. Dose

Age at Diagnosis

Years Since Treatment

Individual Dose

Afterload (Stress on Wall of the Heart)

LV Wall Thickness

LV Dimension

NCI DFCI: Gender Difference

Probability of late decreased contractility 8 years after childhood cancer

Lipshultz et al., NEJM 1995
NCI DFCI: Effect of enalapril in delaying progression of depressed LVFS in long-term survivors of childhood cancer – 6-10 yrs of benefit

Lipshultz, Lipsitz, Sallan, et al., JCO 2002
Conclusion: continuous infusion is not cardioprotective at a mean follow-up of 8.2 yrs post-randomization compared to bolus infusion at a mean follow-up of 8.3 yrs.

Differences between Pre-treatment and Post-treatment Echo Z-scores

<table>
<thead>
<tr>
<th>LV Characteristics</th>
<th>Bolus Infusion Mean follow-up yrs</th>
<th>Continuous Infusion Mean follow-up yrs</th>
<th>P§</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median z-score difference</td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Diastolic Dimension</td>
<td>29</td>
<td>0.21</td>
<td>0.19</td>
<td>39</td>
</tr>
<tr>
<td>Wall Thickness</td>
<td>28</td>
<td>-1.55</td>
<td>0.002</td>
<td>37</td>
</tr>
<tr>
<td>Systolic Dimension</td>
<td>29</td>
<td>1.45</td>
<td>&lt;.001</td>
<td>39</td>
</tr>
<tr>
<td>Fractional Shortening</td>
<td>28</td>
<td>-2.72</td>
<td>&lt;.001</td>
<td>37</td>
</tr>
<tr>
<td>Mass</td>
<td>19</td>
<td>-1.37</td>
<td>&lt;.001</td>
<td>23</td>
</tr>
</tbody>
</table>

§Test that the median z score is equal to 0; †Test that the median z scores are equal for treatments

Lipshultz et al., JCO 2010
Light micrographs showing protective effect of dexrazoxane against DOX-induced cardiac lesions. Toluidine stain, x 400. Myocardial vacuolization and myofibrillar loss are less severe in rats treated with dexrazoxane/DOX 12 mg/kg (C) and dexrazoxane/DOX 7 mg/kg (D) than in rats treated with 12 mg/kg DOX (A) or 7 mg/kg DOX (B) alone.

Herman, Lipshultz, et al., JCO 1999
Myocardial genes

DOX induced changes in myocardial genes occur early and are abrogated by DEX.

Thompson, Lipshultz, et al., Cancer Chemother Pharmacol 2010
Many mitochondrial genes are down-regulated at 9 inj, reflecting extensive damage to this organelle by DOX.
Preventive Strategies: Progressively less effective as the number increases. 
Primary prevention is possible at number 1. 
Secondary prevention is possible at numbers 2, 3, and 4.

Treatment Strategies: Greater impact with higher numbers but longer effects with lower numbers. 
Treatment is possible at numbers 4 and 5 to reduce sequelae.

Biomarkers/Surrogate Endpoints: 
Potentially more useful with lower numbers for alteration of course with interventions. 
Potentially more useful with higher numbers for decisions about transplantation.

Lipshultz et al., Prog Pediatric Cardiol 2000
Potential biomarkers for heart failure*

**Neurohormones**
- Adiponectin
- Aldosterone
- Endothelin
- Norepinephrine
- Renin
- Resistin

**Inflammation**
- Fas (APO-1)
- Interleukin-1
- Interleukin-2
- Interleukin-6
- Interleukin-8
- Interleukin-18
- Osteoprotegerin
- Tumor necrosis factor

**Myocyte injury**
- Creatinine kinase MB fraction
- Heart-type fatty-acid protein
- Myosin light chain kinase

**Oxidative stress**
- Isoprostanes
- Myeloperoxidase
- Oxidized LDL
- Plasma malondialdehyde
- Serum uric acid
- Urinary biopyrrins

**Matrix remodeling**
- Matrix metalloproteinases
- Plasma procollagen type III
- Propeptide procollagen type I
- Tissue inhibitors of metalloproteinases

*Categorized according to putative function.*
Validation of cTnT as a Pediatric Myocardial Injury Marker

1. Can cTnT elevations, with developmentally regulated isoform diversity, be measured in children of all ages? Yes.

2. Do cTnT levels correlate with known severity of myocardial injury in children? (A positive control group). Yes.

3. Is cTnT absent in children without myocardial injury? (A negative control group). Yes.

4. Low cTnT levels may be important in children. The analytic validity/sensitivity of the cTnT assay at low levels was established.

5. Is cTnT elevated in children receiving doxorubicin? Low level cTnT elevations noted.

6. What is the time course of cTnT elevations in children receiving doxorubicin? A serial time course study was conducted.

7. Do cTnT elevations in children receiving doxorubicin relate to late echo abnormalities? A correlative study with 1 year of follow-up was conducted and showed significant correlations.

8. What is the specificity of doxorubicin associated cTnT elevations for myocardiocyte injury? Immunohistochemistry using the cTnT antibody from the assay demonstrated cTnT leaving doxorubicin injured rat myocardiocytes.

9. Does a doxorubicin dose-cTnT elevation relation exist? A dose response effect was demonstrated in rat heart.

10. Does a doxorubicin histologic injury score (a gold standard)-cTnT elevation relation exist? Blinded histologic scoring and cTnT measurement correlated significantly in rat heart.

11. Will agents known to be cardioprotective against doxorubicin cardiotoxicity result in reduced cTnT elevation? Yes in the rat heart. We remain blinded in active randomized clinical trials in children.

12. Will the magnitude or timing of cTnT elevations correlate with late echo abnormalities, symptomatic heart disease or cardiac mortality in doxorubicin-treated long-term survivors of childhood cancer? Such studies are in progress.
**NCI DFCI 9501 cohort: myocardial injury**

Day of doxorubicin treatment
- **Doxorubicin**
- **Dexrazoxane/Doxorubicin**

Lipshultz et al., NEJM 2004
NCI DFCI ALL 9501 cohort: Left ventricular end systolic dimension in doxorubicin-treated children, by gender

*p-value ≤ 0.05 vs Dexrazoxane +

Girls

Boys

Dexrazoxane -

Dexrazoxane +

Dexrazoxane -

Dexrazoxane +

Lipshultz et al., Lancet Oncol 2010
NCI DFCI ALL 9501 cohort: Left ventricular fractional shortening in doxorubicin-treated children, by gender

* p-value ≤ 0.05 vs Dexrazoxane +

Girls

Boys

Mean Z-Score

Mean Z-Score

Time post treatment (years)

Time post treatment (years)

Dexrazoxane +

Dexrazoxane -

Normal

Normal

Lipshultz et al., Lancet Oncol 2010
NCI DFCI ALL 9501 cohort: Left ventricular end diastolic posterior wall thickness in doxorubicin-treated children, by gender

Girls

*\( p\)-value ≤ 0.05 vs Dexrazoxane +

Boys

\[ \text{Mean Z-Score} \]

\[ \text{Time post treatment (years)} \]

Lipshultz et al., Lancet Oncol 2010
Ventricular Remodeling in Systolic and Diastolic Heart Failure as a Function of Time
NCI DFCI ALL 9501 cohort: Left ventricular thickness to dimension ratio in doxorubicin-treated children, by gender

*p-value ≤ 0.05 vs Dexrazoxane +

Girls

Boys

Dexrazoxane +

Dexrazoxane -

Normal

Mean Z-Score

Time post treatment (years)

Lipshultz et al., Lancet Oncol 2010
NCI DFCI: Myocardial injury (measurable serum cardiac troponin T, \( \geq 0.01 \text{ng/ml} \)) during doxorubicin therapy is significantly related to lower left ventricular mass, wall thickness, and remodeling by echo more than 5 years later.

<table>
<thead>
<tr>
<th>Fractional Shortening</th>
<th>Mass</th>
<th>Posterior Wall Thickness</th>
<th>Thickness: Dimension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury</td>
<td>Injury</td>
<td>Injury</td>
<td>Injury</td>
</tr>
<tr>
<td>No Injury</td>
<td>No Injury</td>
<td>No Injury</td>
<td>No Injury</td>
</tr>
<tr>
<td>Z-Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.4</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>-1.2</td>
<td>**</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>-1</td>
<td></td>
<td>***</td>
<td>**</td>
</tr>
<tr>
<td>-0.8</td>
<td></td>
<td>***</td>
<td>**</td>
</tr>
<tr>
<td>-0.6</td>
<td></td>
<td>***</td>
<td>**</td>
</tr>
<tr>
<td>-0.4</td>
<td></td>
<td>***</td>
<td>**</td>
</tr>
<tr>
<td>-0.2</td>
<td></td>
<td>***</td>
<td>**</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P=0.47</td>
<td>P=0.01</td>
<td>P=0.005</td>
<td>P=0.004</td>
</tr>
</tbody>
</table>

Myocardial injury vs No Injury

Lipshultz, JCO 2009

\( * p \leq 0.05 \text{ vs } 0 \)

\( ** p \leq 0.001 \text{ vs } 0 \)
NCI DFCI cohort: proportion NT-proBNP abnormal during therapy - cardiomyopathy neurohormone

**Post Dox Tx**

*\(p\)-value ≤ 0.05
**\(p\)-value ≤ 0.001

<table>
<thead>
<tr>
<th>Time point</th>
<th>.00-.25</th>
<th>.25-.50</th>
<th>.50-end tx</th>
<th>end tx-.12 post (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dox Only</td>
<td>631/68</td>
<td>386/59</td>
<td>73/29</td>
<td>30/23</td>
</tr>
<tr>
<td>Dox/Dex</td>
<td>692/74</td>
<td>432/65</td>
<td>60/31</td>
<td>27/18</td>
</tr>
</tbody>
</table>

Lipshultz et al., Circ 2007

**Overall test for dex effect**

- Period
  - During tx: <0.001
  - After tx: 0.2405

**Age >1 yr abnormal ≥ 100 pg/ml**
**Age < 1yr abnormal ≥ 150 pg/ml**
NCI-DFCI: Abnormal NT-proBNP (Age ≥ 100 pg/mL; Age < 1 yr abnormal ≥ 150 pg/ml) during the first 90 days of doxorubicin therapy is not significantly related to lower left ventricular mass, wall thickness, and remodeling but is related to thickness to dimension ratio by echo 4 years later.

<table>
<thead>
<tr>
<th>Fractional Shortening</th>
<th>Mass</th>
<th>Posterior Wall Thickness</th>
<th>Thickness: Dimension</th>
</tr>
</thead>
</table>

**Mean Z-Score**

<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Normal</th>
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<tbody>
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<td></td>
</tr>
</tbody>
</table>

* p ≤ 0.05 vs 0. ** p ≤ 0.001 vs 0.

Lipshultz, JCO 2009
Hemochromatosis Gene Mutations

Miranda et al. found that the heterozygous HFE knockout mice (HFE+/−) showed mitochondrial degradation and increased mortality as compared to wild-type mice after chronic doxorubicin exposure.
NCI DFCI: Associations between HFE mutations and myocardial injury during DOX therapy

C282Y mutations were significantly associated with 8-fold increased risk of elevations in cTnT

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>OR*</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H63D</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormal cTnT</td>
<td>0.39</td>
<td>0.05-3.30</td>
<td>0.39</td>
</tr>
<tr>
<td>abnormal NT-proBNP</td>
<td>0.59</td>
<td>0.17-2.09</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>C282Y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abnormal cTnT</td>
<td>8.79</td>
<td>1.08-71.46</td>
<td>0.04</td>
</tr>
<tr>
<td>abnormal NT-proBNP</td>
<td>1.49</td>
<td>0.31-7.19</td>
<td>0.62</td>
</tr>
</tbody>
</table>

OR: Odds Ratio
Abnormal cTnT: >0.01ng/ml;
Abnormal NT-proBNP: ≥150 pg/mL in infants younger than 1 year or ≥100 pg/mL in children aged 1 year or older

* Adjusted for dexrazoxane
Carriers showed more dilated left ventricles, LV dysfunction, thinner posterior wall thickness, and reduced LV mass than normal.
Red lines highlight HCM mutations, many of which also cause DCM (green hexagons). Interactions with known hypertrophy pathways (Kegg, Mouse phenotypes) can be constructed. Pathway interactions for cardiomyocyte metabolism, cardiac/z-disk structure, extracellular matrix remodeling, adhesion, and fibrosis will be mapped using this approach.
NCI DFCI: Candidate serum biomarkers of doxorubicin-induced cardiotoxicity in pediatric acute lymphoblastic leukemia assessed by nanoparticle-capture mass spectrometry

Blinded SELDI-TOF MS Profile Testing Results

<table>
<thead>
<tr>
<th>Troponin Status</th>
<th>N</th>
<th>Classification by Fingerprint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>High TnT</td>
</tr>
<tr>
<td>High TnT</td>
<td>14</td>
<td>13 (93%)</td>
</tr>
<tr>
<td>Low TnT</td>
<td>38</td>
<td>4 (11%)</td>
</tr>
</tbody>
</table>
NCI DFCI: Nanoparticle-MS is able to uncover these candidate protein biomarkers previously implicated in cardiac dysfunction, remodeling, fibrosis and hypertrophy.

- **Inflammation/Acute Phase Reactants**
  - Serum amyloid A1 isoform 1
  - Serum C-reactive protein pentraxin related

- **Innate Immunomodulation Against Inflammation**
  - Serum A gamma globulin

- **Cytokine-mediated Inflammation**
  - Myocardial Contractility Depressant – Cardiomyopathy
    - Serum HIV type 1 enhancer b

- **Myocardial Injury**
  - Serum cardiac muscle actin proprotein

Petricoin, Lipshultz, JCO 2010
NCI DFCI: Significant Fold Increases in Serum Proteins from cTnT+ versus cTnT- Doxorubicin-Treated Children with ALL

<table>
<thead>
<tr>
<th>Protein</th>
<th>Fold Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Amyloid A1.isoform1</td>
<td>22.8</td>
</tr>
<tr>
<td>Serum C-reactive Protein</td>
<td>12.9</td>
</tr>
<tr>
<td>Serum A-Gamma Globulin</td>
<td>38.1</td>
</tr>
<tr>
<td>Serum HIV-type1 Enhancer-b</td>
<td>10.3</td>
</tr>
<tr>
<td>Serum Cardiac Muscle Actin Proprotein</td>
<td>4.8</td>
</tr>
</tbody>
</table>
Candidate serum biomarkers may increase the predictive value of conventional markers for earlier detection of cardiac damage.

Identifying heart derived tissue proteins associated with myocardial injury would have profound implications on the earlier detection and clinical monitoring for doxorubicin cardiotoxicity before irreversible damage and loss of cardiomyocytes occurs.

Additional studies evaluating the efficacy of nanoparticle-capture mass spectrometry are needed.
LV Wall Thickness identified a population at risk 18-24 months before death and may be useful as an independent short-term predictor of mortality.

NHLBI P²C² HIV Study: Longitudinal Change in LV Wall Thickness Z-score for Survivors and Non-survivors (64 dead, 129 alive)

Lipshultz et al., Circulation 2000
Mildly increased LV Mass is a risk marker for early HIV mortality even though it is still inadequate for LV dimension.

NHLBI P²C² study: Cumulative Mortality Among 113 HIV-infected Children by Degree of LV Mass Abnormality

- Mildly Increased LV Mass: 76% mortality
- 22% mortality
LV Fractional Shortening showed abnormalities for up to 3 years before death and may be useful as an independent predictor of mortality.

NHLBI P²C² HIV Study: Longitudinal Change in Fractional Shortening Z-score for Survivors and Non-survivors (64 dead, 129 alive)
A 2 SD fall in LV FS from 34% to 30% in a 10-year old, levels that most cardiologists would not consider to be action values, is associated with an increase in 5-year mortality from 15% to 55%.

NHLBI P²C² study: cumulative mortality among HIV-infected children not on HAART by degree of LV fractional shortening abnormality.

Depressed LVFS

55%

15%

Lipshultz et al., Circulation 2000
Fisher, Lipshultz et al., Am Heart J 2005
ART+ measurements were consistently 1.42 SD lower than ART- through the first 2 years of life (p<0.001).
ART+ measurements were 0.46 SD lower than ART- group at birth (p=0.005). At 6 months ART+ measurements were 1.02 SD lower than ART- (p<0.001) and remained so up to 2 years of age.

Lipshultz et al., JACC 2011
NHLBI-CHAART-1: Multi-ART use is Associated with Impaired LV Relaxation

Peak myocardial early diastolic velocity for the ART+ cohort was below normal at all ages (p=0.01) consistent with impaired relaxation.

Lipshultz et al., JACC 2011
MV E:A measurements for the ART+ cohort were above normal at 1, 12, and 24 months of age indicative of impaired compliance (p=0.01, p<0.0001, p=0.0008, respectively).

For the same pressure, with decreased compliance, there is less filling.

Lipshultz et al., Circulation 2010
Unsuspected myocardial injury in otherwise healthy newborns (normal newborn nursery)

- Umbilical cord serum: 76%
- Neonatal serum: 94%
- Ill older children: 6%

Source: Lipshultz et al., Am J Cardiol 2008
Lipshultz et al., Am Heart J 2006
Myocardial injury was significantly associated with:

- Younger gestational age/lower birth weight
- Longer hospitalization
- Non-Caucasian race
- Positive cervical culture
- Elevated serum highly sensitive C-reactive protein

Lipshultz et al., Am J Cardiol 2008
1. Serum biomarkers or functional and structural markers can detect preclinical cardiotoxic injury and assess protection from anthracycline cardiotoxicity.

2. Biomarkers measured during anthracycline therapy or cardioprotective treatment are associated with cardiac status in survivors.

3. Whether tailoring therapy to individual children based on monitoring data is beneficial is unknown.
4. We also do not know whether serial assessment of these markers is more important than a single measurement.

5. We do not know which biomarkers best detect early cardiovascular disease.

6. The role of cardiac imaging in early detection of cancer-related heart disease is unknown and includes strain and strain rate, tissue Doppler velocities, and remodeling and fibrous matrix/collagenous activation.

Lipshultz et al., JCO 2010
7. Cell death pathway indicators and markers of substrate use or metabolic control are also underappreciated and underused.

8. Many important questions are without answers and include: Can we predict cardiovascular events? Can we improve cardiovascular outcomes in a cost-effective manner? Can new biomarkers or combinations of biomarkers predict acute or chronic heart failure?
9. There has been great enthusiasm for creating guidelines for cardiac monitoring and treatment, but the question is, will these guidelines improve care and combined outcomes that include multisystem morbidity and mortality, quality of life, and cost?

10. Validated biomarkers for cardiovascular diseases
   – How can genomic and proteomic techniques be applied to discovering biomarkers?
   – How does transcriptional regulation of normal and abnormal cardiovascular development work and how do epigenetic mechanisms control transcriptional regulatory expression in cardiac development and disease

Lipshultz et al., Curr Opinion in Pediatrics 2009
Lipshultz et al., JCO 2010
11. Sub-clinical myocardial injury occurs in apparently healthy newborns, but whether this injury is pathologic or a response to the stress of the immediate perinatal period or to other prenatal factors remains to be determined.

12. We need to identify validated biomarkers as surrogate endpoints for clinically important cardiovascular disease.