CMR Techniques to Detect Cardiac and Vascular Injury after Treatment for Cancer

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In patients with cancer, review cardiovascular magnetic resonance (CMR) assessments of:

- LV volumes, mass, ejection fraction, strain
- Myocardial injury
- Myocardial interstitial fibrosis
- Vascular stiffness

Feasibility of performing multi-center initiatives to develop predictive models of CV risk using CMR

Ongoing NIH studies to investigate cardiotoxicity
MRI methods (left ventricle)

A multi-phase, multi-slice cine white blood sequence was used to measure LV volumes and ejection fraction using a modified Simpson’s Rule Method.

Mean, mid-wall circumferential strain using tissue tagging.
**Comparison to 2D planar imaging incorporating area-length formulae**

<table>
<thead>
<tr>
<th></th>
<th>Echo</th>
<th>CMR</th>
<th>↓ sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV, 10 ml</td>
<td>121</td>
<td>12</td>
<td>90%</td>
</tr>
<tr>
<td>ESV, 10 ml</td>
<td>53</td>
<td>10</td>
<td>81%</td>
</tr>
<tr>
<td>EF, 3%</td>
<td>102</td>
<td>15</td>
<td>85%</td>
</tr>
<tr>
<td>Mass, 10 g</td>
<td>273</td>
<td>9</td>
<td>97%</td>
</tr>
</tbody>
</table>

Two potential manifestations of LVEF decline: 
EDV decrease vs. ESV increase

Baseline LVEF measurements

LVEF 60%

EDV 100 - ESV 40

EDV 100

Potential mechanisms of LVEF decline

LVEF 52%

EDV 83 - ESV 40

EDV 100

Volume depleted patient; Non-acute

Serious reduction in end-systolic volume from Adj-C

From 112 participants receiving potentially cardiotoxic chemotherapy, 26 participants experienced baseline to 3 months LVEF drops of >10% or a decline to an absolute value of <50%

n=5 ↓ EDV - ESV
Suggested Intravascular Volume Depletion (19.23%)

n=1 ↓ EDV ↑ ESV
Suggested Intravascular Volume Depletion + LV Systolic dysfunction (3.85%)

n=15 - EDV ↑ ESV
LV Systolic dysfunction (59.69 %)

n=5 - EDV - ESV
Minor changes in either LV EDV or LV ESV (19.3%)

Melendez, et al., Global Cardio-Oncology Summit 2016
Reductions in LVEDV can impair LV strain 3 months after initiating cardiotoxic chemotherapy

101 participants aged 50 yrs, 70% women, 50% breast cancer 32% lymphoma, 12% leukemia: 74% with anthracycline chemotherapy.

Jordan, et al., Global Cardio-Oncology Summit 2016
**Patho-physiology**

**Exposure**
- Disrupted mitochondrial function & actin-myosin interaction
- Intra- and extracellular edema, inflammation, cell injury
- Impaired regional LV function
- Myocellular death, collagen deposition, LV remodelling
- Decreased LVEF, cardiac output
- Neurohormonal activation, CHF

**Surveillance**
- + MRI contrast signal intensity
- MRI T2 signal
- + serum cardiac Troponin I
- Abnormal regional function
- + serum BNP measurement
- Decreased LVEF
- Exercise capacity
ROC Curves Comparing Characteristics of Signal Intensity Change the Forecast Future Events

- Optimal cutpoint mean signal intensity of 8.2
- Optimal cutpoint (if signal intensity increases by 1 or more during time interval preceding an event)
- Optimal cutpoint (if signal intensity increases by more than 2.9 relative to baseline)

Lightfoot, et al., *Circ Cardiovasc Imag* 2010
Early changes in CMR tissue characterization with late gadolinium enhancement occur concurrently with subclinical declines in LVEF

Study population:

n=67 participants receiving cardiotoxic chemotherapy

Aged 51±12 years
87% women
76% breast cancer
55% anthracyclines

Cardio-Oncology

Anthracycline-Associated T1 Mapping Characteristics Are Elevated Independent of the Presence of Cardiovascular Comorbidities in Cancer Survivors

Jennifer H. Jordan, PhD, MS; Sujethra Vasu, MD; Timothy M. Morgan, PhD; Ralph B. D’Agostino, Jr, PhD; Giselle C. Meléndez, MD; Craig A. Hamilton, PhD; Andrew E. Arai, MD; Songtao Liu, MD; Chia-Ying Liu, PhD; João A.C. Lima, MD; David A. Bluemke, MD, PhD; Gregory L. Burke, MD, MSc; W. Gregory Hundley, MD

n=310
Total study participants enrolled from rural communities of northwest NC, southwest VA, and east TN

n=236
Control Subjects

n=37
Cancer Patients Pre-Treatment

n=37
Cancer Survivors Post-Anthracycline Treatment

Myocardial fibrosis is elevated in adult survivors 3 years after anthracycline treatment relative to comparators.
**CMR findings of elevated fibrosis persist even after accounting for other risk factors such as age, the presence of cancer, or coexistent cardiovascular comorbidities**

<table>
<thead>
<tr>
<th>Model</th>
<th>Covariates</th>
<th>ECV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Group</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Model 2</td>
<td>Group + Age, Race, Gender, Age*Gender</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Model 3</td>
<td>Model 2 + Weight, Heart Rate, Systolic BP, CAD, DM, DysL, HTN</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Model 4</td>
<td>Model 3 + LVEF, LV Mass Index</td>
<td>p &lt; 0.0001</td>
</tr>
</tbody>
</table>
Progressive 3-Month Increase in Left Ventricular Myocardial Extracellular Volume Fraction After Receipt of Anthracycline-Based Chemotherapy
(n= 56; 66% women; 71% white and 29% black; aged 52 ± 13 years).

Moving beyond the heart: Relevance of abnormal pulse wave velocity for predicting CV events in population-based studies

<table>
<thead>
<tr>
<th>Study population (n)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly subjects</td>
<td>2488</td>
<td>1.80 1.10–2.80</td>
</tr>
<tr>
<td>Hypertensive subjects</td>
<td>1045</td>
<td>1.34 1.01–1.79</td>
</tr>
<tr>
<td>Hypertensive subjects</td>
<td>1715</td>
<td>1.72 1.48–1.81</td>
</tr>
<tr>
<td>Diabetic subjects</td>
<td>571</td>
<td>1.08 1.03–1.14</td>
</tr>
<tr>
<td>ESRD subjects</td>
<td>241</td>
<td>1.39 1.19–1.62</td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>492</td>
<td>4.24 1.39–12.96</td>
</tr>
</tbody>
</table>

P=0.0165
P=0.0043

Utility of CMR to define etiology of LV dysfunction: 63 yo woman with multiple myeloma with past history of CAD, HTN presents 5 weeks after treatment with new proteosome inhibitor with dyspnea and LVEF of 40%? What is her diagnosis?
<table>
<thead>
<tr>
<th>Test</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localizers (x2)</td>
<td>0:30</td>
</tr>
<tr>
<td>Tagging</td>
<td>0:30</td>
</tr>
<tr>
<td>T1 and T2 Maps</td>
<td>1:00</td>
</tr>
<tr>
<td>Aorta Phase Contrast</td>
<td>2:00</td>
</tr>
<tr>
<td>Aorta Wall Thickness</td>
<td>0:30</td>
</tr>
<tr>
<td>Aorta Distensibility</td>
<td>0:30</td>
</tr>
<tr>
<td>LV Cine Stack</td>
<td>3:00</td>
</tr>
<tr>
<td>Total Time</td>
<td>8-12 min</td>
</tr>
</tbody>
</table>
Wake Forest NCORP Research Base

- One of two Cancer Center Prevention and control Research Bases in U.S.

- Initially funded in 1999, now operating on 4th competing renewal

- 41 individuals at Wake Forest funded by Research Base grant
  - Executive Steering Committee
  - Protocol Office
  - Data Management Center
  - Research Nursing
  - Cores: Biostatistics, Biospecimen

- Large Network of Community Hospital systems that perform clinical research. Cardiovascular MRI operative across 25 of these community hospitals.
Implementation of clinical CMR studies involving community hospitals

- Our effort is focused on translational science approaches to diagnose, prevent and manage CV disease in patients treated for cancer.

<table>
<thead>
<tr>
<th>#</th>
<th>Title</th>
<th>Status</th>
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<tbody>
<tr>
<td>R21 CA 109224</td>
<td>MRI Detection of Doxorubicin Induced Cardiotoxicity</td>
<td>Completed</td>
</tr>
<tr>
<td>R33 CA121296-02</td>
<td>Optimized CMR Imaging of Chemotherapy Cardiotoxicity</td>
<td>Completed</td>
</tr>
<tr>
<td>Komen BCTR0707769</td>
<td>Early Detection of Chemotherapy Associated Cardiotoxicity in Women with Breast Cancer</td>
<td>Completed</td>
</tr>
<tr>
<td>R01 CA167821-01</td>
<td>Early Imaging Detection of CV Injury after Cancer (n=110)</td>
<td>Awarded through 2017</td>
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<tr>
<td>R43 CA174261</td>
<td>Advanced imaging detection of cardiac injury in high risk cancer patients</td>
<td>Awarded through 2016</td>
</tr>
<tr>
<td>R01 HL119980-01</td>
<td>CV injury, exercise intolerance, fatigue and risk prediction after chemotherapy for breast cancer (n=1000)</td>
<td>Awarded through 2020</td>
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<tr>
<td>R01 HL118740-01</td>
<td>Preventing anthracycline CV toxicity with statins (n=240)</td>
<td>Awarded through 2018</td>
</tr>
<tr>
<td>R43 HL120486-01</td>
<td>Community hospital ID of CV risk patients during cancer</td>
<td>Awarded through 2017</td>
</tr>
</tbody>
</table>
Summary

- In individuals treated for cancer, cardiovascular magnetic resonance measures of left ventricular structure and function are useful for identifying subclinical cardiovascular disease associated with adverse CV events.

- New initiatives are extending this technology into clinical healthcare delivery systems that facilitate patient care in community hospitals where a large proportion of the individuals with cancer are treated in the US.

- These new CMR techniques are commensurate with those used in other large NIH population based studies thus allowing for comparisons between individuals with cancer and others at risk for CV disease. Initiatives are underway to utilize risk prediction modeling to determine the utility of several of the new CMR metrics for forecasting CV events after treatment for cancer.