Cardio-oncology: Applying new echo technology to guide therapy

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Disclosures

• Janssen Advisory Board
• Takeda Advisory Board
Outline

- 3D echocardiography in cardio-oncology
- Myocardial strain to potentially guide treatment
  - Baseline risk
  - Early detection and treatment
- Trials to guide practice

Consequence of Myocardial Injury

Abdel-Qadir et al, JAMA Cardiology Oct 2016
Thavendiranathan et al, JCO; 2016, Apr 18.
Detection of Cardiotoxicity
3D Left Ventricular EF

Dorosz JL et al. JACC, 2012; 15:1799

Detection of Cardiotoxicity
3D Left Ventricular EF

Detection of Cardiotoxicity
Left Ventricular EF

Thavendiranathan et al, JACC 2013 Jan 8;61(1):77-84.

Detection of Cardiotoxicity
Left Ventricular EF

EXPERT CONSENSUS STATEMENT

Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

2.1. LV systolic function.
- Echocardiography is the method of choice for the evaluation of patients before, during and after cancer therapy.
- Accurate calculation of LVEF should be done with the best method available in the echocardiography laboratory (ideally 3DE).
- When using 2DE, the modified biplane Simpson technique is the method of choice.
3D Echocardiography Gaps

• Does 3D echocardiography identify cardiotoxicity earlier or more accurately?
• Does it provide incremental prognostic value?
• Does it guide earlier treatment?

Question

Which of the following is true about myocardial strain imaging?

1. Pre-cancer therapy strain can be used to guide cancer therapy
2. Cardiac meds guided by strain imaging prevents heart failure
3. Cardiac meds guided by strain imaging in survivors prevents LV systolic dysfunction
4. GLS measurements are more reproducible than 3D LVEF
Myocardial strain

1. Pre-treatment risk assessment
2. Early detection of myocardial injury
3. Prediction of LVEF recovery
4. Subclinical disease in survivors

Pre-treatment risk assessment

Narayan HK et al, JACC: Cardiovascular Imaging, 2016
**Pre-treatment risk assessment**

Every 1% difference in Circumferential strain at baseline 31% increase in odds of cardiotoxicity

<table>
<thead>
<tr>
<th>TABLE 2: Associations of Strain, Strain Rate, and Ventricular-Arterial Coupling Parameters With Odds of CTRCD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Model 1</strong></td>
</tr>
<tr>
<td><strong>Strain</strong></td>
</tr>
<tr>
<td>Longitudinal strain, %</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change*</td>
</tr>
<tr>
<td>Circumferential strain, %</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change*</td>
</tr>
<tr>
<td>Radial strain, %</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change*</td>
</tr>
<tr>
<td><strong>Ventricular-arterial coupling</strong></td>
</tr>
<tr>
<td>Elast =&lt;</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change*</td>
</tr>
</tbody>
</table>

Narayan HK et al, JACC: Cardiovascular Imaging, 2016

**Pre-treatment risk assessment**

- 450 patients
- Hematological malignancy
- Anthracycline treated
- Followed for median 15 days
- 6% developed cardiac events (HF or death)
- Pre-treatment echo

Pre-treatment risk assessment

Kalam K and Marwick TH, European J of Cancer 2013

"Subclinical" Cardiac Injury

- 158 patients – various cancers, Adriamycin Rx
- Higher biopsy grades in pts with normal EF - even with moderate cumulative dose of Rx
Early Detection of Myocardial Dysfunction

N=43, 21% CTOX, AC followed by TZM
Sawaya H et al. Am J Cardiol 2011;107:1375

N=81, 30% CTOX, All trastuzumab, 40% A
Negishi K et al, JASE 2013, 26: 493-8

Prognosis

<table>
<thead>
<tr>
<th>Study/First Author (Ref, #)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folli-Nail et al. (44)</td>
<td>78%</td>
<td>93%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>Reduced (10% relative) decrease in LVEF</td>
<td>78%</td>
<td>93%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>Reduced (10% relative) decrease in EF</td>
<td>67%</td>
<td>93%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>Elevated LVEF &gt; 55%</td>
<td>79%</td>
<td>97%</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>Elevated EF &gt; 55%</td>
<td>79%</td>
<td>97%</td>
<td>97%</td>
<td></td>
</tr>
</tbody>
</table>

Thavendiranathan et al., JACC 2014
Management

Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

Juan Carlos Plana, MD, FASE, Chair, Maurizio Galderisi, MD, FESC, Co-Chair, Ana Barac, MD, PhD.

- Chemotherapy (n=320)
  - Anthracyclines with age >65, cardiac Hx, radiotherapy, other cardiotoxic (eg trastuzumab)

- Randomize Reduced EF
  - ACEi and B-blocker n=29
    - CTX (17)
    - Cardiotoxicity (22). (40-18)
  - Normal EF, normal strain No treatment n=91

- Strain guidance (160)
  - EF guidance (156)
  - EF guidance (138)
  - EF guidance (138)

- Reduced EF
  - Strain guidance (138)
  - EF guidance (160)
  - EF guidance (156)
  - EF guidance (138)

- Normal EF
  - No treatment n=320

- Allow for 22% to dropout

Study PI: Dr. Thomas Marwick - Tom.Marwick@bakeridi.edu.au
North American PI: Dr. P. Thavendiranathan – dinesh.thavendiranathan@uhn.ca

The Promise of a Healthy Heart.

UHN Peter Munk Cardiac Centre
TED ROGERS CENTRE FOR HEART RESEARCH

Treatment - SUCCOUR - RCT
Myocardial strain – recovery of ventricular function

• Newly diagnosed breast cancer, AC followed by trastuzumab (N=95)
• CTOX (ASE) in 19 (20%)
• Reversibility as per ASE = 13

Patients with GLS at nadir absolute <15.8 less likely to recover – HR 0.39 (95% CI 0.18-0.74)

Hong-wen F et al. Echocardiography 2016

Strain in pediatric cancer survivors

N=1820

Armstrong GT et al, JACC 2016
Multi-center Reproducibility

<table>
<thead>
<tr>
<th></th>
<th>Core Lab value</th>
<th>Site value</th>
<th>Bias</th>
<th>LOA</th>
<th>ICC [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLS, %</td>
<td>-21.0±2.4</td>
<td>-20.4±2.1</td>
<td>0.7</td>
<td>3.1</td>
<td>0.845 [0.692, 0.919]</td>
</tr>
<tr>
<td>EF2D, %</td>
<td>61.7±3.5</td>
<td>63.8±5.3</td>
<td>2.0</td>
<td>9.8</td>
<td>0.513 [0.147, 0.725]</td>
</tr>
<tr>
<td>EF3D, %</td>
<td>61.6±4.6</td>
<td>62.0±4.7</td>
<td>0.5</td>
<td>8.0</td>
<td>0.750 [0.536, 0.866]</td>
</tr>
</tbody>
</table>

Negishi T et al, JACC CV Imaging, 2016, Oct 6
58 Readers from North America, Europe, Asia and Oceania

Experience and Reproducibility

No = 0 cases
Limited = 1-20
Intermediate = 21-100
High >100 cases
Expert > 1000 cases

Negishi T et al, JACC CV Imaging, 2016, Oct 6
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Image Quality and Reproducibility

<table>
<thead>
<tr>
<th>Image quality for measurement</th>
<th>GLS</th>
<th>EF</th>
<th>p (GLS vs. EF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.996 [95%CI 0.990, 0.999]</td>
<td>0.962 [0.900, 0.994]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Good</td>
<td>0.997 [95%CI 0.990, 1.000]</td>
<td>0.961 [0.875, 0.997]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Borderline</td>
<td>0.993 [95%CI 0.965, 1.000]</td>
<td>0.868 [0.421, 1.000]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p (Good vs. Borderline)</td>
<td>0.01</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Negishi T et al, JACC CV Imaging, 2016, Oct 6

Question

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Case Example

- 51 year old woman, high risk HER2+, left sided breast cancer
- Treatment
  - Mastectomy, Epirubicin (300mg/m²), Trastuzumab (17 cycles), refused radiation therapy, hormonal therapy
- No cardiovascular disease history, no CV risk factors, non-smoker, no medications, excellent functional capacity
- Baseline peaks systolic Circumferential strain - 19.6% (mildly reduced)
### Case - Summary

<table>
<thead>
<tr>
<th>Time</th>
<th>3D EF</th>
<th>MRI EF</th>
<th>GLS</th>
<th>E/A</th>
<th>E/e'</th>
<th>HsTpl</th>
<th>NYHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>61</td>
<td>56.7</td>
<td>-21.5</td>
<td>0.9</td>
<td>7.0</td>
<td>2</td>
<td>I</td>
</tr>
<tr>
<td>Post A</td>
<td>53</td>
<td>50.5</td>
<td>-17.9</td>
<td>1.1</td>
<td>8.7</td>
<td>48</td>
<td>I</td>
</tr>
<tr>
<td>1 month H</td>
<td>48</td>
<td>47.4</td>
<td>-15.1</td>
<td>1.6</td>
<td>11.3</td>
<td>102</td>
<td>II-III</td>
</tr>
<tr>
<td>6 weeks</td>
<td>56</td>
<td>55.5</td>
<td>-19.2</td>
<td>1.0</td>
<td>4.4</td>
<td>17</td>
<td>I</td>
</tr>
<tr>
<td>6 months</td>
<td>54</td>
<td>52.6</td>
<td>-17.8</td>
<td>1.2</td>
<td>6.1</td>
<td>8</td>
<td>I</td>
</tr>
<tr>
<td>9 months</td>
<td>53</td>
<td>-</td>
<td>-18.1</td>
<td>1.3</td>
<td>8.0</td>
<td>3</td>
<td>I</td>
</tr>
<tr>
<td>12 months</td>
<td>53</td>
<td>53.0</td>
<td>-17.1</td>
<td>1.3</td>
<td>5.0</td>
<td>2</td>
<td>I</td>
</tr>
<tr>
<td>24 months</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>I</td>
</tr>
</tbody>
</table>
Strain echo vs LVEF MRI

Summary

- Limited data - ?immunotherapy/ proteosome inhibitors? / immunomodulators?
- 3D EF more accurate reproducible
- Value of strain
  - Circumferential strain – pre treatment risk
  - Longitudinal strain – LV dysfunction / recovery
  - LS / CS identifies subclinical disease in survivors
  - Strain is more reproducible than LVEF
- We need data on using these techniques to guide therapy and modify prognosis!
Thank you