Monitoring for Chemo-Related Cardio-toxicity

B K Tamarappoo, MD, PhD
Co-Director, Cardio-Oncology Center
Section of Cardiovascular Imaging
Department of Cardiovascular Medicine
Cleveland Clinic
No disclosures
Outline

• CTRCD definition and mechanisms of toxicity
• Echocardiographic evaluation of the patient undergoing cancer therapy
• Early detection of toxicity
• Other modalities
• Integrated approach
Case study

• 47 year old female
• Invasive ductal carcinoma (ER-, PR-, Her2-neu+)
• Docetaxel, Carboplatinum and Trastuzumab followed by mastectomy
• Is this patient vulnerable?
• How do I predict cardiotoxicity?
• How do I monitor?
• How do I treat?
1. CTRCD: Definition and Mechanisms of toxicity
Cancer therapeutics-related cardiac dysfunction

Type I CTRCD
- Cellular death
- Biopsy changes
- Cumulative dose-related
- Permanent damage
- Model: doxorubicin

Type II CTRCD
- Cellular dysfunction
- No biopsy changes
- Not cumulative dose-related
- Reversible
  Model: trastuzumab
Cancer

Cancer Therapeutics

Regimen potentially associated with Type I toxicity
- Doxorubicin
- Epirubicin
- Idarubicin
- Mitoxantrone

Regimen potentially associated with Type II toxicity
- Trastuzumab
- Lapatinib
- Pertuzumab
- Imatinib
- Sorafenib
- Sunitinib
- Bevacizumab
- Bortezomib
Cancer therapeutics related cardiac dysfunction (CTRCD)

- Decrease in the **LVEF** of greater than 10 % to a value below the reference value of normal (EF 53%).
- LVEF decrease may be further categorized as symptomatic or asymptomatic, or with regard to reversibility
Prediction and Monitoring Techniques

Statistical models – large scale population based, examine patient characteristics and identify risk factors unique to patients affected by cardiotoxic medications

Biomarkers – Large scale studies using serum or blood to examine enzymes/proteins that are found more often in patients with cardiotoxicity than in unaffected controls

Imaging – Assess imaging techniques that can identify cardiac dysfunction and test their ability to predict long-term effects
Echocardiographic evaluation of the cancer patient
Topics

• How reproducible is LVEF-for sequential imaging?
• Are there other echo-based measures to monitor subclinical dysfunction?
• Reproducibility of global longitudinal strain (GLS)
• What is the threshold of GLS that signals cardiotoxicity
• Once you detect cardiotoxicity what can you do?
Reproducibility of Echocardiographic Techniques for Sequential Assessment of Left Ventricular Ejection Fraction and Volumes

Application to Patients Undergoing Cancer Chemotherapy

Paaladinesh Thavendiranathan, MD, MSc, Andrew D. Grant, MD, Tomoko Negishi, MD, Juan Carlos Plana, MD, Zoran B. Popović, MD, PhD, Thomas H. Marwick, MD, PhD, MPH

Cleveland, Ohio
Figure 3  Temporal Variability in EF

The temporal variability is defined as the standard error of measurement (SEM) and 95% confidence intervals (CIs) for each technique for the entire follow-up period. Noncontrast 3D had the lowest temporal variability and 95% CI for EF measurements (lower panel) compared with all methods (p < 0.01 for all comparisons against noncontrast 3D). *p < 0.05 for comparison of contrast enhanced to noncontrast acquisition for the respective technique. Abbreviations as in Figure 1.
Among 56 patients (all female, 54 ± 13 years of age), noncontrast 3D EF, end-diastolic volume, and end-systolic volume had significantly lower temporal variability than all other methods. Contrast only decreased the temporal variability of LV end-diastolic volume measurements by the 2D biplane method. Our data suggest that a temporal variability in EF of 0.06 might occur with noncontrast 3DE due to physiological differences and measurement variability, whereas this might be >0.10 with 2D methods. Overall, 3DE also had the best intra- and inter-observer as well as test-retest variability.
Early detection of toxicity
Global longitudinal strain is evaluated by frame by frame tracking of the speckles.
GLS in the prognosis of subsequent LV dysfunction
Objective

• To evaluate the ability of strain imaging to prognosticate downstream reductions in ejection fraction
Assessment of Echocardiography and Biomarkers for the Extended Prediction of Cardiotoxicity in Patients Treated With Anthracyclines, Taxanes, and Trastuzumab

Heloisa Sawaya, MD, PhD; Igal A. Sebag, MD; Juan Carlos Planas, MD; James L. Januzzi, MD; Bonnie Ky, MD, MSCE; Timothy C. Tan, MBBS, PhD; Victor Cohen, MD; Jose Banchs, MD; Joseph R. Carver, MD; Susan E. Wiegers, MD; Randolph P. Martin, MD; Michael H. Picard, MD; Robert E. Gerszten, MD; Elkan F. Halpern, PhD; Jonathan Passeri, MD; Irene Kuter, MD; Marielle Scherrer-Crosbie, MD, PhD

Clinical Perspective on p 603

The cardiotoxicity of anthracyclines is well recognized. Transient increases in cardiotoxicity of anthracycline treatment, with left ventricular (LV) dysfunction noted in 20% of patients, may occur after ceasing anthracycline therapy. More sensitive and specific markers of anthracycline-induced cardiac dysfunction or response to therapy are needed. This article describes ongoing research in this area. The National Institutes of Health has recently begun a large, multicenter trial comparing doxorubicin to an experimental agent, the drug candesartan, to determine whether candesartan can reduce the cardiotoxicity attributable to doxorubicin. In addition, several sets of biomarkers of anthracycline-induced cardiotoxicity are being studied, including plasma levels of biomarkers of myocardial injury and oxidative stress. These biomarkers may be useful for monitoring anthracycline therapy and determining cardiotoxicity.
Questionnaire/ Echocardiogram / Biomarkers

Baseline 3 mo (post Anthracyclines) 6 mo 9 mo 12 mo 15 mo

Athracyclines Trastuzumab Paclitaxel Trastuzumab
Assessed for eligibility: 99 patients

Excluded (n=3)
- refused enrollment (n=2)
- baseline LVEF <50% (n=1)

96 patients

Baseline only (n=15)
- HER2 - on further test (n=2)
- Change in scheduled treatment (n=2)
- Followed-up in other institutions (n=11)

Completed protocol (n=81)

All follow-up visits (n=69)

Partial follow-up visits (n=12)
(number of visits=4.9±0.3)

Figure 2. Consort diagram of the study protocol. LVEF indicates left ventricular ejection fraction; HER2, human epidermal growth factor receptor 2.
Results

• 81 consecutive patients
• 26 patients developed cardio-toxicity (32%)
• 3 at the end of anthracyclines, 23 while on Trastuzumab
• 5 (6%) of the patients were symptomatic
Cardio-toxicity by month of presentation

Asymptomatic
Symptomatic
<table>
<thead>
<tr>
<th>Predictors (Measured At the Completion of Anthracyclines)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long strain &lt;19%</td>
<td>17/23 (74%) (0.51–0.90)</td>
<td>40/55 (73%) (0.59–0.84)</td>
<td>17/32 (53%)</td>
<td>40/46 (87%)</td>
</tr>
<tr>
<td>usTnl &gt;30 pg/mL</td>
<td>11/23 (48%) (0.27–0.68)</td>
<td>40/55 (73%) (0.59–0.84)</td>
<td>11/26 (44%)</td>
<td>40/52 (77%)</td>
</tr>
<tr>
<td>Long strain &lt;19% and usTnl&gt;30 pg/mL</td>
<td>8/23 (35%) (0.16–0.57)</td>
<td>51/55 (93%) (0.82–0.98)</td>
<td>8/12 (67%)</td>
<td>51/66 (77%)</td>
</tr>
<tr>
<td>Long strain &lt;19% or usTnl&gt;30 pg/mL</td>
<td>20/23 (87%) (0.66–0.97)</td>
<td>29/55 (53%) (0.39–0.66)</td>
<td>20/46 (43%)</td>
<td>29/32 (91%)</td>
</tr>
</tbody>
</table>

PPV indicates positive predictive value; NPV, negative predictive value; and usTnl, ultrasensitive troponin I.
Long strain is peak systolic longitudinal myocardial strain.
The 95% exact CIs are provided in brackets.
Results

- LVEF measured at the completion of anthracyclines was not predictive of later cardio-toxicity (P=0.075)
- Change in EF was not predictive
- Peak GLS was predictive of cardio-toxicity (P=0.0003)
- Neither radial nor circumferential were predictive (P=0.25 and 0.67 respectively)
What are normal values for GLS?
Normal Range of Left Ventricular 2-Dimensional Strain
– Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) Study –

Kiyohiro Takigiku, MD; Masaaki Takeshi, MD; Chisato Izumi, MD; Satoshi Yuda, MD; Konomi Sakata, MD; Nobuyuki Ohto, MD; Kazuaki Tanabe, MD; Satoshi Nakatani, MD on behalf of the JUSTICE investigators

Despite the rapid adoption of this new technology, the normal range of LV 2-D strain has been traditionally measured in a small number of subjects. Little information exists regarding the equivalence of the normal ranges of LV 2-D strain when comparing ultrasound systems from different vendors, manufacturers, and software versions. Therefore, our study aimed to establish the normal range of LV 2-D strain in a large number of healthy subjects using the same ultrasound system and software from different vendors. The study included 200 subjects (100 men and 100 women) aged 18-79 years. The normal range of LV 2-D strain was determined using a custom-made software program, which incorporates both systolic and diastolic phases of the cardiac cycle. The results of our study showed that the normal range of LV 2-D strain is significantly different between the different vendors, manufacturers, and software versions. Therefore, it is recommended to establish the normal range of LV 2-D strain in each center using the same ultrasound system and software from the same vendor. This will improve the accuracy and reliability of the measurement of LV 2-D strain.
Table 3. Effect of Age and Gender on Global Longitudinal Strain vs. Vendor

<table>
<thead>
<tr>
<th>Age group</th>
<th>0–19 years</th>
<th>20–29 years</th>
<th>30–39 years</th>
<th>40–49 years</th>
<th>50–59 years</th>
<th>≥60 years</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>-22.1±2.4</td>
<td>-21.2±1.9</td>
<td>-21.1±2.1</td>
<td>-21.4±2.0</td>
<td>-21.0±2.2</td>
<td>-20.3±1.9</td>
<td>0.0218</td>
</tr>
<tr>
<td>Male</td>
<td>-21.7±3.1</td>
<td>-20.9±1.9</td>
<td>-20.6±1.9</td>
<td>-20.9±1.8</td>
<td>-21.0±1.9</td>
<td>-19.7±1.4</td>
<td>0.1982</td>
</tr>
<tr>
<td>Female</td>
<td>-22.4±1.6</td>
<td>-22.3±1.6</td>
<td>-22.8±1.8</td>
<td>-22.6±2.1</td>
<td>-23.3±1.9</td>
<td>-20.9±2.1</td>
<td>0.0348</td>
</tr>
<tr>
<td>P (M vs. F)</td>
<td>0.4292</td>
<td>0.0316</td>
<td>&lt;0.0001</td>
<td>0.0178</td>
<td>0.0029</td>
<td>0.1381</td>
<td></td>
</tr>
<tr>
<td>V2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>-19.9±2.5</td>
<td>-19.0±2.1</td>
<td>-19.5±2.2</td>
<td>-18.2±2.5</td>
<td>-17.6±2.5</td>
<td>-16.7±2.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>-19.4±2.7</td>
<td>-18.8±2.0</td>
<td>-19.1±2.3</td>
<td>-17.9±2.8</td>
<td>-16.9±2.3</td>
<td>-15.8±1.4</td>
<td>0.0019</td>
</tr>
<tr>
<td>Female</td>
<td>-20.5±2.2</td>
<td>-20.6±2.3</td>
<td>-20.2±2.0</td>
<td>-19.3±0.9</td>
<td>-20.4±1.5</td>
<td>-17.3±2.3</td>
<td>0.0002</td>
</tr>
<tr>
<td>P (M vs. F)</td>
<td>0.1349</td>
<td>0.0248</td>
<td>0.1083</td>
<td>0.4316</td>
<td>0.0294</td>
<td>0.0928</td>
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</tr>
<tr>
<td>V3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>-21.4±1.7</td>
<td>-20.2±2.1</td>
<td>-20.4±2.3</td>
<td>-19.4±2.2</td>
<td>-18.5±2.6</td>
<td>-17.8±2.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>-21.6±2.0</td>
<td>-20.2±2.0</td>
<td>-20.4±2.2</td>
<td>-19.8±2.3</td>
<td>-18.7±2.6</td>
<td>-16.3±3.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>-21.2±1.5</td>
<td>-20.2±2.4</td>
<td>-20.4±2.8</td>
<td>-18.7±1.8</td>
<td>-18.3±2.8</td>
<td>-18.6±2.3</td>
<td>0.0141</td>
</tr>
<tr>
<td>P (M vs. F)</td>
<td>0.6076</td>
<td>0.9787</td>
<td>0.9201</td>
<td>0.1415</td>
<td>0.7374</td>
<td>0.0688</td>
<td></td>
</tr>
</tbody>
</table>

817 subjects, Males >16.8 % / Females >18.6%
Reproducibility
Reproducibility of Speckle-Tracking-Based Strain Measures of Left Ventricular Function in a Community-Based Study

Susan Cheng, MD, Martin G. Larson, ScD, Elizabeth L. McCabe, MS, Ewa Ospiuk, MD, Birgitta T. Lehman, RDMS, Plamen Stanchev, MD, Jayashri Aragam, MD, Emelia J. Benjamin, MD, ScM, Scott D. Solomon, MD, and Ramachandran S. Vasan, MD, Framingham, Boston, and West Roxbury, Massachusetts
<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average coefficient of inter-observer variation</td>
<td>&lt; 4%</td>
</tr>
<tr>
<td>Average coefficient of intra-observer variation</td>
<td>&lt; 6%</td>
</tr>
</tbody>
</table>

2 sets of 20 patients used for the study
Optimal myocardial deformation index and cut-off values
Objectives

We sought the optimal myocardial deformation index for prediction of cardio-toxicity at 12 months.
Independent and Incremental Value of Deformation Indices for Prediction of Trastuzumab-Induced Cardiotoxicity

Kazuaki Negishi, MD, PhD; Tomoko Negishi, MD; James L. Harc, MBBS, PhD; Brian A. Halaska, PhD; Juan Carlos Plana, MD, and Thomas H. Marwick, MBBS, PhD, MPH. Cleveland, Ohio; Brisbane and Hobart, Australia
Methods

• 100 women (51±12 y) receiving chemotherapy

• 46 received simultaneous anthracycline and trastuzumab.

• Conventional echo (mitral annular s’ and e’ velocity) and myocardial deformation indices (global longitudinal peak systolic strain [GLS], strain rate [SR-s] and early diastolic strain rate [SR-e]) from speckle tracking were measured at baseline, 6 and 12m.

• Cardiotoxicity was defined by a decrement of EF >10%
Figure 1: Receiver operating characteristic curves to predict subsequent decrease in EF. Discriminative abilities of the deformation parameters were evaluated to predict a >10% decrease in EF at 12 months.
<table>
<thead>
<tr>
<th></th>
<th>Cut-off (%)</th>
<th>Sen (%)</th>
<th>Spe (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔGLS</td>
<td>-11</td>
<td>65</td>
<td>94</td>
</tr>
<tr>
<td>ΔGLSR-E</td>
<td>10.0</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>Δs'</td>
<td>-3.4</td>
<td>100</td>
<td>34</td>
</tr>
<tr>
<td>Study</td>
<td>Cut-off</td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>MDACC/MGH</td>
<td>-19%</td>
<td>74%</td>
<td>73%</td>
</tr>
<tr>
<td>CCF/Brisbane</td>
<td>-11.95% CI(8-15)</td>
<td>65%</td>
<td>94%</td>
</tr>
</tbody>
</table>
V. Integrated approach
Case presentation

• Follow up EF at 3 months 58%
• What to do?
Early detection of sub-clinical LV dysfunction using GLS

Drop of 10 points to LVEF <53% → Yes → CTRCD

Relative drop of GLS as compared to baseline

- < 8%
  - No evidence of subclinical LV dysfunction

- > 15%
  - Subclinical LV dysfunction*

* The data supporting the initiation of cardioprotection for the treatment of subclinical LV dysfunction is limited.
Change in strain: 25-5 - 19 / 25.5 = 25%
Cardioprotective Effect of β-Adrenoceptor Blockade in Patients With Breast Cancer Undergoing Chemotherapy
Follow-Up Study of Heart Failure

Sinziana Seicean, MD, MPH, PhD; Andreea Seicean, PhD, MPH; Nima Alan, BS; Juan Carlos Plana, MD; G. Thomas Budd, MD; Thomas H. Marwick, MBBS, PhD, MPH
920 consecutive patients with breast cancer (age $52.3 \pm 11.0$ y) with normal EF prior to receiving A/TT therapy at our institution between 2005 and 2010. Using a propensity score and a 5 to 1 matching algorithm, **106 of these patients on continuous BB during cancer treatment were matched with 212 patients from the same pool with similar characteristics but not on continuous BB.**

During a median follow-up of $3.2 \pm 2.0$ years, 32 incident HF admissions were identified in these 318 patients with breast cancer, while 28 cancer-related (non-cardiac) deaths occurred prior to any incident HF.

Cumulative incidence regression models and cause-specific hazards of new HF events were estimated from competing-risk Cox models of time-dependent covariates.

While trastuzumab therapy showed significant association with incident HF, independent of anthracycline-related cardiotoxicity (HR=9.0, 95% CI: 3.0-27.0, p<0.0001), **continuous use of BB was associated with lower risk of new HF events (HR=0.2, 95% CI 0.1-0.5, p=0.003).**

Secian S, Plana JC. Circ Heart Failure. Pub ahead of print
• Coincidental, continuous use of BB is associated with lower incidence of HF in patients with breast cancer and normal baseline ejection fraction in a competing risk framework, and after matching for demographics, clinical, and cancer related treatment characteristics. Prospective randomized clinical trials to validate these findings are warranted.
EXPERT CONSENSUS STATEMENT

Expert Consensus for Multi-Modality Imaging Evaluation of Adult Patients During and After Cancer Therapy: A Report from the American Society of Echocardiography, the European Association of Cardiovascular Imaging

Juan Carlos Plana, MD, FASE, Chair, Maurizio Galderisi, MD, FESC, Co-chair, Ana Barac, MD, PhD, FASE, Michael S. Ewer, MD, JD, Bonnie Ky, MD, FASE, Marielle Scherrer-Crosbie, MD, PhD, FASE, Javier Ganame, MD, PhD, Igal A. Sebag, MD, FASE, Deborah A. Agler, RCT, RDCS, FASE, Luigi Badano, MD, FESC, Jose Banchs, MD, FASE, Daniela Cardinale, MD, Joseph Carver, MD, Manuel Cerqueira, MD, Jeanne M. DeCara, MD, FASE, Thor Edvardsen, MD, PhD, FESC, Scott Flamm, MD, MBA, Thomas Force, MD, Brian P. Griffin, MD, Guy Jerusalem, MD, PhD, Jennifer E. Liu, MD, FASE, Andreia Magalhães, MD, Thomas Marwick, MBBS, PhD, MPH, Liza Y. Sanchez, RCS, FASE, Rosa Sicari, MD, PhD, FESC, Hector Villaraga, MD, FASE, Patrizio Lancellotti, MD, PhD, FESC, Cleveland, Ohio; Naples, Padua, Milan, and Pisa, Italy; Washington, DC; Houston, Texas; Philadelphia, Pennsylvania; Boston, Massachusetts; Hamilton, Ontario and Montreal, Quebec, Canada; Chicago, Illinois; Oslo, Norway; Liege, Belgium; New York, New York; Lisbon, Portugal; Hobart, Tasmania, Australia; Rochester, Minnesota

(J Am Soc Echocardiogr 2014; XX:XX-XX.)

Keywords: Chemotherapy, doxorubicin, trastuzumab, left ventricular dysfunction, three-dimensional echocardiography, early detection, strain, biomarkers
Conclusions

• Echo may be used for sequential imaging 3D volumes and EF

• GLS may be a sensitive measure of changes

• Change of more than 15% in strain may predict onset of LV dysfunction (small study of 100 patients).

• Initiation of BB may be first step

• If strain becomes abnormal with drop in LVEF >10%, consider change in therapy