Cardiotoxicity Effects of Chemotherapeutic Drugs

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* No conflicts to declare
CCF Cardio-Oncology Center

- Joint collaboration of HVI and Cancer (Taussig) Institute

- Mission:
  - to address the cardiovascular side effects of cancer therapy
  - to maximise cardiovascular outcomes for cancer survivors

- Multi-disciplinary Team including Cardiologists, Oncologists, Radiation Oncologists
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

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Expert Consensus

- CTRCD definition and mechanisms of toxicity
- Echocardiographic evaluation of the patient undergoing cancer therapy
- Early detection of toxicity
- Other modalities
- Integrated approach
CTRCD: Definition and Mechanisms of toxicity
Cancer therapeutics related cardiac dysfunction (CTRCD)

- Decrease in the LVEF of greater than 10 percentage points 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.
Cancer therapeutics-related cardiac dysfunction

**Anthracyclines**

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

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

**Herceptin**

**Tyrosine kinase (RTK) inhibitors**

**VEGF inhibitors**
Echocardiographic evaluation of the cancer patient
2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

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### Table 6  Proposed diagnostic tools for the detection of cardiotoxicity

<table>
<thead>
<tr>
<th>Technique</th>
<th>Currently available diagnostic criteria</th>
<th>Advantages</th>
<th>Major limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography:</strong></td>
<td>• LVEF: &gt;10 percentage points decrease to a value below the LLN suggests cardiotoxicity.</td>
<td>• Wide availability.</td>
<td>• Inter-observer variability.</td>
</tr>
<tr>
<td>- 3D-based LVEF</td>
<td>• GLS: &gt;15% relative percentage reduction from baseline may suggest risk of cardiotoxicity.</td>
<td>• Lack of radiation.</td>
<td>• Image quality.</td>
</tr>
<tr>
<td>- 2D Simpson’s LVEF</td>
<td></td>
<td>• Assessment of haemodynamics and other cardiac structures.</td>
<td>• GLS: inter-vendor variability, technical requirements.</td>
</tr>
<tr>
<td>- GLS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nuclear cardiac imaging (MUGA)</strong></td>
<td>• &gt;10 percentage points decrease in LVEF with a value &lt;50% identifies patients with cardiotoxicity.</td>
<td>• Reproducibility.</td>
<td>• Cumulative radiation exposure.</td>
</tr>
<tr>
<td><strong>Cardiac magnetic resonance</strong></td>
<td>• Typically used if other techniques are non-diagnostic or to confirm the presence of LV dysfunction if LVEF is borderline.</td>
<td>• Accuracy, reproducibility.</td>
<td>• Limited structural and functional information on other cardiac structures.</td>
</tr>
<tr>
<td><strong>Cardiac biomarkers:</strong></td>
<td>• A rise identifies patients receiving anthracyclines who may benefit from ACE-I's.</td>
<td>• Detection of diffuse myocardial fibrosis using T1/T2 mapping and ECVF evaluation.</td>
<td>• Limited availability.</td>
</tr>
<tr>
<td>- Troponin I</td>
<td>• Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs further investigation.</td>
<td>• Accuracy, reproducibility.</td>
<td>• Patient’s adaptation (claustrophobia, breath hold, long acquisition times).</td>
</tr>
<tr>
<td>- High-sensitivity Troponin I</td>
<td></td>
<td>• Wide availability.</td>
<td></td>
</tr>
<tr>
<td>- BNP</td>
<td></td>
<td>• High-sensitivity.</td>
<td></td>
</tr>
<tr>
<td>- NT-proBNP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

Sequential measurement of ejection fraction (EF) is used in a variety of conditions, perhaps most commonly in the assessment of potential cardiotoxicity from chemotherapy or immune therapy in patients with malignancies (1). Cardiotoxicity is most commonly defined as a reduction of the left ventricular (LV) EF of \( \leq 5\% \) to \( < 55\% \) with symptoms of heart failure or asymptomatic reduction of the LVEF of \( > 10\% \) to \( < 55\% \) (2). Because decisions regarding cessation of lifesaving therapy (3) are based on changes in EF values (4,5), it is important that EF measurement should not only be accurate but also have the lowest temporal variability such that a change in EF truly represents cardiotoxicity.

References

From the Department of Cardiology, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received June 30, 2013; revised manuscript received August 24, 2013; accepted September 6, 2013.

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Echocardiography remains the most common modality for EF measurement, but the method for EF measurement with the lowest temporal variability is unknown. Although 3-dimensional echocardiography (3DE) has been shown to be more accurate than 2-dimensional echocardiography (2DE) for both ventricular volume and EF measurements when compared with cardiac magnetic resonance imaging (6,7), no head-to-head comparison of 3DE with 2D meth...
Even in experimental conditions, the minimal detectable difference by 2DE is greater than the magnitude of change used to adjudicate CTRCD (10%) - posing concerns that LVEF by 2DE may fail to detect small changes in LV contractility.

- 3DE has the best intra- and inter-observer as well as test-retest variability.

- 3DE contrast not recommended - blooming and attenuation artifacts may hinder the delineation of structures such as the mitral valve, with the resultant variability in contouring of the left ventricle.
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.
3D with Contrast
Early detection of toxicity
Normal values
Normal Range of Left Ventricular 2-Dimensional Strain
– Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) Study –

Kiyohiro Takigiku, MD; Masaaki Takeuchi, MD; Chisato Izumi, MD; Satoshi Yuda, MD; Konomi Sakata, MD; Nobuyuki Ohte, MD; Kazuaki Tanabe, MD; Satoshi Nakatani, MD on behalf of the JUSTICE investigators
### Justice Study

**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>
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</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>
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<td></td>
<td></td>
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</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>
<td></td>
</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>0.0668</td>
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</table>

Males >16.8 % / Females >18.6%
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 Plana, 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
<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>usTnI &gt;30 pg/mL</td>
<td>11/23 (48%) (0.27–0.69)</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 usTnI &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 usTnI &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 usTnI, ultrasensitive troponin I.
Long strain is peak systolic longitudinal myocardial strain.
The 95% exact CIs are provided in brackets.
Independent and Incremental Value of Deformation Indices for Prediction of Trastuzumab-Induced Cardiotoxicity

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

5% or an asymptomatic 10% reduction to an EF <55%1,3,8 However, EF is an imperfect parameter for the detection of cardiotoxicity because of its inherent variability; the 95% confidence interval (CI) for EF measurement exceed 0.10. Moreover, EF fails to detect early subtle changes, and when reduced, it reflects a marker of advanced myocardial damage accompanied by a poor prognosis.1,2,5 Deformation parameters such as strain and strain rate have been useful to detect subclinical myocardial dysfunction1,2,6 but the incremental value to traditional clinical variables and EF is unknown. Thus, we sought (1) to elucidate the optimal parameter for early recognition of cardiotoxicity and (2) to ascertain whether deformation indices are incremental to clinical risk factors and baseline...
<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>-11.1% (95% CI 8-15) change</td>
<td>65%</td>
<td>94%</td>
</tr>
</tbody>
</table>
Recommended frequency of testing

ANTHRACYCLINES:

Initiation of regimen potentially associated with Type I toxicity

Baseline evaluation of LVEF
- 3DE (preferred) / 2DE (consider contrast)
- GLS, Troponin I

LVEF < 53%
- GLS < LLN
- + Troponins

Cardiology consultation

LVEF > 53%
- GLS > LLN
- - Troponins

F/U at completion of therapy, and 6 months later

HERCEPTIN:

Initiation of trastuzumab after regimen associated with Type I toxicity

Baseline evaluation of LVEF
- 3D (preferred) / 2D (consider contrast)
- GLS, Troponin I

LVEF < 53%
- GLS < LLN
- + Troponins

Cardiology consultation

LVEF > 53%
- GLS > LLN
- + Tn I

F/U every 3 months during therapy, and 6 months later
Suggested Echo definitions

- **CANCER THERAPEUTICS-RELATED CARDIAC DYSFUNCTION**
  - A decrease in LVEF of >10% to a value <53% confirmed by repeated cardiac imaging 2 to 3 weeks later.

- **SUBCLINICAL LV DYSFUNCTION**
  - A relative decrease in GLS of >15% confirmed by repeated cardiac imaging 2 to 3 weeks later.

* The data supporting the initiation of cardioprotection for the treatment of subclinical LV dysfunction is limited.
Integrated approach
Case Presentation

- 47 year old female
- Invasive ductal carcinoma (ER-, PR-, Her2-neu+)
- Docetaxel, Carboplatinum and Trastuzumab followed by mastectomy
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
Initiation of trastuzumab

Baseline evaluation of LVEF
3DE (preferred) / 2DE (consider contrast)
GLS or Troponin I

LVEF < 53%*
GLS < LLN**
+ Troponins

Cardiology consultation

LVEF > 53%
GLS > LLN**
- Troponins

F/U every 3 months
during therapy

* Consider confirmation with CMR.
** LLN = Lower limit of normal. Please refer to Table 4 for normal GLS values based on vendor, gender and age.
Case Presentation

• Baseline 3D EF 65%
Case presentation

- Follow up EF at 3 months 58%
- What to do?
Subclinical LV Dysfunction

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%
Figure 3. Stages in the development of HF and recommended therapy by stage.

At Risk for Heart Failure

**STAGE A**
- At high risk for HF but without structural heart disease or symptoms of HF

- e.g.: Patients with
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesity
  - Metabolic syndrome
  - Using cardioactive agents
  - With family history of cardiomyopathy

**THERAPY**
- Goals:
  - Heart healthy lifestyle
  - Prevent vascular, coronary disease
  - Prevent LV structural abnormalities

- Drugs:
  - ACEI or ARB as appropriate
  - Beta-blockers as appropriate

- In selected patients:
  - ICD
  - Revascularization or valvular surgery as appropriate

**STAGE B**
- Structural heart disease but without signs or symptoms of HF

- e.g.: Patients with:
  - Previous MI
  - LV remodeling including LHF and low EF
  - Asymptomatic valvular disease

**THERAPY**
- Goals:
  - Control symptoms
  - Improve HRODL
  - Prevent hospitalization
  - Prevent mortality

- Drugs for routine use:
  - Diuretics for fluid retention
  - ACEI or ARB
  - Beta-blockers
  - Aldosterone antagonists

- Drugs for use in selected patients:
  - Metformin/dapagliflozin
  - ACEI and ARB
  - Digoxin

- In selected patients:
  - CRT
  - ICD
  - Revascularization or valvular surgery as appropriate

**STAGE C**
- Structural heart disease with prior or current symptoms of HF

- e.g.: Patients with:
  - Known structural heart disease and HF signs and symptoms

- Development of symptoms of HF

- Refractory symptoms of HF despite GDMT

- e.g.: Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

**THERAPY**
- Goals:
  - Control symptoms
  - Improve HRODL
  - Reduce hospital readmissions
  - Establish patient's end-of-life goals

- Options:
  - Advanced care measures
  - Heart transplant
  - Chronic therapies
  - Temporary or permanent MCS
  - Experimental surgery or drugs
  - Palliative care and hospice
  - ICD deactivation
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

Background—Chemotherapy with trastuzumab and anthracycline is associated with incident heart failure (HF) in patients...
920 consecutive patients with breast cancer (age 52.3±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±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).
• Conclusions—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.
Improvement in LV Dysfunction
Current concerns

- Cost-effectiveness data on sequential imaging studies is lacking
- Borderline adequate test-re-test variability vs. echo cut-offs used to define real interval change
- Limited data re course of action once you detect cardio-toxicity?
Conclusions

- Limited data

- LVEF $\Delta 10\%$ on rpt testing defines echo-based CTRCD

- GLS $\Delta 15\%$ may be used to detect subclinical LVD

- Repeat study 2-3 weeks later

- Initiation of BB is first step