Potential use of cardiac biomarkers in cardio-oncology

Antonio Buño Soto
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Hospital Universitario La Paz – Madrid
D Cardinale said:

“The best treatment for chemotherapy-induced cardiotoxicity is its prevention in the first earliest stages”
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“The **best treatment for chemotherapy-induced cardiotoxicity is its prevention in the first earliest stages**”
Biomarkers

WHO definition
Any substance, structure, or process that can be measured in the body (or its products) that influences or predicts the incidence or outcome of disease → can include physiologic tests, clinical images, genetic variants, and biopsies of tissue specimens.

Ideal biomarker in blood samples
- Sensitivity (baseline close to zero; rapid rise when illness)
- Specificity (exclusivity of a disease; rise in accordance to injury severity)
- Easy to measure (analytics and preanalytics)
- 24h available with short TAT
- Low individuality index
- Low biological variation
- Good balance cost / efectivity
Cardiac biomarkers and cardiotoxicity

Injury biomarkers
- Cardiac troponins
  - Conventional
  - High sensitivity

Function biomarkers
- Natriuretic peptides
  - NT-proBNP
  - BNP

Other biomarkers
- Myeloperoxidase
  - Galectine 3
  - GDF-15
Cardiac biomarkers and cardiotoxicity

**Injury biomarkers**
- Cardiac troponins
  - Conventional
  - High sensitivity

**Function biomarkers**
- Natriuretic peptides
  - NT-proBNP
  - BNP

**Other biomarkers**
- Myeloperoxidase
- Galectine 3
- GDF-15
Troponina cardiaca

- Complejo troponina:
  - transmisión señal intracelular del Ca²⁺
  - interacción actina-miosina

- Presente en músculo estriado y cardiaco (no en liso)

- Hay isoformas específicas de músculo cardiaco (genes distintos)

- Un 7% TnT y 4% TnI disuelto citoplasma miocardiocito → liberación bifásica

- Rápida liberación

- cTnI libera 4-6h del daño → 7-10 días

- cTnT → 7-14 días
Analytical Methods (I or T)

- Conventional
- Improved sensitivity
- High sensitivity troponin
- New high sensitivity troponin
High sensitivity troponin
Conventional troponin

NATURE REVIEWS CARDIOLOGY; 2017
Cardiac troponin

Improved sensitivity troponin

Conventional

Improved sensitivity

Plasma troponin concentration

Young, healthy
Elderly, chronic disease
Myocardial injury
Myocardial infarction
High sensitivity troponin

Conventional

Improved sensitivity

High sensitivity
New high sensitivity troponin

Conventional

Improved sensitivity

High sensitivity

New high sensitivity
Cardiac troponin: causes of increase

TROPONIN IS AN INJURY BIOMARKER
**High sensitivity troponin**

- CV <10% at p99
- Measures troponin values in at least 50% of healthy individuals

<table>
<thead>
<tr>
<th>Company/platform/assay</th>
<th>LoD, ng/L</th>
<th>99th, M/F, ng/L</th>
<th>% CV at 99th</th>
<th>10% CV, ng/L</th>
<th>% Normals Measurable &gt;LoD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott ARCHITECT hs-cTnl</td>
<td>1.2</td>
<td>34/16</td>
<td>5</td>
<td>3</td>
<td>83</td>
</tr>
<tr>
<td>Beckman Coulter Access hs-cTnl</td>
<td>2.5</td>
<td>52/23</td>
<td>&lt;10</td>
<td>8</td>
<td>80</td>
</tr>
<tr>
<td>Ortho-Clinical Diagnostics hs-cTnl</td>
<td>1.0</td>
<td>19/16</td>
<td>&lt;10</td>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>Singulex Errena hs-cTnl</td>
<td>0.09</td>
<td>36/30</td>
<td>5</td>
<td>0.9</td>
<td>100</td>
</tr>
<tr>
<td>Siemens Vista hs-cTnl</td>
<td>0.8</td>
<td>55/33</td>
<td>5</td>
<td>3</td>
<td>86</td>
</tr>
</tbody>
</table>
• Recommended as cut-off threshold for clinical use

• Imprecision (CV) below 10%

• Factors that influence:
  – Gender: men higher than women
  – Age: higher overall above 60y

• Very important, how to define healthy population

• Calculated according to guidelines
## Table 2. Measurable values among hs-cardiac troponin assays using sex-specific cutoffs.

<table>
<thead>
<tr>
<th>Manufacturer-analyzer-assay</th>
<th>No. of results</th>
<th>LoD, ng/L</th>
<th>99th percentile, ng/L</th>
<th>Excluded values above the 99th percentile, n</th>
<th>Measurable values ≥LoD–99th percentile</th>
<th>Proportion of undetectable values (&lt;LOD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott ARCHITECT hs-cTnl</td>
<td></td>
<td>1.9</td>
<td>F: 16</td>
<td>F: 2</td>
<td>F: 67% (168/250)</td>
<td>F: 33% (82/250)</td>
</tr>
<tr>
<td>Beckman Access 2 hs-cTnl</td>
<td></td>
<td>2.5</td>
<td>F: 9</td>
<td>F: 12</td>
<td>F: 73% (175/240)</td>
<td>F: 27% (65/240)</td>
</tr>
<tr>
<td>Roche Cobas e601 hs-cTnT</td>
<td></td>
<td>5</td>
<td>F: 14</td>
<td>F: 1</td>
<td>F: 7% (17/251)</td>
<td>F: 93% (234/251)</td>
</tr>
<tr>
<td>Siemens Dimension Vista hs-cTnI</td>
<td></td>
<td>0.5</td>
<td>F: 33</td>
<td>F: 5</td>
<td>F: 82% (191/234)</td>
<td>F: 18% (43/234)</td>
</tr>
<tr>
<td>M: 264</td>
<td></td>
<td>M: 55</td>
<td></td>
<td>M: 3</td>
<td>M: 90% (234/261)</td>
<td>M: 10% (27/261)</td>
</tr>
<tr>
<td>Singulex Erenna hs-cTnl</td>
<td></td>
<td>0.1</td>
<td>F: 15</td>
<td>F: 8</td>
<td>F: 100% (244/244)</td>
<td>F: 0% (0/0)</td>
</tr>
<tr>
<td>M: 272</td>
<td></td>
<td>M: 27</td>
<td></td>
<td>M: 5</td>
<td>M: 100% (267/267)</td>
<td>M: 0% (0/0)</td>
</tr>
</tbody>
</table>

* F, female; M, male.
Serum cardiac biomarkers (troponins, natriuretic peptides)

- Useful in the surveillance and monitoring during and after treatment in patients at risk for cardiac dysfunction
- Use of BNP and NT-proBNP in asymptomatic patients with cancer remains largely investigational
- Need for additional studies to clarify the role of troponins and NPs assessment during cancer therapy
Serum cardiac biomarkers (troponins, natriuretic peptides)

- CV evaluation before anticancer treatment
- CV monitoring during and after anticancer treatment
- Although it is not yet established whether their routine monitoring is useful in predicting cardiotoxicity, and this needs to be examined in prospective studies, there is a strong case to incorporate their use in the clinical trial setting.
Algorithm for the management of cardiotoxicity in patients receiving anthracyclines
**What the guidelines say**

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

European Heart Journal (2016) 37, 2768–2801

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Proposed diagnostic tools for the detection of cardiotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technique</strong></td>
<td><strong>Currently available diagnostic criteria</strong></td>
</tr>
<tr>
<td>Cardiac biomarkers: - Troponin I - High-sensitivity Troponin I - BNP - NT-proBNP</td>
<td>• A rise identifies patients receiving anthracyclines who may benefit from ACE-Is. • Routine role of BNP and NT-proBNP in surveillance of high-risk patient needs further investigation.</td>
</tr>
</tbody>
</table>
Serum cardiac biomarkers (troponins, natriuretic peptides)

- Possible use for monitoring during and after anticancer treatment
Serum cardiac biomarkers (troponins, natriuretic peptides)

- Elevated troponins in patients receiving cardiotoxic chemotherapy may be a sensitive measurement for the early detection of toxicity.

- Serum NPs, although likely reflective of elevated filling pressures, may be less consistent in the early identification of Cancer therapeutics–related cardiac dysfunction.
Cardiovascular Disease in Survivors of Childhood Cancer: Insights Into Epidemiology, Pathophysiology, and Prevention

What the guidelines say

Cardiovascular Disease in Survivors of Childhood Cancer: Insights Into Epidemiology, Pathophysiology, and Prevention

What surveillance modality should be used?

Echocardiography is **recommended** as the primary cardiomyopathy surveillance modality for assessment of left ventricular systolic function in survivors treated with anthracyclines and/or chest radiation.

Radionuclide angiography or cardiac magnetic resonance imaging may be **reasonable** for cardiomyopathy surveillance in at risk survivors for whom echocardiography is not technically feasible/optimal.

Assessment of cardiac blood biomarkers (e.g., natriuretic peptides and troponins) is **not recommended** as the primary cardiomyopathy surveillance in at-risk survivors.

“What the guidelines say... cardiac blood biomarkers... **is not recommended** for surveillance in survivors.”
The role of cardiac biomarkers in cardio-oncology

Elizabeth Riddell, MD, PharmD, Daniel Lenihan, MD*

Cardio-Oncology Center of Excellence, Cardiovascular Division, Washington University in St. Louis, St. Louis, MO
**Table 1**  
Selected clinical studies investigating troponin as a tool for detecting cardiotoxicity.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient population</th>
<th>Patient sample size</th>
<th>Chemotherapy regimen</th>
<th>Value cutoff for troponin</th>
<th>Timing of measurement</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ye et al</td>
<td>HER2 breast cancer</td>
<td>78</td>
<td>Doxorubicin, cyclophosphamide, paclitaxel, trastuzumab</td>
<td>≥30 pg/mL</td>
<td>Biomarkers measured at baseline, 3, and 6 mo; IVEF was measured at baseline, 3, 6, 9, 12, and 15 mo</td>
<td>Tnl and MPO rise at 3 mo was associated with subsequent cardiotoxicity</td>
</tr>
<tr>
<td>Savaya et al</td>
<td>HER2 breast cancer</td>
<td>81</td>
<td>Anthracycline, paclitaxel, trastuzumab</td>
<td>≥0.41 ng/mL</td>
<td>Biomarkers were measured at baseline, 3, 6, 9, 12, and 15 mo</td>
<td>Elevated Tnl at 3 mo was predictive of subsequent cardiotoxicity</td>
</tr>
<tr>
<td>Onitilo et al</td>
<td>HER2 breast cancer</td>
<td>54</td>
<td>Trastuzumab adjuvant</td>
<td>≥0.01 ng/mL</td>
<td>Biomarkers measured at baseline, then every 3 wk up to 1 y</td>
<td>-Only hs-CRP was associated with a clinically significant decline in IVEF -Tnl was not predictive of subsequent cardiotoxicity</td>
</tr>
<tr>
<td>Morris et al</td>
<td>HER2 breast cancer</td>
<td>95</td>
<td>Doxorubicin, cyclophosphamide, paclitaxel, trastuzumab</td>
<td>&gt;0.04 ng/mL (DP/HCC)</td>
<td>Biomarkers measured every 2 wk during chemotherapy and at 6, 9, and 18 mo</td>
<td>-Tnl rise (peak ~14 wk) preceded max decline in IVEF but did not predict or relate to max IVEF decline -CRP did not correlate with IVEF</td>
</tr>
<tr>
<td>Cardinale et al</td>
<td>Breast cancer</td>
<td>251</td>
<td>Anthracycline, cyclophosphamide, paclitaxel, trastuzumab</td>
<td>&gt;0.08 ng/mL</td>
<td>Biomarkers were assessed at baseline, every 3 mo during therapy, and every 6 mo after</td>
<td>-Troponin level did not correlate with LV dysfunction</td>
</tr>
<tr>
<td>Feola et al</td>
<td>Breast cancer</td>
<td>53</td>
<td>Cyclophosphamide, epirubicin, fluorouracil ± locoregional XRT</td>
<td>&gt;0.03 ng/mL</td>
<td>Biomarkers and MUGA were assessed at baseline, 1 mo, 1 y, and 2 y</td>
<td>-Troponin level did not correlate with LV dysfunction</td>
</tr>
</tbody>
</table>
### Troponin as a tool for detecting cardiotoxicity

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient population</th>
<th>Chemotherapy regimen</th>
<th>Value cutoff for troponin</th>
<th>Timing of measurement</th>
<th>Results</th>
</tr>
</thead>
</table>
| Cardinale et al[^1] | Advanced or primary resistant breast CA (326), high grade NHL (264), myeloma (44), poor prognosis Hodgkin’s disease (30), relapsed or refractory ovarian CA (16), SCCL (10), germ-cell tumors (8), and Ewing’s sarcoma (5) | High-dose chemotherapy (Some regimens did not contain an anthracycline) | >0.08 ng/mL | -Troponin was measured soon after chemo administration and 1 mo after  
-LVEF by TTE was evaluated at baseline, 1, 3, 6, and 12 mo after treatment  
-A persistent Tnl increase was associated with a greater incidence of cardiac events  
-PPV was 84% for patients with persistent troponin elevation  
-NPV was 99% for patients without troponin elevation | Positive Tnl was associated with a reduction in LVEF during 12 mo of follow-up. |
| Cardinale et al[^2] | High risk breast cancer                       | Epirubicin, Taxotere, ifosfamide, Carboplatin, Etoposide, Cyclophosphamide (Some regimens did not contain an anthracycline) | >0.05 ng/mL | - Tnl was measured before, immediately after, and then 12, 24, 36, and 72 h after every single cycle of chemo | -Tnl was measured before, immediately after, and then 12, 24, 36, and 72 h after every single cycle of chemo  
-Tnl elevation predicted future decline in LVEF |
| Kremer et al[^2]  | Various malignancies (pediatric): 16 with solid tumor and 22 with leukemia or lymphoma | Anthracyclines (33) or mitoxantrone (5)                                                                                         | >0.01 ng/mL | -TnlT was measured prior to each chemo cycle, 4.6 h after each chemo cycle and 24 h after each chemo cycle.  
-Measurement of LV shortening fraction was measured using M-mode echo before, during, and after chemo | -Tnl was measured in the first 24 hours after administration of chemotherapy did not predict cardiotoxicity or cardiac dysfunction |
| Cardinale et al[^2] | Breast Cancer, ovarian cancer, SCCL, Hodgkin’s lymphoma, NHL | Various regimens with epirubicin, etoposide, taxotere, carboplatin, and cyclophosphamide | >0.5 ng/mL | Tnl was measured before, immediately after, and then 12, 24, 36, and 72 h after every single cycle of chemo  
-TTEs were performed at baseline, 1, 2, 3, 4, and 7 mo after chemo | -Tnl elevation predicted future decline in LVEF |
Natriuretic peptides for the monitoring of cardiotoxicity

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient population</th>
<th>Patient sample size</th>
<th>Chemotherapy regimen</th>
<th>Normal reference value</th>
<th>Timing of measurement</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Iulis et al(^{22})</td>
<td>Breast CA</td>
<td>100</td>
<td>Anthracyclines, Taxanes, trastuzumab</td>
<td>Not defined</td>
<td>NT-pro BNP and LVEF were measured at baseline, 3, 6, and 12 mo</td>
<td>Significant increase in NT-proBNP (P &gt; 0.0001) was seen before LVEF decrease became evident. There was a correlation between increased NT-proBNP after chemo and predicted 1 year mortality. BNP was superior for the detection of cardiac events than LVEF. BNP and LVEF independently predicted hospitalization for CHF. Only BNP showed prognostic value in predicting mortality. Neither baseline levels of BNP or change in level of BNP during therapy were predictive of change in LVEF. BNP cannot replace measurement of LVEF. Persistent increase in NT-proBNP was associated with development of cardiac dysfunction.</td>
</tr>
<tr>
<td>Lenihan, D et al(^{25})</td>
<td>Sarcoma, lymphoma, breast cancer</td>
<td>109</td>
<td>Anthracyclines</td>
<td>BNP &gt; 100 pg/mL</td>
<td>Pre- and postcycle</td>
<td></td>
</tr>
<tr>
<td>Skovgaard et al(^{26})</td>
<td>Breast CA, hematologic malignancies, uterine/ovarian CA</td>
<td>333</td>
<td>Anthracyclines</td>
<td>BNP &lt; 100 pg/mL</td>
<td>No standard intervals for measurement</td>
<td></td>
</tr>
<tr>
<td>Daugaard et al(^{28})</td>
<td>Various advanced cancers (malignant disease)</td>
<td>107</td>
<td>Anthracyclines</td>
<td>Not defined</td>
<td>No standard intervals for measurement but started after 1/2 cumulative dose of anthracycline was administered</td>
<td></td>
</tr>
<tr>
<td>Sandri et al(^{24})</td>
<td>Various aggressive malignancies</td>
<td>52</td>
<td>High-dose chemo-based on study institution protocol</td>
<td>NT-pro BNP cutoff values differed based on age and gender. &gt;153 ng/mL for women &lt; 50 y; &gt;88 ng/mL for men &lt; 50 y; &gt;334 ng/mL for women &gt; 50 y; &gt;227 ng/mL for men &gt; 50 y</td>
<td>NT-pro BNP levels were drawn at baseline (before each treatment), at the end of chemo infusion, and 12, 24, 36, and 72 h after the end of each chemo cycle. TTE was performed at baseline and at 4 and 12 mo after treatment</td>
<td></td>
</tr>
<tr>
<td>Suzuki et al(^{23})</td>
<td>Hematologic malignancies</td>
<td>27</td>
<td>Anthracyclines</td>
<td>BNP &lt; 19 pg/mL</td>
<td>BNP levels were drawn at baseline and after chemo administration</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient population</th>
<th>Patient sample size</th>
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<th>Normal reference value</th>
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<th>Results</th>
</tr>
</thead>
</table>
“Current clinical research in cardio-oncology **has not firmly established** these biomarkers as effective screening tools for cardiotoxicity in a broad range of populations or cancer therapeutics but the **future is bright for these markers as indicators of cardiac risk as well as tools to ensure cardiac safety**.”
Potential explanations

• The timing of serum troponin collection
• Studies with chemotherapy regimens that are now out of date
• Different methods for troponin measurement
• Several cut-offs used to consider a test as positive
• Percentage of cardiac injury of chemotherapy agents is variable
• 703 pacientes con cáncer y QT a altas dosis sin cardiopatía previa

• Troponina medida por método convencional. Cut-off 0,08 ng/mL

• Medición de TnI basal y al mes del tto (inmediatamente después, 12, 24, 36, 72h)
  Considera el valor más alto:
  o Al terminar 33%; tras 12h 22%; tras 24h 8%; tras 36h 24%; tras 72h 13%
Potential explanations

Prognostic Value of Troponin I in Cardiac Risk
Stratification of Cancer Patients Undergoing
High-Dose Chemotherapy

Daniela Cardinale, MD; Maria T. Sanchi, MD; Alessandro Colombo, MD; Nicola Colombo, MD;
Matteo Boeri, MD; Giuseppina Lunetta, MD; Massimiliano Civelli, MD; Fedro Pecorari, MD;
Giovanni Marzetti, MD; Cesare Formentini, MD; Carlo M. Cipolla, MD

Figure 3. Cumulative cardiac events rate in 3 study groups. 
\( P < 0.001 \) for Tnl\(^{++} \) vs Tnl\(^{+/-} \) and Tnl\(^{-/-} \), and for Tnl\(^{+/-} \) vs Tnl\(^{-/-} \).
Advantages of cardiac biomarkers

- “Easy to use” - availability
- Minimally invasive
- Costs less than echocardiogram and than a nuclear LVEF assessment
- Without direct damage for patient
- Interpretation of results doesn't depend on the experience of an operator
- Early detection of potential cardiotoxicity
- Potential high negative predictive value → allows identification of low-risk patients who will not require further cardiac monitoring
- TnI-positive patients require more strict surveillance
Possible utilities of cardiac biomarkers

• Identify patients at risk **before** cancer therapy (chemo or radio): unknown cardiac diseases vs cancer damage?

• Identify patients that develop myocardial injury **during** cancer therapies (surveillance and monitoring )

• **Monitoring** of the cardioprotective **effect** preventive treatments (dexrazoxane, nebivolol, valsartan, ...)

• Long term **follow up** of patients after cancer treatment: “personalization” of the frequency of cardiac function monitoring

• **Prognostic** value → prediction of future LVD severity
Proposal of a biomarker algorithm

Early detection

High negative predictive value
# Proposal of how to use a biomarker

<table>
<thead>
<tr>
<th>Before cancer treatment</th>
<th>After cycle 1</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>1 year follow up</th>
<th>2 years follow up</th>
<th>3 years follow up</th>
<th>4 years follow up</th>
<th>5 years follow up</th>
<th>n years follow up??</th>
</tr>
</thead>
<tbody>
<tr>
<td>hs-cTn</td>
<td>*hs-cTn</td>
<td>*hs-cTn</td>
<td>*hs-cTn</td>
<td>*hs-cTn</td>
<td>*hs-cTn</td>
<td>*hs-cTn</td>
<td>*hs-cTn</td>
<td>*hs-cTn</td>
<td>*hs-cTn</td>
<td>*hs-cTn</td>
</tr>
<tr>
<td>hs-cTn + CV risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Plus NT-proBNP / BNP when needed

10 hs-troponins in 5 years ≈ 25-30 €

* High sensitivity troponin is better than conventional, but conventional is better than nothing.
• Doxorribicina (n: 100/75) vs doxorribicina y dexrazoxano (n: 105/81)
• cTnT (cualquier valor medible) y NT-proBNP (>150 pg/mL en <1a y >100 pg/mL en >1a)
• Clara asociación entre % de aumento de BM y hallazgos ecocardiográficos
Cardiotoxicidad en la infancia

Novel approaches to the prediction, diagnosis and treatment of cardiac late effects in survivors of childhood cancer: a multi-centre observational study

Fig. 1 Data and specimen acquisition from the Acute Cohort. BIOMKR: Serum for biomarkers, ECHO: Echocardiogram, DNA: Blood or saliva for DNA, CLIN: Gather baseline clinical data

Fig. 2 Data and specimen acquisition from the Survivor Cohort. BIOMKR: Serum for biomarkers, ECHO: Echocardiogram, DNA: Blood for DNA, CMR: Cardiac Magnetic Resonance, CLIN: Gather baseline clinical data
Biomarkers has the potential to anticipate other diagnostics techniques (cell injury level)

High sensitivity troponin (not conventional) is the preferable biomarker but we need to learn how to use it

Results with natriuretic peptides are controversial

Other biomarkers are less practicable and results are inconclusive

Possible roles:
  a) Identify patients at risk before and during cancer therapy
  b) Monitoring cancer treatment or cardioprotective treatments
  c) Surveillance after treatment
  d) Prognostic value

But ... there are many questions to be solved with future investigations
Thank you