Guidelines to manage the risk of heart disease in cancer patients will soon be published by the American Society of Echocardiography. These new recommendations will guide clinicians in the use of strain imaging with echocardiography for early detection of cardiotoxicity resulting from therapies used to treat cancer.

“The goal is not to stop cancer therapy but to identify cardiotoxicity early and to protect the heart with medications so heart failure does not become a problem and the cancer treatment can be continued,” states Dr. Juan Carlos Plana, a leading echocardiologist focusing on cardiotoxicity at the Cleveland Clinic. “Currently, 17% of patients receiving treatment for the most aggressive form of breast cancer have to stop therapy due to heart issues. The sensitivity of strain echo allows early detection, so oncologists can treat their patients without fear of the downstream effects of the therapies.”

“We have learned that toxicity is not a global phenomenon, that the entire heart is not compromised,” Plana told MedPage Today in an interview. “So, a global indicator like ejection fraction could miss specific toxicity. Strain imaging, on the other hand, assesses each segment of the heart separately, even color-coding the segments, which would give physicians a much more accurate indication of cardiotoxicity as a result of cancer therapy.”

“We have been pleasantly surprised at strain imaging’s ability to prognosticate a future drop in cardiac function,” Plana said. “We have shown that strain imaging gives information three months in advance of a drop in ejection fraction.” “This type of “early warning” opens the opportunity to treat patients sooner than traditionally would be possible with cardioprotective therapies,” Plana said.

A study published in 2011 in the American Journal of Cardiology by Dr Heloisa Sawaya and colleagues, concluded that longitudinal strain echocardiography, along with plasma concentrations of cardiac troponin, predicted the development of cardiotoxicity in patients treated with anthracyclines such as Doxorubicin and Trastuzumab. They noted that as breast-cancer survival increases, cardiotoxicity with the chemotherapeutic agents becomes a more significant issue, but the two parameters might be “useful to detect chemotherapy-treated patients who may benefit from alternative therapies, potentially decreasing the incidence of cardiotoxicity and its associated morbidity and mortality.”

**Issue at Hand**

Until now, the most common non-invasive monitoring measure for cardiotoxicity among cancer patients has been left ventricle (LV) ejection fraction (EF). EF can be calculated from an echo study or a Multi Gated Acquisition (MUGA) nuclear exam. However, using standard EF tracing methods of an echo study can be prone to error (>15% variability). Research and trends indicate strain imaging provides a high quality measure for possible earlier detection of cardiotoxicity; a clinically useful, reliable and workflow-oriented strain imaging is needed for practice integration and improved patient management.
About Measurement Variability

When assessing patients undergoing therapy, clinicians evaluate change in cardiac function typically by comparing monitoring studies to the baseline study – recorded before the start of therapy. To determine if change in function is due to degradation and not to measurement variability, all measures that are derived from the speckle tracking algorithm need to be characterized and reduced in order to provide optimal monitoring for cardiotoxicity.

Figure 1 below demonstrates an example of measurement variability. The red curves depict the probability of strain measures for a patient prior to therapy (baseline) and the blue curves show the probability of strain measures at the monitoring time point (follow-up). The peaks of the curves represent the “true” strain measurement for this patient. The variation about truth can be due to variability in data acquisition, operator analysis, strain imaging processing, patient physiological condition, etc. The shift in true strain from baseline to follow-up indicates a reduction of mechanical function associated with toxicity. When a strain measurement is recorded (i.e., a value is selected from the distribution), a decision whether the patient has developed cardiotoxicity is made by the clinician. The threshold for this decision is indicated by the solid black line in figure 2. In this case, the measurement fell below the threshold line (i.e., near the baseline measurement distribution) resulting in the decision that the patient did not develop toxicity. This incorrect result is due to the large range of possible measurements indicated by the wide measurement distribution. Low measurement variability, like shown in top panel of figure 1, reduces probability of incorrect assessment.

**Red** = Baseline Measurement  
**Blue** = Follow-up Measurement

Acquisition Variability

Patients that undergo an echo study may be scanned using different ultrasound equipment operated by different technicians on each visit, introducing measurement variability. In addition, the sonographer and technique may be different on these visits. Finally, the heart itself does not always contract consistently the same way from beat to beat based on the patient’s physiology.

Speckle Tracking Analysis Variability

For every echo study, clinicians may trace the endocardium to calculate the EF and strain differently (inter-observer). In addition, even a specific clinician may trace the same endocardium differently from one time to the next (intra-observer).

Importance of Strain Imaging for Reduced Variability

The inherent difficulty with EF is the variability of the measurement process, both inter-observer and intra-observer. In addition, a noticeable change in EF will occur when the myocardium has already sustained substantial damage. Alternatively, strain imaging has the ability to detect changes in myocardium mechanics before global changes occur and has lower variability than EF measures (iii).

Recently, research has been completed to determine the efficacy of using longitudinal strain to detect cardiotoxicity. These studies indicate that a 15-20% change in longitudinal strain from the baseline study is a good indicator of cardiotoxicity. (See a summary of study data below).

<table>
<thead>
<tr>
<th>Author</th>
<th>Change in Strain for Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganame (v)</td>
<td>15%</td>
</tr>
<tr>
<td>Sawaya (iii)</td>
<td>15%</td>
</tr>
<tr>
<td>Fallah-Rad (vi)</td>
<td>17%</td>
</tr>
</tbody>
</table>
**Echolnsight for Cardio Oncology – Reduced Variability Validation**

Echolnsight for Cardio Oncology provides simultaneous strain and EF measurements in a workflow efficient manner using speckle tracking of standard DICOM image loop (i.e., vendor neutral). In order to characterize the variability of strain measurements using Echolnsight for Cardio Oncology, several research studies were conducted.

Initial studies were completed at Oregon Health Sciences University using excised pig hearts and with embedded sonomicrometry crystals. The crystals provide accurate measurements of tissue motion (invasively), and were used as the gold standard comparator for the ultrasound based strain measurements. Each heart was scanned using a GE, Siemens and Philips scanner, thus providing variability measures between different acquisitions. The results demonstrated a high agreement between each acquisition platform and with the microcrystals.(vii)

Once the ex-vivo feasibility study was completed, evaluations in a clinical setting were performed to measure variability. The first study was conducted with 7 subjects scanned with both GE and Philips scanners. These paired sets of data allow measurement of the test/re-test (i.e., sequential measurement) variability. In order to determine the inter-observer variability, two readers analyzed the data by (tracing) the myocardium on all subjects at two different times. In addition, one reader traced the myocardium on multiple heart cycles for all subjects to determine the variability induced by the heart motion alone. The variability characterization from the study is listed in the table below.

<table>
<thead>
<tr>
<th>Measure (Global)</th>
<th>Inter-Observer</th>
<th>Intra-Observer</th>
<th>Test/Re-test</th>
<th>Beat to Beat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strain</td>
<td>6.68%</td>
<td>4.34%</td>
<td>7.2%</td>
<td>5.8%</td>
</tr>
<tr>
<td>EF</td>
<td>2.72%</td>
<td>2.05%</td>
<td>6.4%</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

The key highlights from study are:
- Strain variability was below 10%
- Auto-EF (current method) was very reproducible (<7% for all variabilities)

To complete the variability characterization of Echolnsight for Cardio Oncology, data from Brigham and Women’s Hospital (BWH) was collected and analyzed. In addition to intra-observer and inter-observer variability strain characterization using Echolnsight, two other strain packages were characterized, TomTec and GE.

<table>
<thead>
<tr>
<th>Strain Correlations</th>
<th>Echolnsight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-observer</td>
<td>0.92</td>
</tr>
<tr>
<td>Inter-observer</td>
<td>0.91</td>
</tr>
</tbody>
</table>
Introducing EchoInsight for Cardio Oncology

Until now, strain imaging has traditionally been research-oriented, cumbersome to use and usually vendor specific. EchoInsight is a validated vendor-neutral software platform that provides visualization and analysis with practical strain imaging for streamlined workflow in the clinical environment. Developed in collaboration with cardiologists, EchoInsight aids clinicians in transforming the way they analyze and interpret echo studies.

EchoInsight for Cardio Oncology assists clinicians to quickly and easily integrate strain imaging into their program, and improve patient management. Features include automated processing, rapid serial study comparison, global and regional longitudinal strain and EF trending with percent change from baseline, clear, concise, highly reliable and detailed visual-based reporting to aid patient management and customized integration to customer healthcare IT workflow.


