In the September issue of the Journal of the American Society of Echocardiography, Juan Carlos Plana, et al. published “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.”(i) These recommendations include echocardiographic assessment and monitoring of the heart using strain imaging for improved detection and management of oncology patients at risk for cardiotoxicity. Until now, strain imaging has been research-oriented, cumbersome to use and usually vendor specific. Strain imaging is a new technology that provides tissue motion information for improved evaluation of cardiac function.

These new recommendations include echocardiographic assessment and monitoring of LV using EF and strain imaging, along with RV using TAPSE, S’ and FAC for improved management of oncology patients at risk for cardiotoxicity. “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.”(i)

“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.”(ii)

“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.(iii) 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).(iv)
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. However, these comparative measurements are impacted by measurement variability. To determine if a measurement change truly reflects a change in cardiac function, measurement variability must be understood.

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.

Strain 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 typically only occur when the myocardium has already sustained substantial damage. Alternatively, strain imaging has the ability to detect changes in myocardium mechanical function 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 greater than 10-11% change in longitudinal strain from a 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>Negish (v)</td>
<td>≥11%</td>
</tr>
<tr>
<td>Sawaya (iii)</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Fallah-Rad (vi)</td>
<td>&gt;10%</td>
</tr>
</tbody>
</table>
**EcholInsight – Reduced Variability Validation**

EcholInsight 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 EcholInsight for Cardio Oncology, several research studies were conducted.

In addition to the ex-vivo feasibility study, 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 allow assessment of the test/re-test (i.e., sequential measurement) variability. In order to determine the inter- and intra-observer variability, two readers analyzed the data two different times. In addition, one reader analyzed multiple heart beats for all subjects to determine the variability induced by the beat to beat changes in heart function. 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>
</tbody>
</table>

The low variabilities demonstrated by the study (all <7.2%) allow for repeatable strain measurements, which are critical for monitoring cardiac function.

Further assessment of EcholInsight measurement variability was done at Brigham and Women’s Hospital. Inter-observer and intra-observer correlations were calculated for 24 subjects. The study demonstrated excellent agreement between measurements, with correlations exceeding 0.90.

<table>
<thead>
<tr>
<th>Strain Correlations</th>
<th>EcholInsight</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 EcholInsight**

Until now, strain imaging has traditionally been research-oriented, cumbersome to use, and usually vendor specific. EcholInsight 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, EcholInsight aids clinicians in transforming the way they analyze and interpret echo studies.
Echoln Insights Features

Echoln Insights is designed for the clinical environment and can assist in optimizing your cardio oncology program, and provides:

- Clinical strain imaging for improved confidence in assessment and monitoring of wall mechanics
- Automated linear, volumetric and area measurements for improved efficiency and standardization. RV systolic measurements, such as TAPSE, S’ and FAC, are also automatically included.
- Rapid study comparison for comprehensive assessment and monitoring of patients
- Fast and intuitive features for improved analysis, interpretation and trending
- DICOM structured reporting for improved patient management
- Vendor neutral platform
- Premier consultative customer support

A study presented at ASE 2013, from a team at University of Chicago Medicine, demonstrated improved monitoring of patients at risk for cardiotoxicity using Echoln Insights for Cardio Oncology. (ix) Results indicated Echoln Insights for Cardio Oncology to be a high quality, efficient application for comprehensive assessment and serial comparison of LV function. “Our study demonstrates Echoln Insights for Cardio Oncology offers visualization and analysis that allows for quick, easy and accurate interpretation of LV function over time,” said Dr. Jeanne DeCara, University of Chicago Medicine. “Echoln Insights is a promising software application that may assist in the follow-up of patients undergoing potentially cardiotoxic treatments, such as chemotherapy.”

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