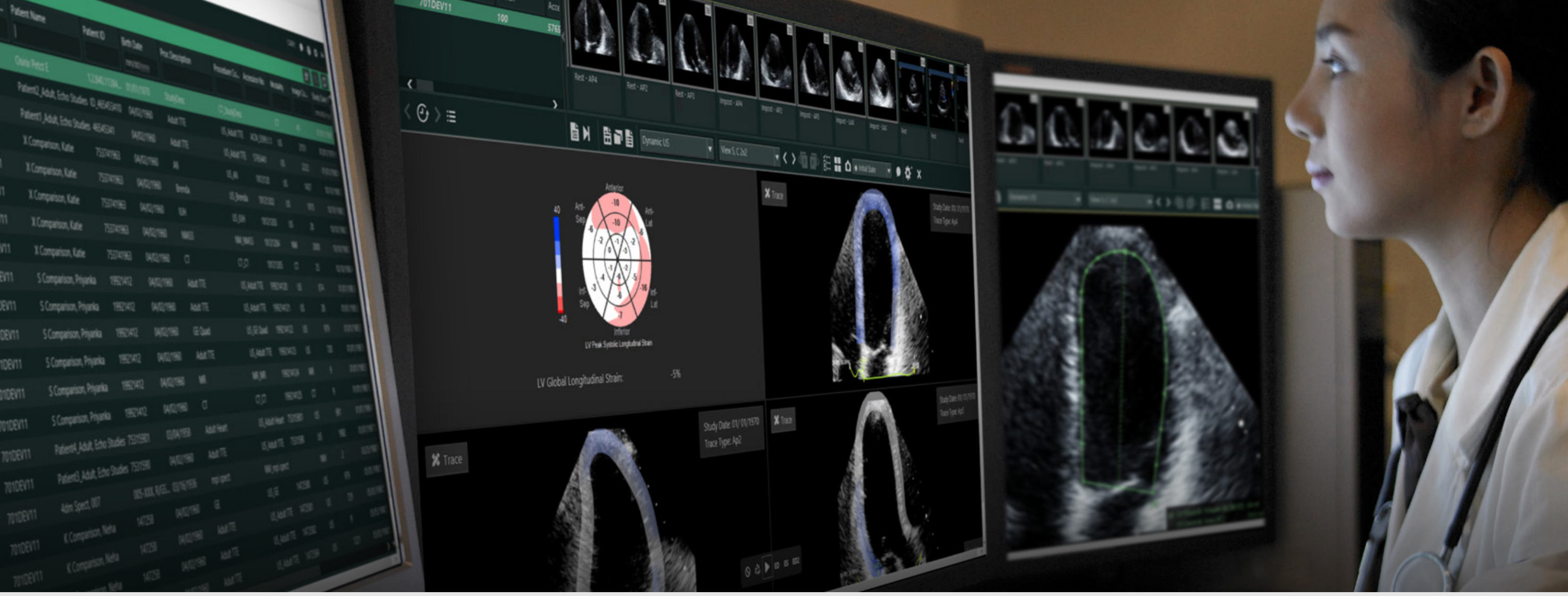


EchoInsight®

EPSILON IMAGING®

Understanding the Importance of Monitoring Cancer Patients for Cardiotoxicity: Strain Imaging

Cancer patients have on average a 2-6 times higher mortality risk due to cardiovascular disease than the general population.(i) Globally, cancer is diagnosed in 12.7 million patients annually, and cancer incidence is projected to increase by 40% in high-income countries from 2008 to 2030.(ii) Chemotherapy is the main treatment for most cancers and improves survival, but is associated with significant cardiotoxicity.(ii) In recent years, hospitals have implemented cardio-oncology programs that combine cardiac and cancer care enabling patients to continue with their cancer treatment while minimizing damage to the heart.

Echocardiography, specifically myocardial strain imaging, plays a central role in detecting the early signs of cardiotoxicity in the field of cardio-oncology. Strain imaging brings valuable benefit to the clinical setting, which is changing the way clinicians diagnose and provide therapy.

In 2014, recommendations for imaging evaluation of patients undergoing cancer therapy were published in the Journal of the American Society of Echocardiography by Juan Carlos Plana, et al. entitled, “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.”(iii) 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. The recommendations include echocardiographic assessment and monitoring of LV using strain imaging EF 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 echo cardiologist 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.” (iii)

“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.

Issue at Hand

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) While traditional imaging based assessment of left ventricular ejection fraction still has its place in cardiac monitoring, more advanced echocardiographic modalities, in particular, myocardial deformation imaging with speckle tracking strain analysis, show great potential for detecting early signs of cardiotoxicity.(v) 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 typically evaluate change in cardiac function 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

Figure 1

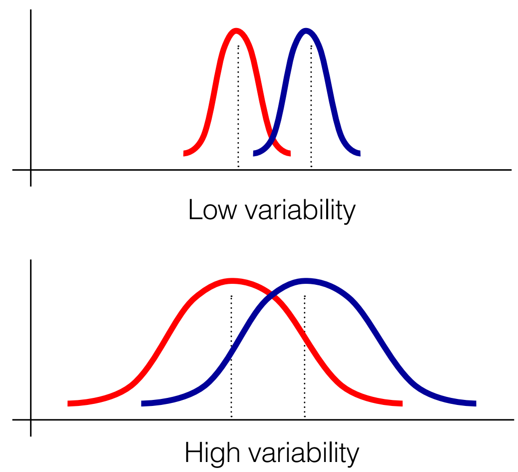
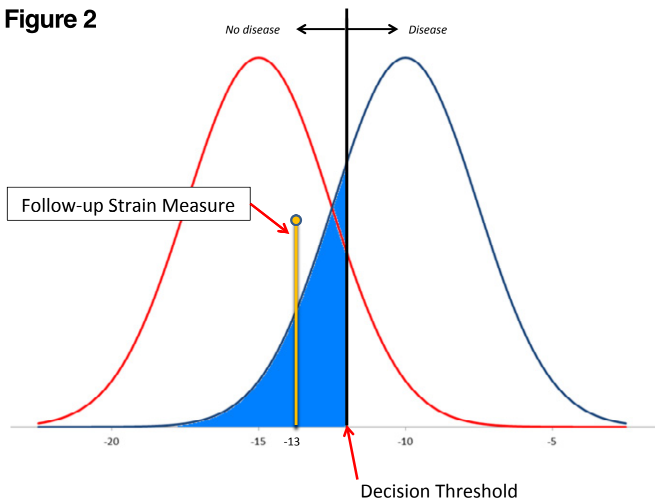


Figure 2



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

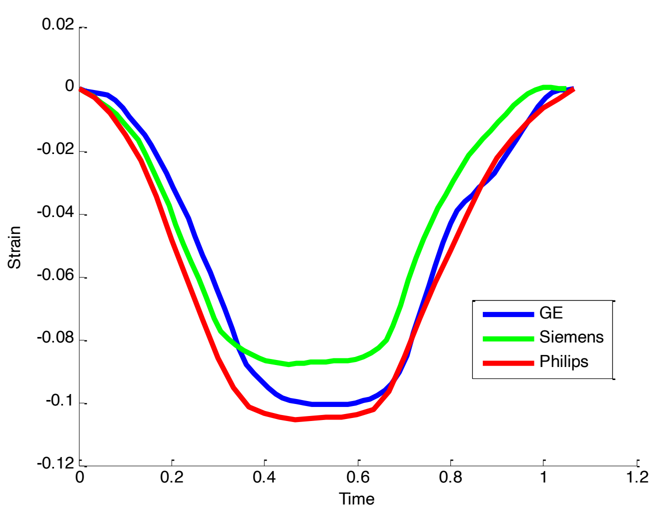
The inherent difficulty with EF is the variability of the measurement process, both inter-observer and intra-observer. In addition, a noticeable change in EF will typically only occur when the myocardium has already sustained substantial damage. Alternatively, strain imaging has the ability to detect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

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)..

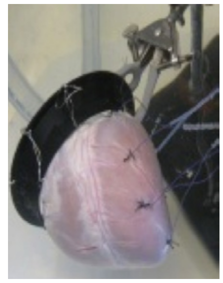
Author	Change in Strain for Detection
Negishi (ix)	≥11%
Sawaya (vi)	>10%
Fallah-Rad (x)	>10%

EchoInsight – Reduced Variability Validation

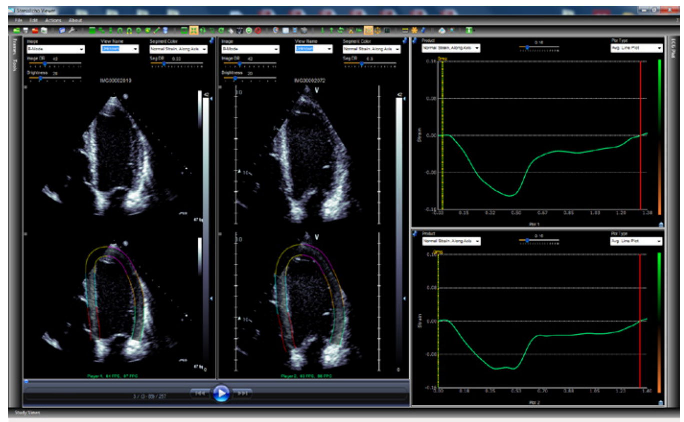
EchoInsight provides simultaneous strain and EF measurements in a workflow efficient manner using speckle tracking of standard DICOM image loop (i.e., vendor neutral). In order to characterize the variability of strain measurements using EchoInsight for cardio-oncology, several research studies were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



Corr. w/ Crystals	GE	Philips	Siemens
Strain	0.99	0.98	0.99
Strain Rate	0.93	0.98	0.96



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)



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.

Measure (Global)	Inter-Observer	Intra-Observer	Test/ Re-test	Beat to Beat
Strain	6.68%	4.34%	7.2%	5.8%

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 EchoInsight 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.

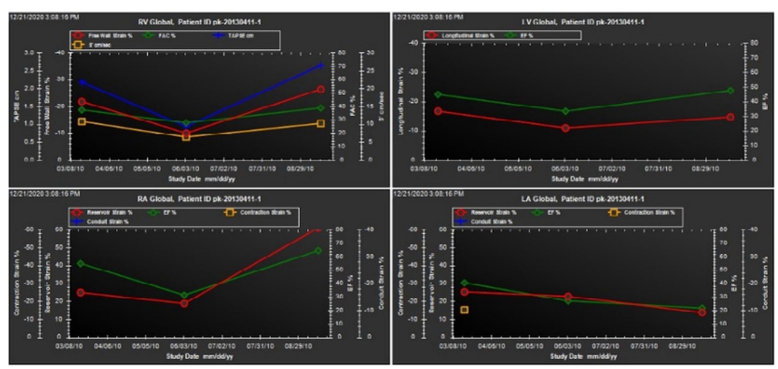
Strain Correlations	EchoInsight
Intra-observer	0.92
Inter-observer	0.91

Reimbursable CPT Code Available

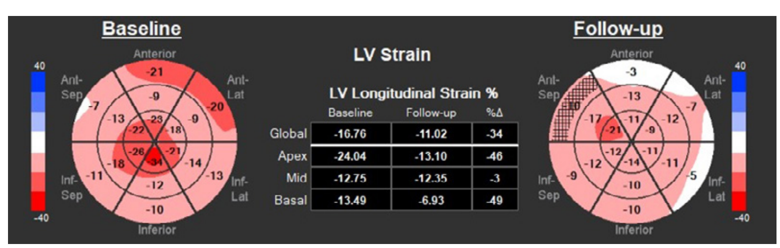
The clinical benefits in the use of strain imaging in cardio-oncology has been published in many studies which demonstrate its value. Systematic cardiac surveillance with more sensitive technologies and a higher frequency of measurements will lead to a greater incidence of detected cardiotoxicity. (viii) Patients can receive treatment of their cancer while simultaneously addressing and evaluating for cardiotoxicity, which may lead to better patient outcomes – the common goal of a cardio-oncology program. Since there are many benefits gained by using strain imaging with echo, a reimbursable Current Procedure Terminology (CPT) code +93356 to report myocardial strain imaging by speckle tracking has been established by the American Medical Association (AMA).

The myocardial strain imaging code is intended to report +93356 in conjunction various transthoracic echocardiography procedures 93303, 93304, 93306 and 93308 in addition to stress echocardiography services 93350 and 93351. (xi) Additionally, the intent is for this code to be reported once per imaging session. (xi)

EchoInsight®: Making it Easy to Incorporate Strain Imaging into a Cardio-Oncology Program



EchoInsight visualization and analysis is a vendor agnostic software platform providing clinical strain imaging and automated cardiac measurements based on ASE guidelines, along with efficient serial study comparison capabilities. With dual visualization of prior and current study data, and fast and easy analysis, EchoInsight helps enable improved confidence in assessment and monitoring of wall mechanics of patients undergoing treatment. By seamlessly integrating into healthcare IT infrastructure as a DICOM compliant system with structured reporting available on any web-enabled workstation, EchoInsight makes it easy to incorporate strain imaging into a cardio-oncology program.



Useful Features for Cardio-Oncology Studies Include:

- Patented strain imaging technology for analysis of DICOM clips
- Straight-forward clinical strain imaging applications
- Automated linear, volumetric and area measurements based on American Society of Echocardiography (ASE) guidelines
- Bull's Eye Diagram
- Serial comparison capabilities for efficient monitoring of changes in cardiac function
- Ability to analyze contrast-enhanced echo studies
- Scalable architecture to meet demands of growing echo practice
- DICOM structured reporting

Benefits Include:

- Robust strain imaging enabling improved analysis and interpretation of studies
- Improved efficiency and standardization with the automation of cardiac function measurements
  - The EchoInsight RV application has demonstrated to save 3.5 minute per study when providing analysis of FAC, TAPSE and basal and mid-cavity diameters and length compared to conventional methods(xii)
  - The EchoInsight LV application has demonstrated to save 1 minute per study when providing analysis of volumes and EF with strain when compared to conventional methods (xiii)
- Improved IT support/management with reduced memory and processing power requirements for client workstations
- Consolidation of quantification data and other patient data for AI tools in efforts to offer predictive approaches to patient management

Supportive Research

In a 2020 issue of JACC entitled, "Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy," published a research study by Paaladinesh Thavendiranathan et al., in which a randomized controlled trial had 331 anthracycline-treated patients with another heart failure risk factor randomly assigned to cardioprotective therapy (CPT) initiation guided by either ≥12% relative reduction in GLS or >10% absolute reduction of LVEF. These patient's EF and development of cancer therapy-related cardiac dysfunction (CTRCD) were monitored for 1 year. The study showed that the LVEF changes were not different between the 2 arms collectively compared to patients who received CPT. It also showed that the patients in the GLS-guided arm showed significantly lower reduction in LVEF at the 1 year follow-up. The study concluded that GLS-guided CPT significantly reduces a meaningful fall of the LVEF to the abnormal range. This is supportive in the use of GLS surveillance for CTRCD. (Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes [SUCCOUR]; ACTRN12614000341628)

A recent study, "Beyond Left Ventricular Function – Temporal Changes in Whole Heart in Women with Breast Cancer Receiving Cancer Therapy: An Emrace-MRI Substudy," published in JASE by Paaladinesh Thavendiranathan, et. al from the Peter Munk Cardiac Centre at the Toronto General Hospital used EchoInsight to assess changes in full-heart cardiac function with strain imaging in breast cancer patients undergoing therapy. The study concluded that with women receiving anthracyclines and trastuzumab therapy for breast cancer, there is a reduction in the function of all cardiac chambers during treatment. These changes were more significant in those who experience cardiotoxicity.

"The Use of Two-Dimensional Speckle-Tracking Strain in Monitoring Cardiotoxicity in Older Patients with Acute Myeloid Leukemia (AML)," by Nausheen Akhter, et al. from Northwestern Memorial Hospital published in JASE in 2015 analyzed 25 AML patients enrolled in the ECOG2906 study (standard cytarabine and daunorubicin vs. clofarabine (Genzyme/Sanofi). Echo studies were performed before and after induction of therapy. 2D speckle-tracking echo was performed using EchoInsight. The study concluded 4-ch longitudinal strain can be used to follow cardiotoxicity in patients undergoing induction 7+3 chemotherapy. Patients treated with 7+3 were noted to have both subclinical and clinically significant changes in LV function. These changes were not seen in the clofarabine group. These findings suggest that changes in LV function occur shortly after exposure to relatively low doses of anthracycline in older patients with AML.

A study from a research team at MD Anderson Cancer Center at the International Society of Amyloidosis (ISA) Symposia in Sweden entitled, "Outcomes of Patients With

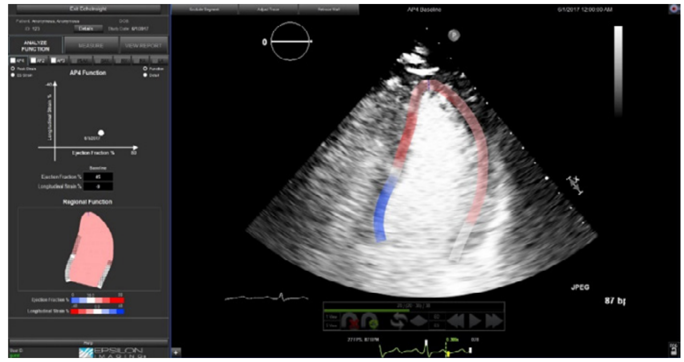
At the University of California San Diego Sulpizio Center, Dr. Narezkina along with Monet Strachan, Manager & Technical Director CV Imaging and Megan Kraushaar, Supervisor Non-Invasive CV Services were tasked with launching a strain imaging clinic to bring strain imaging into routine clinical echo study management. The initial patient populations to be monitored were with cardio-oncology and a focus on breast cancer patients. Megan Kraushaar commented, **"a unique feature of EchoInsight is the ability to analyze retrospective data, allowing for streamlined enrollment into the strain imaging clinic. This is critical, along with the serial comparison capabilities, to properly assess cardiac function in these vulnerable and important patient populations."**

Cardiac Amyloidosis After Autologous Hematopoietic Stem Cell Transplantation and its Association With Longitudinal Strain Analysis Per Speckled Tracking Echocardiography," presented by W Yusuf, J Banchs, RA Quintana-Quezada, et al. utilized EchoInsight to determine the software's clinical use in improving patients outcomes with cardiac amyloidosis after autologous hematopoietic stem cell transplantation. The study concluded that the use of longitudinal strain (LS) values used in assessment and monitoring of this demographic could provide useful clinical information that may improve overall management and care in this population.

A study published on Computing in Cardiology in 2014 entitled, "Vendor-Independent Software for Rapid Comprehensive Assessment of Changes in Left Ventricular Function During Serial Echocardiographic Studies," presented by Gillian Murtagh, et. al used EchoInsight to evaluate the software's unique abilities to monitor patients at risk of cardiotoxicity. Results indicated that interpretation of EchoInsight displays integrating changes in EF and GLS data from serial studies is feasible and accurate. Importantly, this approach was found to provide a time saving alternative to the conventional methodology. Incorporation of EchoInsight displays into clinical practice may improve follow-up of cardiac function in patients receiving therapies such as potentially cardiotoxic chemotherapy. EchoInsight demonstrated improved monitoring of patients at risk for cardiotoxicity in this study.

In some cancer patients, it may be common to experience challenges in properly visualizing myocardial tissue due to physiology and/or image quality, and in this case a contrast agent may be administered to improve visualization. A unique benefit of EchoInsight is it has been validated to produce reliable GLS with contrast echo studies resulting in the ability to monitor all patient studies with GLS. Supportive studies, include:

- "Contrast-Enhanced Echocardiographic Measurement of Longitudinal Strain: Accuracy and its Relationship with Image Quality" was published in the International Journal of Cardiovascular Imaging in 2019 was presented by Karagodin, I., Genovese D., Kruse, E. et al. The study enrolled 25 patients undergoing CMR imaging who also had a transthoracic echocardiography exam (TTE) with and without low-dose contrast injection (1-2 mL Optison/3-5mL saline IV). EchoInsight was used to measure GLS from the non-contrast and contrast enhanced images. Measurements were compared to each other and found that the GLS of contrast-enhanced was in close agreement with the GLS of non-enhanced images ($r = 0.95$; bias: $-0.2 \pm 1.5\%$). The study found the agreement with CMR was better for contrast enhanced GLS ($r = 0.87$; bias: $1.1 \pm 2.2\%$) when compared to that of non-enhanced GLS ($r=0.80$; bias: $1.3 \pm 2.7\%$). Twelve of the twenty-five patients with suboptimal TTE images where GLS was difficult to measure showed better agreement with contrast enhanced GLS with CMR than non-enhanced GLS ($r=0.88$ vs. 0.83). This study concluded that contrast enhanced TTE images improves the accuracy and reproducibility of GLS measurements. Patient's with suboptimal acoustic windows have better agreement in CMR images. This study and methodology may help in the analyzation of LV function in this patient population.

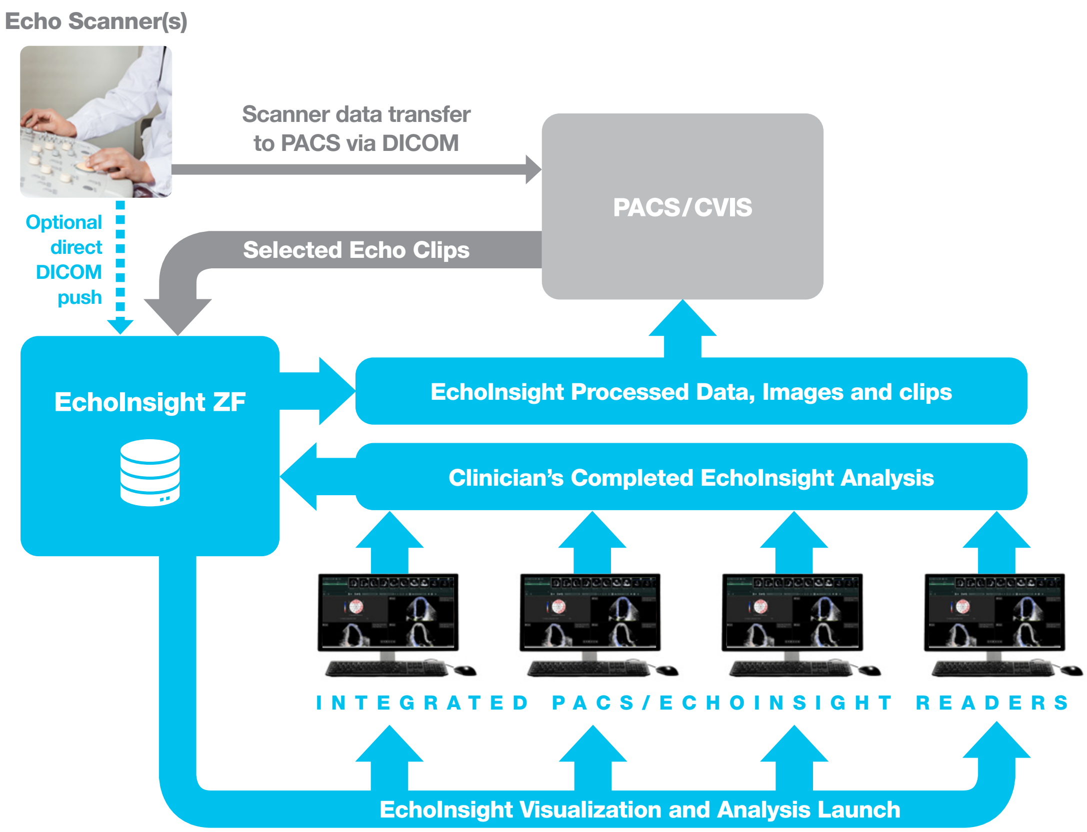


- In a 2017 issue of JASE, "Feasibility of Global Longitudinal Strain Measurements in Contrast-Enhanced Images," published a research study from Lang, Roberto, Mor-Avi, Victor and Medvedofsky, Diego, et al. from the University of Chicago. The methodology of the study included 26 patients referred for a contrast-enhanced echo study, because of suboptimal image quality. Half the manufacturer recommended dose of a commercial contrast agent (Definity/Optison) was used to provide partial contrast enhancement with lower bubble density than typically used for LV opacification. Higher than normal mechanical indices (0.6-0.7) were used for imaging. GLS was measured with EchoInsight at midsystole in the left ventricle (LV) 4-chamber view on both contrast-enhanced and non-enhanced images. Manual corrections were performed as needed to optimize boundary tracking throughout the cardiac cycle. The study resulted with the algorithm failing in three patients with hyperdynamic LV function, due to inadequate contrast enhancement, and manual corrections were needed to optimize tracking with contrast in all remaining 23 patients. GLS measurements were in good agreement between contrast and non-contrast images ($r=0.85$) in University of Chicago's cohort of patients with a wide range of GLS values.

Cardio-Oncology and Beyond: EchoInsight is Designed for A Wide Variety of Indications

The EchoInsight platform offers a suite of applications designed for managing a wide variety of clinical indications across echocardiography programs. EchoInsight provides improved visualization and analysis of echo studies assisting clinicians achieve better standardization, quality, and workflow in patient management. Applications includes LV, LV Contrast, RV, Full Heart, Stress Echo and Research. These applications are equipped to meet the demands of echo labs of any size.

How EchoInsight Works



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