



**ASE**

**American Society of  
Echocardiography**

---

**Echocardiographic Myocardial Strain Imaging for Early  
Detection of Cardiotoxicity in Patients Receiving Potentially  
Cardiotoxic Chemotherapy**

Contact Information

American Society of Echocardiography · 2100 Gateway Center Boulevard, Suite 310 · Morrisville, NC 27560  
Irene Butler · P: 919.297.7162 F: 919.882.9900 (Fax) email: [ibutler@asecho.org](mailto:ibutler@asecho.org) website: [www.asecho.org](http://www.asecho.org)

Saint Luke's Hospital of Kansas City · Michael L. Main M.D., F.A.C.C. · Chairman, Department of Cardiovascular Diseases ·  
Medical Director, Cardiovascular Ultrasound Imaging Laboratory · P: 816-751-8545 Email: [mmain@saint-lukes.org](mailto:mmain@saint-lukes.org)

## About the American Society of Echocardiography

The American Society of Echocardiography (ASE), founded in 1975, is the largest global non-profit organization for cardiovascular ultrasound imaging professionals. Comprised of 16,000 members including physicians, sonographers, nurses, and scientists, ASE is the leader and advocate, setting standards and guidelines for the profession.

ASE is committed to excellence in cardiovascular ultrasound and its application to patient care through education, advocacy, research, innovation and service to our members and the public. We advocate the use of ultrasound to provide an exceptional view of the cardiovascular system to enhance patient care.

ASE members are heart and circulation ultrasound specialists dedicated to improving their patients' health and quality of life. ASE is open to all "echo enthusiasts" and is not specialty-specific. The majority of ASE's membership is physician-based, but the organization has been representative of the entire echo lab team since its inception. Therefore a large component of allied health professionals is represented in membership and in board positions.

ASE strives to write guideline and standards publications that are significant, long-lasting and move the field forward. In addition to guidelines and standards, ASE helped develop Appropriate Use Criteria (AUC) for cardiac imaging procedures. Studies have shown that adhering to these AUC resulted in a reduction in the number of inappropriate or rarely appropriate studies.

ASE is also a sponsor of ABIM Foundation's *Choosing Wisely*<sup>®</sup> campaign. This national initiative aims to promote quality and patient safety by reducing unnecessary medical procedures. In addition to its benefits for patients and physicians, the *Choosing Wisely*<sup>®</sup> campaign also seeks to reduce duplicate and unnecessary procedures that waste healthcare resources in the U.S.

## Double Edged Sword of Cancer Chemotherapy

Advances in the diagnosis and treatment of cancer have markedly improved survival. The US National Cancer Institute estimates that 13.7 million cancer survivors were alive in 2012, and that this number will approach 18 million by 2022. However, some cancer treatments adversely impact the cardiovascular system. For example, anthracyclines, trastuzumab, and some tyrosine kinase inhibitors have detrimental effects on myocardial function, and radiation therapy to the thorax can damage heart valves, coronary arteries, and the pericardium. Thus, many cancer survivors are at potential risk for cardiac disability from their cancer treatments. In addition, as successfully treated cancer patients age, they are subject to the same common cardiac diseases as the general population.

A clinical case from Saint Luke's Mid American Heart Institute illustrates the double edged sword of cancer chemotherapy. A 46 year-old woman was initially diagnosed with right sided breast cancer, and underwent modified radical mastectomy with 2/11 nodes positive. She subsequently underwent a prophylactic left mastectomy and adjuvant chemotherapy. She was diagnosed with metastatic breast cancer 3 years later, and was treated with multiple chemotherapeutic agents including adriamycin and trastuzumab. She subsequently presented with acute systolic heart failure, with NYHA class IV symptoms and a left ventricular ejection fraction of 10%. She required several days of inpatient treatment for parenteral diuresis, and initiation of a low dose beta-blocker and an angiotensin converting enzyme inhibitor. Her left ventricular systolic dysfunction was attributed to chemotherapy related cardiotoxicity. Several months later, her left ventricular ejection fraction normalized, and her heart failure symptoms abated.

A case like this is not rare. Bowles and colleagues demonstrated an approximate 15% incidence of heart failure and/or cardiomyopathy at 5 years following initiation of an anthracycline plus trastuzumab (1). Pinder et al described a 40% prevalence of congestive heart failure in women aged 66 to 70 years at 120 months following initiation of adjuvant anthracycline therapy (2). In fact, in older women diagnosed with breast cancer, cardiovascular disease is actually the leading cause of death (3). Adjuvant radiotherapy for breast cancer also contributes to cardiovascular morbidity and mortality. A cumulative dose of 16 Gy is associated with a > 100 percent increase in major coronary events (including myocardial infarction, coronary revascularization and death from ischemic heart disease) in comparison with patients who did not receive radiation therapy (4). Despite evidence that up to 28% of women may manifest cardiotoxicity following treatment with trastuzumab (5), and prescribing information recommendations (6) that patients undergo echocardiography at baseline, and then every 3 months while on therapy, and every 6 months for at least 2 years following completion of trastuzumab, monitoring is suboptimal in a large proportion of patients (7).

### **Role of Echocardiography, and a New Technology, Myocardial Strain Imaging**

There are several roles for cardiovascular ultrasound during potentially cardiotoxic cancer treatment regimens. First, prior to potentially cardiotoxic chemotherapy, echocardiography can ensure that patients do not already have impaired cardiac function. Second, during chemotherapy, cardiovascular ultrasound can monitor ventricular function to exclude chemotherapy induced dysfunction. Last, during follow-up treatment, cardiovascular ultrasound can determine if new symptoms are potentially due to cardiac disease.

Early detection of decreased ventricular function allows modification in the chemotherapy regimen, either by increasing the interval between doses or reducing the

total cumulative dose of a potentially toxic agent. In addition to routine monitoring of left ventricular systolic function (including use of advanced techniques such as contrast enhanced imaging and 3D imaging for more accurate and reproducible measurements of left ventricular systolic function) a new technology, echocardiographic myocardial strain imaging, allows detection of subclinical left ventricular systolic dysfunction before it is manifest as heart failure symptoms, or a reduction in left ventricular ejection fraction. Early detection of cardiotoxicity (in the subclinical phase) as a sequela of cancer treatment results in less disability, higher quality of life, fewer future cardiac complications, and lower subsequent costs for care. Early detection will not stop or typically even delay cancer treatment. Patients can continue to receive the care they need to treat their cancer while simultaneously addressing the cardiotoxicity.

Although strain correlates with other measures of left ventricular systolic function (such as left ventricular ejection fraction), it offers incremental diagnostic information, and acts as a “canary in the coal mine” for detection of cardioxicity, with strain abnormalities predating declines in ejection fraction and onset of clinical symptoms. James D. Thomas M.D. uses the following simple example to explain the concept of strain:

“Imagine a rubber band that is 10 cm long. If that rubber band is then stretched to 12 cm, then we say that rubber band has undergone 20% strain. If we relax the rubber band back to 8 cm, then, relative to the original 10 cm length, we say the rubber band has experienced a -20% strain”

The left ventricular myocardium undergoes 3 fundamental types of strain or deformation. During systole it shortens along the longitudinal and circumferential axis, and thickens in the radial dimension. Longitudinal strain appears to be the most reproducible (and correlates best with clinical outcomes) with normal values in the range of -20%. “Speckle tracking strain”, now commercially available through all major equipment vendors, tracks the motion of tiny myocardial features (“speckles”) within the myocardium to derive strain values. The ASE recently published an expert consensus statement titled “Current and Evolving Echocardiographic Techniques for the Quantitative Evaluation of Cardiac Mechanics: ASE/EAE Consensus Statement on Methodology and Indications” (8). This comprehensive document describes the current and potential clinical applications of strain, including use in detection of subclinical cardiotoxicity in patients undergoing chemotherapy. A category III CPT™ code (+0399T) was published for myocardial strain on July 1, 2015, and will be active on January 1, 2016.

## **Evidence for Myocardial Strain to Detect Cardiotoxicity in Patients Undergoing Chemotherapy**

The American College of Cardiology/American Heart Association defines four stages (A-D) of heart failure. Stage A= at high risk for heart failure, but without structural heart disease or symptoms, Stage B = structural heart disease but without signs or symptoms of heart failure, Stage C = structural heart disease with prior or current symptoms of heart failure, and Stage D = refractory heart failure. Currently, cardiotoxicity in patients receiving chemotherapy is typically diagnosed in Stage B to C. Myocardial strain imaging offers the potential to diagnose cardiotoxicity much earlier, in Stage A. This would likely result in much better clinical outcomes for patients, and reduced healthcare costs. There is now substantial peer reviewed published literature which describes the use of echocardiographic myocardial strain imaging to detect subclinical left ventricular dysfunction in patients undergoing potentially cardiotoxic chemotherapy,

Thavendiranathan and colleagues (9) recently published a systematic review which described myocardial deformation parameters in 1504 patients during or after cancer chemotherapy for 3 clinically relevant scenarios. All studies of early myocardial changes with chemotherapy show that changes in strain precede declines in left ventricular ejection fraction; global longitudinal strain using speckle tracking strain appears to be the optimal modality, with a 10-15% early reduction in strain the most useful parameter for prediction of cardiotoxicity. Multiple individual studies have confirmed these overall findings.

Mornos et al (10) studied 74 patients (mean age 51 years) who had received anthracyclines. Echocardiography was performed pre, post and at 6, 12, 24 and 52 weeks. A relative change in global longitudinal strain of 13.1% at 6 weeks had 79% sensitivity and 73% specificity for predicting cardiotoxicity at 24 to 52 weeks.

Negishi and colleagues (11) studied 81 patients (mean age 50 years) who had received trastuzumab or doxorubicin for breast cancer, with echocardiography performed prior to therapy and at 6 and 12 months. A global longitudinal strain change of  $\geq 11\%$  had 65% sensitivity and 95% specificity for toxicity at 12 months.

Baratta (12) et al studied 36 patients with breast cancer who had received trastuzumab or doxorubicin with echocardiography performed at baseline, 2, 3, 4 and 6 months after initiation of therapy. A global longitudinal strain decline  $\geq 15\%$  at 3 months had a sensitivity of 86% and a specificity of 86% for detecting cardiotoxicity.

Sawaya (13) studied 81 patients with breast cancer who had received an anthracycline or trastuzumab with imaging performed at baseline, and at 3, 6, 9, 12, and 15 months. An absolute decline in global longitudinal strain at 3 months of -19% had a sensitivity of 74% and a specificity of 73% for toxicity.

In a separate publication Sawaya and colleagues (14) studied 43 patients with breast cancer who were treated with an anthracycline or trastuzumab. Imaging was performed at baseline and at 3 and 6 months. A fall in global longitudinal strain >10% at 3 months had a sensitivity of 78% and a specificity of 79% for cardiotoxicity at 6 months.

Fallah-Rad (15) described 42 patients treated with an anthracycline or trastuzumab. Imaging was performed at baseline, and at 3, 6, 9, and 12 months. An absolute global longitudinal strain fall of 2.0 % had a sensitivity of 79% and a specificity of 82% for subsequent cardiotoxicity.

Hare et al (16) studied 35 patients who had received an anthracycline or trastuzumab. Echocardiography was performed at baseline, post anthracycline, and at 3 months. A > 1 standard deviation drop in global longitudinal strain rate predicted toxicity at a mean follow-up of  $22 \pm 6$  months.

Mavinkurve-Groothuis (17) and colleagues studied 60 patients who had received an anthracycline. Echocardiography was performed at baseline, and at 10 weeks and 12 months. In this particular study, the cardiotoxicity rate was 0%, and strain values were of course not predictive of cardiotoxicity.

Additionally, Tan (18) and colleagues recently reported strain values remain impaired > 2 years after cessation of trastuzumab therapy suggesting long term underlying myocardial injury, and the need for prolonged monitoring.

### **Professional Society Recommendations for Strain Imaging in Cardio-Oncology**

The ASE recently published an expert consensus document titled “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” (19) which incorporates strain imaging into the management of patients receiving drugs with the potential for either Type I cardiotoxicity (i.e. anthracyclines) or Type II cardiotoxicity (i.e. trastuzumab). In both cases, echocardiography with strain imaging is recommended at baseline. For drugs with the potential for Type I toxicity, echocardiographic imaging, including strain, is recommended at completion of therapy and 6 months later. For drugs with the potential for Type II toxicity, echocardiography with strain imaging is recommended every 3 months during therapy. In both cases, a relative decline in global longitudinal strain > 15% is defined as indicative of subclinical left ventricular dysfunction and should prompt cardiology consultation and potential initiation of cardio-protective drugs (20,21) as well as chemotherapy dosing modifications.

A recent clinical case at Saint Luke’s Mid America Heart Institute illustrates the value of this approach. A 54 year-old woman with invasive ductal breast carcinoma underwent bilateral mastectomy, with a baseline echocardiogram performed prior to initiating weekly Taxol and Trastuzumab revealing normal global longitudinal strain

(-24.0%). A follow-up echocardiogram after 12 doses of these agents showed a significant reduction in strain to -17.8% (a relative reduction of 23% from baseline), although left ventricular systolic function was unchanged. These findings prompted a cardiology consultation and consideration of cardio protective medications including a beta-blocker, ACE inhibitor, and close clinical monitoring.

### **American Society of Echocardiography Request**

The ASE requests that payers consider limited coverage of CPT™ code +0399T - myocardial strain imaging (quantitative assessment of myocardial mechanics using image based-analysis of local myocardial dynamics). Current evidence as outlined above supports coverage for this add on echocardiography code when performed in association with the following ICD-9 codes:

- V58.11 - echocardiography performed for initial examination prior to chemotherapy
- V67.1 echocardiography performed for follow-up examination, following radiotherapy
- V67.2 - echocardiography performed for follow-up examination, following chemotherapy

CPT™ code +0399T is billed in conjunction with the following base echocardiography services Transthoracic 93303, 93304, 93306, 93307, 9330; and Stress 93350, 93351, 93355.

The ASE suggests CPT™ +93320 - spectral Doppler as an appropriate cross walk as it is similar in clinical staff and resource utilization.

### **Value Proposition for Payers**

Potential benefits to payers associated with limited coverage of this code as detailed above include the following:

- Potential to reduce hospitalizations and overall healthcare costs in patients receiving potentially cardio toxic chemotherapy
- Opportunity to help women with advanced breast cancer (the majority of patients receiving anthracyclines, trastuzumab)
- Congruent with most payers core principle of innovation
- Low risk proposition (for example V67.2 comprised just 3% of indications for echocardiography at Saint Luke’s Mid America Heart Institute in 2014)

## References

1. Bowles EJ et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. *J Natl Cancer Inst* 2012;104:1293-1305.
2. Pinder MC et al. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol* 2007;25:3808-3815.
3. Patnail JL et al. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer Research* 2011;13:R64.
4. Darby SC et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987-998.
5. McArthur HL and Chia S. Cardiotoxicity of trastuzumab in clinical practice. *N Engl J Med* 357;94-95.
6. Herceptin Prescribing Information. Available at: [http://www.gene.com/download/pdf/herceptin\\_prescribing.pdf](http://www.gene.com/download/pdf/herceptin_prescribing.pdf) accessed August 21, 2015.
7. Chavez-MacGregor M et al. Cardiac monitoring during adjuvant trastuzumab-based chemotherapy among older patients with breast cancer. *J Clin Oncol* 2015;33:1-10.
8. Mor-Avi V et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications. *J Am Soc Echocardiogr* 2011;24:277-313.
9. Thavendiranathan P et al. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after chemotherapy. *J Am Coll Cardiol* 2014; 63:2751-2768.
10. Mornos C and Petrescu L. Early detection of anthracycline-mediated cardiotoxicity: the value of considering both global longitudinal left ventricular strain and twist. *Can J Physiol Pharmacol* 2013;91:601-607.
11. Negishi K et al. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. *J Am Soc Echocardiogr* 2013;26:493-498.
12. Baratta S et al. Serum markers, conventional Doppler echocardiography, and two-dimensional systolic strain in the diagnosis of chemotherapy-induced myocardial toxicity. *Rev Argent Cardiol* 2013;81:151-158.
13. Sawaya H et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes and trastuzumab. *Circ Cardiovasc Imaging* 2012;5:596-603.
14. Sawaya H et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. *Am J Cardiol* 2011;107:1375-1380.



15. Fallah-Rad N et al. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy. *J Am Coll Cardiol* 2011;57:2263-2270.
16. Hare JL et al. Use of myocardial deformation imaging to detect preclinical myocardial dysfunction before conventional measures in patients undergoing breast cancer treatment with trastuzumab. *Am Heart J*; 158:294-301.
17. Mavinkurve-Groothuis AMC et al. Myocardial 2D strain echocardiography and cardiac biomarkers in children during and shortly after anthracycline therapy for acute lymphoblastic leukaemia (ALL): a prospective study. *Eur Heart J Cardiovasc Imaging* 2013;14:562-569.
18. Tan TC et al. Time trends of left ventricular ejection fraction and myocardial deformation indices in a cohort of women with breast cancer treated with anthracyclines, taxanes, and trastuzumab. *J Am Soc Echocardiogr* 2015;28:509-514.
19. Plana JC et al. 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. *J Am Soc Echocardiogr* 2014;27:911-939.
20. Kalay N et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol* 2006;48:2258-2262.
21. Cardinale D et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibitors. *Circulation* 2006;114:2474-2481.