

Echocardiography for Evaluation of Oncology Therapy-Related Cardiotoxicity

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Advances in cancer therapy have improved the outcomes and survival rate of oncology patients.¹ As patient survival is extended, early detection and in-time intervention of therapy-related cardiotoxicity are becoming increasingly important. The cardiotoxicity varies by the type of treatment utilized and the mechanisms of cardiac damage involved.² Type 1 cardiotoxicity is caused by the notorious anthracyclines with cumulative dose effects.³ Anthracyclines such as doxorubicin and epirubicin inhibit topoisomerase II β in cardiomyocytes and induce deoxyribonucleic acid double strand breaks and transcription changes.³ The myocardial damage caused by such type 1 agents is often permanent and irreversible. Patients who are treated with type 1 agents are at an increased risk for significant myocardial dysfunction, subsequent heart failure and death during the follow-up. Type 2 cardiotoxicity is typically caused by target-therapy agents such as trastuzumab.³ Here, trastuzumab blocks human epidermal growth factor receptor 2 (HER-2), expressed on cardiomyocytes in addition to tumor cells, leading to the loss of HER-2 – mediated survival pathways.⁴ There is no cumulative dose effect and the cardiotoxicity is likely to recover after drug withdrawal.³

Two-dimensional echocardiography (2DE) remains the technique of choice for the evaluation of therapy-related cardiotoxicity in oncology patients.^{3,5,6} Left ventricular (LV) ejection fraction (EF) evaluated with the modified Simpson's method by 2DE is the most commonly used parameter for cardiac function assessment.^{6,7}

LVEF has a central role in the management of heart failure (HF), identifying patients with a reduced LVEF (< 40%) for guideline-directed medical therapy and for patients who may benefit from device therapy including cardiac resynchronization therapy and implanted defibrillators.⁸ In fact, LVEF has proved to be a powerful predictor of adverse cardiovascular outcomes in patients with HF.^{9,10} However, LVEF with 2DE usually fails to detect subtle LV dysfunction.^{3,11,12} Once the LVEF has decreased to a significant extent that can be detected, it may be too late to reverse the process of cardiotoxicity and the subsequent development of HF.¹³ The other limitations of LVEF by 2DE are the large temporal and observer variability in the measurements (Table 1).¹⁴ The measurement variability in LVEF with 2DE has been shown to be > 10% equivalent to the > 10% change in LVEF that defines cardiotoxicity in asymptomatic subjects.^{3,14}

Three-dimensional echocardiography (3DE) derived LVEF and speckle-tracking echocardiography (STE) – derived global longitudinal strain (GLS) are two promising indices which may overcome the limitations inherent in the use of 3DE-derived LVEF.^{6,7} 3DE has been shown to be more accurate than 2DE in detecting LVEF < 50% on cardiac magnetic resonance (CMR) imaging in childhood cancer survivors.¹² Moreover, non-contrast 3DE demonstrates better reproducibility and less variation for sequential measurements of LVEF than contrast or non-contrast 2DE.¹⁴ The superiority of LVEF with 3DE over 2DE may be explained by the fact that 3DE can avoid the errors induced by geometric assumption or LV foreshortening with 2DE.⁷ However, LVEF by 3DE has several limitations (Table 1).³ 3DE is not widely available because of cost, and post-procedure analysis still requires high-quality images and a trained operator to achieve the superior performance over 2DE.³

Myocardial deformation is now readily used with routine 2DE.^{3,6,7} The ability of strain analysis to detect

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subtle LV dysfunction and the prognostic value of strain indices have been shown in several clinical situations.¹⁵⁻¹⁹ Among the deformation indices derived from speckle-tracking analysis, LV GLS is the most commonly used and consistent index to detect subclinical myocardial changes and to predict subsequent cardiotoxicity.^{3,11,13,20} In the absence of a reduction in LVEF, a reduction in LV GLS between 9% and 19% is commonly observed during or immediately after chemotherapy.^{13,21,22} Though similar reductions in radial strain, circumferential strain or longitudinal strain rate can also be found after chemotherapy,^{13,23,24} where higher variability and lower reproducibility of these measurements make the detection of a meaningful reduction in each index from pre- to post-therapy more questionable.^{3,21} A recent meta-analysis on the use of myocardial strain imaging indicated that the reduction in LV GLS preceded the reduction in LVEF and persisted during the subsequent therapy.²¹ The

meta-analysis also suggested that a relative 10-15% reduction in LV GLS by STE may be used to predict subsequent cardiotoxicity based on the results from 8 studies involving 452 patients with 6 months to one year of follow-up.^{11,13,20,21,25-28} However, it should be noted that the measured strain value is vendor and software specific (Table 1).^{3,29} When applying STE for the serial follow-up of patients with cancer therapy, the same machine and software should be used. The problems of 2DE image quality and reproducibility are also concerns in the use of GLS derived from 2DE.²¹ Reliable measurements of GLS cannot be obtained in patients with poor 2DE imaging. The reported variability of LV GLS is 8.3-11%, which is similar to the measurement variability of 2DE derived LVEF.^{14,21}

In contrast to the extensive studies on LV function changes after oncology therapy, there are only a few studies that focus on right ventricular (RV) function.³⁰⁻³³

Table 1. Comparison of echocardiographic indices for detection of cardiotoxicity

	Strengths	Limitations
LVEF by 2DE	<ul style="list-style-type: none"> • Current standard and guideline recommended • Widely available and feasible • A powerful predictor of death and adverse outcomes in HF 	<ul style="list-style-type: none"> • Not a sensitive index to detect subclinical cardiotoxicity • Higher temporal and observer variability compared with 3DE • Load-dependent
LVEF by 3DE	<ul style="list-style-type: none"> • Better accuracy in detecting LVEF < 50% compared with 2DE • Better reproducibility compared with 2DE • Lower temporal variability compared with 2DE 	<ul style="list-style-type: none"> • High reliance on imaging quality • Less availability compared with 2DE • Lack of long-term randomized trials evaluated the ability to predict persistent decreases in LVEF or HF • Need for training of operators
GLS by 2DE	<ul style="list-style-type: none"> • Ability to detect subclinical cardiotoxicity in early stage • Superior prediction of mortality compared with 2DE EF • Improved risk stratification in HF patients • Reproducible when performed by experienced operator • Less load dependence than LVEF 	<ul style="list-style-type: none"> • Dependence on imaging quality • Lack of long-term randomized trials evaluated the ability to predict persistent decreases in LVEF or HF • Lack of reproducibility in nonacademic centers • Vendor and software specific
RVFWLS by 2DE	<ul style="list-style-type: none"> • Ability to detect subclinical cardiotoxicity in early stage • Superior ability to detect occult RV dysfunction compared with conventional RV parameters 	<ul style="list-style-type: none"> • Highly reliance on image quality • Lack of long-term randomized trials evaluated the ability to predict persistent decreases in LVEF or HF • Prognostic value has not been examined • Lack of reproducibility data • Vendor and software specific

2DE, two-dimensional echocardiography; 3DE, three-dimensional echocardiography; EF, ejection fraction; GLS, global longitudinal strain; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; RV, right ventricular; RVFWLS, right ventricular free wall longitudinal strain.

Abnormality in RV function may occur due to preexisting RV dysfunction, tumor involvement or cardiotoxicity induced by chemotherapy. In this issue of *Acta Cardiologica Sinica*, Chang et al. report on echocardiographic assessments of RV- and LV-function changes after epirubicin treatment in a prospective cohort of 35 breast cancer patients.³⁴ Among the echocardiographic parameters, LV GLS and RV free wall longitudinal strain (RVFWLS) significantly worsened post epirubicin treatment.³⁴ In contrast to the strain parameters, 2DE-derived LVEF failed to reflect the myocardial changes after epirubicin treatment. The authors also demonstrated a dose-response relationship between the severity of dyspnea and the decline in RVFWLS.³⁴ This study confirms again the limitation of LVEF derived from 2DE and highlights the value of strain imaging in early detection of subclinical cardiotoxicity.

The effect of chemotherapy on the RV function was first shown in a study of 52 doxorubicin-treated patients where RV wall motion abnormalities were more commonly observed than LV wall motion abnormalities by radionuclide ventriculography (19.9% vs. 9.0%, $p < 0.001$).³¹ A CMR imaging study also demonstrated that RV dysfunction was more common than LV dysfunction (34% vs. 26%) at the 12-month follow-up in 46 breast cancer patients receiving anthracyclines and/or trastuzumab.³² Significant functional changes of both the left and right ventricles can be found at 4 months, which persisted at the 12-month follow-up.³² A recent study of 30 breast cancer patients treated with trastuzumab with or without anthracyclines, RV dysfunction was only seen in 10% of the patients by RV fractional area change (a measure similar to LVEF) but in > 40% of the patients based on strain analysis by STE; this demonstrated the sensitivity of STE strain measures to identifying subtle RV dysfunction.³³ In addition, the opportunity of LV functional recovery was lower in patients who have concomitant RV dysfunction compared to those who have preserved RV function (17% vs. 40%), implying the detected RV dysfunction by RV strain reflects more severe myocardial damages induced by cancer therapy.³³

According to the updated recommendations on cardiac chamber quantification from The American Society of Echocardiography and The European Association of Cardiovascular Imaging, RV longitudinal strain should be measured by the RV-centered 4-chamber view.⁷ The width

of the region of interest should be limited to the RV myocardium, excluding the pericardium, which may be difficult due to the thin RV free wall. In general, RV systolic strain can be measured as RV GLS or RVFWLS. RV GLS is the average of RV systolic strain of the 3 RV free wall segments and 3 septal segments, whereas RVFWLS refers to the average of RV systolic strain of the 3 RV free wall segments (Figure 1). RVFWLS has been shown to have prognostic value in pulmonary hypertension, acute myocardial infarction, HF, and amyloidosis.³⁵⁻³⁸ However, the prognostic value of RV dysfunction in oncology patients and its persistence during follow-up still need to be evaluated in further studies. Similar to LV GLS, RV strain by STE is also limited by image quality and the measured value is vendor and software specific (Table 1). The lack of reproducibility data is also a concern in the application of RV strain for the assessment of cardiotoxicity.

With the use of STE, we can detect subtle changes in LV or RV function after therapy. However, the benefit of early identification of subtle myocardial dysfunction is still not clear. Further studies are needed to examine the progression of LV and RV dysfunction to clinical car-

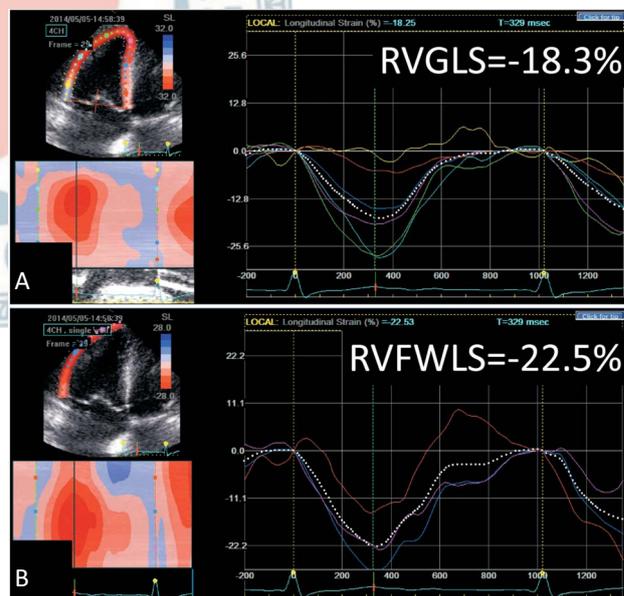


Figure 1. Measurements of right ventricular (RV) systolic strain from the apical four-chamber view by 2-dimensional speckle-tracking echocardiography. (A) Right ventricular global longitudinal strain (RVGLS) is calculated from the average of right ventricular systolic strain of the 6 segments: 3 RV free wall and 3 septal segments. (B) Right ventricular free wall longitudinal strain (RVFWLS) is calculated from the average of right ventricular systolic strain of the 3 RV free wall segments.

diomyopathy and to determine whether early intervention in these patients will lead to improvements in long-term outcomes.

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