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STATE-OF-THE-ART PAPERS

Use of Myocardial Strain Imaging by Echocardiography for the Early Detection of Cardiotoxicity in Patients During and After Cancer Chemotherapy

A Systematic Review

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The literature exploring the utility of advanced echocardiographic techniques (such as deformation imaging) in the diagnosis and prognostication of patients receiving potentially cardiotoxic cancer therapy has involved relatively small trials in the research setting. In this systematic review of the current literature, we describe echocardiographic myocardial deformation parameters in 1,504 patients during or after cancer chemotherapy for 3 clinically-relevant scenarios. The systematic review was performed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using the EMBASE (1974 to November 2013) and MEDLINE (1946 to November 2013) databases. All studies of early myocardial changes with chemotherapy demonstrate that alterations of myocardial deformation precede significant change in left ventricular ejection fraction (LVEF). Using tissue Doppler-based strain imaging, peak systolic longitudinal strain rate has most consistently detected early myocardial changes during therapy, whereas with speckle tracking echocardiography (STE), peak systolic global longitudinal strain (GLS) appears to be the best measure. A 10% to 15% early reduction in GLS by STE during therapy appears to be the most useful parameter for the prediction of cardiotoxicity, defined as a drop in LVEF or heart failure. In late survivors of cancer, measures of global radial and circumferential strain are consistently abnormal, even in the context of normal LVEF, but their clinical value in predicting subsequent ventricular dysfunction or heart failure has not been explored. Thus, this systematic review confirms the value of echocardiographic myocardial deformation parameters for the early detection of myocardial changes and prediction of cardiotoxicity in patients receiving cancer therapy. (J Am Coll Cardiol 2014;63:2751–68) © 2014 by the American College of Cardiology Foundation

The mortality rate among patients with cancer has decreased over the past 20 to 30 years (1,2). However, cardiac toxicity (cardiotoxicity) from cancer therapy has become a leading cause of morbidity and mortality in survivors (3,4). In patients who develop heart failure (HF) from cancer therapy, the mortality rate is as high as 60% by 2 years (5). Therefore, contemporary management of patients with cancer should include careful consideration of potential cardiotoxicity during therapy, with a focus on early detection and intervention (6).

Historically, several definitions of cardiotoxicity have been proposed (7). The most commonly used definition is a ≥5% reduction in symptomatic patients (or ≥10% reduction in asymptomatic patients) in the left ventricular ejection fraction (LVEF) from baseline to an LVEF <55% (8). Early detection of cardiotoxicity has predominantly relied upon serial cardiac imaging to identify a reduction in left ventricular (LV) function without signs or symptoms of heart failure (stage B HF) (9). The use of LVEF has important limitations. First, the measurement of LVEF is subject to technique-related variability, which can be higher than the thresholds used to define cardiotoxicity (8,10). Second, the reduction in LVEF is often a late phenomenon, with failure to recover systolic function in up to 58% of patients despite intervention (11–15). Hence, there has been a growing interest in markers of early myocardial changes (i.e.,

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Abbreviations and Acronyms

2D = 2-dimensional
3D = 3-dimensional
echo = echocardiography
GCS = global circumferential strain
GLS = global longitudinal strain
GRS = global radial strain
HF = heart failure
LV = left ventricular
LVEF = left ventricular ejection fraction
RT = radiotherapy
SR = strain rate
STE = speckle tracking echocardiography
TDI = tissue Doppler imaging

changes with normal LVEF) that may predict the development of subsequent LVEF reduction or the progression to HF, so that preventive strategies with established cardioprotective medications such as beta-blockers, angiotensin-converting enzyme inhibitors, or dexrazoxane could be implemented.

Myocardial deformation can now be readily measured during routine echocardiography, and its value in detecting subclinical ventricular dysfunction, as well as its prognostic value, has been demonstrated in several clinical scenarios (16). A growing body of literature supports the use of myocardial deformation parameters to detect early myocardial injury and to forecast ventricular dysfunction (cardiotoxicity) in patients receiving cancer therapy. This systematic review seeks to summarize the existing data for the following clinically relevant scenarios: 1) detection of early myocardial changes; 2) prediction of subsequent cardiotoxicity; and 3) detection of late consequences of therapy (>1 year post-treatment).

Methods

Search strategy. The search method adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for reporting systematic reviews (17). An EMBASE (1974 to November 7, 2013) and MEDLINE (1946 to November 7, 2013) search was performed by an experienced information specialist using the terms "antineoplastic agents," "radiotherapy," "cardiac toxicity," "echocardiography," and their variations as key words in the OVID search engine without language or species limitations (Fig. 1). References of all selected papers and reviews were screened to identify additional studies.

Inclusion and exclusion criteria. Any prospective or retrospective study of at least 10 patients that used echocardiographic (echo)-based myocardial deformation parameters as the primary method to detect cardiotoxicity during or after cancer therapy was included. In order to be included in this systematic review, studies had to provide data on changes in deformation parameters and LVEF during therapy. Studies that did not provide data on the type of chemotherapy or the timing of imaging were excluded.

Myocardial deformation. Echocardiographic measures of LV strain have become a robust method to measure myocardial deformation (16,18). Strain is a dimensionless index reflecting the total *deformation* of the ventricular myocardium during a cardiac cycle as a percentage of its initial length (reported as percentage). Strain rate (SR) is the *rate of*

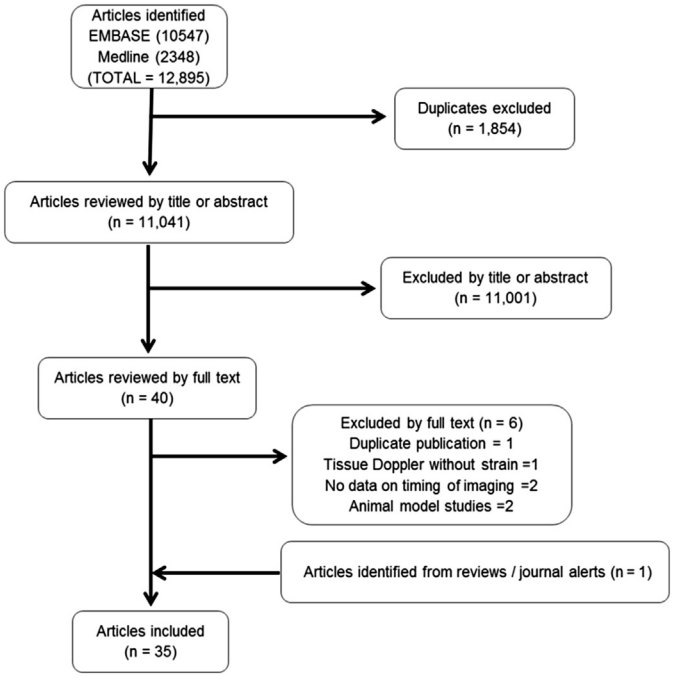

Figure 1 Literature Search Flow Diagram