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● *Review Article*

CANCER THERAPY-INDUCED CARDIOTOXICITY: ROLE OF ULTRASOUND DEFORMATION IMAGING AS AN AID TO EARLY DIAGNOSIS

Donato Mele,* Paola Rizzo,† Alberto V. Pollina,* Andrea Fiorencis,* and Roberto Ferrari*‡

*Department of Cardiology, University Hospital of Ferrara, Ferrara, Italy; †Department of Medical Sciences, University Hospital of Ferrara, Ferrara, Italy; and ‡Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy

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Abstract—In the last decade, ultrasound deformation imaging, based on both Doppler and speckle tracking echocardiography techniques, has emerged as a more sensitive tool to identify subtle and subclinical left ventricular systolic dysfunction in several clinical settings compared with ejection fraction. In this article, we review the evidence relative to the application of ultrasound deformation imaging to the oncologic field for detection of left ventricular systolic dysfunction induced by cardiotoxic treatments with the aim of verifying whether this approach may actually help in early diagnosis of chemotherapy-induced cardiotoxicity. (E-mail: donatomele@libero.it) **© 2014 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Speckle tracking echocardiography, Cardiotoxicity, Chemotherapy, Trastuzumab, Anthracyclines.**

INTRODUCTION

Modern oncologic treatments have led to a reduction in the mortality rate among patients with cancer (Coleman et al. 2011). However, some anti-neoplastic therapies may also have toxic effects on the heart and lead to the development of a number of cardiovascular complications (such as heart failure, myocardial ischemia, hypertension, thromboembolism and arrhythmias), which may have significant consequences on patient outcomes. For example, a survival rate of about 50% at 2 y has been reported for patients who develop heart failure and cardiomyopathy from anthracycline treatment (Felker et al. 2000). This subject has forced both cardiologists and oncologists to deal with the early detection of cardiotoxicity to set up strategies to prevent irreversible cardiac damage and heart failure (Jurcut et al. 2008b; Monsuez 2012; Schwartz et al. 2013; Wu 2008).

Cancer therapy-induced cardiotoxicity may vary in terms of mechanisms, pathophysiology, presentation and prevalence depending on several factors, including the types of drugs used (*e.g.*, anthracyclines, trastuzumab, cyclophosphamide) (Yeh and Bickford 2009). Anthracyclines, such as doxorubicin and epirubicin, which are employed in both solid and hematologic malignancies, directly damage the myocardium mainly through production of oxygen free radicals, leading to left ventricular (LV) systolic dysfunction and, in some cases, an irreversible cardiomyopathy. This toxicity is cumulative and dose dependent. A 3%–26% incidence of LV systolic dysfunction has been associated with doxorubicin utilization (Yeh and Bickford 2009). Trastuzumab is a humanized monoclonal antibody against the extracellular domain of the human epidermal growth factor receptor 2 (HER2) and is part of the standard treatment for breast cancer with HER2 overexpression and/or amplification. The incidence of LV systolic dysfunction ranges from 2% to 7% when trastuzumab is used as monotherapy and may be as high as 27% when it is used concurrently with anthracyclines plus cyclophosphamide (Yeh and Bickford 2009). Many other anti-cancer drugs may determine cardiotoxicity, with variable incidence rates, and dedicated reviews can be consulted for specific information in this regard (Curigliano et al. 2010; Yeh and Bickford 2009).

Cardiotoxicity is generally evaluated assessing the LV ejection fraction (LV-EF), which is defined as the LV (end-diastolic volume minus the end-systolic volume)/end-diastolic volume. Generally, the LV-EF is obtained using 2-D echocardiography, which has the advantage of being a widespread technique. On the basis of the Cardiac Review and Evaluation Committee of Trastuzumab-Associated Cardiotoxicity (CREC) (Seidman et al. 2002), cardiotoxicity is defined as a reduction in LV-EF of ≥5% to <55% with symptoms

Address correspondence to: Donato Mele, Department of Cardiology, Azienda Ospedaliero-Universitaria, Via Aldo Moro 8, 44124 Cona, Ferrara, Italy. E-mail: donatomele@libero.it

of heart failure or an asymptomatic reduction in LV-EF of ≥10% to <55%. According to the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines (Bovelli et al. 2010), in patients undergoing anti-cancer therapy with anthracyclines and their derivates or monoclonal antibodies, a reduction in LV-EF of ≥20% from baseline despite normal function or a LV-EF <50% necessitates re-assessment or discontinuation of therapy and further frequent clinical and echocardiographic checks.

A reduction in LV-EF of less than 10%–20% from baseline in asymptomatic patients, as suggested by the ESMO and CREC recommendations, is not sensitive enough to reveal subclinical or regional myocardial dysfunction when 2-D echocardiography is used for calculation (Manisty and Francis 2008; Mele 2011; Thavendiranathan et al. 2013). To improve accuracy and reproducibility, 3-D echocardiography was introduced for evaluation of LV-EF. In patients undergoing cancer chemotherapy, it has been found that non-contrast 3-D LV-EF has better intra-observer, inter-observer and test–retest variability than 2-D echocardiography (Thavendiranathan et al. 2013). However, even 3-D LV-EF can be less sensitive for recognition of subtle LV systolic dysfunction compared with other imaging techniques assessing LV myocardial rather than cardiac pump function (Hare et al. 2009). Therefore, the use of LV-EF, despite its high feasibility when calculated by 2-D echocardiography, and the increased accuracy and reproducibility of measurements when obtained by the 3-D echocardiography approach, may be still questionable for early detection of cardiotoxicity, mainly because of its intrinsic limitations (Manisty and Francis 2008).

In recent years, ultrasound deformation imaging, obtained by both Doppler and speckle tracking echocardiography (STE) techniques, has been proposed for detection of myocardial dysfunction as an alternative to LV-EF (Mondillo et al. 2011; Yip et al. 2011). This approach has emerged as a more sensitive tool with which to identify subtle and subclinical LV systolic dysfunction in several clinical settings (Biswas et al. 2013), including assessment of anti-neoplastic treatments (Stoodley et al. 2011b; Thavendiranathan et al. 2014). In this article, we review the evidence on application of ultrasound deformation imaging in the oncologic field to verify whether it may actually help in the early diagnosis of chemotherapy-induced cardiotoxicity.

ULTRASOUND DEFORMATION IMAGING

Left ventricular contraction is complex and generates multiple myocardial deformations in different spatial directions. In brief, during the ejection phase of systole, the LV myocardium shortens in the longitudinal and circumferential directions and thickens in the radial direction (Fig. 1). In a normal contracting LV, these regional myocardial deformations occur synchronously. Also, normally the LV base and apex rotate in opposite directions during ventricular ejection (clockwise for the base and counterclockwise for the apex), thus generating torsional motion of the whole LV (Fig. 1). This is due to the characteristic helical architecture of the LV myocardium (Buckberg 2002). A reduction in systolic twisting and twisting velocity (and/or diastolic untwisting and untwisting velocity) indicates LV systolic dysfunction (and/or diastolic dysfunction). Reversed apical rotation as a marker of disease severity has been described in dilated cardiomyopathy (Popescu et al. 2009).

Longitudinal, circumferential and radial deformations are generally expressed in terms of strain, that is, the percentage of deformation, which is positive if the deformation is elongation or negative if the deformation is shortening. Strain rate is the rate at which strain changes and is expressed per second (or in hertz, *i.e.*, the change in strain per unit time). Normally, LV longitudinal and circumferential strain and strain rate are negative, whereas radial strain and strain rate are positive. Basal and apical LV rotation is expressed in degrees, as is twisting, which is their algebraic sum; torsion is obtained by dividing twisting by the length of the LV cavity in degrees per centimeter. Systolic rotation and twisting velocity can also be measured in degrees per second (Cheung et al. 2011; Motoki et al. 2012).

Myocardial deformations can be studied non-invasively by magnetic resonance imaging (MRI) using

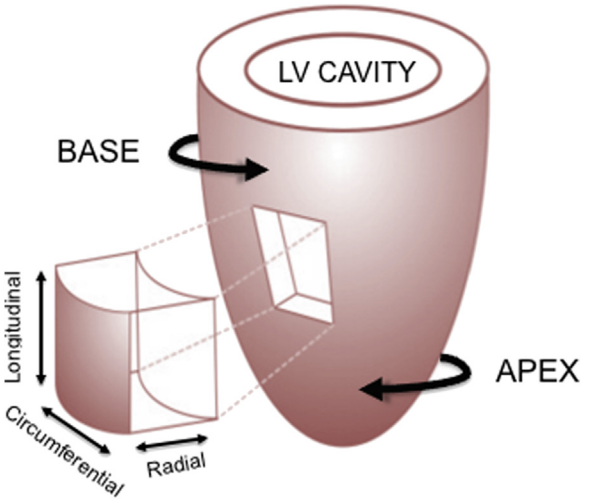

Fig. 1. Schematic of the left ventricle (LV) with the three main directions of the myocardial deformation: longitudinal, circumferential and radial. *Thick arrows* indicate the opposing rotational motion of the left ventricular base and apex, generating a twisting movement of the whole LV.