Early Detection of Epirubicin-Induced Cardiotoxicity in Patients with Breast Cancer

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Background: Epirubicin is a cytotoxic drug, widely used in patients with breast cancer, but its application is limited by its cardiotoxicity. Assessment of left ventricular (LV) ejection fraction (EF) is performed to demonstrate cardiac dysfunction. Because normal EF can mask LV impairment, the aim of this study was to evaluate whether deformation and rotation assessed using speckle-tracking echocardiography represent better markers of early epirubicin-induced cardiotoxicity.

Methods: Forty women with breast cancer (mean age, 51 ± 8 years), scheduled to be treated with epirubicin-based chemotherapy, were prospectively enrolled. All patients underwent conventional echocardiography, tissue velocity imaging, and speckle-tracking echocardiography to evaluate LV geometry and EF, S′, deformation (longitudinal, circumferential, and radial strain and strain rate), and rotation. Patients were reevaluated after the third and sixth cycles of epirubicin (mean cumulative dose, 268 ± 22 g/m^2).

Results: After the sixth cycle of treatment, 14 patients (35%) had developed epirubicin-induced cardiotoxicity (a decrease in EF of ≥10% to an EF of <55%; group I), and 26 patients (65%) did not fulfill the criteria for cardiotoxicity (group II). In the entire study population, after the third cycle of epirubicin, there were reductions in diastolic and longitudinal function, but patients in group I had significantly lower S′, longitudinal strain, and longitudinal strain rate than those in group II. Although after the third cycle of treatment, radial and circumferential deformation and rotation remained unchanged, these parameters showed significant reductions after the sixth cycle of epirubicin. A decrease in longitudinal strain after the third cycle of epirubicin was the best independent and accurate predictor of cardiotoxicity after the completion of treatment.

Conclusions: Assessment of myocardial longitudinal deformation detects subclinical LV dysfunction and can predict further changes in EF and therefore can be used to monitor epirubicin-induced cardiotoxicity. (J Am Soc Echocardiogr 2014;27:83-92.)

Keywords: Epirubicin-induced cardiotoxicity, Myocardial deformation and rotation, Speckle-tracking echocardiography

Breast cancer represents the most frequent form of neoplasia in women worldwide, responsible for 1.6% of deaths each year.[1] Therefore, it is a major public health issue, and research in this field should be a priority. Chemotherapeutic drugs are extremely potent tools that, alone or in association with radiotherapy, increase survival and lower the recurrence rate of cancer.[2] As a consequence of increased life expectancy, it is essential that chemotherapy be safe.[3]

Epirubicin, a type of anthracycline, is a potent and widely used drug in different therapeutic regimens. However, the applicability of this drug is limited by the risk for cardiotoxicity.[3-5] Cardiotoxicity is one of the most important adverse reactions to epirubicin, leading to increases in morbidity and mortality.[6] Epirubicin-induced cardiotoxicity may be augmented by the cumulative dose, by other associated cytotoxic drugs, or by advanced age.[7] Moreover, the cardiac changes are frequently subclinical, and they can appear early (during therapy), late (during the first year after therapy), or very late (>1 year after finishing therapy).[6] Consequently, early diagnosis of epirubicin-induced cardiotoxicity in patients with breast cancer is essential for close cardiac monitoring during chemotherapy, as well as for starting antiremodeling drugs to reduce the progression of myocardial injury.[3]

Although a growing body of research is now focused on cardiovascular events associated with chemotherapy, a clear definition and diagnosis of cardiotoxicity are lacking.[8,9] The current definition of chemotherapy-induced cardiotoxicity is based on the measurement of left ventricular (LV) ejection fraction (EF) with serial transthoracic echocardiography.[10] However, assessment of EF is dependent on hemodynamic conditions and allows only the late diagnosis of cardiac dysfunction, which might already be irreversible.

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Abbreviations
EF = Ejection fraction
FS = Fractional shortening
HF = Heart failure
LS = Longitudinal strain
LSR = Longitudinal strain rate
LV = Left ventricular
ROC = Receiver operating characteristic
STE = Speckle-tracking echocardiography
TVI = Tissue velocity imaging

Tissue velocity imaging (TVI) and speckle-tracking echocardiography (STE) are noninvasive and accurate techniques allowing the early detection of LV systolic dysfunction, before a decrease in EF.[11,12] TVI and STE have been evaluated primarily in the clinical setting of doxorubicin-induced and trastuzumab-induced cardiac dysfunction.[13,14] Although a few studies, using tissue Doppler principles, have described alterations of longitudinal LV deformation during treatment with epirubicin, the early detection of cardiac injury using an integrated assessment with TVI and STE in patients with breast cancer treated with epirubicin remains to be investigated.

We hypothesized that changes in myocardial systolic velocities, assessed by TVI,[15] and deformation and rotation, evaluated by STE,[16] might represent early markers of subclinical LV dysfunction and can predict epirubicin-induced cardiotoxicity. The novelty of this hypothesis is due to two aspects: (1) epirubicin, a regimen thought to be less toxic than doxorubicin, is evaluated, and (2) the prognostic value of LV mechanics halfway through treatment is assessed.

METHODS

Study Group

Forty consecutive female patients (mean age, 51 ± 8 years) with breast cancer, scheduled to be treated with epirubicin, were enrolled prospectively in the study. Inclusion criteria were (1) age > 18 years, (2) provision of written informed consent signed, (3) previous untreated HER2-negative breast cancer scheduled for treatment with chemotherapy according to international standardized protocols, and (4) EF > 50%. Exclusion criteria were (1) any history of cardiovascular disease and/or active cardiovascular treatment, (2) diabetes mellitus, and (3) mediastinal irradiation. All subjects were informed about the procedures and provided informed consent. The study protocol was approved by the local ethics committee.

All subjects were evaluated at baseline using conventional echocardiography, TVI, and STE. All measurements were averaged from ≥3 consecutive cardiac beats. The full echocardiographic protocol was repeated in all patients within 24 hours of the end of the third and sixth cycles of chemotherapy (63 ± 6 and 126 ± 12 days after baseline, respectively). Cardiotoxicity was defined as reduction in EF of ≥10% to an EF of <55%, without signs or symptoms of heart failure (HF), compared with baseline, after the sixth cycle of treatment. According to the reduction in EF after the completion of treatment, two groups were defined: patients who developed cardiotoxicity (group I) and patients without cardiotoxicity (group II).

Echocardiography

Examinations were performed using a commercially available ultrasound machine equipped with TVI and STE, using a 2-MHz to 4-MHz transducer (Vivid 7 Dimension; GE Medical Systems, Milwaukee, WI). Digital echocardiographic data were acquired during passively held end-expiration for offline analysis using a dedicated software package (EchoPAC version 9.0.1 for PC; GE Medical Systems). Heart rate and blood pressure were measured just before the study. A one-lead electrocardiogram was recorded simultaneously.

Conventional echocardiography consisted of M-mode, two-dimensional, and Doppler blood flow measurements to assess LV structure and global function. All measurements were taken in accordance with the current guidelines of the American Society of Echocardiography.[17] M-mode tracings from the parasternal long-axis view were used to measure systolic and diastolic septal and posterior wall thickness and LV diameters and to calculate fractional shortening (FS). Two-dimensionally guided M-mode echocardiography of mitral annular motion (medial and lateral) was also performed. The systolic amplitude in the long axis was measured from the onset of annular movement toward the apex, at the peak of the QRS complex, to the maximal systolic displacement; mean displacement (mitral annular plane systolic excursion) was calculated by averaging the two sites. Cross-sectional images were recorded from the apex, and end-diastolic and end-systolic areas and LV lengths were measured from the apical four-chamber and two-chamber views (using the modified biplane Simpson's method) for the calculation of EF. Diastolic function was assessed using pulsed-wave Doppler of the transmitral flow; the E/A ratio was calculated. LV inflow was recorded using color M-mode echocardiography, and flow propagation velocity was measured.

Online pulsed-wave tissue velocity traces were recorded from the six basal segments (from the apical four-chamber, two-chamber, and three-chamber views) to assess longitudinal function. Peak myocardial velocities in systole (S′) and early diastole (E′) were measured, and their six-segment mean was calculated. The E/E′ ratio was calculated as a marker of LV filling pressure.

STE was used to assess systolic myocardial deformation in all three directions (longitudinal, circumferential, and radial) and rotation, according to current recommendations.[18] Frame rates of 70 to 80 frames/sec were used, with optimal sector width and depth. The frame in which the LV endocardium was best defined was identified, and the border of the endocardium was traced manually to identify the region of interest between the endocardial and epicardial borders. After definition of the region of interest in the long-axis or short-axis views, the postprocessing software automatically divided the ventricle into six equally distributed segments. All LV segments were tracked optimally in each echocardiographic view. Cardiac time intervals were measured using pulsed-wave tracings from the LV outflow tract (aortic valve opening and aortic valve closure). We calculated peak longitudinal strain (LS) and strain rate (LSR) as means of the 18 ventricular segments from the apical views (four-chamber, two-chamber, and three-chamber views), peak circumferential strain and strain rate, and peak radial strain and strain rate from the six ventricular segments, from the short-axis view at the level of the papillary muscles. "LV twist" refers to the rotation of the short-axis views of the left ventricle as viewed from the apical end and is defined as the absolute apex-to-base gradient rotation along the longitudinal axis of the left ventricle, expressed in degrees.[19] We measured apical rotation, a counterclockwise rotation during LV ejection and the most important part of LV twist, using the short-axis apical view well beyond the papillary muscle and basal rotation, which is significantly lower in magnitude than apical rotation and opposite in direction, at the basal short-axis view. Subsequent recoil of twist deformation, so-called untwist, is associated with the release of restoring energy and contributes to LV diastolic relaxation and early diastolic filling.[20] As a parameter of a diastolic mechanic function, we measured early untwist rate (degrees per second) as the mean difference between