Tissue-Doppler Assessment of Cardiac Left Ventricular Function during Short-Term Adjuvant Epirubicin Therapy for Breast Cancer

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Background: It has been hypothesized that the extent of acute anthracycline-induced cardiotoxicity reflects the risk for late development of heart failure. The aim of this study was to examine if short-term changes in cardiac function can be detected even after low-dose adjuvant epirubicin therapy for breast cancer when using Doppler tissue imaging of longitudinal left ventricular function.

Methods: Eighty consecutive women in good cardiopulmonary health scheduled to undergo adjuvant treatment for breast cancer were included. They were examined using echocardiography and Doppler tissue imaging before and after three treatment series of epirubicin (mean cumulative dose, 273.7 ± 46.6 mg/m^2; median time interval, 9 weeks; range, 47–113 days).

Results: Apart from a marginal reduction in E/A ratio, none of the conventional Doppler echocardiographic or Doppler tissue imaging indices of systolic and diastolic function were affected during epirubicin treatment.

Conclusions: In contrast to several previous studies using tissue Doppler and conventional echocardiography, this study did not document relevant short-term effects of low-dose epirubicin treatment on heart function. (J Am Soc Echocardiogr 2011;24:200-6.)

Keywords: Tissue Doppler echocardiography, Anthracycline, Epirubicin, Adjuvant treatment, Breast cancer, Cardiotoxicity, Cardiomyopathy, Heart failure

Anthracyclines are effective antineoplastic drugs used in the treatment of breast cancer and in many other malignant diseases, including childhood tumors, soft tissue sarcomas, lymphomas, and leukemias. The use of anthracyclines is limited by serious side effects, the major being cardiotoxicity with resulting chronic heart failure (CHF). The mechanism behind the development of anthracycline-induced cardiomyopathy is complex and probably multifactorial. However, the formation of free radicals with oxidative damage seems to play a central role.[1] The risk for the development of CHF is accentuated by several risk factors, the most important being the cumulative anthracycline dose.[2,3]

The development of CHF is often postponed by several months to years after the end of anthracycline treatment. After high-dose regimens, the risk for heart failure has been reported to approach 20% to 50%, but even during the treatment course, deterioration of heart function can be seen, with reductions in left ventricular ejection fraction (EF) up to 10%.[4] Heart failure is uncommon during low-dose regimens (Table 1[5-14]), but a risk for the development of CHF seems to persist many years after treatment.[15-18]

It has been hypothesized that the extent of acute treatment-induced cardiotoxicity reflects the risk for the late development of heart failure and that impairment of systolic left ventricular function is preceded by subclinical deterioration. This has been supported by studies showing that a decrease in left ventricular EF during treatment predicted the development of CHF.[4] Serial measurements of EF by radionuclide ventriculography (multigated acquisition) or echocardiography are recommended in various treatment guidelines.[19-21] A recent study, however, indicated that this approach is inadequate to predict late left ventricular impairment. A search has been prompted for a more sensitive monitoring method with prognostic information that can detect the individuals at risk, enabling closer follow-up, early treatment, and possibly the development of prophylactic treatments.[22] Tissue Doppler velocities of the mitral ring have been found in several settings to possess independent and supplementary prognostic information to the standard evaluation of the left ventricular function.[23-25]

Several groups have studied short-term changes in cardiac tissue Doppler parameters during low-dose anthracycline treatment. Early reductions in the range of 10% to 20% have been described in regional deformation variables, strain rate and strain, and in tissue velocities E′ (early diastolic mitral ring velocity) and S′ (peak systolic mitral ring velocity) (Table 1).

Traditional Doppler velocity measurements of mitral flow E (peak early diastolic flow velocity) and A (peak flow velocity during atrial contraction) waves reflect the diastolic function of the left ventricle but are also affected by filling pressures. In individuals with various

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Abbreviations

CHF = Chronic heart failure

DTI = Doppler tissue imaging

EF = Ejection fraction

Vp = Flow propagation velocity

cardiovascular diseases, E′ (early diastolic mitral ring velocity) and flow propagation velocity (Vp) are less preload sensitive markers of left ventricular relaxation, and they are inversely correlated with the time constant of isovolumic pressure decay. These parameters have been combined in indices providing information on left ventricular filling pressures.

Our aim was to examine whether subtle short-term changes in cardiac function can be detected even during low-dose adjuvant anthracycline therapy for breast cancer when using Doppler tissue imaging (DTI) of longitudinal left ventricular function. In addition, changes in other Doppler echocardiographic indices were studied.

METHODS

Study Population

The protocol was approved by the local ethics committee, and all participants gave their written informed consents.

Calculation of the necessary sample size was based on statistical power >80%; minimal relevant changes of 0.75 cm/sec in tissue velocities, 0.75 mm in maximal systolic displacement, and 5% in EF; spontaneous individual variability in a group of 34 healthy volunteers; and a 5% level of statistical significance. The observed statistical power is displayed in Table 2.

The subjects were 80 women consecutively recruited among patients who had received curative surgery for primary breast cancer and were scheduled for standard adjuvant chemotherapeutic treatment with a regimen containing epirubicin (cyclophosphamide and epirubicin). Prior treatment with cardiotoxic drugs, radiation therapy, or heart rhythm other than sinus rhythm were exclusion criteria. According to local treatment guidelines, none of the patients had a history of heart disease before epirubicin treatment was planned; hypertension was accepted. All subjects came from the same geographical suburban area. All but one were Caucasian. Demographic and clinical data of the participants are displayed in Table 3. Participants were examined before and after a total of three series of epirubicin and cyclophosphamide infusions. Standard and tissue Doppler echocardiography was performed as outlined below. Of 85 included individuals, one was excluded because she was previously treated with anthracyclines, two left the study because of recurrence of malignant disease, and two chose not to complete the final examination. Eighty participants completed the study.

Table 1 Studies of myocardial function with echocardiography and/or DTI

Study	Population	*n*	Design	Follow-up time (mos)	Anthracyclines	Cumulative dose (mg/m^2)	Modality	Early or late deterioration	CHF
Jurcut *et al.* (2008)[8]	A	16	P	5	Pegylated liposomal doxorubicin	180	Echo, DTI	SR, E′	0
Dodos *et al.* (2008)[7]	A	100	P	12	Doxorubicin	230	Echo	Early EF, FS, Tei index	0
Karakurt *et al.* (2008)[9]	I	32	C	28	Doxorubicin, daunorubicin	50–300	Echo, DTI	E′, E/E′, MPI	0
Mantovani *et al.* (2008)[5]	A	31	P	18	Epirubicin	200–400	Echo, DTI	Early SR, E′/A′; late S′	0
Nagy *et al.* (2008)[10]	A	40	R	12	Doxorubicin, epirubicin	300	Echo, DTI	E/A, E′/A′	0
Belham *et al.* (2007)[11]	A	61	R	6	Doxorubicin	300	Echo, DTI	EF, Tei index	5%
Ganame *et al.* (2007)[12]	I	13	P	3	Daunorubicin, doxorubicin, idarubicin	90–225	Echo, DTI	E, E′, IVRT, SR, ϵ, Tei index	0
Mercuro *et al.* (2007)[6]	A	16	P	9–18	Epirubicin	200–400	Echo, DTI	Early SR; late E′, E′/A′	0
Corapcioglu *et al.* (2006)[13]	I	21	P	3	Doxorubicin, daunorubicin, epirubicin, idarubicin	240–600	Echo, MUGA	EF, FS, PFR	5%
Tassan-Mangina *et al.* (2005)[14]	A	20	P	42	Doxorubicin	210	Echo, DTI	Early E/A, E′; late EF, S′	0

A, Adults; *I*, infants; *C*, case-control; ϵ, peak systolic strain; *FS*, fractional shortening, *IVRT*, isovolumetric relaxation time; *MUGA*, multigated acquisition nuclear ventriculography; *P*, prospective, *R*, retrospective; *SR*, peak systolic strain rate.

Echocardiography

A single investigator (J.M.A.) performed all echocardiographic studies and subsequent analyses. All studies were stored on an external server for later analyses offline, blinded for all clinical data. All examinations were done in the left lateral decubitus position corresponding to the time of end-expiration. A Vivid 7 ultrasound unit (GE Vingmed Ultrasound AS, Horten, Norway) with a 2.5-MHz probe was used for all examinations. Second-harmonic imaging was applied. EchoPAC PC ′08 (GE Vingmed Ultrasound AS) was used for analysis of the echocardiographic studies.

Echocardiographic studies were performed according to guidelines.[21,26,27] Valvular function was screened using standard two-dimensional imaging as well as pulsed-wave and color Doppler imaging. Three cardiac cycles of two-dimensional two-chamber and four-chamber grayscale images were recorded from an apical view. From the apex, pulsed-wave Doppler traces were collected from an area between the tips of the mitral leaflets in the four-chamber view and from the aortic valve in the five-chamber view using continuous-wave Doppler. Also from an apical four-chamber view, color M-mode recordings of diastolic left ventricular filling were obtained as described by Sessoms *et al.*[28] The excursions of the tricuspid ring corresponding to the free right ventricular wall were assessed using grayscale M-mode images. Color DTI was performed in the apical two-chamber and four-chamber views. Loops of three consecutive beats were stored. The areas depicted included the anterior, posterior, lateral, and septal sections of the mitral ring. The sector was reduced