The Clinical Value of Echocardiography and Acoustic Cardiography to Monitor Patients Undergoing Anthracycline Chemotherapy

Stefan Toggweiler, MD; Yvonne Odermatt, MD; Andreas Brauchlin, MD; Thilo Zander, MD; Andrea Müller, MD; Michel Zuber, MD; Ralph Winterhalder, MD; Paul Erne, MD
Department of Cardiology (Toggweiler, Odermatt, Brauchlin, Müller, Zuber, Erne) and
Department of Oncology (Zander, Winterhalder), Luzerner Kantonsspital, Lucerne, Switzerland

ABSTRACT

Background: Investigate the usefulness of echocardiography and acoustic cardiography to monitor patients exposed to anthracycline chemotherapy.

Hypothesis: Serial echocardiographies to monitor systolic function may not be necessary in all patients undergoing anthracycline chemotherapy.

Methods: In a prospective study, consecutive patients undergoing anthracycline-containing chemotherapy were evaluated with echocardiography and acoustic cardiography at baseline, after completion of chemotherapy, and after a median follow-up of 3.8 years. Systolic dysfunction was defined as a left ventricular ejection fraction $\leq 50\%$.

Results: A total of 187 patients (83% female) with a mean age of 55 ± 14 years underwent chemotherapy for breast cancer (73%), malignant lymphoma (23%), and sarcoma (4%). None of the patients had systolic dysfunction at baseline. Patients were treated with doxorubicin 276 ± 74 mg/m² or epirubicin 317 ± 55 mg/m². After chemotherapy, 170 (91%) had normal systolic function, 8 (4%) developed systolic dysfunction, and 9 (5%) had died. Of those 8 patients with systolic dysfunction, 4 (50%) improved to normal systolic function, 1 (13%) remained unchanged, and 3 (37%) died. Patients with normal systolic function after chemotherapy had a mortality rate of 3.5%, and 1.8% developed late systolic dysfunction. Acoustic cardiography-derived percent electromechanical activation time $>12.4\%$ had a sensitivity of 88% and a specificity of 84% to identify patients with systolic dysfunction (area under the receiver operating characteristic curve 0.87).

Conclusions: Patients with systolic dysfunction early after anthracycline treatment had worse outcome. Acoustic cardiography was able to identify these patients with a high sensitivity and specificity. Based on the findings of this study, we propose a simple algorithm to monitor patients undergoing anthracycline-containing chemotherapy.

Introduction

Monitoring of left-ventricular function in patients exposed to anthracyclines is currently recommended for early detection and treatment of cardiotoxicity.^{1,2} However, there are no clear guidelines on timing and frequency of left ventricular monitoring, and the best parameter to evaluate left ventricular function is unknown.

Acoustic cardiography (AudiCor; Inovise Medical Inc., Portland, OR) has been proposed as a noninvasive method to assess left ventricular function in a wide spectrum of patient care.^{3–8} In particular, electromechanical activation time (EMAT) has been shown to allow accurate detection of left ventricular dysfunction. Therefore, we investigated the clinical value of echocardiography and

acoustic cardiography in patients undergoing anthracycline-containing chemotherapy.

Methods

Study Population and Chemotherapy Regimen

Between January 2007 and December 2010, a total of 189 patients underwent anthracycline treatment for breast cancer, malignant lymphoma, or sarcoma at the Luzerner Kantonsspital, Lucerne, Switzerland. A total of 2 patients were excluded because of missing baseline examination, leaving a study population of 187 patients.

The anthracyclines were given in standard combination regimens. Patients received epirubicin or doxorubicin every third week. Total duration of chemotherapy was 12, 18, and 18 weeks for patients with breast cancer, lymphoma, and sarcoma, respectively. Patients with breast cancer received adjuvant chemotherapy according to international standards: doxorubicin 60 mg/m² and cyclophosphamide

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600 mg/m². In some, doxorubicin was replaced by epirubicin 90 mg/m². Some patients received doxorubicin 50 mg/m², cyclophosphamide 500 mg/m², and docetaxel 75 mg/m². Trastuzumab was used in the approved adjuvant setting for HER2-positive patients (8 mg/kg body weight loading dose, 6 mg/kg body weight maintenance for 1 year). For lymphoma patients, doxorubicin 50 mg/m², cyclophosphamide 750 mg/m², vincristine 1.4 mg/m², and prednisolone 100 mg was described. Hodgkin patients received doxorubicin 25 mg/m², bleomycin 10 mg/m², vinblastine 6 mg/m², dacarbazine 375 mg/m². All sarcoma patients who were included in the study were treated with an epirubicin dose of 150 mg/m² in combination with other chemotherapeutic agents.

This prospective study was approved by the local ethics committee and all patients provided written informed consent.

Data Collection and Definitions

Patients were evaluated at baseline, after completion of anthracycline-containing chemotherapy, and at long-term follow-up after a median of 3.8 years (1st and 3rd quartiles [Q1, Q3] = 2.8, 4.7). Clinical and echocardiographic data were obtained and entered into a dedicated database at each visit.

Transthoracic echocardiography was performed according to the guidelines of the American Society of Echocardiography.⁹ Left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson method.

The principle of acoustic cardiography has been previously described.⁵ Briefly, the patient was placed in the supine position and connected to an Audicor device to record acoustic cardiography parameters. A 10-second Audicor recording was obtained and analyzed by the computerized algorithm for the EMAT. EMAT was measured as the time from the onset of the Q wave to the mitral component of the first heart sound. The percentage of EMAT (%EMAT) was calculated by dividing EMAT by the RR (R wave to R wave) interval.

End points were mortality and new onset systolic dysfunction. Mortality was defined as death from any cause. Systolic dysfunction was defined as LVEF ≤50%.

Statistical Analysis

Continuous variables were described using means ± standard deviation or medians with Q1 and Q3 quartiles in cases of skewed distributions. Categorical variables were described by frequencies and percentages. Differences between independent groups were tested using the χ^2 test for categorical variables, the *t* test for continuous variables, and the Mann-Whitney *U* test for comparison of continuous variables with a small sample size. In cases where the samples were paired, the paired *t* test was used. Survival rates at 5 years were estimated and graphed using the Kaplan-Meier method. A Cox regression model was used to estimate hazard ratios and 95% confidence intervals of baseline characteristics on mortality. Variables were included in the multivariate model if they were univariately significant at *P* < 0.10. Analyses were conducted with IBM

Figure 1. Kaplan-Meier estimates of survival in patients with breast cancer, lymphoma, and sarcoma.

SPSS version 18 (IBM Corp., Somers, NY) and tested using 2-sided tests at a significance level of 0.05.

Results

A total of 187 patients (83% female) with a mean age of 55 ± 14 years underwent anthracycline-containing chemotherapy for breast cancer (73%), malignant lymphoma (23%), and sarcoma (4%). Relevant comorbidities were infrequently present and included arterial hypertension in 24 (13%) and coronary artery disease in 6 (3%). None of the patients had systolic dysfunction at baseline. All patients received doxorubicin (a mean dose of 276 ± 74 mg/m²) or epirubicin (a mean dose of 317 ± 55 mg/m²). In addition, 104 (56%) had left chest wall radiation, 67 (36%) received trastuzumab, and 23 (12%) received rituximab.

Outcome

Five-year survival rates in patients with breast cancer, lymphoma, and sarcoma were 93%, 80%, and 50%, respectively (log-rank *P* for overall comparison < .01, figure 1).

Mean LVEF decreased from 64 ± 5% at baseline to 61 ± 6% after chemotherapy (*P* < 0.01 vs baseline) and remained at 61 ± 5% at late follow-up (*P* < 0.01 vs baseline). Late LVEF was 62 ± 4% in patients receiving trastuzumab, 58 ± 9% in patients receiving rituximab, and 61 ± 5% in patients without monoclonal antibody treatment (*P* = 0.09). Late LVEF was 61 ± 5% in both patients with and without chest wall radiation.

After chemotherapy, 170 (91%) had an LVEF >50%, 8 (4%) developed systolic dysfunction, and 9 (5%) had died. The majority of patients who had a preserved LVEF after chemotherapy maintained a preserved LVEF at late follow-up. Only 3 (2%) developed new systolic dysfunction, and 6

(4%) had died. All patients with systolic dysfunction after chemotherapy were started on an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. None had clinical signs of heart failure, but 2 (25%) had shortness of breath on exertion (New York Heart Association class II). Outcome was worse in patients with systolic dysfunction. Four (50%) improved to normal systolic function, 1 (13%) remained unchanged, and 3 (37%) died. Figure 2 and Table 1 summarize these findings.

Only 4 (2%) patients had a cumulative anthracycline dose ≥ 450 mg/m². All 4 patients survived and maintained a normal systolic function. A total of 5 (2%) patients had a borderline LVEF ($>0\%$ and $<55\%$) after chemotherapy. All survived, and 1 (20%) developed systolic dysfunction at late follow-up. Four patients (2.1%) developed new persistent atrial fibrillation.

Acoustic Cardiography

Mean EMAT increased from 80 ± 14 ms at baseline to 84 ± 15 ms after chemotherapy ($P < 0.01$) and increased

Figure 2. Outcome stratified by systolic function and survival. Abbreviations: EF, ejection fraction.

further to 89 ± 19 ms at late follow-up ($P < 0.01$ vs baseline, $P = 0.02$ vs after chemotherapy). Mean %EMAT increased from $9.6 \pm 2.1\%$ at baseline to $10.9 \pm 3.3\%$ after chemotherapy ($P < 0.01$) and remained $10.6 \pm 3.4\%$ at late follow-up ($P < 0.01$ vs baseline). Relative changes in %EMAT correlated with relative changes in LVEF ($r = -0.33$, $P < 0.01$).

Table 1. Characteristics and Outcome of the 8 Patients With Systolic Dysfunction After Chemotherapy

Diagnosis	Age, y	Chemotherapy	Dose, mg/m ²	LVEF at Baseline, %	LVEF After Chemotherapy, %	%EMAT at Baseline	%EMAT After Chemotherapy	Long-term Outcome
Lymphoma	63	Doxorubicin	285	63	42	8.6	12.7	Patient died
Breast CA	50	Doxorubicin	237	61	50	10.3	14.5	Improved LVEF 52%
Breast CA	74	Epirubicin	336	57	43	6.6	12.4	Improved LVEF 63%
Lymphoma	86	Epirubicin	299	55	43	8.7	17.9	Patient died
Lymphoma	74	Epirubicin	389	63	34	8.7	17	Patient died
Breast CA	73	Epirubicin	438	54	44	12.2	35.8	Improved LVEF 53%
Breast CA	71	Epirubicin	286	51	50	8.4	9.3	Improved LVEF 57%
Breast CA	72	Doxorubicin	153	55	41	9.5	23.6	Worsened LVEF 35%

Abbreviations: CA, cancer; EMAT, electromechanical activation time; %EMAT, percentage of electromechanical activation time; LVEF, left ventricular ejection fraction.

Table 2. Baseline Characteristics of Patients With and Without Systolic Dysfunction After Chemotherapy

Variable	Normal Systolic Function (N = 170)	Systolic Dysfunction (n = 8)	P Value ^a
Age (y)	54 ± 14	70 ± 10	<0.01
Female sex (%)	147 (87)	6 (75)	0.31
Coronary artery disease (%)	4 (2)	2 (25)	0.02
Arterial hypertension (%)	20 (12)	3 (38)	0.03
Chemotherapy with doxorubicin (%)	75 (44)	3 (38)	0.71
Cumulative dose (mg/m ²)	303 ± 61	303 ± 88	0.56
LVEF at baseline (%)	64 ± 4	57 ± 4	<0.01
EMAT at baseline (ms)	81 ± 14	75 ± 14	0.27
%EMAT at baseline (%)	9.8 ± 2.1	9.0 ± 1.7	0.31

Abbreviations: EMAT, electromechanical activation time; %EMAT, percentage of electromechanical activation time; LVEF, left ventricular ejection fraction.
^aMann-Whitney U test was used due to the small sample size of patients with systolic dysfunction.

Predictors of Systolic Dysfunction

Patients who developed systolic dysfunction after chemotherapy were older, had a lower LVEF at baseline, and presented more often with arterial hypertension or coronary artery disease (Table 2). An LVEF <61% at baseline had a sensitivity of 75% and a specificity of 72% to identify patients with systolic dysfunction after chemotherapy. %EMAT >12.4% after chemotherapy had a sensitivity of 88% and a specificity of 84%, and EMAT >95 ms after chemotherapy had a sensitivity of 75% and a specificity of 84% to identify patients with systolic dysfunction after chemotherapy (Figures 3 and 4).

Figure 3. Receiver operating characteristic curves for LVEF at baseline, EMAT, and %EMAT after chemotherapy to identify patients with systolic dysfunction after chemotherapy. Abbreviations: AUC, area under the receiver operating characteristic curve; EMAT, electromechanical activation time; %EMAT, percentage of electromechanical activation time; LV-EF, left ventricular ejection fraction.

Predictors of Survival

In univariate analysis, survival was significantly better in women and in patients with breast cancer as opposed to lymphoma or sarcoma (Figure 1, Table 3). In multivariate analysis, female sex was the only significant predictor for improved survival (Table 3).

Discussion

With the relatively low doses of anthracyclines used in this study, the rate of systolic dysfunction after chemotherapy was 8/187 (4.8%), and this rate was further reduced to 2.4% at long-term follow-up. No patient developed clinical signs of heart failure. Half of the patients improved their ejection fraction with early initiation of heart failure treatment, but 3 (37%) died, and 1 (13%) did not improve ejection fraction. Outcome in patients with normal systolic function after chemotherapy was favorable, with a mortality rate of 3.5% and a late systolic dysfunction rate of 1.8%. Acoustic cardiography was able to identify patients with an LVEF ≤50% after chemotherapy with a sensitivity of 88% and specificity of 84%. Baseline characteristics that predicted systolic dysfunction were a higher age, a lower ejection fraction, and the presence of arterial hypertension or coronary artery disease. In multivariate analysis, female sex was the only significant predictor of survival.

Chemotherapy Dose and Regimen

It is well known that the incidence of anthracycline-related cardiotoxicity correlates with cumulative dose.^{10–12} With cumulative doses of doxorubicin of 500 to 550 mg/m², clinically manifest heart failure rate has been reported in 4% to 5%, but only in 1.6% with lower doses of 240 to 360 mg/m².^{12,13} The cumulative dose of anthracyclines was limited in the present study, and only 4 patients received a cumulative dose ≥450 mg/m². This explains why no patient developed signs of heart failure and also explains the low rate of patients who developed systolic dysfunction.

Figure 4. The principle of acoustic cardiography. In addition to a regular electrocardiogram (ECG), acoustic cardiography simultaneously records heart sounds. (A) Time domain (ECG, heart sound) as well as frequency domain (heart sound only) illustration. (B) Baseline examination of a study patient. At that time, left ventricular ejection fraction was 63%, electromechanical activation time (EMAT) was 86 ms, and percentage of EMAT was 8.6%. Abbreviations: Q, onset of electrical depolarization in ECG; S1, first heart sound; S2, second heart sound.

Table 3. Univariate and Multivariate Predictors of Mortality

Variable	Univariate Models		Multivariate Model	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (per year)	1.02 (0.99-1.06)	0.16		
Female sex	0.15 (0.06-0.37)	<0.01	0.29 (0.09-0.98)	0.046
Breast cancer ^a	0.18 (0.07-0.45)	<0.01	2.62 (0.75-9.18)	0.13
Coronary artery disease	4.12 (0.95-17.88)	0.06	1.36 (0.30-6.22)	0.69
Arterial hypertension	1.83 (0.61-5.51)	0.28		
LVEF at baseline (per %)	0.92 (0.84-1.02)	0.10		
EMAT at baseline (per ms)	1.00 (0.97-1.03)	0.92		
%EMAT at baseline (per %)	0.95 (0.76-1.19)	0.65		

Abbreviations: CI, confidence interval; HR, hazard ratio; EMAT, electromechanical activation time; %EMAT, percentage of electromechanical activation time; LVEF, left ventricular ejection fraction. ^aAs opposed to lymphoma or sarcoma.

Furthermore, additive administration of trastuzumab or chest wall radiation did not affect LVEF.

Usefulness of Echocardiography

In current guidelines, surveillance of cardiac function by echocardiography was given a class I indication by the task force of the American College of Cardiology, the American Heart Association, and the American Society of Echocardiography,¹ but the usefulness of screening all patients at baseline is controversial.^{14–16} In our study, a lower baseline LVEF was predictive of later systolic dysfunction, but none of the patients had systolic dysfunction at baseline, and baseline LVEF did not predict mortality. On the other hand, patients with systolic dysfunction after chemotherapy had a significantly worse outcome with a higher mortality rate, and therefore echocardiography after chemotherapy provided important information regarding prognosis, at least in a subset of patients. A total of 3/170 patients with normal systolic function after chemotherapy had systolic dysfunction at long-term follow-up, suggesting delayed cardiotoxicity. Currently, LVEF is the most widely used parameter for monitoring, but other measurements, such as strain, strain rate, and speckle tracking, have been proposed.^{17–19} However, these studies included a low number of patients with only short-term follow-up. In consequence, the clinical value of these parameters is unknown. In addition, cardiac magnetic resonance imaging has been proposed in patients with poor echocardiographic quality or conflicting results.²⁰

Usefulness of Acoustic Cardiography

Acoustic cardiography has been proven useful to monitor cardiac function and to detect changes in left ventricular function. EMAT is the interval in milliseconds from the onset of the QRS to the point of peak intensity of the first heart sound. It measures the amount of time that the left ventricle requires to generate sufficient force to close the mitral valve.⁵ It has been shown that EMAT and %EMAT are closely related to left ventricular contractility.^{21,22} Reduced

Figure 5. A simple algorithm to monitor cardiac function during and after anthracycline-containing chemotherapy. Abbreviations: %EMAT, percentage of electromechanical activation time; LV-EF, left ventricular ejection fraction.

left ventricular contractility is present in patients with heart failure, and may precede the development of reduced ejection fraction.^{23,24} Performing an acoustic cardiography evaluation is simple, fast, and can be done without referral to a cardiologist. Therefore, it might be a cost-effective and time-efficient alternative to echocardiographic monitoring. The value of performing acoustic cardiography before initiation of chemotherapy appeared to be limited because it did not identify patients at risk for systolic dysfunction after chemotherapy. However, after exposure to anthracycline-containing chemotherapy, acoustic cardiography had a high sensitivity and specificity to identify patients with systolic dysfunction. Therefore, instead of referring all patients to a cardiologist for routine echocardiography, we suggest performing a baseline echocardiogram only in patients with

a history of cardiac disease, hypertension, or clinical signs of heart failure. After chemotherapy, acoustic cardiography is recommended for all patients. An echocardiogram may only be necessary in patients with an acoustic cardiography-derived %EMAT >12.4%. The proposed algorithm is shown in Figure 5. However, this algorithm will not identify patients who develop late systolic dysfunction (1.8% of patients with normal systolic function after chemotherapy).

Study Limitations

The rate of patients who developed systolic dysfunction was low. This limited the power of our study to identify additional predictors of systolic dysfunction. In addition, we did not have enough patients to validate the proposed algorithm. Therefore, our results should be confirmed in a larger study. Natriuretic peptides such as B-type natriuretic peptide (BNP) or N-terminal proBNP were not measured. Newer echocardiographic parameters such as strain, strain rate, or speckle tracking were not analyzed. Because the cause of death was not clear in all, we analyzed all-cause mortality (which was determined by the underlying malignant disease, anthracycline cardiotoxicity, comorbidities, and other factors) and not cardiovascular mortality.

Conclusion

With relatively low doses of anthracyclines administered in this study, no patient developed clinical signs of heart failure, and the rate of new onset systolic dysfunction after chemotherapy was only 4.8%. However, patients with systolic dysfunction had a worse prognosis, and mortality was high despite early initiation of medical treatment. Acoustic cardiography was able to identify patients with systolic dysfunction after chemotherapy with a high sensitivity and specificity. Based on these findings, we proposed a simple cost-effective and time-efficient algorithm to monitor patients undergoing anthracycline-containing chemotherapy.

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