

Equilibrium radionuclide ventriculography in the assessment of cardiotoxicity of chemotherapy and chemoradiotherapy in patients with breast cancer

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Abstract

BACKGROUND: Multidrug chemotherapy increases the efficacy of the treatment, but at the same time rises its cardiotoxicity. The majority of cardiac complications are caused by anthracyclines. Radiation therapy may intensify cardiotoxicity. The aim of this study was to determine early changes of cardiac function using radionuclide ventriculography in patients with breast cancer and to compare the toxicity of AC and AT chemotherapy programs. **MATERIAL AND METHODS:** The study included 71 patients with breast cancer between the ages of 38 and 71 years. All patients after surgery were qualified for chemotherapy, and for 37 (52%) of them subsequent irradiation treatment was planned. Patients received chemotherapy according to the scheme: AC — 47 patients (66%) and AT — 24 patients (34%). Patients were irradiated using a photon beam (4 to 6 MeV) and an electron

beam (6–15 MeV). In all patients, before and six months after the treatment, radionuclide ventriculography was performed.

RESULTS: In all 71 patients a reductions in left ventricular ejection fraction (EF) and in peak filling rate (PFR) as well as an increase in the end-systolic and end-diastolic volumes (ESvol, EDvol) were observed. AC chemotherapy, where cumulative anthracycline dose was higher, significantly decreased left ventricular ejection fraction and PFR and increased ESvol. After AT chemotherapy the EF reduction proved to be smaller. Radiotherapy did not significantly lower the value of EF as compared to the group of patients who underwent chemotherapy.

CONCLUSIONS: Radionuclide ventriculography is a useful method of evaluating the cardiotoxicity of the treatment. Early indicators of myocardial damage are EF, PFR, ESvol and EDvol. AC chemotherapy, where the average cumulative dose of anthracyclines was higher, caused more cardiotoxic effects than AT chemotherapy.

Applying additional radiotherapy did not significantly increase the cardiotoxicity of the treatment.

Key words: radionuclide ventriculography, cardiotoxicity, breast cancer, chemotherapy, chemoradiotherapy

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Introduction

Multidrug chemotherapy used in variety of cancers increases the effectiveness of the treatment, but is also associated with toxicity, including cardiotoxicity. The majority of cardiac complications is caused by anthracyclines, regarded as one of the most effective anti-tumor agents. Anthracycline-induced cardiotoxicity

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Table 1. Average cumulative dose of anthracyclines received by patients in each group [mg/m²]

	Whole group	ACtotal	AC (only)	AC + rth	ATtotal	AT (only)	AT + rth
ADM dose	375	395	390	400	330	340	320

is directly related to the cumulative dose of anthracyclines received, and is irreversible [1].

Radiation-induced heart disease includes coronary artery disease, valvular disease, constructive pericarditis and myocardial dysfunction [2]. Radiotherapy is often associated with late, developing over the years, side effects. First cardiac complications occur within 12 to 24 months after the treatment [3]. Combination therapy — chemoradiotherapy may intensify the toxicity of both methods of cancer therapy.

Nowadays, the problem of cardiotoxicity is particularly important due to the effectiveness of oncological treatment in some patients, resulting in long-term remission or overall survival. Drug- and radiation-induced damage to the heart can lead to congestive heart failure, and as a result significantly limit and impede the normal functioning of the patient.

Echocardiography is commonly used to monitor cardiac complications of cancer therapy. It is a non-invasive and widely available method, that provides valuable information about systolic and diastolic left ventricular function, morphological changes in cardiac structures and the degree of hemodynamic changes [4]. However, in many patients after therapy, postsurgery or postradiation changes impede or even prevent the execution or interpretation of the study.

Radionuclide ventriculography is a noninvasive, useful method for the quantitative measurement of the left ventricular function and the assessment of the regional wall motion [5].

The aim of this study was to determine early changes in cardiac function using radionuclide ventriculography in patients with breast cancer after chemotherapy and chemoradiotherapy and to compare the toxicity of AC and AT chemotherapy regimens.

Material and methods

The study included 71 patients with breast cancer between the ages of 38 and 71 (mean — 54; median — 53 years). All patients that underwent surgery (mastectomy) were qualified for adjuvant chemotherapy.

Patients received chemotherapy according to the schemes:

- AC [adriamycin (ADM) 60 mg/m² *i.v.* and cyclophosphamide (CTX) 600 mg/m² *i.v.* — every 3 weeks]. Patients received from 4 to 8 courses;
- AT [adriamycin (ADM) 50–60 mg/m² *i.v.* and docetaxel 70 mg/m² (15 patients) or paclitaxel 175 mg/m² (9 patients) — every 3 weeks]. Patients received from 4 to 6 courses (Table 1).

Of the 71 patients who underwent chemotherapy or combined therapy:

- 47 (66%) were treated according to the AC regimen, with 22 (47%) qualified for radiotherapy;
- 24 (34%) were treated according to the AT regimen, with 15 (62%) qualified for radiotherapy.

Of all 71 patients after AC or AT chemotherapy 37 (52%) underwent radiotherapy. In this group in 19 (51%) patients tumor was located in the right breast and in 18 (49%) patients in the left breast.

Patients were irradiated using a photon beam with an energy range from 4 to 6 MeV and the electrons beam with an energy 6–15 MeV in one, two or three of the following fields:

- field of scar + parasternal lymph nodes — irradiated with electrons beam individually matched to the thickness of the chest wall, in a fractional dose of 200–225 cGy/90% to a total dose of 5000 or 4500 cGy/90%;
- supraclavicular field — irradiated with photon X (4–6 MeV) in a fractional dose of 200–225 cGy to a total dose of 5000 cGy or 4500;
- posterior axillar field — irradiated with photon X (4–6 MeV) to a total dose of 4500 cGy or 5000 calculated in the middle of the armpit.

Study protocol

Scintigraphic examination was performed using the *in vivo* method of red blood cells labeled with ^{99m}Tc. 20 minutes after stanous (II) chloride injection patients received intravenously 740–925 MBq (20 - 25 mCi) ^{99m}Tc pertechnetate (^{99m}TcO₄).

Gated acquisition was performed using dual-head gamma-camera, with low-energy and high resolution collimator (LEHR), 30 minutes after the administration of radiopharmaceutical. The energy analyzer was set to 140 keV and the width of the energy window was ± 10%.

Images were obtained using the left anterior oblique projection 45° (LAO 45) in order to better separate the chambers of the heart. Additionally, 10–15° caudal tilt was applied to separate left atrium from left ventricle [6]. Computer reconstruction of the image was made 2–3 times using a semi-automatic method.

In the study the following parameters were assessed: ejection fraction (EF); peak filling rate (PFR); peak ejection rate (PER); end-diastolic volume (EDvol); end-systolic volume (ESvol).

In all post-surgery patients radionuclide ventriculography was performed before and six months after chemo- and chemoradiotherapy.

Statistical analysis

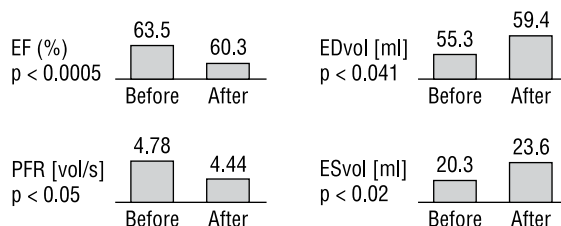
The statistical analysis of the results was made using the computer program STATISTICA Version 8. All values are expressed as the mean ± SD. Student's test was used for comparison between baseline and post treatment values in each group and a *p* value < 0.05 was considered statistically significant. In cases of distribution other than normal the Mann-Whitney test was used.

Correlation of normally distributed variables with equal variances was evaluated using Pearson's correlation coefficient and in cases of distribution other than normal with Spearman's coefficient. The data were also assessed using a multivariate analysis of variance (MANOVA).

Table 2. Haemodynamic parameters with significant changes 6 months after the treatment, as compared to baseline values (changes in other parameters showed no statistical significance NS)

	ACtotal group (n = 47)		
	Before	After	p
EF	62.7 ± 4.4	59.5 ± 6.1	P < 0.004
PFR	4.7 ± 1.6	4.3 ± 1.0	P < 0.016
ESvol	21.6 ± 7.9	24.9 ± 9.9	P < 0.09

	ATtotal group (n = 24)		
	Before	After	p
EF	63.7 ± 5.2	61.7 ± 5.3	P < 0.028
ESvol	17.5 ± 7.1	21.5 ± 7.9	P < 0.012
EDvol	48.5 ± 16.4	56.3 ± 17.2	P < 0.043

**Figure 1** Hemodynamic parameters with significant changes 6 months after the treatment, as compared to baseline values.**Table 3. Comparison of changes in EF in patients irradiated for the left and right sides 6 months after the treatment**

	Before	After	p
Right side	63.5 ± 4.2	62 ± 4.1	NS
Left side	62.5 ± 5.2	58.5 ± 6.9	P < 0.001

Results

Half year after the treatment in all 71 patients a decrease of ejection fraction (EF) from 63% to 60% and a reduction of peak filling rate (PFR) from 4.78 to 4.44 vol/s were observed. Moreover, end-systolic volume (ESvol) increased from 20 to 24 ml and end-diastolic volume (EDvol) from 55 to 59 ml (Figure 1).

In patients after AC chemotherapy (n = 47, including 22 patients additionally subjected to radiotherapy), significant reduction in EF and PFR as well as increase in ESvol were found.

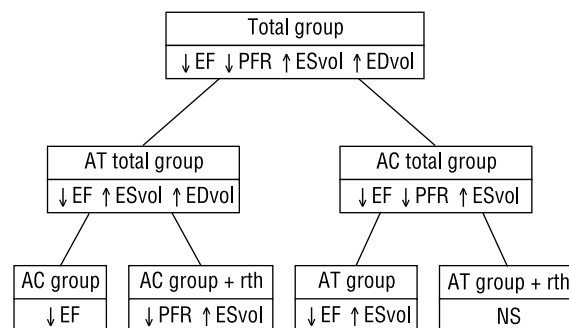
In patients after AT chemotherapy (n = 24, including 15 patients who received rth), there was also a significant decrease in EF, but it was smaller than in AC arm. Moreover, ESvol and EDvol an increase and PFR reduction were observed.

However, it should be noted that the cumulative dose of anthracyclines in the group of patients treated according to AC chemotherapy was significantly higher than in patients treated with AT chemotherapy (390 mg/m² vs. 330 mg/m²) (Table 2).

Additional radiotherapy in 37 patients after AC or AT chemotherapy did not significantly decrease EF compared to 34 patients who received only chemotherapy.

However, in patients with left-sided irradiation lower EF and an increase in ESvol were observed as opposed to patients with right-sided irradiation (Table 3, Figure 1).

Additionally, a correlation between the cumulative dose of the drug and the reduction of PFR was found — the higher the cumulative dose of anthracycline, the lower the PFR. What is more, a connection between a higher radiation dose and an increased

**Figure 2.** Graphic representation of significant changes in haemodynamic parameters 6 months after the treatment.

EDvol as well as a higher radiation dose and a decreased PFR was observed.

Discussion

Cardiotoxic effects of chemotherapy in women with breast cancer

Our study, carried out before and 6 months after the treatment, has demonstrated an adverse effect of chemotherapy and combined treatment — chemoradiotherapy in the group of patients with breast cancer.

As a result of the treatment in all patients both abnormal systolic and diastolic left ventricular function were found. A significant reduction in EF and PFR as well as an increase in ESvol and EDvol were noted.

According to some authors, in patients treated with anthracyclines, despite the absence of cardiac clinical signs and cardiac changes visible on echocardiography, early left ventricular diastolic dysfunction was observed. That may indicate that diastolic dysfunction is an early marker for anthracycline cardiotoxicity [7–9].

Massing et al [10] in their evaluation of the toxicity of anthracyclines, in a short period of time (4 weeks after the treatment), noted a significant decrease in the maximal velocity of early diastolic filling time, as well as a less significant decrease in ejection fraction. Suzuki et al. [11] assessing the cardiac function 2 and 4 weeks after the administration of anthracyclines also have not observed any significant change in EF, whereas diastolic parameters such as the initial 1/3 of peak filling rate corrected by the end-diastolic count (1/3 PFR/EDC) and the initial 1/3 of the filling fraction (1/3 FF) decreased significantly.

However, in the literature there are reports showing that even in the early period after chemotherapy both systolic and diastolic parameters change.

Cottin and colleagues [12], in their work conducted on a group of 60 patients treated with anthracycline-containing chemotherapy, observed a significant decrease in ejection fraction, PFR and PER already one month after the treatment. They came to the conclusion that both systolic and diastolic left ventricular function parameters are subject to early changes after the treatment.

In our study, changes of systolic and diastolic parameters were noted after six-months observation period, even though the patients had no symptoms of heart failure. As in the case of anthracycline-induced myocardial damage clinical symptoms of heart failure usually develop over a period of several years following the treatment [13]. It may be expected that in at least part of all patients heart failure will develop over the years.

We evaluated cardiotoxic effect of two regimens of anthracycline-containing chemotherapy — AC and AT. In the AC group the average cumulative dose of the drug was 395 mg/m², and thus was higher than in the AT group — 330 mg/m². Radionuclide ventriculography 6 months after the treatment showed a reduction of ejection fraction in both groups, but the decrease was higher in the AC group, which confirms the dependence of cardiotoxicity on the cumulative dose of anthracyclines.

It is worth mentioning that paclitaxel and cyclophosphamide used in the treatment of breast cancer can also have toxic effects on the myocardium.

In another study, carried out by Gehl et al. [14], 30 patients with advanced breast cancer underwent adjuvant combined chemotherapy (doxorubicin — 369 mg/m² and paclitaxel). Although the anthracycline dose did not exceed the acceptable values a decrease of ejection fraction of left ventricular below normal levels in 50% of all patients was noted, while 20% of all patients developed congestive heart failure. Other studies have also demonstrated that the combination of paclitaxel with doxorubicin intensifies the cardiotoxicity of the treatment [15, 16].

After 6 months of observation, no evidence of significant adverse effects of irradiation on the parameters of the left ventricle function were found in comparison with the group of patients who were subjected only to chemotherapy. What proves to be interesting, is that many previous studies proved that radiotherapy intensifies cardiotoxic effect of chemotherapy [17].

However, the group of patients with left-side chest-wall irradiation, as compared to patients with right-side irradiation, showed a significant reduction in ejection fraction and an increase in end-systolic volume of left ventricle.

Cardiotoxicity of chemoradiotherapy in patients with breast cancer

Radiation therapy is often associated with late complications remaining silent for several years. In the initial period after the radiotherapy the cardiac dysfunction triggers compensatory mechanisms. Sympathetic nervous system stimulation prevents deterioration of myocardial function [18]. This mechanism may explain why in our study there was no significant change in the ejection fraction in patients who additionally underwent radiotherapy. Only reduced peak filling rate (PFR) and increased end-systolic volume (ESvol) were observed in patients after AC chemotherapy, which may indicate future development of cardiac dysfunction.

Complications after radiotherapy may depend on several factors, including the irradiated heart volume, total irradiation dose per

fraction and the presence of pre-existing cardiovascular risk factors [19]. Patients treated with radiation therapy during 1970–1985 for left-sided breast cancer were found to have a higher mortality rate, due to myocardial infarction, than patients with right-side tumours [20].

It may seem that the reason for such high risk of heart damage was mainly due to deficiencies of planning and treatment techniques used in those times.

The type of radiotherapy proved to be significant in the development of cardiac complications. In the study 37 patients were irradiated using a photon beam with an energy range from 4–6 MeV and electrons with an energy of 6–15 MeV in fractional doses to a maximum dose of 50 Gy.

Megavoltage therapy, used currently, is less harmful for the body than the conventional X-rays therapy (with an energy of 250 kV). New techniques such as three-dimensional treatment planning and improved dosimetric planning are associated with lower cardiac morbidity [21]. Computerized three-dimensional treatment planning system (3D) allows to customize the type and dose of radiation to the patient's anatomy and the size and shape of the irradiated area [22]. This can also explain why in our study in patients, who underwent radiotherapy, no significant decrease in the evaluated parameters was noted.

Rutqvist et al. [23] found no indication of increased risk of acute myocardial infarction in the group of 684 patients after mastectomy and radiotherapy, which was given with tangential photon fields (total dose 48–52 Gy, given with 2 Gy daily fraction) in comparison with 4996 patients treated with mastectomy.

Monitoring of cardiotoxicity of antineoplastic agents (particularly anthracyclines) should be included in the strategic treatment planning for most patients. The appearance of early indicators of myocardial damage allows rapid intervention, modification of the treatment, inclusion of cardioprotective treatment as well as cardiac supervision in this group of patients. This is especially important with a positive prognosis on the length of survival after the treatment.

Nowadays, it is recommended to perform the baseline radionuclide ventriculography in patients admitted to anthracycline-containing chemotherapy, and then to control the EF after a cumulative dose of 400 mg/m² in patients with known heart disease or 450 mg/m² in patients without this risk factor. In patients whose EF declines below 50% or decreases 10% of its baseline value a change of the treatment regimen is recommended [24].

Conclusions

Our Findings confirm that already in the early period after chemotherapy the cardiotoxic effects of the treatment using non-invasive method such as radionuclide ventriculography can be assessed.

Among early indicators of myocardial damage are primarily ejection fraction and peak filling rate and, to a lesser extent, end-systolic and end-diastolic volume of the left ventricular function.

Chemotherapy according to the AC regimen, where the mean cumulative anthracycline dose was higher, proved to cause more cardiotoxic effects than AT chemotherapy.

The additional use of radiotherapy did not significantly increase the cardiotoxicity of the antitumor therapy.

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