Cardiotoxicity of anthracycline in young breast cancer female patients: the possibility of detection of early cardiotoxicity by TDI

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Tissue Doppler imaging (TDI) was investigated for its applicability for detecting cardiac function and early cardiotoxicity in breast cancer patients treated with anthracyclines. A total of 40 women (age range 18 to 65 years) were enrolled, who had not received anthracyclines previously and had normal systolic and diastolic cardiac function. All healthy patients in the control group were of the same age.

Each patient underwent not only standard echocardiographic measurements (ventricular dimensions and wall thickness, ejection fraction, E-wave deceleration time (DT), E/A ratio), but also specific imagings (E-septum separation, pulmonary venous flow), and in addition the myocardial velocity of many segments of mitral anulus obtained with pulsed wave tissue Doppler imaging were performed during the one year of observation period.

Based on the results we found that systolic left ventricular function did not change significantly – neither in the study nor in the control group. Diastolic left ventricular function was impaired in 39 patients (97.5%), and 30 (75%) of these showed clear changes by means of both the traditional E/A ratio and TDI. Diastolic dysfunction in 9 patients (22.5%), however, could be detected only with TDI. The analysis of myocardial velocity in different segments showed that diastolic dysfunction does not develop in a homogeneous way but in a different way in segments. Diastolic function was intact in the control group during the study.

The detectable myocardial damage occured in the study group of young female patients without risk factors as a result of one year anthracycline therapy was so severe that the possible outcome might be serious congestive heart failure or death. Our results confirmed our assumptions that TDI is a more precise and useful examination method than traditional ones (E/A ratio or deceleration time) to demostrate isolated diastolic dysfunction as a result of chemotherapy. Relevant extra information might be given by TDI compared to parameters describing diastolic functions depending on several changing values. TDI may become a regularly and more widely used noninvasive method to detect subclinical cardiotoxicity emerging after chemotherapy.

Key words: *anthracycline, tissue Doppler imaging, cardiotoxicity*

Myocardial damage as a result of doxorubicine therapy was already described in 1967 in children suffering of leukaemia [1]. Since then an increasing number of examinations have been published about this entity and disease [2, 3]. More and more attention has been devoted to cardiotoxicity as to a potential side effect of chemotherapy. Although a remission can be reached in several kinds of tumor-related diseases by exposing patients to an agressive or combinative anti-tumor treatment, we may have to pay a high price for this. Several data have been published in medical literature about the harmful complications of widespreadly used anthracyclines like doxorubicine and epirubicine [4–6]. These were mostly

Abbreviations: AC – doxorubicin and cyclophosphamide; EC – epirubicin and cyclophosphamide; ECG – electrocardiography; EF – ejection fraction; IVSs – thicknesses of the left ventricular septum in systole; IVSd – in diastole; LVPWs – thicknesses of the left ventricular posterior wall in systole; LVPWd – in diastole; LVEDd – left ventricular end-diastolic dimension in diastole; LVEDs – left ventricular end-systolic dimension in systole; TDI – tissue Doppler imaging.

acute myocardial damages which resulted in the deterioration of ejection fraction and cardiac function and manifested themselves in symptoms of heart failure. Due to the administration of lower dose and frequency, these acute damages became avoidable. The rate of so called late cardiotoxicity has, however, become higher, mainly in subclinical form, causing often progressive, especially in children potentially severe and occasionally even fatal cardiac event [7]. There are two sub-types of chronic cardiotoxicity, early or late chronic progressive cardiotoxicity, the former emerging within a year, the latter as long as decades after treatment [8].

Fight against cardiotoxicity has been given special emphasis as survival rates have significantly increased in spite of the original cancer disease, but due to the previous chemical treatment, a secondary damage to organs has been detected at a later clinical stage – such as cardiomyopathy with a consequence of progressive heart failure, which might lead to fatal outcome. This is the reason why more and more attention is being paid to this subject both by oncologists and cardiologists. Early detection of subclinical cardiotoxicity may help to choose the appropriate medication at an early stage, thus enhancing the chance of long term survival [9]. It was BURSTEIN and WINER who emphasised, in their publication in 2000, the necessity of long term follow up and a multidisciplinary care of women surviving breast cancer [10].

Several methods have been applied in order to detect myocardial damage caused by chemotherapy [11]. Information about the extent of myocardial damage can be provided by ECG, definition of variability of heart frequency, determination of ventricular repolarization time index and echocardiography as non-invasives study methods [12]. Among lab tests monitoring the increase of specific biomarkers of myocardial damage (CK, CK-MB, Troponin I and T) and the estimation of certain natriuretic peptides in the detections of subclinical cardiotoxicity are mentioned in literature [13]. Antimyosine (In-111-antimyosin-Fab antibody) and Thallium 201 perfusion scintigraphic examinations are the most common procedures demonstrating direct myocardial damage through image. Ejection fraction can be measured by radionuclid ventriculography. Sequential MRI may result in a better image than different isotop techniques. Nevertheless the noninvasive echocardiography is the most widespread method which can be repeated several times, provides valuable data and is applicable for the definition of both systolic and diastolic left ventricular function. By means of the above, echocardiography is used as a gold standard [14] to demonstrate the ejection features of myocardium for its well defined measurements. Problematic field is the estimation of diastolic function which gives information of the possible damage of relaxation with an approximate preciseness only [15] – though, first of all, precise information would be essential in order to get earlier information about myocardial damage. Secondly – in case of subclinical cardiomyopathy – for systolic function may remain normal for a long time in spite of the late emergence of symptoms of heart failure. Although it was the invasive catheter technique that was applied as a standard for a long time to measure diastolic function [16], the evaluation of Doppler curve of mitral inflow has become more and more important as echocardiography was developing [17]. In addition to the left ventricular diastolic features there are other factors that influence the traditional E/A mitral inflow curve: preload, afterload, frequency, atrioventricular delay, ventricular interaction, viscoelastical features, and pericardial restrictive factors. As a result, it is easy to define mitral inflow curve, but the above factors must be taken into consideration when we evaluate it. In many cases not even pulmonal venous flow but deceleration time do not help either. It was the tissue Doppler image – first described in 1989 – which was a new method [18]. A method that was suitable not only to measure regional myocardial function [19] and – by measuring velocity of systolic mitral annulus – to get values that can be compared to global left ventricular function [20], but with pulsatile Doppler techniques it was likewise suitable to measure precisely even the diastolic functions of the relevant part of the myocardium [21] – regardless of the presence of the above mentioned influencing factors. In our study we were trying to find the answer whether and to what extent tissue Doppler imaging is applicable in the early diagnosis of subclinical cardiomyopathy of breast cancer patients treated with anthracycline.

Patients and methods

Study population. Forty female patients were recruited for the study in the age of 31 to 65 years (mean 50±9 ys), after surgery for malignant breast cancer, and did not have any cardiovascular risk factors previously and no previous chemotherapy (Tab. 1). The breast cancer was on the right side of the patients, thus no patient underwent mediastinal or left sided thoracic irradiation.

Table 1. Exclusion criteria

hypertension (severe or mild)
anaemia
diabetes mellitus
coronary heart disease
left ventricular hypertrophy
severe aortic stenosis
mitral valve disease
cardiomyopathy
irradiation of the left side of the thorax or thoracic cage

The patients with lower or medium risk of invasive breast cancer underwent postoperative chemotherapy, consisting of 4 series of EC, or AC infusions. The cumulative dose of the doxorubicin was 240 mg/m^2, and the cumulative dose of the epirubicin was 360 mg/m^2.

The control group consisted of twenty healthy women in the same age between 33 and 62 years (mean 49±10 ys) and were observed with the same protocol.

The supportive therapy of the cancer disease was not an exclusion criterion (e.g. palliative irradiation in other localization, painkillers, antiemetics, and biphosphonates).

The cardiac evaluation was performed at the following stages: before initiation of the chemotherapy (T0); 3 months after the second chemotherapy, around the middle of the total treatment (T1); just after the fourth chemotherapy, which means the end of the total therapy (6 months) (T2); and 1 year after the start of chemotherapy (T3).

Study protocol.Besides the cardiological history, the findings of the physical examinations, especially the cardiovascular conditions were recorded. A standard 12-lead ECG was recorded and blood pressure was measured at rest. In order to adequately reproduce data, both the study and the control groups were examined by the same cardiologist. During echocardiography, ECG was simultaneously recorded.

Echocardiographic study. The echocardiograms were performed with a commercially available echocardiographic device (Vivid 3, GE Medical System, Horten, Norway) in the echolaboratory of the cardiology department. For the purposes of comparability and further processing, images were recorded digitally.

M-mode recordings were performed in parasternal long-axis view at the level under the apex of mitral valves. The aortic root, LV end-diastolic dimension (LVEDd) and end-systolic dimension (LVEDs); the thicknesses of the left ventricular septum and posterior wall in systole (IVSs and LVPWs) and in diastole (IVSd and LVPWd); and the atrial dimension were measured. LV end-diastolic and end-systolic volumes as well as the ejection fraction (EF) were calculated according to the modified Simpson rule.

Doppler gain and filters were adjusted to obtain the best spectral recordings. Mitral flow velocities were recorded from an apical four-chamber view by placing the pulsed-wave Doppler sample volume between the tips of the mitral valves in the centre of the flow stream. The following parameters were derived: peak early (mitral E velocity) and atrial (mitral A velocity) flow velocities, E/A ratio, deceleration time of the E wave. From the apical 4-chamber view, the pulmonary venous flow velocities were recorded by placing the pulsed-wave Doppler sample volume approximately 1 cm into the right upper pulmonary vein. The pulmonary venous peak systolic (pulmonary S) and peak diastolic (pulmonary D) flow velocities, S/D ratio, and peak reverse flow velocity and duration due to left atrial systole were recorded.

In all views, wall motion, valves disorders, and the occurance of accidental pericardial effusion were examined.

Tissue Doppler imaging (TDI). By activating the TDI function in the same echocardiographic machine, recordings of the mitral annular velocities were made with pulsed-wave TDI. To obtain the best quality recordings, filter settings and gains were adjusted at the minimal optimal level to minimize noise and eliminate the signals produced by the transmitral flow. On the apical 4-chamber view, four different sites at the mitral anulus were selected. By placing the TDI cursor at the septal side of the mitral anulus (septal) and having the movement of the mitral anulus align with the sample volume line, the recordings of anular velocity at the interventricular septum were obtained along the long axis of the left ventricle. From the apical 4-chamber view, the mitral anular velocities of the LV lateral wall were also recorded by moving the sample volume at the lateral site (lateral) of the mitral anulus. The velocities at the anterior (anterior) and inferior (inferior) sites of the mitral anulus were also recorded from the apical 2-chamber view in a similar way. Three major velocities were recorded from all 4 mitral anular sites, one of them was a positive systolic velocity (S velocity) when the mitral ring moved toward the cardiac apex. The other 2 negative diastolic velocities were recorded when the mitral annulus moved toward the base away from the apex, the early phase of diastole (Ea diast.vel.), and the late phase of diastole (Aa diast.vel.).

In a chemotherapy related cardiomyopathy, not only the global systolic and diastolic function deteriorate and has to be monitored, but the regional wall motion also. In the pulsed DTI, the sample has to be placed in the middle of the septal (septal') and posterior wall (posterior) in parasternal long axis view.

A mean of 3 consecutive cycles was used to calculate all tissue Doppler echocardiography parameters.

Statistics. Data are presented as mean value ±SD. Comparisons of baseline characteristics between the groups were assessed using an independent *t* test. For the analysis of the changes in heart rate, blood pressure, and standar echo parameters, as mitral inflow and annulus velocity parameters in each time point, paired *t* test was used in each group. Sotfware (SPSS, Version 10,0, SPSS Inc., Chicago, III) was used for the statistical analysis and a p value of 0.05 or less was considered statistically significant.

Results

Forty female patients having surgical treatment of malignant breast cancer were recruited for the study, who were compared to a control group similar to them in terms of sex, age as well as negative cardiac anamnesis and risk factors. In addition to the examination of systolic and diastolic function by common echocardiography, tissue Doppler imaging was used as well. We show in Table 2 basic data and standard echocardiographic parameters of patients and control group at the begining of the study and one year later (Tab. 2). There was no discrepancy at the begining between the two groups. When examining them one year later pulse rate in the patient group was significantly higher. However, the elevated pulse in our study is neither clinical, nor as a risk factor for diastolic dysfunction relevant. Arrhytmias were not detected in any cases. As for blood pressure, there were not significant differences. This finding is an important fact to prove that change in blood pressure could not cause diastolic dysfunction in either of the groups.

As far as standard echo parameters (aortic root, left atrium, E-septum separation, LVEDd) a considerable difference was ascertainable after one year. Due to the cardiotoxic effect in the patient group, chamber sizes have become bigger. This was, however, not accompanied by clinical symptoms or deterioration of systolic function since ejection fraction (EF) did not fall under 60%. Based on the evaluation of clinical cardiological examinations, ECG and the symptoms – despite the measurable differences of the anatomical data – we can declare that no remarkable difference could be found in the cardiovascular state of the two groups after one year of therapy.

Values, indicating traditional diastolic dysfunction (mitral E velocity, mitral A velocity, E/A ratio, Deceleration Time, S/D ratio) at the end of the study show significant difference within the patient group as compared to the initial values. Significant difference was to be seen between the last measures of patients and women of the control group. The signs of diastolic dysfunction based on E/A ratio, deceleration time were observed in 30 patients (74%), it means that diastolic dysfunction is supposed to have occured only in 74% of the group (Fig. 1). TDI measurements are represented in the third table (Tab. 3) according to the different segments at the begining when compared with the end of the study (1 year later) both in patient and control groups. It is clear that no difference could be seen in TDI values before chemotherapy as compared to control group. However, a visible difference developed between pa-

Table 2. Basic data and standard echocardiographic parameters of patients

	Begining			After 1 year		
	Patient (n=40)	Control (n=20)	p	Patient (n=40)	Control (n=20)	p
Gender (year)	49.2 ± 10.1	50.1 ± 8.5	ns			
Heart rate (1/min)	78.7 ± 12.6	72.6 ± 9.5	ns	83.0 ± 11.3	72.1 ± 15.5	0.003
Blood pressure (mmHg)	131/81 ± 16/8	128/77 ± 11/6	ns	128/78 ± 13/7	124/77 ± 10/4	ns
Aortic root (cm)	2.64 ± 0.26	2.52 ± 0.36	ns	2.58 ± 0.25	2.44 ± 0.27	ns
Left atrium (cm)	3.83 ± 0.45	3.97 ± 0.37	ns	4.89 ± 0.32	4.40 ± 0.87	0.030
LVEDd (cm)	5.11 ± 0.56	5.09 ± 0.53	ns	5.41 ± 0.43	5.06 ± 0.52	0.007
E-septum separation (cm)	0.50 ± 0.18	0.46 ± 0.12	ns	0.51 ± 0.13	0.45 ± 0.09	0.070
EF (Simpson) %	66.9 ± 5.8	64.2 ± 4.7	ns	65.7 ± 3.6	67.7 ± 2.8	0.030
Mitral E velocity (m/s)	0.78 ± 0.13	0.78 ± 0.09	ns	0.65 ± 0.11	0.76 ± 0.09	0.001*
Mitral A velocity (m/s)	0.62 ± 0.13	0.59 ± 0.12	ns	0.73 ± 0.10	0.57 ± 0.08	0.001*
E/A ratio	1.30 ± 0.29	1.35 ± 0.26	ns	0.91 ± 0.18	1.33 ± 0.23	0.001*
Deceleration time (ms)	253 ± 49	275 ± 53	ns	301 ± 42	280 ± 56	ns
Pulmonary S (m/s)	0.56 ± 0.10	0.59 ± 0.08	ns	0.43 ± 0.12	0.57 ± 0.08	0.001*
Pulmonary D (m/s)	0.36 ± 0.09	0.38 ± 0.08	ns	0.55 ± 0.14	0.36 ± 0.11	0.001*
S/D ratio	1.58 ± 0.29	1.57 ± 0.27	ns	0.87 ± 0.51	1.55 ± 0.11	0.001*

*means significant difference in values within the patient group at the end as compared to the initial status

Table 3. TDI measurements at the beginning vs at the end of the study both in patients and control groups

	Begining			After 1 year		
	Patient (n=40)	Control (n=20)	p	Patient (n=40)	Control (n=20)	p
Septal						
S velocity (cm/s)	9.96 ± 2.21	10.32 ± 1.92	ns	8.18 ± 1.67	10.28 ± 1.96	0.001
Ea diast. vel. (cm/s)	9.97 ± 1.95	10.80 ± 1.78	ns	6.13 ± 1.33	11.18 ± 2.05	0.001
Aa diast. vel. (cm/s)	6.11 ± 1.35	6.25 ± 1.28	ns	9.41 ± 2.23	6.50 ± 1.30	0.001
Ea/Aa ratio	1.65 ± 0.24	1.74 ± 0.21	ns	0.70 ± 0.31	1.72 ± 0.16	0.001
Posterior						
S velocity (cm/s)	7.22 ± 1.59	7.64 ± 1.12	ns	6.54 ± 1.07	7.24 ± 0.95	0.004
Ea diast. vel. (cm/s)	11.68 ± 2.27	11.60 ± 1.70	ns	7.09 ± 2.01	11.36 ± 1.80	0.001
Aa diast. vel. (cm/s)	6.61 ± 1.61	6.29 ± 1.09	ns	9.07 ± 1.95	6.43 ± 1.09	0.001
Ea/Aa ratio	1.81 ± 0.37	1.86 ± 0.26	ns	0.84 ± 0.42	1.77 ± 0.17	0.001
Septal'						
S velocity (cm/s)	9.65 ± 1.81	9.91 ± 1.84	ns	8.41 ± 1.37	9.75 ± 1.65	0.002
Ea diast. vel. (cm/s)	12.23 ± 1.89	13.43 ± 1.95	ns	8.10 ± 1.54	13.61 ± 1.56	0.001
Aa diast. vel. (cm/s)	9.11 ± 1.93	8.81 ± 1.56	ns	11.27 ± 2.04	8.47 ± 1.47	0.001
Ea/Aa ratio	1.38 ± 0.27	1.54 ± 0.21	ns	0.74 ± 0.20	1.62 ± 0.19	0.000
Lateral						
S velocity (cm/s)	10.09 ± 2.14	9.88 ± 1.53	ns	8.87 ± 1.54	9.67 ± 1.66	0.070
Ea diast. vel. (cm/s)	14.21 ± 2.21	14.34 ± 2.79	ns	10.06 ± 2.67	14.38 ± 2.55	0.001
Aa diast. vel. (cm/s)	9.32 ± 1.53	8.92 ± 1.55	ns	11.91 ± 2.38	8.87 ± 1.45	0.001
Ea/Aa ratio	1.54 ± 0.27	1.63 ± 0.32	ns	0.90 ± 0.41	1.63 ± 0.22	0.001
Inferior						
S velocity (cm/s)	10.16 ± 1.72	10.13 ± 1.35	ns	9.12 ± 1.28	9.94 ± 1.28	0.020
Ea diast. vel. (cm/s)	15.12 ± 2.40	14.00 ± 1.82	ns	9.88 ± 2.96	13.93 ± 1.35	0.001
Aa diast. vel. (cm/s)	10.03 ± 1.35	9.41 ± 1.64	ns	12.21 ± 1.91	9.11 ± 1.27	0.001
Ea/Aa ratio	1.52 ± 0.28	1.50 ± 0.17	ns	0.84 ± 0.36	1.54 ± 0.18	0.001
Anterior						
S velocity (cm/s)	8.70 ± 1.55	9.14 ± 1.77	ns	7.98 ± 1.46	8.69 ± 1.63	0.090
Ea diast. vel. (cm/s)	10.77 ± 1.94	11.33 ± 1.40	ns	7.58 ± 2.01	11.75 ± 1.29	0.001
Aa diast. vel. (cm/s)	7.04 ± 1.30	6.90 ± 1.12	ns	9.90 ± 2.27	6.65 ± 1.16	0.001
Ea/Aa ratio	1.55 ± 0.28	1.66 ± 0.23	ns	0.82 ± 0.38	1.79 ± 0.24	0.001

Table 4. E/Ea ratio in all segments referring to the left ventricular filling pressure in the groups before the chemotherapy and one year later

	Begining			After 1 year		
	Patient (n=40)	Control (n=20)	p	Patient (n=40)	Control (n=20)	p
anterior	7.46±1.61	7.00±1.04	n.s.	9.14±2.60	6.53±1.01	0.001
inferior	5.24±1.04	5.70±1.07	n.s.	7.05±1.91	5.49±0.85	0.001
lateralis	5.61±1.20	5.68±1.34	n.s.	6.63±2.13	5.81±1.31	n.s.
posterior	6.97±1.69	6.91±1.34	n.s.	9.83±2.86	6.90±1.68	0.001
septalis	8.16±2.12	7.43±1.41	n.s.	11.06±2.70	6.96±1.28	0.001
septalis'	6.56±1.42	5.95±1.04	n.s.	8.25±1.55	5.62±0.76	0.001

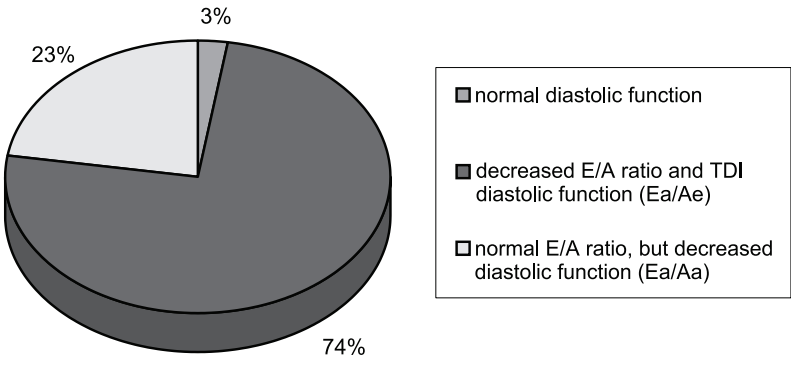

Figure 1. Diastolic function in patients after 1 year

tients and control group after one year, in the velocity of fiber shortening of the given segment both in systolic and diastolic period. In all cases the divergence of the Ea/Aa ratio was significant characterising the diastolic dysfunction of given segment. E/Ea ratio referring to the left ventricular filling pressure was also similar in the groups before the chemotherapy, but showed considerable difference when measured one year later, indicating the increase of filling pressure (Tab. 4).

Discussion

Anthracyclines are a widespreadly used cytostatic drugs in the treatment of different types of cancer diseases, hematological tumors e.g. leukemia, both in lymphocytic and in myelogen lymphomas. But they are also used in non-hematological tumors, like in the Wilms tumor, Ewing sarcoma and in breast cancers, too. However, their use is limited by a toxic cardiomyopathy resulting in irreversible myocyte damage with both acute and subacute manifestations.

The origin of anthracycline induced cardiotoxicity is probably multifactorial. The most investigated mechanism is the free radicals mediated myocytes damage [22, 23].

The myocardium is more sensitive to the harmful effect of free radicals, like other tissues, because there are less free radical scavanger superoxid dismutase and catalase avalaible to protect for the damage [24]. But there are other mechanisms, which are responsible for the injury. Role of circulating proinflammatoric cytokines (histamin, tumor necrosis factor, IL-2) is supposed to contribute to this process. These cytokines have functional receptors on the surface of the myocytes and their release can result in dilated cardiomyopathy [25, 26].

In addition to the mentioned myocadium injury, arrhytmias, sudden death, pericarditis, and temporarily electrophysiological abnormalities, like ST, T deviations, T wave flattern, prolonged QT interval.

Development of heart failure, major arrhythmia, sudden death must be reckoned with as serious complications of manifest cardiotoxicity in patients suffering from malignant tumor and treated with anthracycline [7, 27]. In the recognition of subclinical cardiotoxicity, a special role has been attributed to conventional echocardiography which helped to detect myocardial damage in 20–75% of patients who previously had undergone chemotherapy [28–31]. Myocardial damage can be shown by 2-dimension echocardiography by the increase of size of heart and the appearance of diffuse hypokinesis [14, 32]. Tissue Doppler imaging is a new noninvasive method to measure regional wall motion velocity. It is new as it can show regional disorders at an early stage before any global dysfunction could develop. In contrast with standard echocardiography, TDI is able to measure myocardial tissue velocity both under systole and diastole which directly define contractility and relaxation features of myocardium [19]. The aim of our present study was to have a look at the diastolic dysfunction helping to discover subclinical cardiotoxicity at an early stage – by means of both conventional echocardiography and TDI, comparing reliability of these methods. In early detection of subclinical cardiotoxicity, symptoms, potential heart failure and arrhythmia do not help most of the time. No congestive heart failure has developed in our study during one year, either.

Based on measuring heart frequency, we may declare that the initial similarity between patients and control group has ceased, and the pulse rate was significantly higher in the patient group at the end of the first year of therapy. This observation might be explained by the possible cardiotoxicity. Whereas the cause of the acute stage tachycardia is the direct toxic effect of chemotherapy [33], while after one year of therapy, rather the myocardial damage, the cardiomyopathy, the developing remodelling [34] and accompanying sympaticotony are the reasons for the emergence of arrhytmia.

As for blood pressure, neither patient nor control group showed discrepancies. As it seems, high blood pressure as a risk factor could not lead to diastolic dysfunction. We haven't found any literary data about changes in blood pressure as a consequence of chronic myocardial damage following che-

motherapy. As expected, during treatment we did not see any direct toxic effect with respect to systolic function, similarly to literary data. However, at a very early stage – after half a year follow up during treatment – we could detect and verify cardiotoxicity with objective parameters in the patients group which does not suffer from any other accompanying disease.

The new method seems to be suitable to detect disorders referring to cardiotoxicity, but still without clinical symptoms, one year after the start of the treatment, in women who do not have cardiovascular risk factors and who are chemotherapy-naive. In terms of certain parameters, objective changes can be experienced prior to any clinical deterioration even by treatments with anthracycline of medium dose. We think further examinations are necessary, with aggressive protocols, according to treatment with higher cumulative dose and according to new therapy schemes such as taxane. It would be worth carrying a study on looking through the follow up methods, the special cardiological tests whether they are suitable to diagnose early or late cardiotoxicity in patients suffering from accompanying cardial diseases or other high-risk disorders during invasive oncological treatments.

Due to the development in oncology, as the probability of survival of young patient with a malignant tumor is getting higher, cardiovascular problems occur more and more often – consequently cardiologists must be involved in planning oncological treatment, and they should belong to the interdisciplinary team. The exact time and sensitive methods of cardiovascular examinations must be defined during the oncological treatment and follow up period. More attention must be paid to patients concerning cardiovascular risk factors, too (giving up smoking, metabolic status, blood pressure control, overweight etc.).

Later, we might say that patients getting chemotherapy, without the above mentioned features and habits and healthy otherwise, form an independent group from the point of view of developing cardiovascular diseases. And there are hopeful examinations in terms of cardiovascular therapy, too.

According to literary data, clinically significant congestive heart failure developed in 0.5–1% of patients with breast cancer and treated with standard anthracycline [10]. Elderly people and those with anamnestical heart disease are more prone to this complication.

On the basis of our results compared to these statements mentioned above, we could declare, that not only advanced age and previous heart disease should be taken into consideration referring to emerging cardiac disorders, but young healthy women treated with medium dose of anthracycline also need close cardiac control.

Our opinion is that it would be worth planning additional studies to observe the cardiovascular state of patients getting more agressive chemotherapy, according to new protocols. Further investigation should be done to find the ideal methods for people with high risks or with cardial underlying disease, who have to undergo invasive oncological treatment.

A further question is what kind of cardiological methods might be suitable to detect early or late cardiotoxicity.

Limits and restrictions of pulsatile Doppler technique:

1. necessity of manual settings
2. it gives a limited disintegration, making it impossible to separate subendocardial and subepicardial myocardium velocity
3. a picture of different ventricular segments at the same time is not possible
4. different equipment operate in different frequency ranges with different sensitivity and filters. As a result, comparisons are not reliable.

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