



Possibilities of Early Detection of Cardiotoxicity in Patients with Malignancy

PhD theses

Dr. András Csaba NAGY

Supervisor:

Prof. Dr. Tamás Forster MD, PhD, DsC

2nd Department of Medicine and Cardiology Center, Medical Faculty,
Albert Szent-Györgyi Clinical Center,
University of Szeged

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Introduction

An increasing number of studies have addressed chemotherapy-induced cardiotoxicity. This new entity received increasing attention as a potential chemotherapy-related adverse event. Administering smaller doses at less frequent intervals of anthracyclines (ANT) helped to avoid the acute damages. The so-called late cardiotoxicity became increasingly common, most of the times occurred in a subclinical form, often progressive, potentially severe and sometimes causing fatal heart failure in children.

The fight against cardiotoxicity has come to the fore because survival of the patients significantly improved despite the underlying malignancy.

Later complaints are caused by secondary organ impairment and cardiomyopathy (resulting from previous medication), as well as by progressive heart failure (resulting from cardiomyopathy), and these ultimately lead to fatal outcome.

Anthracycline-induced cardiomyopathy may develop even after many years of the treatment. Some signs have already been described which may be indicative of subclinical cardiotoxicity. Several methods can be used to detect chemotherapy-induced cardiomyopathy.

The predominant method is the non-invasive echocardiography which provides valuable data and can be repeated several times and used to determine both left ventricular systolic and diastolic functions. However, the measurement of the diastolic function provides a measure of the possible damage to the relaxation capacity only with approximate accuracy. Accurate data on this is important because, on the one hand, they provide preliminary information on the damage of the myocardium, and on the other hand, the systolic function can remain normal for a long period of time in the case of subclinical cardiomyopathy.

To detect the diastolic function, the mitral inflow Doppler curve was used for a long time, but this is influenced by many factors that must be taken into account in the evaluation. Tissue Doppler imaging (TDI) was the new method which allowed not only to measure the regional myocardial function and obtain a value comparable to global left ventricular function by measuring the systolic mitral annular velocity, but also made it possible to accurately measure the diastolic properties of a specific portion of the ventricular wall using pulse Doppler technique.

In addition to the management of the above-mentioned risk factors, there is an increasing body of evidence that physical activity plays a role in the prevention in patients with malignancies. Exercise increases cardiovascular efficacy, improves cardiac output and stroke volume, reduces resting pulse rate, and

improves breathing and oxygen transport from the lungs to the cells. Animal studies have confirmed the protective effect of one-time and regular exercise against doxorubicin-induced cardiac damage.

Objectives

Obj. 1. This prospective study attempted to establish whether the anthracycline-containing treatment leads to the development of so-called subclinical myocardial damage in the early stages in female patients with breast cancer and without cardiovascular risk factors.

Obj. 2. Furthermore, this study explored the extent to which tissue Doppler imaging can be used in the early diagnosis of subclinical cardiomyopathy in patients with mammary tumours treated with anthracycline.

Obj. 3. A further objective of this study was to confirm the suitability for use of tissue Doppler echocardiography (TDI) in the early detection of subclinical myocardial damage using long-term measurements.

Obj. 4. The extended study aimed at confirming the preventive effect of regular exercise, already confirmed by literature data, regarding the anthracycline-induced myocardial damage and possible heart failure.

Materials and methods

Obj. 1. Measuring early subclinical damage using traditional methods

A number of 40 women, aged between 31 and 65 years of age (mean age: 50 ± 9 years), treated between April 2003 and January 2006 at the Department of Radiation Oncology of the Uzsoki Hospital, who also received chemotherapy after surgery for malignant mammary carcinoma, were enrolled in this study. The patients had no cardiovascular risk factors. Female patients underwent postoperative chemotherapy, which included 4 series of EC or AC infusions. The cumulative mean dose of doxorubicin and epirubicin was 240 mg/m^2 and 360 mg/m^2 , respectively.

The control group included 20 women with similar age distribution, between 33 and 62 years of age (mean age: 49 ± 10 years), without cardiovascular risk.

Cardiology examination

In addition to the cardiologic history of the patients, their physical status was recorded, ECG and blood pressure measurement was also performed.

Standard echocardiography

This echocardiography was performed using a Vivid 3 ultrasound machine. M-mode measurements, the left ventricular ejection fraction (modified Simpson formula), atrial dimensions were measured, using the mitral inflow curve we looked at the peak velocity of the early (E) and late (A) wave, the E / A ratio, deceleration time (DT).

Schedule of examinations

Examination 1: Before the initiation of the chemotherapy: data collection and recording cardiac status using the methods described above.

Examination 2: 12 months after the initiation of the treatment.

Obj. 2. Measuring early subclinical damage using tissue Doppler imaging

The analysis included the study group and the control group detailed in section Obj. 1, the schedule and methods were developed accordingly.

Tissue Doppler imaging (TDI)

This examination was performed using a Vivid 3 ultrasound machine in TDI mode. The mitral annular velocity (MAV) was measured using pulse TDI from transthoracic view. The lateral velocity patterns were obtained from the proximal annulus of the septal (septum) or lateral wall by placing the TDI cursor on the proximal mitral annulus of the septum in the apical 4-chamber view. Similarly, the anterior and inferior velocity patterns were obtained from the apical 2-chamber view. The mean of velocity values recorded in 3 cycles from this position was used in the statistical calculations. We measured value is the positive systolic velocity (S), the first and the second negative velocity (early diastolic Ea) and (late diastolic Aa) wave, respectively. Similar measurements were performed in the parasternal longitudinal section by placing the Doppler cursor in the middle of the septum and posterior wall. The ratio of the E wave of the traditional inflow and the early (Ea) diastolic wave of the mitral annulus measured with TDI describes the atrial filling pressure well. The Ea/Aa value is considered abnormal below 1, which is an artificial limit, but it provides a good description of the essential damage to the diastolic function.

Obj. 3. Measuring long-term subclinical damage

Our extended study included the study group and the control group detailed in section Obj. 1. Schedule of detailed cardiac examinations: Before the initiation

of the chemotherapy (T0), at 1 month after the first chemotherapy cycle (T1), at 1 month after the second chemotherapy (T2), at 1 year (T3), then at two years (T4) after the initiation of the chemotherapy.

Obj. 4. Preventive effects of physical activity

The extended study included 55 young women with breast cancer and without cardiovascular risk, treated at the Department of Radiation Oncology of the Uzsoki Hospital; most of them were from the study group described above (Obj. 1). Patients were included into two groups depending on whether they were physically active before their disease or not. Intensive physical activity carried out at least 4 or 5 days a week, for at least half an hour, including any individual or team sports, was considered exercise. Based on the above-mentioned definition, 36 patients and 19 patients were included in the physically active group (PA) and the physically inactive group (PNA), respectively. The cardiac examinations were carried out in four phases in this prospective study: before the chemotherapy (T1); at mid-term of the anthracycline therapy (T2); at one year after the first chemotherapy cycle (T3); at 2 years after the first chemotherapy cycle (T4). We assessed the occurrence of symptoms (such as breathlessness, reduced capacity, fatigue, foot swelling, nocturia) indicative of cardiac failure by phone 5 years after the first examination in these patients (T1+5 year).

Results

Obj. 1. Measuring early subclinical damage using traditional methods

The age distribution of the study group and the control group was the same.

There were no differences in the basic data and standard ultrasound measurements between the two groups at baseline. The pulse rate at 1 year was significantly higher in the study group. As regards blood pressure, there was no substantial difference at 1 year, which is important because the change in blood pressure could not cause diastolic dysfunction (DD) in either group.

As regards the traditional measurements of diastolic dysfunction (mitral E velocity, mitral A velocity, E/A ratio, deceleration time, S/D ratio), there was a significant difference within the study group in the values obtained at the end of the study compared to the baseline, and between the study group and the control group at the last measurement. However, the E/A ratio and the deceleration time showed differences indicative of diastolic dysfunction (DD) in only 30 patients

(75% of the cases), in other words, this is the number of patients who supposedly developed diastolic dysfunction within 1 year.

Obj. 2. Measuring early subclinical damage using tissue Doppler imaging

This results show that there were no differences between TDI values before chemotherapy compared to the control group. However, values obtained at 1 year show a clear difference between the patient group and the control group in the fibre shortening velocity values in a specific segment, during both systole and diastole. The resulting Ea/Aa ratio showed a clear significant difference in all cases, which characterized the diastolic dysfunction of a specific segment. The baseline E/Ea ratio indicative of left ventricular filling pressure values were also similar in the groups, and the measurement at 1 year detected a measurable difference indicating an increase in the filling pressure in the study group.

Obj. 3. Measuring long-term subclinical damage

There were no significant differences in standard echocardiographic parameters and values obtained using tissue Doppler measurements in either segment. After therapies, the basic circulation parameters at different time points showed only slight changes.

In the study group, the pulse rate increased after the first (T1) and the second (T2) chemotherapy cycle; this increase reached a significant level only during the one year follow-up period (T3), but was not clinically relevant. During the two-year follow-up period (T4), the pulse rate returned to normal.

We closely monitored the symptoms of circulatory insufficiency. It is clear that neither group had chest complaints or symptoms of circulatory insufficiency. Furthermore, there were no changes in the ECG in the study group.

During the echocardiography, there was no significant change in the ejection fraction in accordance with the clinical condition.

The traditional ultrasound parameters characterized by the diastolic function showed relaxation dysfunction almost right after the first therapy (T1). The peak of the first mitral inflow wave (mitral E wave velocity) began to decrease gradually, and at the same time, the peak of the second wave (mitral A wave velocity) showed an increasing tendency. Accordingly, their ratio (E/A) showed a decrease with a significant change at time point T1. This decrease was detectable during the entire study.

Similarly to the values measured using the traditional method, the Ea and Aa diastolic velocities and their ratio (Ea/Aa), represented by the tissue Doppler echocardiography used to describe the diastolic function, showed a change at time point T1, which remained significant until the end of the study.

It should be noted that in addition to the above mean values, individual analysis of patients showed that 22 patients (55%) had normal diastolic function, and 16 patients (40%) had DD at time point T1 that was detected using the traditional method, while for 18 patients (45%) tissue Doppler imaging had to be used to demonstrate DD. At the end of the study, we confirmed DD in 27 patients (67.5%) using a joint analysis of the traditional mitral inflow pattern and the pulmonary venous pattern, while in the case of 13 patients (32.5%) only a TDI helped.

The analysis of the E/Ea ratio representing the left ventricular filling pressure in the segments showed a significant increase of the filling pressure in all segments after the second chemotherapy cycle.

Obj. 4. Preventive effects of physical activity

The two groups of patients (physically active: n=36 - vs physically inactive: n=19) enrolled in the prospective study had a similar age distribution (49.2 vs 50.1 +/-SD). There were no differences between the two groups in the patients' cardiovascular risk status due to the inclusion criteria.

As regards echocardiographic parameters, there were no significant differences between the two groups and within each group in the aorta width, the end-diastolic diameter of the left atrium and the left ventricle, and the E-septum.

There were more significant and measurable changes in the diastolic function during this study. An evaluation of the mitral inflow patterns showed a clear change in the diastolic function. The decrease of the E/A value was visible at time point T2 in both groups, which already decreased below 1 in the physically inactive group, though the difference between the two groups was not yet significant at that time. However, a significant difference was revealed at T3 both between the two groups and compared to time point T1. The E/A ratio in the physically active group decreased below 1 only at time point T4.

The measurements in different segments of the left ventricle allow a more accurate evaluation of the diastolic function, but they have different sensitivity in the detection of the damage. In this study, the most sensitive measurement in the detection of the damage to the diastolic function was the measurement performed in the sept and sept' segments. In the physically inactive group the Ea/Aa ratio decreased below 1 at time point T2 in the sept segment, while in sept' segment a value below 1 was detected at the same time point in both groups. At time point T3, this value was below 1 in all segments in the physically inactive group, while the same value decreased below 1 only in the sept' and the sept segments in the physically active group. At time point T4, a value below 1 was detected in both groups and all segments.

As regards the change of the parameters over time, the Ea/Aa ratio showed a decreasing trend in all segments in both the sporting and the physically inactive group. This decrease became significant at time point T3 compared to baseline (T1) in both groups, but this significance was confirmed at time point T4, as well. The Ea/Aa value showed a significant decrease at time point T4 compared to time point T2 in the inf, sept', post and ant segments in the physically active groups, which indicates that the diastolic function remained intact for a longer period of time in the physically active group.

The E/Ea sept value, which is a good indicator for the left atrial filling pressure exceeded 10 sooner in the physically inactive group, at time point T2. This limit was reached in both groups at time point T3 and became significant compared to time point T1. This elevation was more marked in the physically inactive group and was significant compared to time point T2. This ratio remained above 10 in both group at time point T4.

Five years after the short term tests, the patients have been asked by phone. According to the responses given, the symptoms of cardiac failure developed in 18.1% of physically active patients while in the case of physically inactive patients, this proportion was significantly higher, 69.2%. 81.2% of physically active patients and only 30.8% of physically inactive patients were free of symptoms.

Discussion

The cardiotoxicity caused by anthracyclines have been described for several decades. One of the most common and most investigated form of cardiotoxicities is myocardial damage (left ventricular dysfunction and heart failure), which received particular attention because it is associated with a far greater mortality than any cardiomyopathy of other etiology. However, it should also be noted that the proportion and relevance of risk factors that contribute to the development of cardiotoxicity is much higher in real life in tumour patients than in the well-defined conditions of prospective randomized studies.

At the beginning, in the 1960s cardiotoxicities were confirmed by establishing the diagnosis of heart failure. Echocardiography became available for routine examination only in 1980s and was used to describe the severity of toxic damage on the basis of the change in the left ventricular EF for several decades. This non-invasive testing method became the gold standard in the detection of cardiotoxicities as well. Nevertheless, due to the heart's substantial reserve capacity, the systolic function (LVEF) showed a significant decrease that can be easily detected using ultrasound scan only years or decades after the toxic damage caused by the treatment. Early detection of subclinical cardiotoxicity

and prevention of the resulting heart failure has always been a great challenge in oncology care. It has become increasingly obvious that the improvement of non-invasive diagnostic methods led to an increase in the incidence of asymptomatic myocardial damage caused by cumulative low doses of anthracycline.

The rate of subclinical cardiotoxicity detected with traditional methods is estimated by various papers to be between 20% and 75%. In addition to limiting the dose of the anthracyclines used and amending the therapeutic protocol, the attempt to minimize the extent of the myocardial damage also required routine cardiac monitoring and detailed knowledge of the cardiovascular risk status. The incidence of heart failure related to the anthracycline treatment is 15-20% and 2% in patients with risk factors and patients without risk factors, respectively. These data emphasise not only the importance of evaluating cardiovascular status and systematic follow-up, but also require a method which can be used to detect cardiotoxicity as early as possible.

The first stage of the cardiac damage is the diastolic damage. The most commonly used method to evaluate the diastolic function, available in routine clinical settings, is echocardiography. Doppler echocardiography can be used to measure mitral filling velocity in early and late diastole. One technique that can be very easily performed and is becoming increasingly accessible is tissue Doppler imaging (TDI), which measures and represents the moving velocity of a specific segment (most commonly the septal and lateral segment) proximal to the mitral annulus as a function of time.

The principle of this method is to measure the contraction and relaxation rate of the subendocardial longitudinal fibers. The ratio of the two negative waves (diastolic waves, E_a/A_a) is a representation of the diastolic function just as the traditional mitral inflow curve. Furthermore, it is important to mention the mitral E/E_a ratio used to evaluate the left ventricular filling pressure, which contributes to the exploration of the diastolic dysfunction by measuring high filling pressure, irrespective of the systolic function. Contrary to the standard Doppler echocardiography, TDI can measure myocardial tissue velocity during both systole and diastole, which directly describe myocardial contractility and relaxation properties.

This study aimed at detecting the diastolic dysfunction to help early detection of subclinical cardiotoxicity using both traditional echocardiography and tissue Doppler imaging by comparing the accuracy of these methods.

In female patients treated with chemotherapy, without cardiovascular risk factors, changes indicative of cardiotoxicity not yet associated with clinical symptoms could be detected very early, after only one year after the initiation of the treatment, using TDI.

The extended study attempted to find out whether there will be any changes in the above-mentioned diastolic dysfunction that can be detected only one year after chemotherapy. Tassan-Mangina *et al.* found that after anthracycline-containing therapy in patients with different tumours, early diastolic dysfunction can be detected using TDI, followed by systolic dysfunction in some cases after many years.

A comparison of the traditional method and the new method used to measure diastolic dysfunction showed that both methods are suitable to detect late-onset subclinical cardiotoxicity after anthracycline-containing chemotherapy in young female patients without risk factors. Both methods confirmed significant changes in the traditional parameters (E, A, E/A, S/D) and the TDI parameters (Ea, Aa, Ea/Aa) used to detect diastolic dysfunction.

The advantages of the modern TDI method were clearly revealed by the individual analysis of the patients. Our data clearly shows that TDI is more a sensitive method for it could detect diastolic dysfunction in 18 patients (45%) in contrast to the 16 patients (40%) evaluated using the traditional method. The difference in the sensitivity of the two methods became even more obvious at time point T4 (27 versus 40 patients).

The diastolic dysfunction is an individual clinical entity, similarly to diastolic heart failure. A joint position of the European Association of Echocardiography (EAE) of the European Association of Cardiology (EAC) and the American Society of Echocardiography (ASE) addresses in detail the possibilities to analyse and detect the diastolic function. In addition to traditional methods (E/A, DT, S/D, left atrial volume), it emphasises the role of the tissue Doppler imaging (Ea, E/Ea), and considers that these methods should be used together. It also notes the role of myocardial strain in measuring regional contractility and diastolic function. A position published by the above-mentioned associations in 2014 addresses in detail the possibilities of using multimodal testing of patients with tumour.

According to the current recommendations, it can be stated that in the early detection of cardiotoxicity is based primarily on the 3D EF measurement and the change in the global longitudinal strain (GLS), but these methods are barely accessible in clinical settings. An acceptable alternative for detecting myocardial damage caused by the antitumour treatment is an accurate 2D EF measurement and diastolic parameters measurement. Nevertheless, there is limited evidence available on whether the diastolic parameters have prognostic power for cardiotoxicity. An additional large-scale study is required in order to demonstrate the above.

This study demonstrated that the deterioration of the diastolic function could be detected in patients with intact heart after the initiation of chemotherapy both in the fit (physically active) and the unfit (physically inactive) groups; in the

physically inactive group this deterioration occurred earlier and it could be detected after only one year, while in the physically active group it could be detected only after two years. The difference in the diastolic function between the two groups became significant after one year. This study evaluated the function of different segments and found that the septal segment is the first to be damaged in both groups. In the physically inactive patients, there were significantly more cases with symptoms indicative of heart failure based on the phone interview conducted 5 years after the completion of the short term studies.

During the tissue Doppler imaging (TDI), as regards the change of the parameters over time, the Ea/Aa ratio showed a decreasing trend in all segments in both the physically active and physically inactive groups. This decrease became significant at time point T3 compared to baseline (T1) in both groups, but this significance was confirmed at time point T4, as well. A study published by Lisi et al. presented similar findings, according to which TDI is more sensitive in the detection of diastolic dysfunction than the traditional E/A measurement.

The measurements in different segments of the left ventricle allow a more accurate evaluation of the diastolic function, but they have different sensitivity in the detection of the damage. A comparison of the values of the two groups showed that the Ea/Aa values were lower in the physically inactive group than in the physically active group in all segments beginning with time point T2.

The E/A ratio in the physically active group decreased below 1 only at time point T4. In the physically inactive group, diastolic dysfunction could be measured as early as the expected time of the subacute damage (T2). In contrast, in the physically active group diastolic dysfunction defined according to the ESC Guideline became apparent only in measurements performed after one year (T3-T4). Similar dynamics was observed in connection to the change in the left atrial filling pressure. The E/Ea sept value, which is a good indicator for the left atrial filling pressure exceeded 10 sooner in the physically inactive group, at time point T2. This study measured the elevation of the filling pressure; however, it did not confirmed signs indicative of more serious damages which could have caused the elevation of the filling pressure.

During the longer term follow-up (5 years after the completion of the chemotherapy), there were significantly more cases with symptoms of heart failure in the physically inactive group, which may have an impact on quality of life and life expectancy.

Based on the phone interview conducted 5 years after the completion of the short term studies, symptoms of heart failure occurred in 19.45% of physically active patients and 68.42% of physically inactive patients, that is, in significantly more cases. Conversely, 80.55% of physically active patients were

free of symptoms, while only 31.58% of physically inactive patients remained free of symptoms. The positive physiological effects and function of physical activity in ameliorating the cardiovascular risk have been long known. The studies published over the last decade provided evidence that physical activity plays an important role in the prevention of breast cancer. In addition to primary prevention, regular physical activity may also play an important role in the secondary prevention, that is, the prevention of cardiotoxicities occurring during the chemotherapy administered in the treatment of malignancies. The positive/preventive effects of physical activity are explained by several physiological factors. A number of human clinical studies also demonstrate the positive effect of physical activity performed during and after the antitumour treatment on the cardiac and pulmonary function and quality of life.

The Framework PEACE study distinguishes six key stages of malignancies (pre-screening, screening, pre-treatment, treatment, post-treatment and resumption), in each of which the positive effect of physical activity can be demonstrated. During pre-screening and screening, exercise can help with the diagnosis of malignancies by directly influencing the sensitivity and specificity of the method used to detect them, and by indirectly improving the adherence to cancer screening. Furthermore, one of the positive effects of physical activity is that it improves the physical fitness of cancer patients before the treatment. During the treatment, it ameliorates the side effects (such as fatigue, pain, nausea and depression). After the treatment, physical activity is an efficient facilitator of the rehabilitation. This study was conducted both during and after the treatment, and the positive effects of physical activity were observed in both cases.

In summary, the measurement of diastolic dysfunction is a suitable and readily accessible method to ensure early detection of chemotherapy-induced cardiotoxicity. Our additional studies confirmed the positive effects of physical activity in the prevention of cardiotoxic damage.

Conclusions - Theses

Ad 1. Compared to literature data, a new finding is that cardiotoxicity (diastolic dysfunction) can be confirmed using objective parameters 6 months after the treatment in a patient group with no other comorbidity or cardiovascular risk.

Ad 2. In female patients treated with chemotherapy, without cardiovascular risk factors, changes indicative of cardiotoxicity not yet associated with clinical symptoms could be detected very early, after only one year after the initiation of the treatment, using TDI. For some parameters, objective changes can be detected even before the deterioration in the clinical status of the patients.

Ad 3. A comparison of the traditional method and the new method used to measure diastolic dysfunction showed that both methods are suitable to detect late-onset subclinical cardiotoxicity (diastolic dysfunction) after anthracycline-containing chemotherapy in young female patients without risk factors. (One or more years later).

Ad 4. Our additional studies confirmed the positive effects of physical activity in the prevention of cardiotoxic damage.

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List of full papers that served as the basis of the PhD thesis

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- VI. Nagy A., Tolnay E., Cserep Z., Forster T.: Chemoterápia okozta kései szívizomkárosodás előrejelzése: a szöveti Doppler szerepe a diasztolés diszfunkció kimutatásában. Poster Magyar Belgyógyász Társaság 2008 évi Nagygyűlése, Magyar Belorvosi Archivum, 2008. Suppl.