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Early Detection and Prediction of Cardiotoxicity – Biomarker and Echocardiographic Evaluation

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1. Intoduction

In recent years with new anticancer therapies, many patients can have a long life expectancy. According to recently published data there are at present more than 12 million cancer survivors in the United States and in Europe (CDC, 2011; Coleman et al., 2003). These patients are prone to higher risk of cardiovascular death than the risk of tumor recurrence, particularly in childhood cancer survivors in which the cardiac mortality rate is sevenfold higher (Scully et al., 2007). However, cardiac toxicity remains an important side effect of anticancer therapies, leading to increased mortality due to mainly heart failure, but also myocardial ischemia, arrhythmias, hypertension, thromboembolism. The time from early development of cardiac dysfunction to the modification or end of chemotherapy and beginning of heart failure therapy, is an important determinant of the extent of recovery. Using conventional strategies with serial measurement of left ventricular ejection fraction, the time from first asymptomatic cardiac changes to clinical onset of cardiac dysfunction with heart failure may be lost for preventive therapy. This underlines the need for a real-time diagnosis of cardiac injury which represents the main goal for cardiologists and oncologists.

According to the general consensus the definition of chemotherapy-related cardiotoxicity include decrease in left ventricular ejection fraction by more than 20% to a value >50%, a decrease of ejection fraction by more than 10% to a value <50%, or clinical manifestations with signs and symptoms of congestive heart failure. Some of the most accurate clinical criteria of preliminary diagnosis of cardiotoxicity are established by cardiac review and evaluation committee for trastuzumab clinical trials: (1) cardiomyopathy characterized by a decrease in cardiac left ventricular ejection fraction that was either global or more severe in the septum; (2) symptoms of congestive heart failure; (3) associated signs of congestive heart failure, including but not limited to S3 gallop, tachycardia, or both; (4) decline in left ventricular ejection fraction of at least 5% to less than 55% with accompanying signs or symptoms of congestive heart failure, or a decline in left ventricular ejection fraction of at least 10% to below 55% without accompanying signs or symptoms (Seidman et al., 2002). Any of the four criteria was sufficient to confirm a diagnosis of cardiac dysfunction.

The incidence of cardiotoxicity depends on treatment-related factors (type of drug, cumulative dose and schedule of administration, combination of potentially cardiotoxic drugs, or association with radiotherapy) or patient related factors (age, presence of cardiovascular risk factors or coexisting cardiac disease, and previous mediastinal irradiation) (Jurcut et al., 2008b). Heart injury usually is subclinical and may present as acute or early onset during therapy, chronic onset - within the first year, or late onset - 1 year or more after completion of treatment. The later form is usually irreversible, and its prediction is the most important challenge.

The chemotherapeutic class of antracyclines is the most frequently implicated group and can cause an irreversible and sometimes fatal cardiomyopathy. The reported incidence of doxorubicin-induced cardiac dysfunction varies from 4%, at a cumulative dose of 500–550 mg/m², to >36% in patients receiving 600 mg/m² or more (Singal et al., 1998). Moreover, in children, the estimated risk of antracycline-induced clinical heart failure increased with time to 5.5% at 20 years after the start of therapy (van Dalen et al., 2006), and in patients treated with a cumulative antracycline dose of 300 mg/m² or more, the risk was even higher, almost 10%.

For treatment of breast cancers with Her-2 amplification, doxorubicin is administered in combination with trastuzumab - a monoclonal antibody against the Her-2/neu receptor (also known as ErbB2 – epidermal growth factor receptor 2). The results from trials using combination of trastuzumab with anthracycline plus taxane-based adjuvant chemotherapy, suggest that approximately 5% of patients will develop objective evidence of cardiac dysfunction, 2% will develop symptomatic congestive heart failure, and 1% will develop severe heart failure (New York Heart Association class III or IV), (Slamon et al., 2001). Her-2/neu receptors are superexpressed over the carcinoma cells in some kind of breast cancer but they are present at regulation of sarcomeric proteins which define the myocardial changes. However, in contrast to anthracyclines, cardiac failure due to trastuzumab administration appears, to a large extent, reversible.

The therapeutic management of oncologic patients includes combinations of drugs, radiation therapy and surgery. Irradiation with a thoracic field (as used in lymphomas and breast or lung cancer) can damage the myocardium by injuring capillary endothelial cells, which leads to ischemia and then to myocardial cell death and fibrosis. These effects can be amplified by the use of other cardiotoxic chemotherapeutic agents.

Although multiple mechanisms involved in doxorubicin cardiotoxicity have been studied there is no clinically proven treatment established for cardiotoxicity. Several approaches have been studied in order to reduce anticancer therapy-induced cardiotoxicity, from developing newer molecules (e.g., pegylated liposomal anthracyclines) (Batist et al., 2001), to the use of cardioprotective agents (dexrazoxane), and angiotensin converting enzyme inhibitors and β-blockers (Shi et al., 2011). Vascular progenitor cells have been the focus of much attention in recent years, both from the point of view of their pathophysiological roles and their potential as therapeutic agents (Jevon et al., 2008) with the ability to differentiate into mature endothelial and vascular smooth muscle reportedly reside within a number of different tissues - bone marrow, spleen, cardiac muscle, skeletal muscle and adipose tissue. Progenitor cells remain quiescent, until mobilized in response to injury or disease. Mobilized, these progenitor cells enter the circulation and migrate to sites of damage, where they contribute to the remodeling process. The number of circulating endothelial progenitor cells inversely correlates with exposure to cardiovascular risk factors and numbers of animal

models and human studies have demonstrated therapeutic roles for endothelial progenitor cells, which can be enhanced by manipulating them to overexpress vasculo-protective genes (Jevon et al., 2008; Rodriquez-Losada et al., 2008).

Until prophylaxis and therapeutic strategies for chemotherapy-related cardiotoxicity are established, close and accurate monitoring of cardiac function is recommended. Using a robust technique is important for early detection of cardiac dysfunction during anticancer therapy. Most international consensus guidelines for chemotherapy recommend serial measurement of left ventricular ejection fraction at the beginning of anticancer therapy, after administration of the half total cumulative dose and before every subsequent dose, as well as assessment at 3, 6 and 12 months after the end of treatment (Bovelli et al., 2010). Using this monitoring strategy the heart failure risk has been reduced to less than 3% in patients examined with equilibrium radionuclide angiocardiography (Mitani et al, 2003). However, subsequent reduction of ejection fraction by more than 10% or less than 50% as absolute value that was proposed as a criterion for suspending treatment (Schwartz et al., 1987, as cited by Dolci et al., 2008), is a relatively insensitively parameter for early cardiotoxicity detection. The possible explanation is that systolic dysfunction appears after a critical amount of myocardium has become damaged. Furthermore, the lack of reduction of ejection fraction does not exclude development of late cardiotoxicity (Aleman et al., 2007). Regardless of these limitations evaluation of ejection fraction has been used for monitoring left ventricular function in both clinical practice and clinical trials. Currently, there is no consensus statement on the method for efficient identification of patients at high risk for development of chemotherapy related cardiotoxicity.

2. Biomarkers

In recent years the biomarkers - enzymes, hormones, markers of cardiac stress and malfunction, as well as myocyte injury of inflammation, appear to have growing clinical importance and have become the subject of intense inquiry. A biomarker should fulfill three criteria to be useful clinically. First, accurate, repeated measurements must be available at a reasonable cost and with short times; second, the biomarker must provide additional information; and third, knowing the measured level should aid in medical decision making. The biomarkers that were proved to predict heart failure could be divided into six categories according to their origin or effects (inflammation, oxidative stress, extracellular matrix remodeling, neurohormones, myocyte injury, myocyte stress), and a seventh category of new biomarkers that have not yet been fully characterized (Braunwald et al., 2008). Heart failure, including in cardiotoxicity, appears to result from a complex interplay among genetic, neurohormonal, inflammatory, and biochemical changes acting on cardiac myocytes, the cardiac interstitium, or both.

2.1 C-reactive protein

C-reactive protein is an acute-phase reactant synthesized by hepatocytes in response to the proinflammatory cytokine interleukin-6. Increased levels of C-reactive protein correlate with the severity of heart failure and is an independent predictor of adverse outcomes in patients with acute or chronic heart failure (Anand et al., 2008). C-reactive protein has direct effects on the vascular endothelium by reducing nitric-oxide release and increasing endothelin-1 production, as well as by inducing expression of endothelial adhesion molecules (Venugopal

et al., 2005). This marker may be useable in wide population because of the low-cost and high-sensitivity test was developed. In most studies C-reactive protein has been investigated as risk factor and prognostic variable in patients with various malignances. In patients with small cell lung cancer the baseline serum concentrations of the C-reactive protein were raised in most of patients and doubled during induction chemotherapy in chemosensitive patients but it did not in non-responders (Milroy et al., 1989). In prospective study including ninety-five patients with breast cancer treated with dose-dense doxorubicin and cyclophosphamide, than weekly paclitaxel with trastuzumab and lapatinib, the levels of C-reactive protein were measured every 2 weeks during chemotherapy then at months 6, 9 and 18. During chemotherapy a detectable C-reactive protein was seen in 78% but did not correlate with ejection fraction declines (Morris et al., 2010).

2.2 Tumor Necrosis Factor α (TNF-α)

Tumor necrosis factor α (TNF-α) and three interleukins (interleukins 1, 6, and 18) are considered to be proinflammatory cytokines and are produced by nucleated cells in the heart (Anker et al., 2004). According to the cytokine hypothesis of heart failure, proinflammatory cytokines are produced by the damaged myocardium, which is enhanced by stimulation of the sympathetic nervous system. Injured myocardium, as well as skeletal muscle, which is hypoperfused because of reduced cardiac output, activate monocytes to produce the same cytokines, which act on and further impair myocardial function as a result of apoptosis and necrosis. Interleukin-6 induces a hypertrophic response in myocytes, whereas TNF-α causes left ventricular dilatation through activation of matrix metalloproteinases. Interleukin-6 and TNF-α levels could be used to predict the future development of heart failure in asymptomatic elderly subjects (Lee et al., 2005) though blockade of TNF-α has not resulted in clinical benefit in patients with heart failure (Anker et al., 2004). The increased levels of soluble members of the TNF-superfamily of apoptosis-related protein have been reported after a median follow-up of more than 6 years in patients after epirubicin-containing chemotherapy and chest wall irradiation for breast cancer especially after high-dose chemotherapy (Perik et al., 2006). To investigate if high TNF-protein levels are related to cardiac function, 40 breast cancer patients were examined following surgery, one month and one year after epirubicin-based chemotherapy. Significant but transient changes in soluble apoptotic protein levels were obsereved, particularly after high-dose chemotherapy but no relation was found between TNF-proteins and carditoxicity, assessed by electrocardiogram, conventional echocardiography and plasma natriuretic peptid.

2.3 Markers of the oxidative stress

Increased oxidative stress results from an imbalance between reactive oxygen species and endogenous antioxidant defense mechanisms. Since it is difficult to measure reactive oxygen species directly in humans, indirect markers of oxidative stress - plasma-oxidized low-density lipoproteins, malondialdehyde and myeloperoxidase have been sought. In animal models administration of doxorubicin resulted in higher myeloperoxidase activity and lipid peroxidation (Fadillioglu et al., 2004). In twenty-two patients with non-Hodgkin's lymphoma or Hodgkin's disease, treated with doxorubicin-containing regimen the flow-mediated dilation was monitored (Nagi et al., 2001). During the same time biochemical

markers were measured - the marker of lipid peroxidation (malondialdehyde), the amounts of the ratio of reduced to oxidized glutathione and the marker of free radical generating capacity of neutrophils (myeloperoxidase). No significant alterations were found in these biomarkers concentrations after doxorubicin bolus.

2.4 Sympathetic nervous system and renin–angiotensin–aldosterone system

The sympathetic nervous system is activated in patients with heart failure and this lead to higher plasma levels of norepinephrine which was proved as an independent predictor of mortality (Cohn et al., 1984). Attention focused on big endothelin-1, secreted by vascular endothelial cells and then undergoes conversion into the active neurohormone endothelin-1, which is a powerful stimulant of vascular smooth-muscle contraction and proliferation and ventricular and vessel fibrosis. Besides the activation of sympathetic nervous system, the renin–angiotensin–aldosterone system becomes activated in patients with heart failure as well. In the Randomized Aldactone Evaluation Study (RALES) of patients with severe heart failure administration of the aldosterone blocker spironolactone was associated with a reduction of plasma procollagen type III and clinical benefit, but only in patients whose baseline levels of the procollagen were above the median (Zannad et al., 2000). Moreover, in Troponin I positive patients after high-dose chemotherapy, early starting of treatment with enalapril prevent the development of late cardiotoxicity (Cardinale et al., 2006b). Obviously, blockers of rennin-angiotensin-aldosterone system slow the progression of left ventricular dysfunction.

2.5 Natriuretic peptides

Natriuretic peptides – brain natriuretic peptide (BNP) and N-terminal probrain natriuretic peptide (NT-proBNP), are synthesized in the myocytes in response to high wall stress and pressure overload (Yasue et al., 1994). Brain natriuretic peptide causes arterial vasodilatation, diuresis, and natriuresis, and reduces the activities of the renin–angiotensin–aldosterone system and the sympathetic nervous system. Measuring the BNP levels not only increases the accuracy of the diagnosis of heart failure in patients presenting with dyspnea, when a level of more than 400 pg/ml makes the diagnosis likely, but appears to be useful in risk stratification of patients with chronic heart failure (Sugiura et al., 2005) and in screening for acute or late cardiotoxic effects associated with cancer chemotherapy (Suzuki et al., 1998). Normal plasma concentrations exclude heart failure with high negative predictive value of the test. Two studies which have directly compared BNP and NT-proBNP, found that the N-terminal prohormone was slightly superior to BNP for predicting death or rehospitalization for heart failure because of the longer half-life of NT-pro-BNP (Masson et al., 2006).

The predictive role of NT-proBNP in patients treated with high dose chemotherapy was evaluated. In 52 patients after 62 chemotherapy treatments for aggressive malignancies the levels of NT-proBNP were measured before the start of high-dose chemotherapy, at the end of administration, and 12, 24, 36, and 72 h thereafter (Sandri et al, 2005). Thirty three percent of patients had persistently increased NT-proBNP, 36% - only transient increases and 31% had no increased values at 72 h. Only patients with persistently increased NT-proBNP

developed significant worsening of the left ventricular diastolic indexes from baseline to 12 months and of the ejection fraction from 62% to 45.6%. In 44 patients BNP-levels at 6-th month were significantly increased and in 4 patients they exceeded the upper normal limit 100 pg/ml, although the patients were asymptomatic (Krastev et al., 2010a).

2.6 Markers of myocyte injury

Myocyte injury results from severe ischemia usually, but in heart failure it is also a consequence of stresses on the myocardium such as inflammation, oxidative stress, and neurohormonal activation. During the past two decades, the myofibrillar proteins — the cardiac troponins T and I — have emerged as sensitive and specific markers of myocyte injury. Cardiac troponin I was detectable (≥0.04 ng/ml) in approximately half of patients with advanced, chronic heart failure without ischemia and after adjustment it remained an independent predictor of death (Horwich et al., 2003). Cardiac troponin T levels greater than 0.02 ng/ml in patients with chronic heart failure were associated with a hazard ratio for death of more than 4 (Hudson et al., 2004). The serum levels of troponin T have been shown to increase in the early stages of antracyclin therapy and it was associated with diastolic dysfunction of the left ventricle (Kilickap et al., 2005). The ability of troponin I to predict cardiotoxicity has been tested in 251 women with breast cancer treated with trastuzumab (Cardinale et al., 2010c). Positive troponin I was found in 14% of patients and in some of them troponin was already positive at baseline, possibly due to myocardial injury caused by previous chemotherapy. In the rest of patients the levels of troponin increased during therapy with first positive troponin soon after the first trastuzumab cycle. Most patients showed only transient positive troponin that normalized within 3 months. In patients with positive troponins cardiotoxicity occurrence was observed in period from 1 to 8 months after the first detection of positive marker. At multivariate analysis positive troponin was the strongest independent predictor of cardiotoxicity with hazard ratio 17.6. In addition to predict cardiotoxicity, troponin I predicts lack of cardiac function recovery with positive predictive value 65% (lack of ejection fraction recovery in troponin positive patients) and negative predicting value 100% (ejection fraction recovery in patients with normal troponin I level). Therefore, the authors propose troponin as a criterion standard marker for the assessment of cardiac risk of both old and new antineoplastic treatments (Cardinale et al., 2010a).

Other marker is creatine kinase MB fraction (CK-MB) which also circulates in stable patients with severe heart failure and is an accurate predictor of death or hospitalization for heart failure (Sugiura et al., 2005). During preparative regimen and hematopoietic cell transplantation in nineteen patients with acute leukemia, CK-MB mass and troponin T concentrations stayed negative, which mean that there was no detectable damage of cardiomyocyte structure. At the same time persistent N-terminal pro–brain natriuretic peptide elevations were registered, indicated significant cardiotoxicity with risk for development of heart failure (Horacek et al., 2007). In 47 adult acute leukemia patients after first chemotherapy the levels of Troponin I became elevated (above 0.40 μg/L) in 2 (8.3%) patients after first and last chemotherapy with anthracyclines. Both patients with Troponon I positivity had elevated glycoprotein phosphorylase. The CK-MB mass stayed in normal limits (Horacek et al., 2010).

2.7 Heat shock proteins

Heat shock proteins (HSP) are present in cells in normal conditions but are expressed at high levels in high temperature exposition or other stress. HSP27, 70, 90 and 110 increase to become the dominantly expressed proteins after stress (Hickey & Weber, 1982, as cited by Ciocca & Calderwood, 2005). Heat shock proteins become overexpressed in cancer by multiple mechanisms and they are effective biomarkers for carcinogenesis in some tissues and signal the degree of differentiation and aggressiveness of certain cancers. The levels of HSP and anti-HSP antibodies in the serum of cancer patients are useful in tumor diagnosis. Moreover, some HSP are implicated with the prognosis of specific cancers and may also predict the response to some anticancer treatments which was summarized in review by Ciocca et al. (Ciocca & Calderwood, 2005).

Implication of HSP in tumor progression and response to therapy has led to its targeting in therapy by two main strategies: pharmacological modification of HSP expression or molecular chaperon activity, and use of HSPs as adjuvants to present tumor antigens to the immune system. Furthermore, it was established that some heat shock proteins have been increased by doxorubicin treatment. In vivo rat model the levels of HSP90, known ErbB2 (epidermal growth factor receptor-2) protein stabilizer and chaperon, are increased by treatment with doxorubicin, with revealed binding of HSP90 to ErbB2. Registered in vivo increases in HSP90 and ErbB2 cardiac proteins occur even before cardiac dysfunction is detected by echocardiography. If a similar relationships occurs in humans this change could potentially be used to predict which patients receiving anti-ErbB2 treatment are at risk for developing cardiac symptoms. After treatment with HSP90 inhibitor, isolated cardiomyocites are more susceptible to doxorubicin, suggesting the protective role of HSP90 during doxorubicin treatment (Gabrielson et al., 2007). Chronic cyclosporine A treatment also induces in vivo HSP90 expression in the heart and is associated with modulation of protective endothelial nitric oxide synthase signaling (Rezzani et al., 2003). HSP 70 protects the heart from hypoxia or reoxygenation and postinfarction stresses in the heart (Iwaki et al., 1993; Marber et al., 1995). The results about HSP70 dynamic during chemotherapy are contradictive possibly due to the multitude of roles of HSP70s (Kampinga et al., 2010). In animal models the short term cardiotoxicity of dideoxycytidine causes multiple complex reactions and depression of HSP 70 levels (Skuta et al., 1999; Šimončiková et al., 2008).

The new biomarkers which are under investigation are chromogranin A (polypeptide hormone produced by the myocardium), galectin-3 (a protein produced by activated macrophages) and osteoprotegerin (a member of the tumor necrosis factor receptor superfamily) (Braunwald, 2008).

A multimarker approach is proved to be useful in improving the prognostic significance and early detection of development of heart failure. The combination of four biomarkers troponin I, NT-pro-BNP, C-reactive protein, and cystatin C, improved risk stratification for death from cardiovascular causes among elderly men beyond that of the model based on established risk factors (Zethelius et al., 2008).

The new methods, as the evaluation of proteins using mass spectrometric analysis coupled with high-pressure liquid chromatography, is likely to yield totally new classes of biomarkers for development of heart failure (Arab et al., 2006). Large platforms that would

facilitate the study of hundreds of proteins are likely to become available, which may provide a greatly expanded approach to the early detection of ventricular dysfunction, elucidating its pathogenesis and making it possible to monitor the therapy.

3. Echocardiography

Imaging techniques are conventionally applied in monitoring of chemotherapy-related cardiotoxicity to determine left ventricular ejection fraction, on whose drops the definition of cardiotoxicity is based. Endomyocardial biopsy has been accepted as the "gold standart" test for the evaluation of antracycline-induced cardiomyopathy (Friedman et al., 1978). However, the biopsy is an invasive technique with associated risk, which makes it a less acceptable method for monitoring the occurrence of cardiotoxicity.

3.1 Conventional echocardiography

3.1.1 Current recommendations for monitoring cardiac function by ejection fraction and pulsed-wave Doppler echocardiography

Echocardiography has become the dominant cardiac imaging technique due to its portability and versatility. Two-dimensional (2D) echocardiography is currently the first-line imaging modality for assessing global and regional function. 2D echocardiography offers the opportunity to measure end-diastolic and end-systolic volumes (EDV, ESV), and thereby to calculate left ventricular (LV) ejection fraction [1].

$$\text{Ejection fraction} = (\text{EDV} - \text{ESV})/\text{EDV} \quad (1)$$

According to European Society for Medical Oncology (ESMO) clinical practice guidelines, baseline assessment and periodic monitoring of cardiac function with Doppler echocardiography is suggested (Bovelli et al., 2010):

Baseline assessment of left ventricular systolic and diastolic function is recommended before treatment with monoclonal antibodies [III, A] or antracyclines and their derivates in patients aged above 60 years, or with cardiovascular risk factors, or previous treatment with 5-hydroxytryptamine-2B agonists, or documented cardiopathy or previous thoracic radiotherapy [III, A].

In all patients evaluation of ejection fraction is recommended after administration of half the planned dose of anthracycline, or after administration of cumulative dose of doxorubicin 300 mg/m², epirubicin 450 mg/m² or mitoxantrone 60 mg/m² [III, A] or after administration of a cumulative dose of doxorubicin of 240 mg/m² or epirubicin 360 mg/m² in patients aging under 15 years or above 60 years [III, B].

Echocardiography should be repeated before every next administration of anthracycline [III, A], after 3, 6, and 12 months from the end of therapy with anthracycline [III, B].

During echocardiography patterns of PW-Doppler of left ventricular in-flow tract and pulsed Tissue Doppler Imaging (TDI) of mitral annulus should be evaluated to detect initial signs of left ventricular dysfunction that may occur before reduction of ejection fraction. For patients receiving monoclonal antibodies, especially if previously treated with anthracycline, periodic monitoring every 12 weeks is also suggested [III, A].

Assessment of cardiac function is recommended 4 and 10 years after anthracycline therapy in patients who were treated at <15 years of age [III, B], or at age >15 years but with cumulative dose of doxorubicin of >240 mg/m² or epirubicin >360 mg/m² [III, B].

Reassessment or discontinuation of therapy with further frequent clinical and echocardiographic checks are needed in cases with ejection fraction reduction of ≥20% from baseline despite normal function or ejection fraction decline <50%. Mandatory these patients, even asymptomatic, should be aggressively medically treated with ACE inhibitors and β-blockers.

According to the guidelines, biomarkers are not included as routine screening measurements because their predictive role for cardiotoxicity is not well defined yet. Despite all, a persistent increases in cardiac troponin I and BNP levels seem to identify high risk patients for cardiotoxicity but this approach is costly and controversial. Using these methods patients who need further cardiac assessment may be identified [III, C]. Baseline assessment of biomarker concentrations is required and periodic measurements during therapy – at the end of therapy administration, after 12, 24, 36, 72 h and 1 month later for troponin I, and at the end of medical infusion and after 72 h for BNP.

The American Society of Echocardiography together with the European Association of Echocardiography has updated the recommendations for quantifying cardiac chambers. To perform adequate chamber quantification several main requirements should be fulfilled: to achieve minimal translational motion of the image, to maximize image resolution, to avoid apical foreshortening and maximize endocardial border (Lang et al., 2006). The most commonly used for volume measurements is the biplane method of discs (modified Simpson's rule,) and is the currently recommended method of choice. The principle of this method is that the total left ventricular volume is calculated from the summation of a stack of elliptical discs. The height of each disc is calculated as a fraction of the left ventricular long axis based on the longer of the two lengths from the two- and four-chamber views. Normal values of left ventricular ejection fraction are ≥55% for both genders (Lang et al., 2006). The alternative method to calculate volumes when apical endocardial definition is not possible is the area-length method where the left ventricle is assumed to be bullet-shaped. However, the accuracy of measured left ventricular volumes and ejection fraction depends on the expertise of the reader, resulting in large intra- and interobserver variability, and are preload-dependent parameters. If a transthoracic window yield unacceptable cardiac images because of local surgery or radiation-related changes, an alternative imaging modality like radionuclide scanning should be considered (Sengupta et al., 2008). Moreover, ejection fraction is not a very sensitive parameter in detecting early alterations in myocardial function as they occur in early cardiotoxicity (Schmitt et al., 1995).

It was established that cardiotoxocity lead to diastolic dysfunction of the left ventricle which can be registered with Doppler echocardiography before systolic function occurs (Schmitt et al., 1995). The impairement was not lineary related to the cumulative dose of antracyclines, but may persist years after treatment with antracyclines (Bu'lock et al., 1995; Hausdorf et al., 1988). Conventional Doppler echocardiography with measurements of the velocities of mitral inflow (early peak E wave and late peak A wave), deceleration time of early filling and isovolumic relaxation time, characterizes the pattern of left ventricular filling (fig. 1 and fig. 2) but is not sufficient to differentiate pseudonormal from normal filling because of preload dependence.

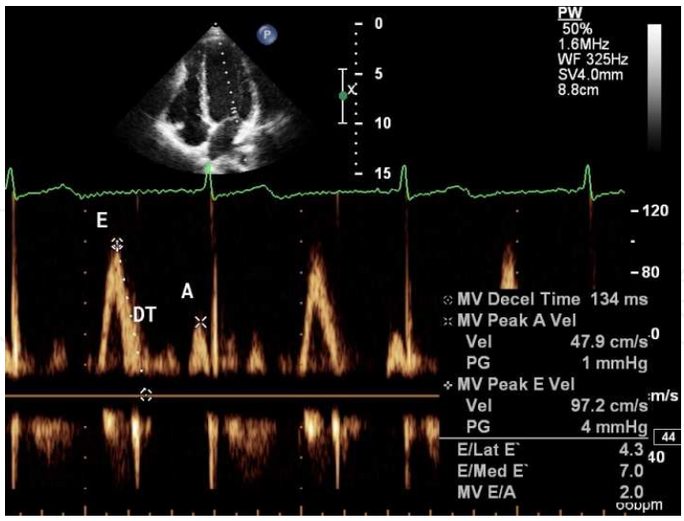

Fig. 1. Pulsed-wave Doppler of mitral filling. E-wave – early diastolic filling, A-wave – late diastolic filling, DT – deceleration time of early mitral filling.

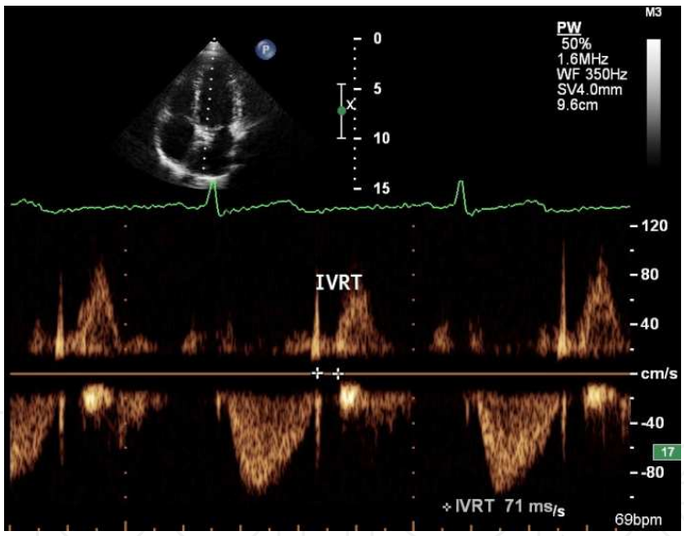

Fig. 2. Isovolumic relaxation time, measured from aortic valve closure to onset of mitral filling.

An algorithm for monitoring cardiac function during trastuzumab therapy is proposed (Sengupta et al., 2008). During chemotherapy, if new diastolic dysfunction, independently of ejection fraction and clinical symptoms manifestation, is detected, patients should be reassessed for risk-benefit of cancer treatment. Heart failure therapy should be started and echocardiography performed every 1 week. If heart failure is presented and worsens, chemotherapy discontinuation should be considered. If symptoms reverse and left ventricular function stabilizes, chemotherapy may be reinstituted. Echocardiographic evaluation of ejection fraction and diastolic function continues once every 8 week.

3.1.2 Additional echocardiographic methods for early detection of cardiac dysfunction

3.1.2.1 Tei-index

Tei-index is a combined index for estimation of systolic and diastolic left venrtricular function, calculated from the ratio of the difference between time interval from the end to the start of transmitral flow (a), and the left ventricular ejection time (b) to the duration of ejection time b [2] (Tei et al., 1995).

$$\text{Tei-index} = (a - b)/b \tag{2}$$

The interval (a) includes the isovolumic contraction time, ejection time and the isovolumic relaxation time, and is derived by pulsed-wave Doppler echocardiography with sample volume at the tips of the mitral valve leaflets in the 4-apical chamber view (fig. 3). The time interval (b) are derived with sample volume in the left ventricular outflow tract from 5-chamber view (fig. 4). Tei-index may also be expressed as [3]:

$$\text{Tei-index} = (\text{IVCT} + \text{IVRT})/\text{ET} \tag{3}$$

IVCT – isovolumic contraction time, IVRT – isovelocity relaxation time, ET – ejection time

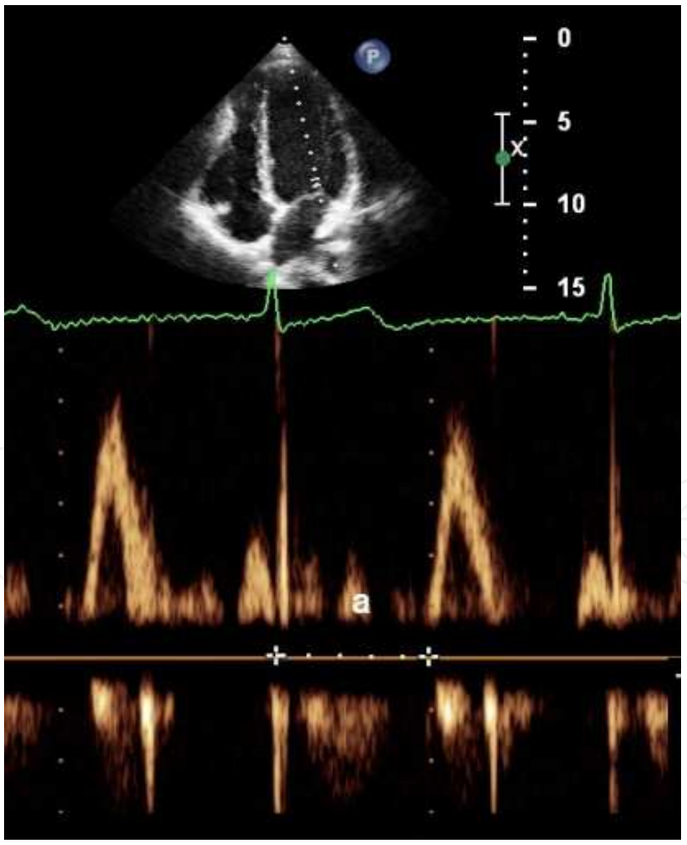

Fig. 3. Measurement of interval (a) which includes the isovolumic contraction time, ejection time and the isovolumic relaxation time. The spectrogram is registered with PW-Doppler at the tips of mitral valve leaflets from apical 4-chamber view.

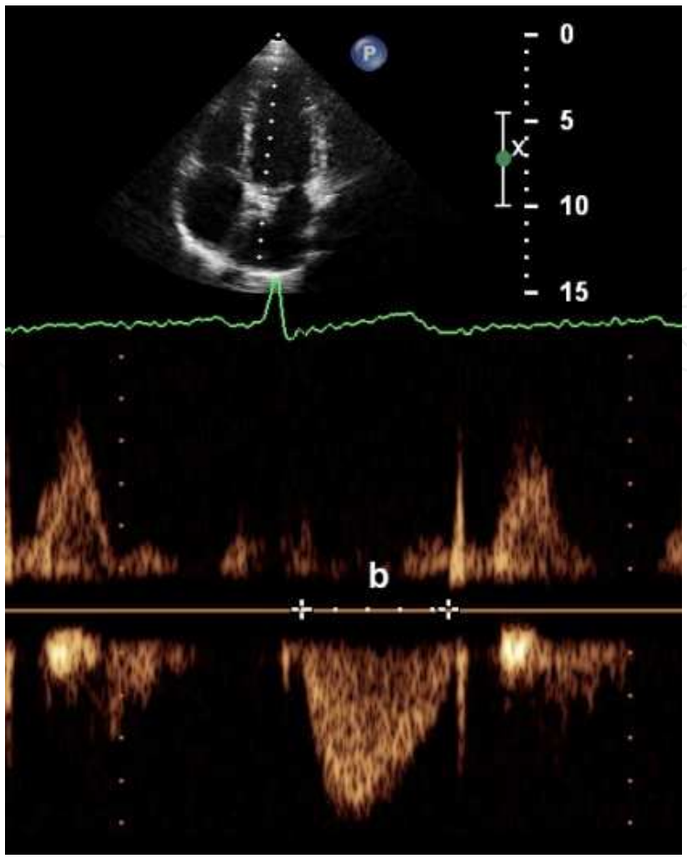

Fig. 4. Measurement of interval (b) which represents the ejection time. The spectrogram is registered with PW-Doppler in the left ventricular outflow tract from apical 5-chamber view.

Calculation of Tei-index is easily obtained and has been proven to be a reliable method for evaluation of left ventricular systolic and diastolic performance, because of its load, heart rate and age independence, although it is not applicable in patients with rhythm and conduction disorders. It appears to be promising parameter for evaluation of myocardial dysfunction in large number of diseases but future studies are needed to confirm its prognostic power (Lakoumentas et al., 2005).

According to the results from serial echocardiographic examination of 23 patients on anthracycline treatment, the Tei-index is a more sensitive indicator of early cardiotoxicity than left ventricular ejection fraction regardless of its value before treatment (Senju et al., 2007). An additional anthracycline dose significantly correlated with a change in Tei-index, in contrast to ejection fraction.

In 61 cancer patients on chemotherapy, the left ventricular Tie index was significantly increased from 0.33 at baseline to 0.44 at 6-th month from chemotherapy, which confirm early changes in cardiac function, undetectable by traditional echocardiography (Krastev et al., 2010c). Moreover, Tei-index calculated for right ventricle was increased also.

In 67 consecutive patients on doxorubicin-containing chemotherapy, 26% of patients developed cardiotoxicity (Belham et al., 2007). The Tei-index detected declines in left ventricular function earlier in the course of anthracycline treatment and to a greater

significance than others standard echocardiographic measurements but did not predict functional cardiotoxicity.

Other authors did not find Tei-index to detect early adriamycin cardiotoxicity in adults in echocardiographic examination performed at baseline, at an-intermediary cycle and at the end of chemotherapy (Rohde et al., 2007). The comparison of its predictive value has been done with left ventricular ejection fraction measured by radionuclide ventriculography.

3.1.2.2 Color-M-mode flow propagation velocity

Flow propagation velocity Vp, measured with color M-mode Doppler echocardiography as a slope of the first color-aliasing from mitral annulus to 4 cm into left ventricular cavity (fig. 5), is a relatively preload and heart rate independent parameter. It has been shown that Vp <45 cm/s to be robust predictor of high left ventricular pressures and cardiovascular mortality (Garcia et al., 2000). Moreover, the ratio of E-wave mitral velocity/propagation velocity (E/Vp) ≥ 1.5 predicts a left ventricular end-diastolic pressure >15 mmHg and differentiates sufficiently pseudonormal from normal left ventricular filling (Garcia et al., 1997). It has been shown that E/Vp ratio to have prognostic value in postmyocardial infarction patients (Moller et al, 2000; Kinova et al, 2004). This method has been validated in a heterogeneous group of pediatric patients by comparing the flow propagation velocity Vp and septal mitral annular myocardial velocity with simultaneously obtained invasive indices of diastolic function (Border et al., 2003). Propagation velocity correlated significantly with the time constant of isovolumic relaxation τ (r= -0.56, p=0.01) and with peak negative dp/dt (r=0.5, p<0.03), and septal mitral annular myocardial velocity – with the time constant of isovolumic relaxation τ (r= -0.58, p=0.01). The E/Vp ratio correlated significantly with left ventricular end-diastolic pressure (r=0.71, p <0.001).

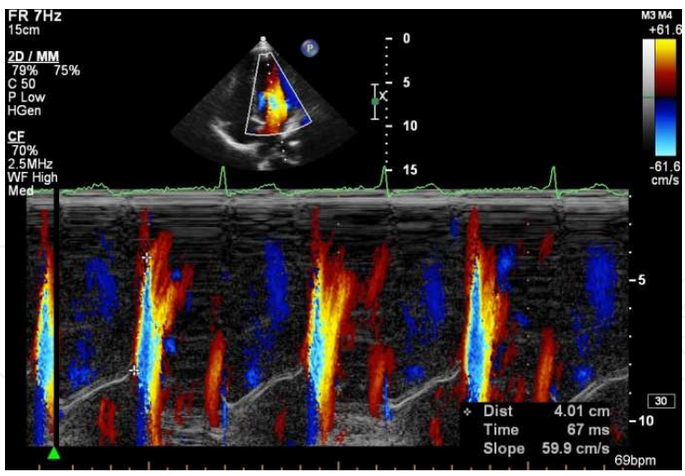

Fig. 5. Color M-mode Doppler flow velocity propagation Vp, measured as the first color aliasing from mitral annulus to 4 cm into left ventricular cavity from 4-chamber apical view.

3.2 Tissue Doppler echocardiography

Tissue Doppler imaging (TDI) uses Doppler principles to measure the velocities of myocardial motion which are lower and have higher amplitude than the velocities of blood flow. Myocardial velocities are measured only in direction of the ultrasound beam and

reflected the absolute tissue motion but with impossibility to discriminate passive from active motion. This is the reason for inability of TDI-velocities to differentiate translation or tethering motion from myofiber shortening and lengthening. Tissue Doppler Imaging can be performed in pulsed-wave and color modes.

3.2.1 Pulsed-wave tissue Doppler imaging

In pulsed-wave (PW) Tissue Doppler Imaging (TDI) the Doppler signal from one sample region is collected. The spectrogram is represented with Doppler frequency on the vertical axis and time on the horizontal axis and it consists of peak systolic myocardial velocity (S-velocity) and early and late diastolic velocities (E' and A' respectively), fig. 6. In apical views PW-TDI measures the long-axis ventricular motion well because the longitudinally oriented endocardial fibers are parallel to the ultrasound beam. The sample volume is placed in the basal myocardial segments adjacent to the annulus and thus PW-TDI has high temporal resolution but does not allow simultaneous analysis of multiple myocardial segments.

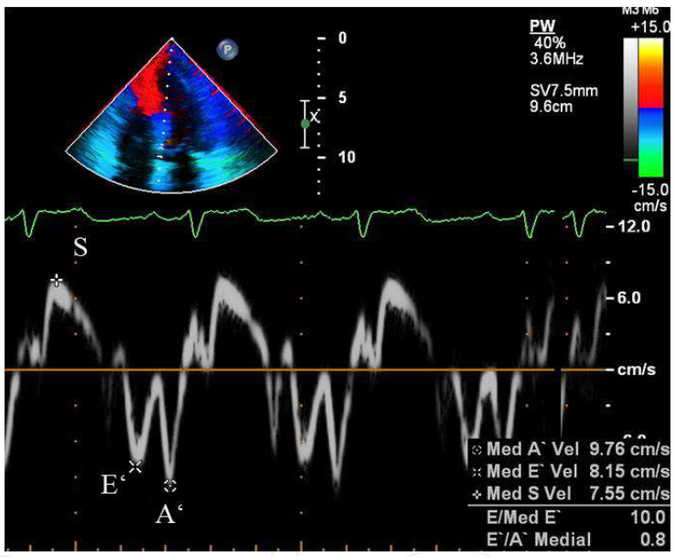

Fig. 6. Pulsed Tissue Doppler of the medial mitral annulus. S – systolic velocity above the baseline as a result of annular movement toward the apex, E'm – early diastolic velocity below the baseline due to annular movement away from the apex, A'm – late diastolic velocity, at the time of atrial contraction.

A heterogeneous pattern of systolic and diastolic myocardial velocities was observed between individual wall segments and between basal and mid segments of each myocardial wall (Galiuto et al., 1998). The velocities are lower in the septum, with higher basal to midwall difference. This heterogeneity should be taken into account in clinical application.

Systolic velocity correlates with peak dp/dt of the left ventricular pressure curve and may be useful for noninvasive evaluation of global left ventricular systolic function (Yamada et al., 1998). Moreover, TDI of the mitral annulus is an established method for assessment of the global diastolic function due to the moving mitral annulus and relatively stationary apex throughout the cardiac cycle. The ratio of early mitral velocity E/early mitral annular

diastolic velocity E′ (E/E′) correlates closely with LV filling pressures (Nagueh et al., 1997; Sohn et al., 1997). Mitral E-wave depends on left atrial driving pressure, left ventricular relaxation and age, and E′ depends mostly on left ventricular relaxation and age. Hence, in the ratio E/E′, effects of left ventricular relaxation and age are eliminated and the ratio becomes a measure of left atrial driving pressure or LV filling pressure. Early diastolic E′-velocity can be conceptualized as the amount of blood entering the LV during early filling, whereas mitral E-wave represents the gradient necessary to make this blood enter the left ventricle. When the ratio E/E′ exceeds 15, left ventricular filling pressures are elevated, and when the ratio is lower than 8, left ventricular filling pressures are low(Paulus et al., 2007).

The early and late anthracycline effects in 20 adults were evaluated with conventional echocardiography and tissue Doppler imaging. Early after chemotherapy (1-3 months) changes in left ventricular diastolic function were observed (Tassan-Mangina et al., 2006). The mitral E peak velocity and early diastolic myocardial velocity Em of the basal segments of lateral and posterior wall decreased significantly. Changes in systolic function with lower ejection fraction and systolic myocardial velocities occurred later (3.5 ± 0.6 years) together with even more pronounced diastolic changes with decline in late diastolic velocities Am of the lateral and posterior wall and early and late diastolic mitral annular velocities. Moreover, a short isovolumic relaxation time <80 ms, measured at the mitral annulus level early after chemotherapy, predicted with accuracy a late decline of LV ejection fraction below 50%.

In patients with breast cancer cardiac function has been monitored using Tissue Doppler imaging which is found to be more sensitive than standard Doppler for assessment of left ventricular diastolic function and 2-dimensional echocardiography for systolic function (Di Lisi et al., 2011). These results show that TDI should be integrate in echocardiographic examination in monitoring chemotherapy-related cardiotoxicity.

The applicability of the conventional and tissue Doppler echocardiography for detection of late or subclinical cardiotoxicity, following anthracycline chemotherapy was compared in forty women (Nagi et al., 2008). After one year diastolic left ventricular function was impaired in 97.5% of patients, and in 25% of them diastolic dysfunction could only be detected with TDI. At the end of the study the rate of undetectable diastolic dysfunction, registered with conventional E/A ratio, rose to 32.5% and TDI was the method for identifying these patients.

In 61 cancer patients treated with cytostatics with known cardiotoxic effects no changes in conventional echocardiographic parameters of systolic and diastolic function were observed. However, at 6-th month systolic velocity of lateral mitral annulus Sl and all medial and lateral annular diastolic velocities (E′m, A′m, E′l, A′l) were significantly reduced (Krastev et al., 2010c). Asymptomatic diastolic dysfunction was developed despite of normal ejection fraction during and after chemotherapy (Krastev et al., 2010b).

Serial evaluation of cardiac function in 37 breast cancer patients revealed progressive decrease in systolic velocity and early diastolic velocity of medial mitral annulus, and early diastolic velocities of inferior and anterior mitral annulus (Tanindi et al., 2011). Pulsed-wave TDI is able to detect even subtle changes in right ventricular function during cancer therapy. Systolic and early diastolic velocity of lateral tricuspid annulus showed significant reduction from baseline to the day after the completion of the first cure, and then to the day after the completion of two cures. Late diastolic velocity decreased later after the second cure of chemotherapy.

Based on the results for possibility of TDI to identify early diastolic changes in left ventricular function in patients on chemotherapy, a randomized clinical trial the Liposomal doxorubicin-investigational chemotherapy-Tissue Doppler imaging Evaluation (LITE) to compare the safety of lisosomal doxorubicin vs. standard epirubicin in terms of clinical and subclinical cardiotoxicity, has been started (Loriontе et al., 2009). The primary end-point will be the comparison of changes from baseline to 12-month follow-up of left ventricular systolic function TDI-parameters and the co-primary end-point will be based on changes in TDI-diastolic parameters.

3.2.2 Color tissue Doppler imaging

Color TDI overcomes the limitations of PW-TDI for performing simultaneous analysis of different myocardial segments. It represents color-coded myocardial velocities of multiple segments at the same time during the cardiac cycle, superimposed on gray-scale 2-dimensional or M-mode images, in a single view. This improves the spatial resolution. Off-line analysis allows derivation of time-velocity plots (fig. 7). Velocities measured off-line represent regional mean velocity and are lower than peak velocity obtained with PW-TDI. The reason is that Doppler signal is collected for each depth and each ultrasound beam which limits the ability to calculate full-signal spectra for each position of the image.

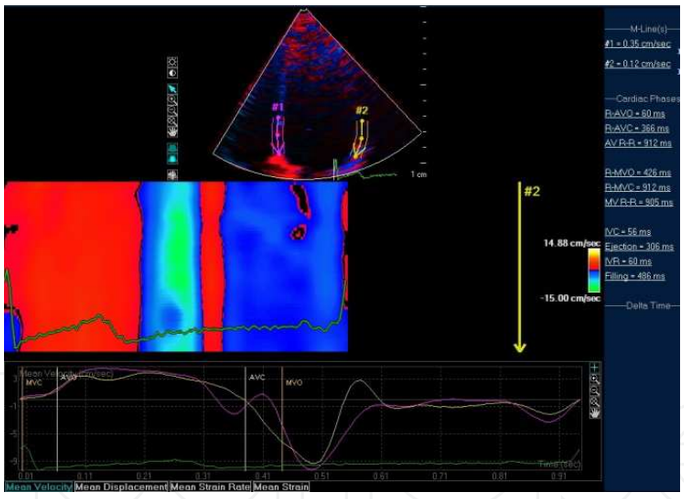

Fig. 7. Tissue Doppler Imaging for assessment of regional myocardial velocities. Apical 4-chamber view with regional analysis of the septal and lateral walls. Region of interest include the basal segments and systolic and diastolic velocities in the averaged cardiac cycle are presented as color M-mode imaging and curves over time.

3.2.3 Strain rate imaging by tissue Doppler

Recently, strain rate imaging, using color-coded tissue Doppler imaging, have emerged as a quantitative technique to estimate myocardial function and contractility (Hashimoto et al., 2003). This method uses Doppler measurements of the myocardium to extract parameters such as deformation, strain rate (fig. 8) and strain (fig. 9).

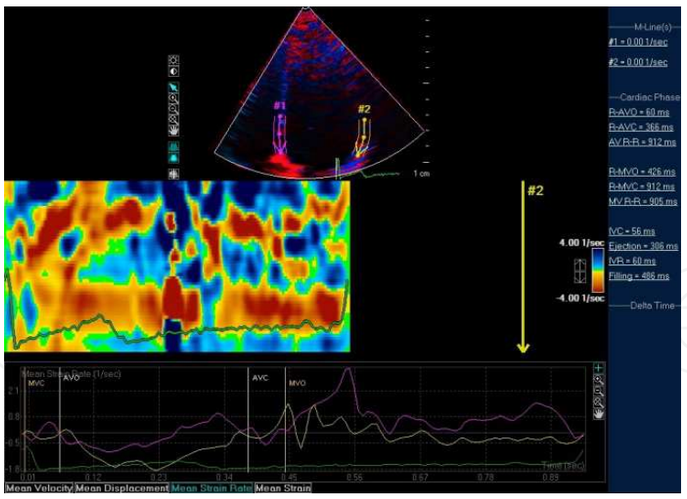

Fig. 8. Color M-mode longitudinal strain rate image and strain rate waveforms obtained from the same region of interest as the velocity curves - basal septal and lateral walls from 4-chamber apical view.

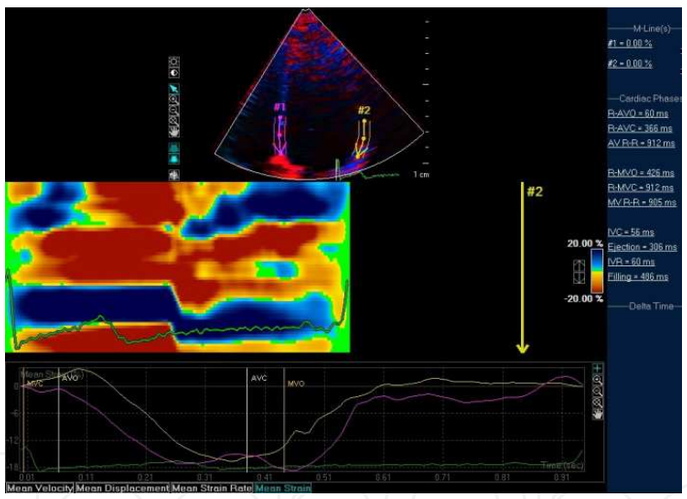

Fig. 9. Color M-mode longitudinal strain image and strain waveforms obtained from the same region of interest as the velocity curves - basal septal and lateral walls from 4-chamber apical view.

TDI-Strain rate provides differentiation of true contractility from passive myocardial motion by accounting relative changes in tissue velocity. Left ventricular function can be assessed in one dimension by the analysis of myocardial wall velocity, or by the analysis of wall deformation of a myocardial segment (strain rate) and deformation over time (strain). These parameters can be measured with sufficient spatial and very good temporal resolution. Using TDI-based Strain rate imaging, derivation of longitudinal strain rate and strain in apical views, and radial strain rate and strain in short axis views is possible. So far, several diseases with subtle impairment of left ventricular function have already been evaluated by Strain rate Imaging (SRI), including cardiomyopaties, hypertensive heart disease, ischemic

heart disease and proved to be more sensitive than conventional measurements (Abraham et al., 2007).

In a population of children treated with anthracyclines myocardial deformation parameters had already changed, while conventional echocardiography did not show any decline in left ventricular ejection fraction or fractional shortening after the first two cycles of treatment (Ganame et al., 2007a). Regional left ventricular longitudinal and radial systolic strain and strain rate were reduced within 2 h after the first dose of anthracyclines.

In 56 late survivors of childhood cancer, previously treated with anthracyclines at supposedly safe doses lower than 300 mg/m², both radial and longitudinal myocardial strain was reduced by 15% in patients compared to controls, while ejection fraction remained within normal limits at a median of 5.2 years after the completion of therapy (Ganame et al., 2007b).

The feasibility and sensitivity of Doppler-based strain rate imaging in detection of cardiac effects of pegylated liposomal doxorubicin have been tested in 16 women with breast cancer at baseline and 6 cycles of treatment (Jurcut et al., 2008a). Longitudinal and radial strain and strain rate were significantly reduced after 6 cycles. Changes in radial function appeared earlier and were more pronounced then longitudinal function.

The angle-dependence of tissue Doppler-based velocities and strain is the main limitation of the method and this makes the measurements of apical segmental velocities and strain difficult. The angle dependency is the reason for inability to analyse anything than movement in longitudinal direction. The inability of TDI-velocities to reflect the motion caused by tethering to adjacent segments is overcome through derivation of strain rate and strain, but spatial resolution is impaired by imaging at high temporal resolution. Higher spatial resolution is achieved by using of a narrow imaging sector and lower depth but decreases the lateral resolution (Marwick et al., 2006). These limitations on lateral resolution significantly limit the ability of this technique to assess longitudinal subendocardial and subepicardial deformation.

3.3 Two-dimensional speckle tracking echocardiography

The real power of speckle analysis is the ability to examine several components or planes (i.e. radial, longitudinal and circumferential) in a single data set (Goffinet et al., 2007; Gorcsan et al., 2011). By analyzing speckle motion each speckle can be identified and tracked by calculating frame to frame changes throughout the cardiac cycle. Speckle tracking echocardiography (STE) offers the opportunity to assess myocardial tissue velocity, strain and strain rate independently of cardiac translation and beam angle. It requires acquiring at least two cardiac cycles for further offline processing and interpretation. Deformation parameters are derived for each left ventricular segment and thus allow regional function assessment. Global circumferential, radial and longitudinal strain is calculated from the mean of all cardiac segments (fig. 10, 11, 12).

Myocardial strain quantification by speckle tracking echocardiography has been well validated, using sonomicrometry and tagged cardiac magnetic resonance as reference methods (Amundsen et al., 2006).

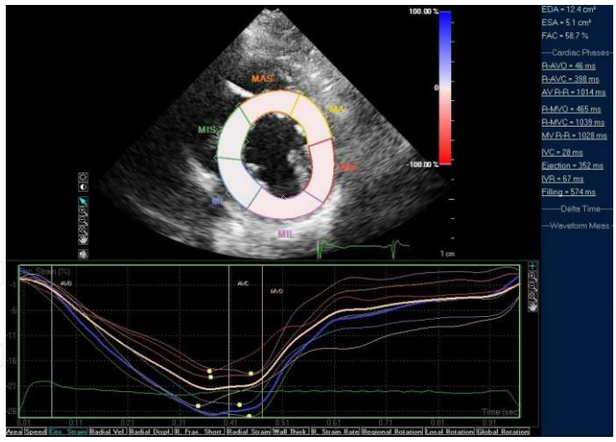

Fig. 10. 2D-speckle tracking analysis of circumferential strain from parasternal short axis view at the level of papillary muscles.

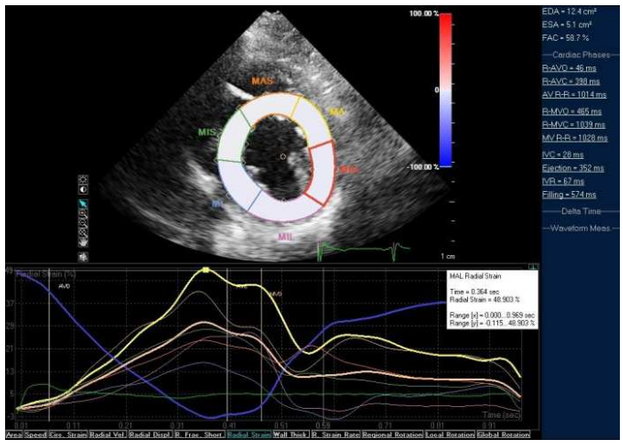

Fig. 11. 2D-speckle tracking analysis of regional and global radial strain from parasternal short axis view at the level of papillary muscles.

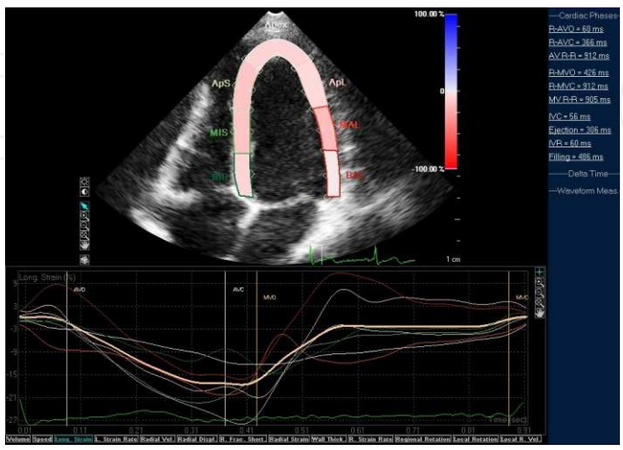

Fig. 12. 2D-speckle tracking analysis of regional and global longitudinal strain from apical 4-chamber view.

Due to the orientation of left ventricular muscle fibers, varying across the left ventricular wall, the shortening of obliquely oriented fibers generates a wringing motion responsible for left ventricular torsion. During the cardiac cycle, a systolic twist and an early diastolic untwist are generated by opposite basal and apical rotations. Twist or torsion (twist/left ventricular length) plays an important role in ejection and in the storage of potential energy at end-systole, the release of this energy as elastic recoil during early diastole assists ventricular suction. Since left ventricular rotation is sensitive to changes in function it is, therefore, of obvious clinical interest to assess left ventricular torsion non-invasively.

Until recently, tagged cardiac magnetic resonance was the only method capable of assessing left venricular torsion non-invasively. Speckle tracking echocardiography has the opportunity to assess torsional deformation of the left ventricle (Notomi et al., 2005).With the advent of speckle tracking echocardiography, left ventricular torsional deformation can be assessed, thus permitting a broader use of this new functional approach. The tissue motion quantification software allows the assessment of rotation in subendocardial, midwall and subepicardial layers at basal and apical levels (fig. 13 and fig. 14) and thus calculating torsion and untwisting.

Myocardial deformation parameters are superior to conventional measures for detection of early subtle alterations in left ventricular function. In 35 female patients treated with trastuzumab, ejection fraction with 2D- and 3D-echocardiography and strain and strain rate with TDI and 2D speckle tracking echocardiography, were measured every 3 months between baseline and 12 months. During the period no overall changes in 2D and 3D ejection fraction, myocardial E-velocity and strain were observed. However, significant reduction in TDI strain rate, 2D longitudinal strain rate and 2D radial strain rate were registered. Three out of 18 patients with reduced longitudinal strain rate had a reduction in ejection fraction ≥10% and another 2 developed a reduction over 20 months follow-up (Hare et al., 2009).

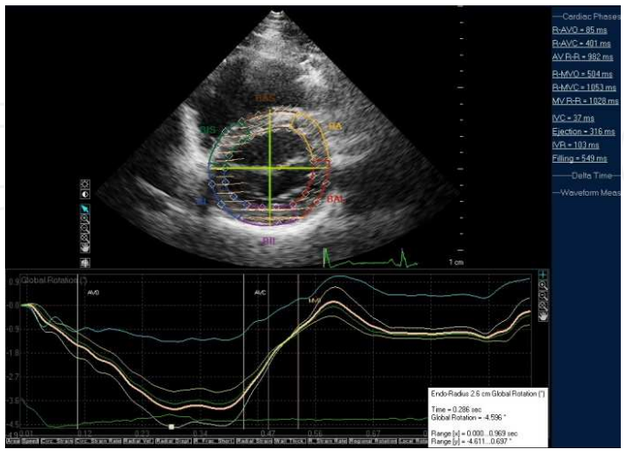

Fig. 13. Rotation by speckle tracking echocardiography.The curves represents rotation in subendocardial, mural and subepicardial layers at the basal left ventricular level from parasternal short axis view.

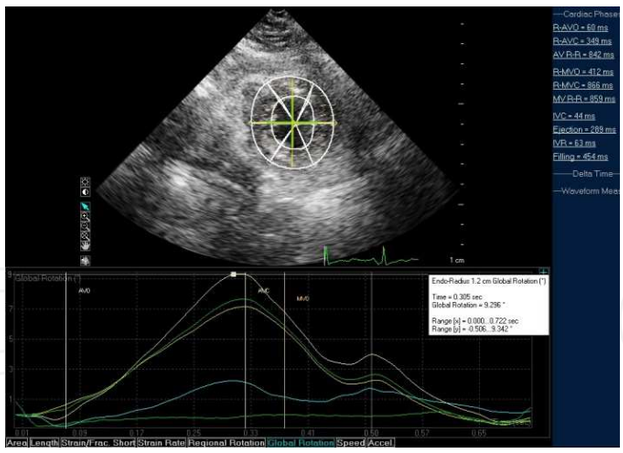

Fig. 14. Rotation by speckle tracking echocardiography. The curves represents rotation in subendocardial, mural and subepicardial layers at the apical left ventricular level from parasternal short axis view.

The data about the possibility of 2D speckle tracking echocardiography to detect early changes in cardiac function during chemotherapy is limited nowadays. However, the results of the currently recruiting participants study "Early detection of anthracycline cardiotoxicity by echocardiographic analysis of myocardial deformation in 2D strain – CA2D" for analysis of myocardial deformation in patients with leukemia, is expected to determine the reliability and reproducibility of this method for diagnosis of cardiotoxicty (University Hospital, Bordeaux, 2011).

3.4 Three-dimensional echocardiography

The interpretation of echocardiographic images requires a complex mental integration of multiple image planes for a true understanding of anatomic and pathologic structures. The representation of images in a 3-dimensional format more closely resembles reality and could therefore enhance image interpretation (Hung et al., 2007). Newer developments use a transthoracic probe technology with volumetric scanning capabilities, which allows simultaneous acquisition of an entire 3D-data set.

3D-reconstructions have also been applied to the color Doppler information allowing a three dimensional representation of jets superimposed on the 3D-grayscale image. Three-dimensional transthoracic imaging can be performed with mechanical steering devices, which are attached to standard transducers. These devices steer the transducer motion causing incremental changes in the scan plane either by rotating, shifting or fanning the probe. The advantage of this technique is that freely definable image planes can be chosen allowing for more flexibility. This method is capable to increase the reproducibility of measured left ventricular ejection fraction as well as is suitable for valve pathology assessment.

Volumetric real-time echocardiography is a recently developed technique based on the design of an ultrasound transducer with a matrix array that instantaneously acquires the image and allows instant (real-time) acquisition of a complete 3-dimensional data set

without complex post-processing (Kisslo et al., as cited by Binder, 2002). 3D-echocardiography is reliable, although image quality can be a problem in some patients. Magnetic resonance imaging is suitable in these patients.

The use of new echocardiographic methods requires additional time to the conventional echo study and further studies are needed to determine the most feasible parameters and their cut-off values, which can be used for prediction of deterioration of global ventricular function with heart failure.

4. Disadvantages of using biomarkers and echocardiography for early cardiotoxicity detection

Most studies have investigated separately echocardiographic variables and biomarkers to identify patients at risk for later cardiotoxicity. There is little information about the ability of both techniques in the same cohort of patients. At present, it is not clear enough which of the investigated parametes – biomarkers or echocardiographic may detect earlier subtle changes in cardiac function.

Measurement of troponins and natriuretic peptides is easy of access in clinical practice. Elevation of troponin may be reliable in prediction of cardiotoxicity but different laboratories use different assays and cut-off values. Elevated troponin I (positive) was defined as any value exceeding the cut-off level of 0.4 ng/ml (Krastev et al., 2010) or 0.08 ng/ml (Cardinale et al., 2010) in different studies. For troponin T was used 0.1 ng/ml as the upper limit of the normal range and in this study elevation of troponon T levels were associated with left ventricular diastolic dysfunction, registered through prolongation of post-treatment isovolumic relaxation time (Kilickap et al., 2005). For BNP and pro-BNP are valid the same conditions in measurement.

Myocardial deformational imaging seems to have increased sensitivity compared to conventional echocardiography in detection of early cardiac changes. This may be related to the possibility of regional character of the cardiotoxicity at the beginning when global function, measured by ejection fraction is preserved. Several questions remain opened. It is not clear enough if regional dysfunction, diagnosed by strain, is clinically essential. If it is important - what are the cut-off values of these parameters for prediction of cardiotoxicity. Larger studies with long-term follow-up of children and adults after chemotherapy, with multivariable approach, are needed to clarify these issues.

5. Conclusions

Biomarkers as Troponin I and natriuretic peptides, measured before starting chemotherapy and after each cure, may be used to predict cardiotoxicity. Large prospective and multicenter studies are needed to define the potential role of new circulating biomarkers in the assessment of chemotherapy-related cardiotoxicity.

In addition to conventional 2D- and Doppler echocardiography, pulsed-wave tissue Doppler echocardiography is a reliable, simple and reproducible method, which may be included in serial echocardiographic evaluation routinely in all patients during chemotherapy. Measurement of mitral annular velocities provides information not only for left ventricular global diastolic function and filling pressures, but detects subtle changes in

systolic function through measurement of systolic velocity. Myocardial deformation imaging may be used in selected patients for more detailed regional and global analysis. Further studies will establish the role of 2D-strain for prediction of cardiotoxicity. 3D-echocardiography overcomes the limits of 2D-echocardiography in measuring ejection fraction which depends on left ventricular geometry.

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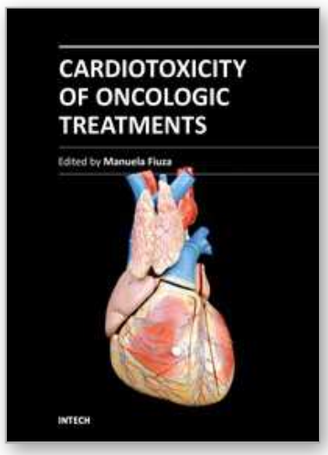

Cardiotoxicity of Oncologic Treatments
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The possibility of getting a cardiovascular disease or cancer increases with advancing age. At the same time, relevant improvements in cancer therapy have resulted in the improvement of quality of life and the increasement of the survival rate of such patients. As a result we have larger number of patients that experience the cardiac side effects of chemotherapy. The extent of cardiotoxicity is variable, depending on the type of drug used, combination with other drugs, prior mediastinal radiotherapy and the presence of cardiovascular risk factors or history of heart disease. Early detection of the patients proneness for developing cardiotoxicity is the key issue to decrease morbidity and mortality. It also facilitates more tailored therapeutic interventions. Therefore, the collaboration and interaction of cardiology and oncology may contribute to reducing the cardiovascular adverse effects and improving the results in the treatment of patients with cancer.

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