THE PLACE OF ECHOCARDIOGRAPHY IN THE ASSESSMENT OF PATIENTS RECEIVING CARDIOTOXIC CANCER THERAPIES: NEW HORIZONS

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ABSTRACT

In the last years cancer treatment has shown an important progress leading to a significant reduction of morbidity and mortality of several kinds of cancer. The therapeutic management of patients with cancer includes multiple combinations of chemotherapy, radiotherapy, and surgery. However, many of these treatments can cause cardiovascular complications such as heart failure (HF), myocardial ischemia/infarction, hypertension, thromboembolism, and arrhythmias. This can negatively affect the quality of life as well as the prognosis of oncologic patients. Chemotherapy-induced cardiotoxicity is of rising concern for both cardiologists and oncologists. Therefore, identifying these effects is crucial to the successful management of cancer patients with cardiovascular complications. The traditional screening of patients with cancer includes cardiologic examination, and both electrocardiography and transthoracic echocardiography at rest. Also biomarkers such as troponine and natriuretic peptides may be useful for early diagnosis of cardiotoxicity.

INTRODUCTION

In the last years cancer treatment has shown an important progress leading to a significant reduction of morbidity and mortality of several kinds of cancer. The therapeutic management of patients with cancer includes multiple combinations of chemotherapy, radiotherapy, and surgery. However, many of these treatments can cause cardiovascular complications such as heart failure (HF), myocardial ischemia/infarction, hypertension, thromboembolism, and arrhythmias. This can negatively affect the quality of life as well as the prognosis of oncologic patients. Chemotherapy-induced cardiotoxicity is of rising concern for both cardiologists and oncologists. Therefore, identifying these effects is crucial to the successful management of cancer patients with cardiovascular complications. The traditional screening of patients with cancer includes cardiologic examination, and both electrocardiography and transthoracic echocardiography at rest. Also biomarkers such as troponine and natriuretic peptides may be useful for early diagnosis of cardiotoxicity.

The most appropriate method of assessing antineoplastic therapy induced cardiotoxicity is transthoracic echocardiography, which can measure cardiotoxicity in a quantitative, non-invasive manner. Standard echocardiography evaluate the global cardiac function. As such, current treatment guidelines emphasize prevention and early intervention for at-risk individuals and individuals with asymptomatic decreased left ventricular ejection fraction (LVEF). Doppler measurements require adequate imaging windows and parallel alignment of the Doppler cursor with blood flow to avoid underestimation of...
Doppler jet velocity and calculated pressure. These parameters are dependent on heart rate and loading conditions and lack validity in patients with preserved EF and are insensitive in detecting the subtle changes in myocardial function which occur in early cardiotoxicity. Newer echocardiographic techniques have enhanced the capability to detect cardiotoxicity at an early stage; in this regard, tissue Doppler imaging (TDI) and bidimensional (2D) strain analysis promise to be particularly useful. The purpose of this review is to summarize the current state of echocardiographic assessment of common cardiovascular complications induced by chemotherapy.

CHEMOTHERAPY AGENTS AND CARDIOTOXICITY

Several therapies for cancer have been associated with the development of LV dysfunction and/or HF. The cumulative dose, the administration schedule, and the concomitant use of other cardiotoxic therapies determine the likelihood of cardiomyopathy. Cardiotoxicity can be divided into four types: acute, sub-acute, chronic and late-onset. Acute complications are usually observed after the first administration of high doses, affect elderly patients, and include electrocardiographic abnormalities (typical ST-T changes, reduced QRS voltages, sinus tachycardia, premature supraventricular and ventricular complexes, QT interval prolongation, or acute myocardial ischemia). These derangements are usually associated with few symptoms, but may be asymptomatic at all, resolving spontaneously several hours or weeks after the completion of chemotherapy in several patients. Sub-acute cardiotoxicity is rare, appears several days or weeks after the last dose of drug and is most frequent manifested as pericarditis or myocarditis. Chronic cardiotoxicity is observed in patients exposed to repeated doses of chemotherapy, occurs several weeks or months after chemotherapy (within 1 year following treatment) with overt congestive HF due to LV dysfunction, has a poor prognosis and its strictly dependent on the total dose administered. Finally, late cardiotoxicity is diagnosed at >1 year following treatment, may be manifested clinically as congestive HF, arrhythmias and conduction abnormalities, but has a more favorable prognosis, rarely leading to sudden death.

Anthracyclines and trastuzumab are the most used antineoplastic drugs with known cardiotoxicity. Anthracyclines (Doxorubicin, Daunorubicin, Epirubicin, Idarubicin), the best studied anticancer drugs, directly damage the myocardium through production of oxygen free radicals, leading to LV dysfunction and, in some cases, an irreversible cardiomyopathy. The onset of cardiotoxicity, even asymptomatic, not only negatively impacts the cardiac outcome of cancer patients, but also seriously limits their therapeutic opportunities. In adults the incidence of HF induced by anthracycline varies from 4% to 5% at a cumulative dose of 500–550 mg/m², to 36% at a cumulative dose 600 mg/m² or more. Data from oncology literature, however, indicate that more than one-half of all patients exposed to anthracycline will show some degree of cardiac dysfunction 10 to 20 years after chemotherapy, and 5% of them will develop HF. On the basis of numerous studies, there is now evidence that many factors predispose to anthracycline-induced cardiomyopathy. Not only the cumulative dose administered, but also sequence and method of administration, simultaneous administration of other antineoplastic agents and patient related factors (age>70 years, female sex, mediastinum radiotherapy, previous exposure to anthracycline agents, arterial hypertension, prior valvular heart disease and/or cardiomyopathy, electrolytic abnormalities, genetic predisposition) predict cardiotoxicity. Importantly, these early studies focused only on patients in whom symptomatic HF developed. A potentially successful strategy for reducing the cardiotoxicity associated with conventional doxorubicin involves liposomal encapsulation, an advanced and versatile drug delivery system which alters the tissue distribution and pharmacokinetics of these agents while preserving antitumor efficacy (liposomal anthracyclines). Monoclonal antibodies (Alemtuzumab, Bevacizumab, Cetuximab, Rituximab, Trastuzumab), modernly applied for treatment of some hematologic malignancies and solid tumors, have toxicity profiles specific to the blocked receptors but all produce arterial hypotension. Trastuzumab, used to treat breast cancer patients with overexpression of human epidermal growth factor receptor 2, has an unclear mechanism for cardiotoxicity. Most likely trastuzumab interferes with normal growth, repair, and survival of cardiomyocytes. Anthracycline exposure is clearly important; cardiotoxicity is worse if trastuzumab is administered in parallel with, rather than following anthracyclines. Due to the known cardiotoxicity of trastuzumab, the package insert recommends baseline LVEF assessment and reassessment every 3 months during and upon completion of this therapy.
injury mediated by a toxic metabolism.\textsuperscript{1,2} Antimetabolites (5-fluorouracil, Clofarabine) and antimicrotubule agents (Docetaxel, Paclitaxel, Vinea Alkaloids) applied also to the treatment of several solid tumors, may induce ischemic syndrome (angina pectoris and myocardial infarction), arrhythmias and cardiomyopathy.\textsuperscript{1,2} Most of the other chemotherapeutic agents (Cytokines, Imatinib mesylate, Etoposide, etc.) have also been correlated with cardiotoxicity, but this was generally rare and reversible.\textsuperscript{1,2} Routine cardiac monitoring is not considered relevant for classes of chemotherapy other than anthracyclines and trastuzumab.

**ELECTROCARDIOGRAPHY AND CARDIOTOXICITY**

Electrocardiography is the traditional support and completion to the clinical examination, but the electrical abnormalities are often non-specific: ST-T changes, decreased QRS voltage and QT-interval prolongation (acute toxicity induced by anthracycline), malignant arrhythmias (cardiotoxicity induced by chronic anthracycline, cyclophosphamide, interferon-\textalpha{} or interleukin-2), or signs of myocardial ischemia (5-Fluorouracil).\textsuperscript{2,13} Increased QT-interval dispersion has been recently found to be a predictor of acute HF after cyclophosphamide therapy and to persist even in late survivors of childhood anthracycline treatment.\textsuperscript{1,2}

**BIOMARKERS**

Natriuretic peptides have been used for the non-invasive assessment of LV function. Increased levels are produced mainly in response to LV wall pressure and volume overload, and are strongly related to symptoms, cardiac events and mortality.\textsuperscript{1,7} In the setting of chemotherapy, however, data regarding the use of natriuretic peptides for monitoring are inconclusive.\textsuperscript{5,7} Although widely used in current oncology studies, its clinical value remains thus to be proven.

Cardiac troponin is a powerful biomarker for the sensitive and specific detection of cardiac injury arising from various causes. Elevations of serum troponin levels have been reported also after anthracycline chemotherapy, indicating myocardial damage and predicting subsequently cardiac morbidity and mortality.\textsuperscript{5,6} The place of troponin and its clinical value on the non-invasive assessment of patients receiving cardiotoxic cancer therapies is also controversial.\textsuperscript{5}

**CONVENTIONAL ECHOCARDIOGRAPHY**

Current common sense is to assess baseline cardiac function before therapy in order to document normal LV function and schedule further regular evaluations to detect signs or symptoms of cardiac involvement. The most appropriate method of assessing chemotherapy induced cardiotoxicity is conventional echocardiography.\textsuperscript{4} In these evaluations, a variety of parameters are applied.

At present, resting LVEF by 2D-echocardiography is the key parameter used to identify and monitor cardiotoxicity. In clinical oncology practice, asymptomatic decreases in LVEF are the most commonly encountered form of cardiotoxicity.\textsuperscript{14,15} LVEF has been validated by comparison with a variety of reference standards, and clear guidelines regarding its acquisition and calculation are published.\textsuperscript{13} However, LVEF presents numerous limitations: it relies on simplified assumptions about cardiac geometry (if the geometry is abnormal, the measurement is open to error), it is dependent on 2D image quality and on the transducer position, is unable to detect subtle regional alterations in myocardial mechanics, and it is influenced by variable preload and afterload conditions.\textsuperscript{11} In many studies, cardiac toxicity is assumed if (a) LVEF drops more than 10% from baseline to values below 50\%, (b) LVEF drops more than 20\% from baseline despite still normal function, or (c) LVEF drops below 45\%. Early decreases in the LVEF after chemotherapy may be associated with significant cardiotoxicity at a later time; the long-term significance of transient decreases in LVEF during cancer therapy is not well-known, although data suggest that the response to injury of various causes is similar, with negative remodeling leading to progressive LV dysfunction over time.\textsuperscript{13} A study performed to investigate possible acute effects in patients with Hodgkin’s lymphoma did not show significant changes of M-mode derived LV end-diastolic diameter, end-systolic diameter and EF but identified regional wall motion abnormalities (hypokinesis) by 2D assessment.\textsuperscript{15}

More recently it has been established that HF can result from abnormalities of diastolic function, where LVEF is relatively preserved. Stodillard et al found that prolonged Doppler-derived isovolumetric relaxation time preceded and reliably predicted anthracycline-induced systolic dysfunction.\textsuperscript{16} Early peak flow velocity to atrial peak flow velocity (E/A) ratio, deceleration time and isovolumic relaxation time were all in more than 50\% of patients treated by anthracyclines, when EF was still normal.\textsuperscript{17} Parameters of diastolic function (E/A ratio, isovolumic relaxation time, and pulmonary...
venous flow pattern) can easily be measured with reasonable accuracy, but are highly sensitive to any change in the circulatory system and, thus, rather unspecific for cardiotoxicity evaluation.\textsuperscript{3}

Myocardial performance index (the sum of isovolumic contraction time and isovolumic relaxation time divided by ejection time), accurate marker of global LV function, may be particularly useful since it appeared significantly altered in patients receiving chemotherapy.\textsuperscript{18-20}

Dobutamine stress echocardiography was tested in several studies to detect subclinical abnormalities of LV function induced by anthracycline cardiotoxicity but studies findings appear insufficient or controversial\textsuperscript{1}. Stress echocardiography, an optimal tool to unmask coronary artery disease in the general population, remains important also in patients treated radiation therapy, which is able to provoke accelerated coronary atherosclerosis.\textsuperscript{1}

Conventional echocardiography is useful to document valvular heart disease, coronary artery disease, pericarditis and/or myocarditis, developing during cancer therapy, but is insensitive in detecting the subtle changes in ventricular function which occur in early cardiotoxicity, before decreasing of LVEF.\textsuperscript{2} Newer echocardiographic techniques have enhanced the capability to detect cardiotoxicity at an early stage; in this regard, myocardial velocity and deformation promises to be particularly useful.

**ADVANCED ECHOCARDIOGRAPHIC TOOLS FOR EARLY DETECTION OF CARDIOTOXICITY**

Tissue Doppler imaging (TDI) has emerged as a complementary method to standard echocardiography, being able to assess the velocity of myocardial segments and other cardiac structures movement. This new method allows the quantification of both regional and global myocardial function. Two important changes were needed to get from standard echocardiography to TDI: a change in the settings of the machines, that allows the recording of low velocities, and avoiding the over saturation that occurs due to the fact that the myocardium is significantly more echo dense than the blood; changing the gain (decreasing) and the reject to shunt the filters of high passage was necessary, so the TDI signal reaches straight to the autocorelator.\textsuperscript{21,22} The filters can be set, in the last generation echocardiography machines, so they ignore the signal reflected by erythrocytes (having low amplitude and high velocity). During the image acquisition time, it is vital to optimize the frame rate by using a narrow sector and an adequate scale of velocities. It is not possible to modify these parameters during off-line analysis. To avoid a series of inconveniences that may occur while recording or analysing the signal, it is recommended to use a frame rate over 100 Hz or even higher if it comes to strain or strain rate techniques.\textsuperscript{21,23}

TDI is currently available on all modern echocardiographic systems, and was proposed by the European Association of Echocardiography to be the standard method of exploring LV function, amongst the EAE guideline recommendations regarding the redaction of the transthoracic echocardiographic result\textsuperscript{24}. There are several methods of measuring myocardial and cardiac structures’ velocities with TDI: Pulsed Doppler, M-Mode Color Doppler or Bidimensional Color Doppler. The ratio between early diastolic transmitral velocity (E) and early mitral annular diastolic velocity (E') has been demonstrated to correlate with LV filling pressure.\textsuperscript{25} (Fig. 1) $E/E'$ is currently used for the non-invasive assessment of LV filling pressure. Several studies showed that TDI-derived parameters ($E/E'$, $E'$) can detect LV dysfunction prior to alterations in conventional indices like heart

![Figure 1](https://example.com/figure.jpg)

*Figure 1*. Bedside measurements of spectral Doppler peak early transmitral inflow (E) velocity (panel a) and spectral tissue Doppler peak early diastolic (E') velocities, respectively peak systolic (S') velocities, at the septal (panel b) and lateral (panel c) corners of mitral annulus. $E/E'$ ratio was calculated ($E/E' = 11.45$). The average of the velocities from septal and lateral mitral annulus was used.
rate, LV end-diastolic pressure, or blood pressure and conventional echocardiography in doxorubicin-induced cardiac injury.\textsuperscript{20-23} Tassin-Mangina et al evaluated the early and late anthracycline effects in adults.\textsuperscript{26} A few months after chemotherapy TDI parameters that explore diastolic function (E, E’, E/A) changed, while changes in systolic function (S’) occurred later. In a recent report, subclinical systolic and diastolic myocardial abnormalities (S’, E’, E/A) were present in asymptomatic breast cancer survivors up to 6 years after standard chemotherapy; adjuvant trastuzumab treatment did not appear to have an additive adverse impact on myocardial function in the medium-long term.\textsuperscript{27} The superiority of TDI parameters can be attributed to the capacity of reduced S’ to identify LV dysfunction in subjects with normal LVEF.\textsuperscript{23} TDI does not require tracing of endocardial borders, unlike LV volumes and LVEF.

Similarly to conventional Doppler echocardiography, for an accurate TDI analysis it is necessary to make a parallel alignment between the ultrasound wave and the movement direction of the analyzed structure.\textsuperscript{22,23} Consequently, the angle between the ultrasound wave and the movement direction must not exceed 20°. Another issue is the complex rotation and translation movement of the heart inside the thorax, with every cardiac cycle, that distorts the measurements of myocardial velocities.\textsuperscript{22,23} All these factors make the interpretation of the images recorded with TDI more complicated, thus a good theoretical and practical preparation of the ultrasound cardiologist is mandatory.

LV function is the results of the contraction and relaxation of helically oriented myofibres.\textsuperscript{28} LV torsion and global longitudinal strain are essential components of cardiac performance.\textsuperscript{28,29}

With technical improvements in the temporal and spatial resolutions of two-dimensional echocardiography, the myocardial deformation and rotation can now be measured using the 2D-strain with the speckle tracking method.\textsuperscript{29,30} Currently, strain measurement is not always a feature of standard ultrasound equipment and strain analysis algorithms differ amongst manufacturers, making comparison between measurements on different ultrasound systems difficult.\textsuperscript{4} Most strain measurements require off-line analysis, are time consuming and involve additional training and expertise. The strain could be measured using TDI or speckle tracking (from 2D images).\textsuperscript{21} (Fig. 2) The latter requires lower frame rates (40–70 frames per second), is relatively angle independent and appears to be more reproducible.\textsuperscript{21}

![Figure 2. Longitudinal regional strain determined by tissue Doppler imaging.](image)

The 2D-strain technique can evaluate LV deformation in 3 planes (longitudinal, radial and circumferential strain) as opposed to TDI derived strain that largely quantifies longitudinal strain.\textsuperscript{21} (Fig. 3) A recently published work suggests that global 2D strain and strain rate are superior predictors of impaired LV filling than the E/E’ ratio (the current standard measurement), highlighting the likely value of strain imaging in the assessment of diastolic function.\textsuperscript{31}

![Figure 3. Global longitudinal strain of the left ventricle determined by 2D strain imaging.](image)
breath-hold at a frame rate of 70–100 frames/s and stored on hard disk for subsequent off-line analysis. Counter-clockwise rotation is marked as a positive value and clockwise rotation as a negative value when viewed from the apex. The LV twist curve is generated by calculating the difference between apical and basal rotations at each corresponding time point. The LV twist represents the peak difference between rotation angles at the apex and base. (Fig. 4) The LV torsion is defined as peak LV twist divided by LV diastolic longitudinal length.

Figure 4. Apical and basal left ventricular rotation and left ventricular twist determined by 2D strain imaging.

Myocardial deformation identifies preclinical myocardial dysfunction earlier than conventional measurements in women undergoing treatment with trastuzumab or epirubicin for breast cancer. Regional LV systolic strain rate and systolic strain were reduced within 2 h after the first dose of anthracyclines in the longitudinal as well as in the radial direction, as showed a recent study. Conventional echocardiography failed to show any decline in LVEF or fractional shortening after the first two cycles of treatment, while myocardial deformation parameters had already changed. These parameters remain reduced at 5 years after the completion of therapy, while EF remained within normal limits. In a study of the efficacy of modified anthracyclines, significant reductions were observed in strain and strain rate after six cycles of the pegylated liposomal doxorubicin, without a significant decrease in LVEF. Ho et al reported that longitudinal strain abnormalities were present in asymptomatic breast cancer survivors up to 6 years after standard chemotherapy, while radial strain was not influenced. 2D-strain echocardiographic parameters provide a more refined tool to evaluate regional and global cardiac function, but their role in clinical practice and their cutoff values must be confirmed in multicenter studies.

In summary, transthoracic echocardiography and particularly TDI and 2D-strain echocardiography can be considered valuable for the early detection of LV dysfunction induced by anticancer therapies. The advantage of these new echocardiographic techniques is that it does not require a separate examination. TDI is available in most of the last generation echocardiography machines and data acquisition adds only a few minutes to the conventional echo study. Myocardial deformation (strain and strain rate) identifies preclinical myocardial dysfunction earlier than conventional measurements in patients undergoing treatment with antineoplastic therapy. Speckle-tracking technique (also referred to as two-dimensional strain method) with its ability to measure systolic and diastolic function, hold great promise for improving the early detection of subclinical myocardial dysfunction due to chemotherapy, but further research is warranted in order to determine its role in this important clinical setting.

ACKNOWLEDGEMENT

This work was supported by CNCSIS–UEFISCU, project number PN II/RU code PD 526/2010.

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