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The Role of Echocardiography in Detection of Chemotherapy-Induced Cardiotoxicity in Breast Cancer Patients

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Abstract

Context: The incidence of breast malignancy is increasing and it became evident that chemotherapy protocols that are based on anthracyclines and trastuzumab, which are being used in these patients, have cardiotoxic effect. Traditional imaging methods could detect the advance stage of chemotherapy-induced cardiomyopathy when cardiac function is significantly impaired. New imaging tools, primarily speckle tracking analysis, could improve detection of cardiotoxicity.

Evidence Acquisition: We searched PubMed, Medline, OVID and EMBASE databases for the studies published from January, 1990 up to May, 2016 in the English language using the following keywords: "chemotherapy", "cardiac toxicity", "left ventricle", "anthracyclines", and "trastuzumab".

Results: Studies show that early signs of chemotherapy-mediated cardiotoxicity in breast cancer patients could be identified even one week after the introduction of anthracycline treatment. Investigations also reported deterioration of the left ventricular mechanics 3, 6 and 12 months after chemotherapy. This suggests that left ventricular strain should be used as an important marker of the left ventricular dysfunction, which might be used simultaneously for detection of cardiotoxicity and for the monitoring of potential improvement of left ventricular function after chemotherapy interruption.

Conclusions: New imaging tools provide insight in cardiac function and mechanics, much better than traditional methods. The ability of mechanical changes to predict subsequent cardiotoxicity needs to be evaluated in larger multicenter and longitudinal studies.

Keywords: Breast Cancer, Echocardiography, Cardiotoxicity, Strain

1. Context

The incidence of malignancies is constantly increasing and there is the large armamentarium of therapeutics that is used nowadays against cancer. There is a very limited number of studies that show the impaired cardiac function even in untreated patients with cancer. On the other hand, a large number of investigations confirm unfavorable effect of different chemotherapy agents on left and right ventricle.

Cancer therapy has significantly developed over the last decades. Typically, chemotherapy medications that are used in the treatment of breast cancer are anthracyclines, antimetabolites, alkylating and anti-mitotic agents. In the last several years appeared new agents-monoclonal antibodies and small-molecule tyrosine kinase inhibitors, which significantly expanded anticancer therapy and provided novel therapeutic approach. Current therapy significantly improves survival and life-quality. However, chemotherapeutic agents are also associated with cardiovascular complications that could result in severe heart failure.

Chemotherapy-induced cardiac dysfunction could be divided into two main groups: (i) agents that induce dose-dependent cardiac dysfunction such as anthracyclines (doxorubicin, epirubicin); and (ii) agents that cause cardiac dysfunction in dose-independent manner (trastuzumab) (1, 2).

Cardiac imaging techniques, especially echocardiographic, have significantly advanced in the last decade and novel imaging tools could detect even incipient cardiac changes in function and mechanics in asymptomatic patients, which was impossible earlier. Some new echocardiographic parameters, particularly longitudinal strain, almost replaced left ventricular ejection fraction as "the holy grail" parameter of left ventricular systolic function in large centers that treat a large number of patients with cancer.

The aim of this review is to provide the short summary of the current knowledge about the role of echocardiography in diagnosis of the chemotherapy-induced cardiac toxicity in the breast cancer patients.

2. Evidence Acquisition

We searched PubMed, Medline, OVID and EMBASE databases for the studies published from January, 1990 up to May, 2016 in English language using the following keywords: "chemotherapy", "cardiac toxicity", "left ventricle", "anthracyclines", "trastuzumab", and "strain".

3. Results

3.1. Mechanisms of Chemotherapy-Induced Cardiac Toxicity

Type 1 of chemotherapy-induced cardiac toxicity in the breast cancer patients is mainly caused by doxorubicin. This agent damages myocardial function through the generation of reactive oxygen species in a cumulative dose-dependent fashion. Electron microscopy of myocardial biopsies reveals different degrees of myocyte damage: vacuolar swelling progressing to myofibrillar disarray and ultimately cell death (3). When myocites death occurs, further regeneration is impossible. These myocites could only be replaced with fibrotic tissue. Therefore, this kind of damage is considered as irreversible, at least at cellular level. This damage could be undetected by traditional echocardiographic methods and left ventricular systolic function could remain preserved. However, it should be emphasized that cardiac function could be improved to some extent, even in those patients who suffered significant cardiac dysfunction after anthracyclines. Immediate interruption of anthracyclin therapy and antiremodeling pharmacologic therapy are necessary in these cases.

Type 2 of chemotherapy-induced cardiac toxicity could be seen in all other chemotherapeutical agents (1). There are several important features related to these medications: (i) they are typically not related with myocites death; (ii) they do not induce the progressive cardiac dysfunction; and (iii) myocardial function is generally completely reversible after their interruption. Trastuzumab is a typical agent that could provoke type 2 chemotherapy-induced cardiac toxicity.

Anthracyclines carry a higher risk for long-term cardiac dysfunction, increased morbidity and mortality (4, 5). The anthracycline monotherapy is related t a 5% - 10% incidence of cardiomyopathy or heart failure (6, 7). This risk ranges between 3 and 12 % with trastuzumab monotherapy (7, 8), whereas the patients who receive concomitant anthracycline and trastuzumab therapy are at the highest risk of cardiotoxicity with 42 % incidence of cardiomyopathy and heart failure (7).

3.2. Left Ventricular Systolic Function

Echocardiography is well-accepted noninvasive, cost-effective and widely available cardiac imaging tool that has been used as the primary screening modality for chemotherapy-induced cardiotoxicity. Left ventricular (LV) systolic function is the most important for every oncologist and cardio-oncologist.

3.3. Left Ventricular Ejection Fraction (LVEF)

The most widely assessed parameter of LV systolic function was ejection fraction (EF). Even current guidelines regarding carditoxicity are based on LVEF (1). Namely, chemotherapy-induced cardiotoxicity is defined as a decrease in the LVEF of > 10%, to a value < 53%. This reduction should be confirmed by repeated echocardiographic exams that are performed 2 to 3 weeks after the baseline diagnostic study showing the initial decrease in LVEF (1). Furthermore, cardiotoxicity could be categorized in 4 various types using LVEF (1): (i) reversible (LVEF reduced < 5%); (ii) partially reversible (LVEF improved by $\geq$ 10% from the nadir but remaining > 5% below baseline); and (iii) irreversible (LVEF improved by < 10% from the nadir and remaining > 5% below baseline).

LVEF cut-off values, used in definitions, are still topic of debate. However, LVEF still remains the most frequently and most widely assessed parameter of LV systolic function in everyday clinical circumstances.

The large study that involved 1,664 breast cancer patients undergoing sequential doxorubicin and trastuzumab therapy showed that both pre-doxorubicin and pre-trastuzumab LVEF, defined by multi-gated acquisition scans, were associated with subsequent development of heart failure (9). The investigators reported that patients with a borderline normal LVEF (50% - 54%) had a greater incidence of heart failure compared to those with an LVEF of 55% - 64% or $\geq$ 65%.

The HERA study also demonstrated that an LVEF of 55% - 60 % was associated with cardiac events, compared to patients with an LVEF $\geq$ 60 %, and similarly for an LVEF of 60% - 65 % compared to an LVEF (10).

However, biplane assessment of LVEF that we perform nowadays has several important limitations: (i) geometric assumptions; (ii) foreshortening; and (iii) it does not take into account all LV walls. Three-dimensional echocardiography could overcome these limitations and provide more accurate calculation of LV volumes and LVEF, comparable with cardiac magnetic resonance (11). A recent study showed that 3D LV volumes and LVEF were more reproducible than the same parameters obtained by both 2DE and contrast-enhanced 2D echocardiography for serial examinations (12).

3.4. Doppler Parameters of Systolic Function

Tissue Doppler imaging might also provide very important information regarding LV systolic function. How-

ever, indices obtained by tissue Doppler are angle- and load-dependent and determine the function of only a small portion of myocardium. This method is used more for evaluation of LV diastolic function than for assessment of LV systolic function.

Previous investigations showed that tissue Doppler indices are good indicators of LV function. Ho et al. showed that peak systolic velocity was significantly decreased in patients receiving anthracyclines and trastuzumab comparing with controls, despite the absence of significant changes in LVEF with anthracycline or trastuzumab therapy (13). Some investigation succeeded to show predictive value of systolic tissue Doppler index in patients with breast cancer who receive anthracycline or trastuzumab therapy. Namely, Fallah-Rad et al. reported that only, comparing with both global longitudinal and radial strain, was able to identify all those patients who developed trastuzumab-induced cardiomyopathy (14).

3.5. Left Ventricular Diastolic Function

The assessment of LV diastolic function should be the obligatory part of echocardiographic examination in cancer patients who are planned for chemotherapy because studies showed that impaired LV diastolic function before treatment is an independent predictor of trastuzumab-mediated cardiotoxicity (15). However, not all agree about the negative effect of trastuzumab on LV diastolic function (16).

Stoodley et al. reported that altered LV diastolic function was observed immediately after the administration of therapeutic doses of anthracycline chemotherapy in breast cancer patient (17). The impairment of LV diastolic function was more pronounced in patients whose LVEF was $< 55\%$ than in patients with LVEF $> 55\%$.

3.6. Left Ventricular Mechanics

Traditional echocardiographic parameters obtained by tissue Doppler imaging have many limitations: relatively low reproducibility, assessment of myocardial deformation only in one dimension, and determination of only regional strain. Most of these limitations are overcome by 2D and 3D speckle tracking imaging which offer comprehensive assessment of myocardial function. Longitudinal and circumferential LV myocardial strains have been shown as particularly accurate and highly reproducible. This is important because LV longitudinal strain deteriorates early, before any change in LV pump function (ejection fraction). What is more important is that longitudinal strain is shown to be an early predictor of cardiactoxicity, as well as an independent predictor of cardiac recovery in chemotherapy-mediated cardiomyopathy in breast cancer patients treated with anthracyclines and trastuzumab (18, 19).

Recently, Tan et al. showed that LV mechanical dysfunction persists $>$ 2 years after the end of anthracycline and trastuzumab treatment, without significant recovery even after the termination of trastuzumab therapy, which suggests long-term underlying cardiac damage and remodeling in these breast cancer patients (20). Khouri et al. reported that 3D LVEF, 2D global longitudinal strain and exercise stress echocardiography, unlike 2D traditional parameters (LVEF), could detect cardiac dysfunction in breast cancer patients treated with doxorubicin-containing adjuvant therapy (21). Sawaya et al. revealed the decrease in LV longitudinal strain only after 3 months of introduction of anthracyclines and trastuzumab therapy (22). The authors reported that a decrease in longitudinal strain from baseline to 3 months was an independent predictor of the development of cardiotoxicity at 6 months.

Stoodley et al. succeeded to show that anthracycline therapy deteriorates LV longitudinal and radial strain immediately after anthracycline treatment (one week) (23). Other investigators showed that myocardial strain imaging is more sensitive than LVEF for the early detection (3 months) and intermediate term (6 months) monitoring of LV systolic function following anthracycline chemotherapy in breast cancer patients (24). Global longitudinal strain normalised by 12 months in the majority of patients. Persistently reduced strain was observed in 16% who had a greater reduction in strain in 6 months ($\leq$ -17.2%), and had received higher cumulative anthracycline doses (24).

Beside longitudinal strain, other mechanical parameters were also shown as very important indicator of myocardial dysfunction in breast cancer patients receiving chemotherapy. Motoki et al. demonstrated that twist, torsion and untwisting rate were impaired even 1 month after anthracycline therapy in breast cancer patients (25). This shows that twist and torsion could be used as even more sensitive indicator of chemotherapy-induced cardiomyopathy than longitudinal strain. An interesting study that followed 74 patients before and after 6, 12, 24, and 52 weeks of anthracycline treatment reported significantly reduced LV longitudinal and radial strain and twist at 6 weeks after initiation of chemotherapy (26). The receiver operating characteristic curves identified early deterioration of global longitudinal strain and twist as the best predictors of later cardiotoxicity (area under curve = 0.93), followed by global longitudinal strain (0.84) and LV apical rotation (0.81) deterioration.

4. Conclusions

There are still many uncertainties regarding the role of cardiovascular imaging in the identification and management of chemotherapy-induced cardiotoxicity. New imaging tools provide insight in cardiac function and mechanics, much better than traditional methods. However, we should be aware that modern imaging machines are not available at every center, as well as the fact that the application of these tools requires additional training. The ability of mechanical changes to predict subsequent cardiotoxicity needs to be evaluated in larger multicenter and longitudinal studies. It should be determined whether strain measurements are required at multiple time-points or a single selected time-point. The long-term effect of strain changes that appear during chemotherapy therapy, and the prognostic significance of these abnormalities in survivors of breast cancer, need to be discovered.

Footnotes

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