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Review

Detection of radiation induced cardiotoxicity: Role of echocardiography and biomarkers☆

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ABSTRACT

We review the role of echocardiography and biomarkers in detection of radiation-induced cardiac toxicity (RICT). RICT is related to micro- and macrovascular damage which induce inflammation, endothelial dysfunction, accelerated atherosclerosis, myocyte degeneration and fibrosis. The process is cumulative dose to the heart and target volume dependent. Furthermore, the damage of the heart is frequently potentiated by the adjunctive chemotherapy. The clinical manifestations of RICT may acutely develop but most often become clinically apparent several years after irradiation. RICT clinical manifestation covers a wide spectrum of pathologies including pericarditis, coronary artery disease (CAD), myocardial infarction, valvular heart disease, rhythm abnormalities, and non-ischemic myocardial and conduction system damages. Echocardiography and cardiac markers are important diagnostic tools for the detection of RICT.

1. Introduction

The progress in the treatment of malignant diseases significantly improved survival of oncological patients. However, the improved survival of oncological patients can be limited by adverse effects associated with intensive antitumorous treatment.[1,2]

Radiation-induced cardiac toxicity (RICT) is related to micro- and macrovascular damage which induce inflammation, endothelial dysfunction, accelerated atherosclerosis, myocyte degeneration and fibrosis. The process is cumulative dose to the heart and target volume dependent.

The risk of developing radiation-induced heart disease after RT has been shown to increase linearly with the mean absorbed dose to the heart by about 7% per Gy.[3,4]

Brosius et al. reported development of radiation associated valvular disease in 81% patients receiving more than 35 Gy to the heart.[5] Similarly, pericardial disease was reported in 91% of patients treated with high doses of mediastinal radiotherapy.

Furthermore, the damage of the heart is frequently potentiated by the adjunctive chemotherapy.[3]

The clinical manifestations of RICT may acutely develop but most often become clinically apparent several years after irradiation. RICT clinical manifestation covers a wide spectrum of pathologies including pericarditis, coronary artery disease (CAD), myocardial infarction, valvular heart disease, rhythm abnormalities, and non-ischemic myocardial and conduction system damages.

In particular, radiation-induced cardiac toxicity may compromise the effectiveness of the anticancer therapy, independently of the oncological prognosis, and can negatively affect survival and quality of life of oncological patients. Therefore, risk stratification and new diagnostic modalities for early detection of RICT are very important.

2. Echocardiography in detection of RICT

2.1. Left ventricular dysfunction

Radiotherapy can induce myocardial dysfunction (systolic and diastolic). Acute changes in left ventricular (LV) function are more frequently caused by acute myocarditis as a result of radiation-induced inflammation and is associated frequently with transient electrocardiogram (ECG) repolarization abnormalities and mild myocardial dysfunction. Chronic changes are the result of diffuse myocardial fibrosis with systolic and diastolic left ventricular dysfunction associated frequently with conduction disturbances and autonomic nervous system dysfunction. In advanced stages, restrictive cardiomyopathy can develop.

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2.1.1. Left ventricular systolic function

Left ventricle systolic function can be evaluated by several methods, but the most frequent method is assessment of the left ventricle ejection fraction (LVEF): LVEF = [(end-diastolic volume) – (end-systolic volume)]/end-diastolic volume. Preferably, the LVEF is assessed by the use of Simpson's biplane method, according to the European Society of Cardiology position paper.[6,7] The lower limit of normal LVEF is 50%, in line with the definition of cardiotoxicity commonly used in registries and trials in patients with cancer. Cardiac toxicity is defined as a significant decrease of LVEF (>10%), to a value below the lower limit of normal. This decrease should be confirmed by repeated cardiac imaging done 2–3 weeks after the baseline diagnostic study showing the initial decrease in LVEF.

Left ventricle fraction assessment by 2D echocardiography has a relatively moderate reproducibility, which can be improved by the use of 3D methods.[6] 2D echocardiographic LVEF assessment is image quality dependent, its inter- and intra-observer variability are reported around 9% and 7%, respectively.[6]

Global systolic longitudinal myocardial strain (GLS) has been reported to predict a subsequent decrease in LVEF. A relative percentage reduction of GLS of >15% from baseline is considered abnormal and a marker of early LV subclinical dysfunction.[7] This promising method has some disadvantages (e.g. inter-vendor and inter-observer variability) (Fig. 1).

Contrast echocardiography can be used in patients with suboptimal echocardiograms with the aim to improve delineation of LV endocardial borders.

2.1.2. Left ventricle diastolic function

LV diastolic dysfunction is frequent in patients with cancer diseases. LV diastolic function is routinely evaluated by the use of Doppler methods (mitral inflow pattern analysis, tissue Doppler techniques analysis of the mitral annulus motion). All these parameters are highly sensitive to any change in the loading conditions.[8,9]

2.2. Pericarditis

2.2.1. Acute pericarditis

Echocardiography is able to detect and to quantify pericardial effusion. Pericardial effusion is usually visualized as echo-free space outside the myocardium (2-d and M-mode echocardiography). In severe cases, cardiac tamponade can develop. Typical 2D features of acute tamponade include collapse of cardiac chambers (while right atrium collapse is commonly observed during systole, right ventricle collapses commonly in diastole), increase of variations in the Doppler velocities (mitral valve: an inspiratory reduction in mitral peak E-wave velocity in cardiac tamponade of at least 25%, tricuspid valve: peak E-wave velocity will drop at least 40% in expiration compared to inspiration; right and left ventricular outflow tracts: variation of the peak velocities in the aorta and pulmonary trunk >10%). The important sign of tamponade seen in 2D echocardiography is dilatation of the inferior vena cava (IVC, >20 mm in an adult size heart), absent inspiratory collapse of IVC and dilatation of the hepatic veins.[6,7,10]

2.2.2. Chronic pericarditis

Chronic pericarditis is associated with pericardial thickening and calcifications. RICT can result in two phenotypes: constrictive or restrictive cardiomyopathy. Echocardiographic findings of constrictive pattern include: thickening of the pericardium, the presence of restrictive diastolic filling pattern of the left ventricle (E/A ratio > 2, mitral valve E-wave <140 ms), PW tissue Doppler of the mitral annulus: peak velocity of medial s > lateral s wave, diastolic septal bounce of interventricular septum, dilatation of inferior vena cava and flow reversal in hepatic veins. Pulmonary artery pressures are normal.

Chronic pericarditis is associated with thickening of the pericardium with increased echogenicity on 2D echocardiography and parallel reflections on the posterior wall on M-mode recordings.[6,7]

2.3. Valvular disorders

Irradiation of the heart can result in valvular heart disease.[11,12] The mechanisms include: fibrosis and calcifications which can affect main parts of the aortic valve (aortic root, valve annulus, valve leaflets), aortic-mitral inter-valvular part of the myocardium, mitral valve (annulus, base and mid-portions of the mitral valve leaflets). The fibrosis and calcifications may be randomly dispersed or contiguous.[11]

Fibrotic changes and calcifications spare the mitral valve tips and commissures.

Evaluation of the severity of the valve disease is based on the recommendations of the European Association of Cardiovascular Imaging and American Society of Echocardiography, but there are some factors which can affect hemodynamics and have to be taken into account:

(1) the presence of restrictive cardiomyopathy and diastolic dysfunction, which can affect the evaluation of mitral valve disease,
(2) significant LV systolic dysfunction as well as low-flow hemodynamics in patients with preserved systolic LV function can affect the evaluation of aortic valve disease.

Furthermore, severe calcifications of the aortic or mitral annulus can affect the evaluation of the regurgitation, also measurements of annulus can be difficult.

2.4. Coronary artery disease

In asymptomatic patients, echocardiography can detect regional wall-motion abnormalities. It has been shown that up to 17% of survivors with Hodgkin's disease treated with mediastinal irradiation (≥35 Gy) had hypokinetic segments of the left ventricle.[13] Darby et al. published analysis of 2168 women who underwent radiotherapy for breast cancer the overall average of the mean doses to the whole heart was 4.9 Gy.[4] They showed that rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray (95% confidence interval, 2.9–14.5; $P < 0.001$), with no apparent threshold. It has been noticed that the hypokinetic region can reflect not only coronary artery disease, but also other intramyocardial processes.

Echocardiography stress tests (dobutamine or exercise echocardiography) can detect epicardial coronary artery stenosis. Inducible ischemia is characterized by new or worsening of wall-motion abnormality. Location, extent, and ischemic threshold should be reported.[6,8,11]

3. Biomarkers in detection of RICT

3.1. Cardiac troponins and natriuretic peptides in detection of RICT

Cardiac troponins (cTnI and cTnT) are sensitive markers of myocyte injury. Both parameters reflect structural changes of thy myocyte. B-type natriuretic peptide (BNP) and N-terminal pro BNP (NT-proBNP) are markers of functional changes of the myocyte.

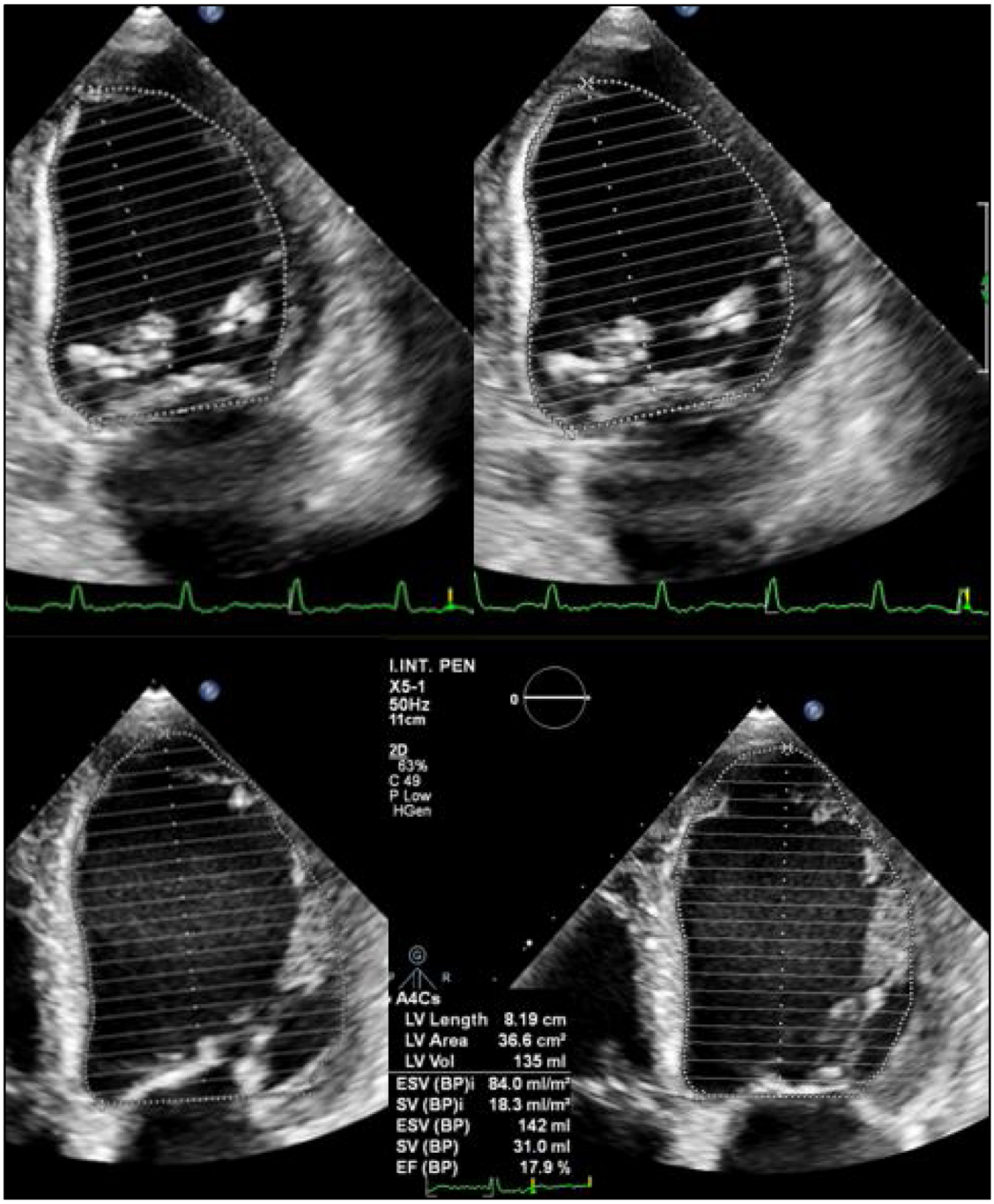

Fig. 1. Biplane Simpson method using the end diastolic and end systolic apical 4- and 2- chamber views for estimation of LV volume and calculation of the ejection the fraction.

Natriuretic peptide synthesis is driven by myocyte stretch during pressure or volume overload; therefore, both markers serve as sensitive markers of myocardial dysfunction. Troponins and natriuretic peptide levels are relatively established sensitive markers of the myocyte injury and dysfunction and have been tested as a promising tool to detect initial forms of chemotherapy induced cardiotoxicity. Furthermore, a role of the serum troponin level in predicting response to heart failure therapy in manifest cardiotoxicity and a benefit of serum troponin in biomarker-guided therapy have been shown in prospective studies with chemotherapy.[14,15] Therefore, cardiac markers have emerged as promising markers also in detection of initial phases of myocardial injury caused by radiation.

Skyttä et al. analyzed the effect of left-sided breast cancer radiotherapy on high sensitive troponin T (hsTnT) levels in a group of 58 patients without previous chemotherapy. Serum hsTnT increased in 21% of patients, the hsTnT increase was associated with radiation dose.[16]

Gomez et al. analyzed troponin I (TnI) level in 25 patients undergoing radiotherapy (more than or equal to 45 Gy to the thorax, with pretreatment estimates of more than or equal to 20 Gy to the heart). Troponin I was increased only in two patients and returned to normal limits during the follow up.[17] Also Serano et al. published non-significant differences in high sensitivity troponin I levels before RT and after RT in patients undergoing thoracic radiation therapy.[18]

Troponins and natriuretic peptides were also studied prospectively in patients undergoing adjuvant breast cancer therapy (PRADA study).[19]

Cardiac markers can serve as markers of myocardial injury caused by stereotactic radiosurgery for ablation of ventricular tachycardias. The accurate and precise delivery of a very high radiation dose to the myocardial arrhytmogenic focus can eliminate the risk of malignant arhythmias. The study of Neuwirth R et al. showed no significant increase of both markers in patients treated with STAR procedure.[20]

Combination of two diagnostic modalities (echocardiography and cardiac markers) seems to be promissing in detection of the early phases of cardiotoxity.[21]

3.2. Other markers tested in detection of RICT

Galectin-3 (Gal-3) is a beta-galactoside-binding lectin that appears to be a marker and mediator of cardiac fibrosis. Gal-3 was tested in patients undergoing thoracic radiation therapy, no significant differences have been detected.[19]

Despite the fact that cardiac biomarkers can detect very early and subclinical stages of cardiotoxicity, the detection of radiation induced cardiotoxicity was much less extensively studied when compared to chemotherapy induced cardiotoxicity Therefore, there is a need for further studies in this field.

4. Conclusion

Improved survival of cancer patients is a result of progress in treatment of malignant diseases. Modern cancer therapy is frequently associated with increased risk of cardiotoxicity. Furthermore, population ageing results in increased number of patients with cardiovascular diseases who must undergo antitumor treatment. Therefore, the risk stratification and detection of initial stages of cardiotoxicity is crucial to improve quality of life and survival of these patients. Echocardiography and assessment of cardiac markers are very helpful to identify patients at risk before therapy and to detect early signs of cardiotoxicity.

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Conflict of interest

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