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DIAGNOSTICS OF THE CARDIO-TOXIC EFFECTS OF ONCOLOGY THERAPIES

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Abstract

Despite the rising trend of cancer disease incidence more and more patients succeed in their fight with the disease. Innovative drugs bring cures or at least improvements to the patient's quality of life. Extensive application of anticancer therapy however brings about the increase of adverse effects of the therapy. Toxic damage of the myocardium remains one of the severest organ damage types with life-threatening consequences. In the last decade, in addition to the known cardio toxicity of traditional cytostatics, specialists have more and more often been facing cardio toxicity caused by targeted oncology therapies.

As myocardium damage is hard to treat when the stage of clinical symptoms is reached, emphasis is laid on the timely diagnosing of this drug-related damage. Diagnostic procedures have been introduced for early detection of risk patients before the therapy has even commenced. Timely diagnosis of myocardium effects in the course of the conservative cancer therapy allows for adjustment of the oncology therapy and lifestyle and timely commencement of treatment of the affected myocardium.

Echocardiograph is considered the basic procedure of patient monitoring during cancer therapy. MRI of the myocardium and CT cardiograph are limited by price and availability despite their uncontentious role in onco-cardiology. Radionuclide ventriculography is considered the gold standard of assessment of the left ventricle function. It is well reproducible and widely available in oncology centres. Laboratory diagnostics of toxic damage of the myocardium focuses on cardinal troponins and natriuretic peptides. This examination performance in clinical practice is undemanding and its application in oncology practice increases.

Key words: *anticancer therapy; cardiotoxicity; diagnostics*

REVIEW ARTICLE

INTRODUCTION

Anticancer therapy efficiency keeps increasing. Its disadvantages include frequent and severe adverse effects. Antiemetics, dietetics, haematogenesis stimulators can manage "common" toxicity. Irreversible organ damage remains a serious issue (Mladosievičová 2015a).

Damaged myocardium is considered one of the severest adverse effects of oncology therapies. Heart failure following therapy with dunorubicine was first described by Tan et al. (1967). In

the 1990s, Von Hoff et al. (1979) confirmed by retrospective analysis the relationship between myocardium damage and cumulative doses of anthracycline cytostatics (Mladosievičová 2015a, b). At present there are around 20 cytostatics with potential cardio toxic effects (Table 1).

Table 1 – Cardio toxicity of cytostatics (Mladosievičová et al. 2014, pp. 120–137)

Standard anticancer drugs	Cardiovascular toxicity
Anthracyclines • doxorubicine • daunorubicine • epirubicine • idarubicine	Acute toxicity: arrhythmias, myocarditis, pericarditis Sub-acute and delayed toxicity: cardiac dysfunction, heart failure, cardiomyopathy
Alkylation cytostatics • cyclophosphamide HD • iphosphamide HD	Myopericarditis, cardiac dysfunction, asymptomatic drop of EFLV, heart failure
Platinum cytostatics • cisplatina • oxaliplatina	Acute toxicity: vasospasms of large and small vessels Delayed toxicity: hypertension, hypercholesterolaemia, angina pectoris
Antimetabolites • fluorouracil • capecitabine • cytarabine	CAD, arrhythmias, hear failure, sudden death, angina pectoris, pericarditis, asymptomatic bradycardia, prolonged QTc interval, extra systoles, drop of EF
Vinkaalcaloids • vincristine • vinblastine	CAD, myocardium infarction
Other antibiotics • bleomycine	CAD
Taxanes • paclitaxel • docetaxel	Asymptomatic sinus bradycardia, ventricular extra systoles, ventricular tachycardia, atrioventricular blockade
Immunomodulation substances • talidomide	Venal thromboembolism
Retinoids • bexarotene	Hypertriacylgycerolaemia, hypercholeserolaemia
Antifolate substances • methotrexate	Angina pectoris, sinus bradycardia, ventricular tachycardia
Cytokines • interferon • interleukin	Arrhythmias, reversible cardiomyopathy, CAD, myocardium infarction, hypotension
Miscellaneous • tamoxifen • arsenic oxide	Venous thromboembolism, prolonged QTc interval, atrioventricular blockade

New targeted therapy products are used in clinical practice. They meet the expectations of increased efficiency and reduced toxicity, except for cardio toxicity (Mladosievičová 2015a) (Table 2).

Risk factors and cardiac toxicity manifestations

According to the time interval, cardiac toxicity is classified as ***acute*** (in 12 hours), ***sub-acute*** (within 12 months after therapy) and ***delayed*** (in a year or more after therapy) (Jurga et al. 2011). Acute and sub-acute toxicity is more frequent. Just some of the drugs generate delayed manifestations of myocardium damage (anthracycline cytostatics, mitomycine, interleukin, interferons, trastuzumab) (Petráková 2011).

The increasing number of cured patients with long survival sub-acute and delayed

Table 2 – Toxicity of targeted therapies (Mladosievičová and Rečková 2013)

Targeted anticancer therapies	Cardiovascular toxicity
Monoclonal antibodies	
rituximab	Arrhythmias, hypotension, myocardium infarction
cetuximab	Arrhythmias, myopericarditis, cardiomyopathy, myocardium infarction, heart failure, sudden death
alentuzumab	Hypotension, heart failure
trastuzumab	Cardiac dysfunction, cardiopmyopathy
bevacizumab	Arterial hypertension, thromboembolism, heart failure
Tyrosine kinase inhibitors	
imatinib	Heart failure, cardiomyopathy
sunitinib	Arterial hypertension, myocardium infarction, heart failure, cardiomyopathy, prolonged QTc interval
sorafenib	Arterial hypertension, CAD, myocardium infarction, prolonged QTc interval
pazopanib	Arterial hypertension, CAD, cardiac dysfunction, prolonged QTc interval
lapatinib	Asymptomatic drop of EFLV, cardiomyopathy
nilotinib	Prolonged QTc interval
Proteasome inhibitor	
bortezomid	Heart failure, prolonged QTc interval, angina pectoris, AV blockade

toxicity substantially affects the quality of life and often also the survival of successfully treated oncology patients. This is the reason why examinations during and after therapy (and care for oncology patients) should be able to diagnose in a timely manner not only the potential recurrence of the underlying oncology disease but also signs of organ damage including the clinically most significant myocardium damage. Timely pharmaceutical therapy and lifestyle adjustment reduce the severity of delayed myocardium damage.

There are several factors increasing the risk of toxic damage to the myocardium by oncology therapy. They include cumulative drug doses (anthracyclines, cisplatina, bleomycine), method and speed of administration (anthracyclines), dosing scheme, preceding or subsequent radiotherapy in the heart area, gender, age, history of heart diseases, race, changes of internal environment during therapy, liver and kidney insufficiency etc. (Mladosievičová 2015b).

Toxic damage to the myocardium by cytostatics may be manifested as cardiomyopathy, arrhythmias, myocarditis, pericarditis, acute coronary syndrome, heart failure and sudden death. In the 25 years after treatment with anthracycline the risk of death by cardiac cause is 8 times higher in these patients in comparison to the rest of the population (Elbl 2002).

Experience in cardiac toxicity of targeted therapies is shorter, with the first published cases not being more than 10 years old. The most frequent types of damage to the cardiovascular system include: left ventricle dysfunction, heart failure, arterial hypertension, thromboembolic incidents, acute coronary syndrome and sudden death of cardiac origin (Ederhy et al. 2011).

Cardiac toxicity of selected drugs

Cytostatics

Anthracyclines (doxorubicine, daunorubicine, epirubicine, idarubicine) are the most common cause of myocardium damage. Delayed toxicity may manifest itself as late as 20 years after treatment, this can happen spontaneously, but more often under stress (work load, exercise, pregnancy, infection). Cardiac toxicity of anthracyclines is proportional to their cumulative dose. Cardiotoxic symptoms may occur after the first administration but there are not many described cases of cardio toxic damage

by cumulative dose below 300 mg/m2. Pathogenesis of anthracycline toxicity is due to damage of the cardiomyocytes with free radicals, inhibition of troponin coding genes, effect on adrenerg mechanisms and the release of cytokines TNF and IL-1. This results in myocardium fibrosis and premature atherosclerosis in the context of metabolic syndrome (Petráková 2011, Mladosievičová 2015a).

Toxic effect of **5-fluorouracil** may be manifested during administration as well as within a couple of hours of the therapy. Toxic manifestations include acute lesion or diffuse CAD and acute heart failure or dilation cardiomyopathy. Patients with cardiac comorbidity and after heart radiotherapy represent the high-risk group. Continual infusion therapy represents a higher risk of cardiac toxicity than bolus administration. Cardiotoxic effects were also observed after oral administration (**capecitabin**). The associated patho-physiological mechanisms are not known. They may include coronary vasospasm caused by the cytostatic and its catabolites, wash off of endothelin from the damaged endothelium, depletion of energy phosphates, induction and autoimmune phenomena and coronaritis (Ederhy et al. 2011).

Taxanes (docetaxel, paclitaxel) cause arrhythmias by stimulation of histamine receptors. A histological image shows the changes in the sarcoplasmatic reticulum, reduced numbers of contractile elements, and vacuolar degeneration of cardiomyocytes. Arrhythmia, CAD or hypotension are also included among the acute and sub-acute side effects of the therapy (Giordano et al. 2002).

Toxic effects of **platinum derivates (cisplatina, oxalipatina)** are most often manifested in the form of chronic CAD in a couple of months to years after the therapy. *In vitro* studies have revealed a potential mechanism of action that might cause heart damage in endothelium damage leading to the early development of atherosclerotic changes. A similar mechanism was also revealed in connection with **bleomycine** (Ederhy et al. 2011).

Targeted anticancer therapies

The benefits of targeted therapy as part of anticancer therapy of multiple tumours are clear. Knowledge of cardiac toxicity of monoclonal antibodies against growth factors, their receptors and tyrosine kinase inhibitors (TKI), against intracellular domains of receptors and signal molecules increases dramatically. An unexpected finding is represented by the fact that multiple signal molecules and transcription factors playing a role in tumour pathogenesis also affect the existence of cardiomyocytes, endothelium and other cells in the heart (Mladosievičová and Rečková 2013).

Trastuzumab is a monoclonal antibody against HER2 receptor, whose excessive expression plays a role in connection with multiple malignancies. HER2 signalling is also important for the survival of cardiomyocytes and in protection against oxidative stress. Heart failure following administration of trastuzumab is caused by damage to myofibrils and failure of the excitation-contractile function. Ewer and Lippmann (2005) call this cardiac dysfunction type II cardiac toxicity, for its difference from anthracycline toxicity and its reversible nature. Toxicity of trastuzumab is potentiated by previous anthracycline therapy, with simultaneous therapy generating a lower risk than concomitant therapy (Slamon et al. 2011). Increased risk of cardiac toxicity is also generated by simultaneous administration with paclitaxel (Giordano et al. 2002, Mladosievičová 2015a). Cardiac dysfunction and failure following trastuzumab therapy incidence is 2–23% (Yeh and Bickford 2009). Treatment of the standard population in "real clinical practice" is assumed to be followed by an even higher incidence of cardiac toxicity (Bowles et al. 2012).

Bevacizumab is a monoclonal antibody against VEGF. The dominant toxicity is represented by arterial hypertension with 4–30% prevalence (An et al. 2010). The pathogenesis mainly includes liver damage and changes in micro vasculature. Risk factors include hyper lipidaemia, cardiovascular disease, diabetes mellitus, smoking, obesity, and insufficient physical activity. Incidence of heart failure caused by hypertension and growth factor blockade in connection with this therapy is 1.5–3% and thromboembolism is developed by 4% of these patients (Ederhy et al. 2011).

Sunitinib is a multikinase TKI. Therapy is connected with increased risk of arterial

hypertension, heart failure and myocardium infarction. As in the case of other antiangiogenic substances, therapy with sunitinib may cause increase of systolic and diastolic pressure, which is considered a predictor of the efficiency of oncology therapy (Force et al. 2007). Data from multiple studies point to a cardiac dysfunction incidence of 6–15%, and to this effect being reversible without clinical consequences by dose adjustment or therapy suspension (Mladosievičová and Rečková 2013). Increased risk of prolongation of QTc interval requires monitoring of this interval during therapy, especially in patients with existing CVS comorbidity. A recently published meta-analysis showed 1.4% of patients with thromboembolism in the TKI (sorafenib, sunitinib) treated group (Ederhy et al. 2011).

Lapatinib is a dual TKI inhibiting intracellular domain of EGFR and HER2 receptors. A pool analysis proved cardiac toxicity in 1.6% of patients under this therapy, mostly represented by asymptomatic reversible EFLV drop (Unitt et al. 2014). The lower incidence of cardiac toxicity in comparison to trastuzumab, blocking the same triad of intracellular signalling, is partly explained by the unfavourable effect of trastuzumab on mitochondria (Azim et al. 2009).

Imatinib BCR/ABL inhibitor is connected with several cases of congestive failure appearing within 2–14 months from the therapy commencement. A retrospective analysis identified 1.7% of patients with signs of heart failure, of which 82% had already suffered from a known CVS disease (Kerkelä et al. 2006, Atallah et al. 2007).

Diagnosing cardiac toxicity of anticancer therapies

Medical history and physical examination

In clinical practice cardiac toxicity is most often diagnosed on the basis of symptoms and EFLV drop. Many symptoms of cardiac damage may be covered by the cancer disease itself but also by other comorbidities of the patient (lung, liver or kidney disorders, obesity and others). These symptoms are assessed in the context with the cardiology finding (Mladosievičová et al. 2014, pp. 120–137).

ECG is the examination most often used in clinical practice. This examination is burdened with low sensitivity and is insufficient for diagnosing specific cardiac toxicity. Results of a higher quality are provided by vector cardiograph, late ventricular potentials, heart frequency variability, and 24-hour monitoring of ECG (according to Holter etc).

ECG is the appropriate method for diagnosing arrhythmias with the use of QT frequency and interval. The QT/QTc interval ratio is a rather straightforward parameter appropriate for finding the presence of conditions for the development of fatal ventricular arrhythmias with sudden death potential. ECG is further appropriate for diagnosing CAD, myocarditis, pericarditis and lung embolism (Bello et al. 2009, Mladosievičová et al. 2014, pp. 120–137).

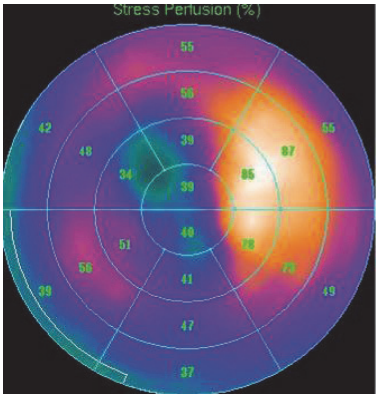
Echo cardiograph is an integral part of oncology patient care. This method is one of the most frequently used in both clinical studies and clinical practice. Diastolic function failure is manifested before the occurrence of systolic dysfunction. The examination assesses changes in heart compartment size, LV wall thickness, LV wall kinetics, presence of pericardiac exudate, and changes of ejection fraction of the left ventricle (EFLV). An EF drop of 20% or below 50% is considered a manifestation of cardiac toxicity. Thanks to modern modalities (contrast echo cardiography, 3D echo cardiography, dobutamine stress echo cardiography, Doppler tissue echo cardiography) the method is also able to diagnose sub-clinical forms of myocardium damage (Jurga et al. 2011). This method is used for patients with an identified risk of cardiac toxicity, for the evaluation of cardio protective procedures and monitoring of patients during and after therapy. At present echocardiography is a standard method in cardio oncology as it provides a wide range of information about heart morphology and function. Assessment of EFLV drop alone is currently considered an insufficiently sensitive method of early cardiac toxicity diagnosing. Diastolic parameters predict the subsequent development of cardiac toxicity better (Mladosievičová et al. 2014).

Magnetic resonance is able to diagnose sub-clinical damage to the myocardium. Its advantages include the accurate assessment of left and right ventricle function, myocardium

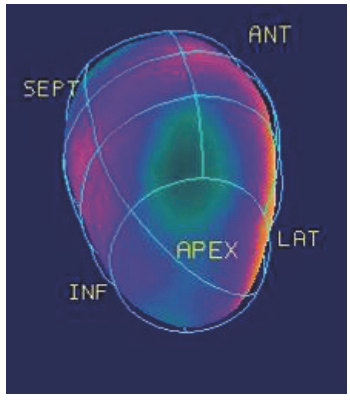
morphology and good reproducibility of the examination. Results of these diagnostic methods are promising despite their so far limited implementation. Magnetic resonance is currently considered one of the most accurate and most promising methods of cardiac toxicity screening in connection with anticancer chemotherapy. Obstacles to a wider sphere of this examination include availability and price of the examination (Mladosievičová 2015a).

Another diagnostic method is represented by **scintigraphy examination of the heart by SPECT method**. Room stress gated myocardium scintigraphy (gated SPECT), or ventriculography performed before, during or after cytostatic therapy allow for diagnosing latent damage to the myocardium. The performed examinations include **stress and room perfusion scintigraphy of the myocardium** (depending on the patient condition) **for myocardium viability specification**. The radiopharmaceutical is applied intravenously, followed by gated SPECT of the myocardium. The qualitative evaluation focuses on radioactivity spread across the left ventricle. Reduced concentration of the radiopharmaceutical indicates perfusion failure in the respective area. SPECT examination uses the bullseye analysis. It is a polar map of the heart in the form of a circle (with the apex in the centre and the left ventricle base on the perimeter). For objective assessment of perfusion disorders the result is compared to normal findings from the database (Figs 1–3).

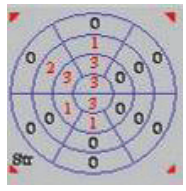
Radionuclide ventriculography allows for the measurement of mechanical function of the right and the left ventricle in the room after stress. After administration of the radiopharmaceutical, by means of a record synchronised with ECG, changes of radioactivity in the individual heart compartments in the course of the heart cycle are observed. Thanks to its reproducibility and reliability of the individual quantitative parameters, this examination may be used for the timely diagnosing of cardiotoxic damage by cytostatic therapy in cases where echocardiography is technically limited (Lacko et al. 2011).



Bullseye image of heart perfusion – the benefits include imaging of perfusion of the whole left ventricle in a single image (the left ventricle is like a "folded umbrella" shown as an "open umbrella" seen from the top by the Bullseye technique). The image shows hypo perfusion of the front and the bottom wall, in the septum and the apex areas.

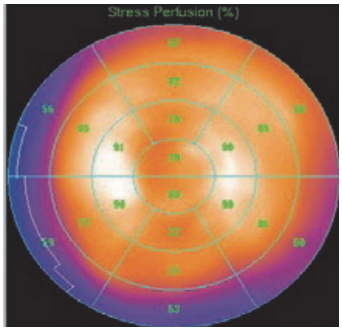


The left ventricle in normal image – you can see the apex, the septum and the front wall, the bottom and the side walls are hidden.

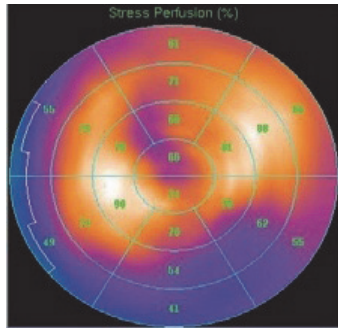


Perfusion comparison to normal image database (0 – normal perfusion, hypo perfusion stage 1–4).the bottom and the side walls are hidden.

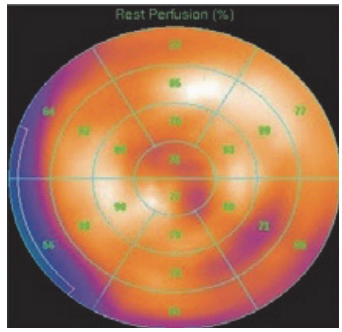
Fig. 1 – Bullseye image of heart perfusion



Polar map of perfusion SPECT of the myocardium ^{99m}Tc tetrofosmin (Myoview) – normal image (shades of brick red colour showing good perfusion).

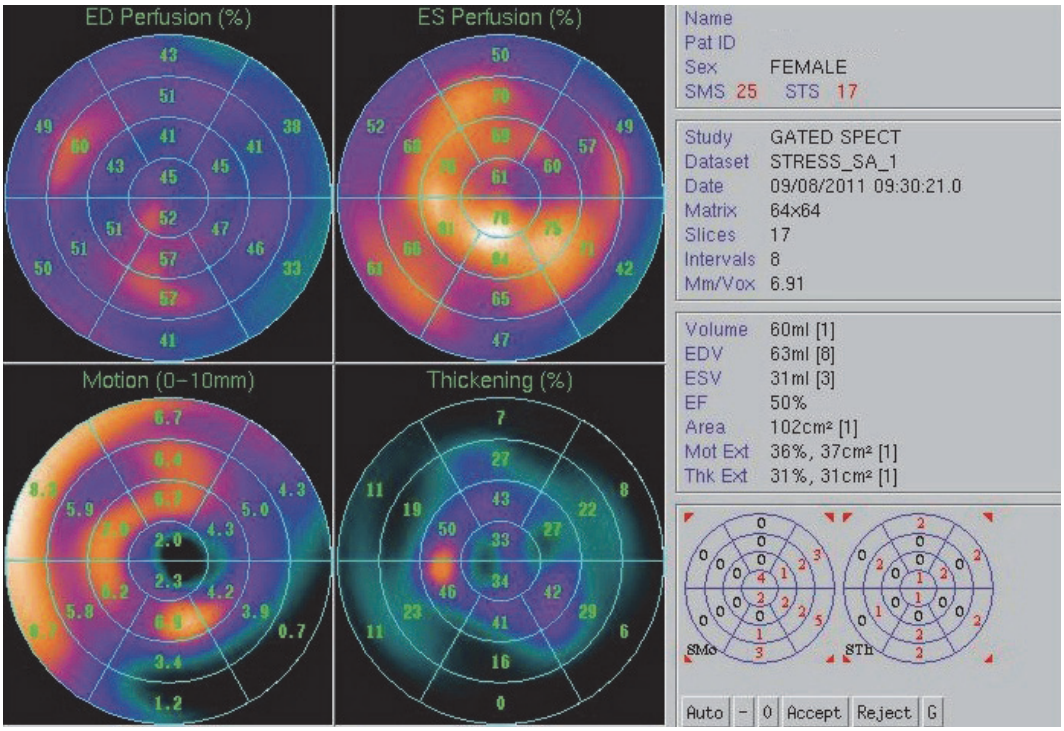


Polar map of perfusion SPECT of the myocardium – changed perfusion in the bottom and the side wall – posterolateral and in the front wall and septum areas anteroseptal (the blue colour shows changed perfusion) in the same patient after cytostatic therapy.



Polar map of perfusion SPECT of the myocardium – persisting minimum change of perfusion in the side wall – posterolateral, after a time post cytostatic therapy.

Fig. 2 – Changes of myocardium perfusion in patients after cytostatic therapy



Note: The top image shows perfusion change in end diastole of the side wall, indicating the presence of subendocardial ischemia. The bottom image shows kinetic disorder of the side wall of the LV and disorder in LV wall thickness.

Fig. 3 – Changes of haemodynamic functions of the left ventricle in a patient after cytostatic therapy

Evaluation of functional parameters of the LV is performed with the help of special programs (QGS), evaluating perfusion changes in end diastole (ED) and end systole (ES). Further evaluations include changed kinetics and the thickening of the LV wall, LV volume in end diastole (EDV), LV volume in end systole (ESV), and ejection fraction (EF) of LV (EFLV).

Radionuclide method using meta-iodinebenzylguanidin (^{123}I-MIBG) allows for specification of sympathetic receptor concentrations in the heart muscle. The autonomous nerve system performs an important role in cardiovascular system regulation. Patients with heart failure show increased levels of noradrenaline, but reduced nerve endings (receptors) in the heart. These changes are reflected in a significant reduction of ^{123}I-MIBG accumulation in the myocardium. The de-nerved but perfused myocardium plays a role in the occurrence of malignant arrhythmias. The examination of ^{123}I-MIBG accumulation allows for finding areas with arrhythmia causing potential in the myocardium. This finding in patients after cytostatic therapy with cardiotoxic effect points to a potential high risk of sudden death. Such myocardium may be identified by a simultaneous image of ^{123}I-MIBG distribution (showing potential de-enervation) and perfusion (showing viability status). Present de-enervation and preserved perfusion represents a discrepancy between the ^{123}I-MIBG and perfusion examination (Fig. 4 and 5). These methods diagnose cardiac damage even before EFLV drop (Lacko et al. 2011, Slart et al. 2015).

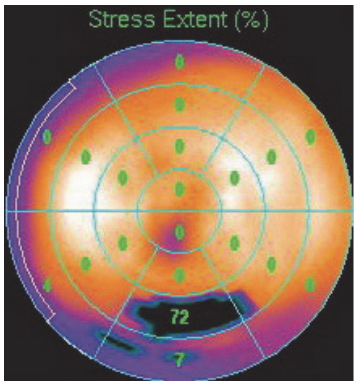


Fig. 4 – Polar map of perfusion SPECT of the myocardium ^{99m}Tc tetrofosmin (Myoview) – normal finding

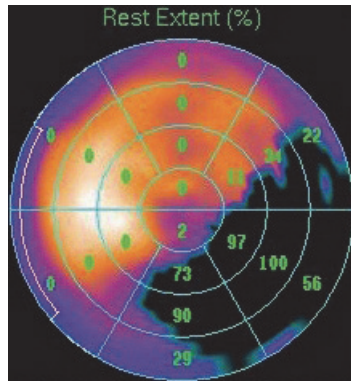


Fig. 5 – Polar map with examination of adrenerg enervation of the myocardium ^{123}I-MIBG

Note: De-nerved myocardium side and bottom wall (areas with arrhythmia causing potential). Comparison of perfusion examination shows signs of discrepancy between perfusion and adrenerg enervation of the myocardium (mismatch) in a patient after cytostatic therapy.

Endocardiac biopsy is a diagnostic method with the highest sensitivity and specificity in diagnosing anthracycline cardiomyopathy. The examination is invasive, performed in selected sites, and the occurrence of serious complications is low (less than 0.5%) (Mladosievičová et al. 2014, pp. 120–137). As for clinical use this examination does not seem to be heading towards becoming a routine examination (Mladosievičová 2015a).

Current laboratory diagnostics of toxic damage to the myocardium focuses on cardiac troponins (cTnT, cTnI), natriuretic peptides (ANP, BNP, NT proBNP) and markers of early atherosclerosis (total cholesterol, LDL-cholesterol, HDL-cholesterol, apolipoprotein A1/B1, CRP, homocysteine) (Urbanová and Mladosievičová 2010). Troponin level increase indicates multiple pathological conditions. Its dynamics in ischemic and cardiotoxic damage is different. Increased troponin levels are found months before

clinical manifestations of cardiotoxic damage caused by chemotherapy (oxidative damage, chronic inflammatory changes in the myocardium). Toxic damage is typically demonstrated by low elevations of troponin levels. The examination possesses a 99% negative prediction value, which means in practice that patients with low troponin levels are exposed to a low risk of development of cardiotoxicity induced by cytostatic therapy.

In a recommendation by the European Society of Cardiologists heart natriuretic peptides are considered important markers in heart failure diagnosing. The American Association of Clinical Oncology and the Panel of Cardiologists and Biochemists included NT examination for BNP as one of the indications in diagnosing anthracyline cardiotoxicity. The negative predictive value of the examination is 98%.

CONCLUSION

Longer life expectancy and the curing of some patients with cancer disease are burdened with myocardium damage by the cancer therapy. Late cardiotoxic manifestations may change the quality as well as the length of life. Reduction of the risk of myocardium damage by the therapy can be affected by compliance with the cumulative dose, speed of administration, adaptation of dosing schemes, and the administration of cytostatics with lower cardiotoxic potential or liposome-bound cytostatics. Due to the limited therapeutic options in connection with toxic damage of the myocardium it is necessary to diagnose the myocardium damage in a timely manner to prevent severe heart failure. There are diagnostic procedures helping with this. Adaptation of the ongoing cancer therapy, lifestyle and timely cardiological therapy can reduce the cardiotoxic effects of cancer therapies.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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