Cardiac troponins – biochemical markers of cardiac toxicity after cytostatic therapy*
Minireview

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Cardiotoxicity is a serious adverse effect of chemotherapy that encompasses a spectrum of disorders, ranging from relatively benign arrhythmias to potentially lethal conditions such as myocardial ischemia/infarction and cardiomyopathy. The toxicity of chemotherapeutic drugs can cause loss of myocytes' sarcolemmal integrity, release of bioactive markers into the extracellular environment (tissue and circulation) and ultimately leading to the necrosis of myocytes. The extent and severity of the necrosis can be monitored by the levels of bioactive markers.

Therefore current research is aimed at finding biochemical markers with absolute cardiac specificity, high sensitivity and predictive value that can be used in early detection of patients with treatment-induced myocardial damage. Routinely used biomarkers like CK, CK-MB, and myoglobin do not meet the stated criteria. Their role in early diagnosis of chemotherapy-induced myocardial toxicity is controversial and limited.

However, cardiac troponins, new nonconventional markers, have shown promising results in assessment and monitoring of both, early and late, clinical and subclinical damage to myocardium after chemotherapy.

The article reviews clinical studies evaluating the role of cardiac troponins in the diagnosis of cardiotoxicity and their use in the management of cancer survivors.

Key words: cardiotoxicity, troponins, cardiac troponins, dexrazoxane

Cardiac morbidity after anticancer therapy has become an important health problem of oncologic patients. Cardiotoxicity of chemotherapeutic agents encompasses a spectrum of disorders, ranging from relatively benign arrhythmias to potentially lethal conditions such as myocardial ischemia/infarction and cardiomyopathy. The most common health issue among oncologic patients has been cardiomyopathy following treatment with anthracyclines (ANT). The pathogenesis of anthracycline-associated toxicity has been well described. Anthracycline-induced cardiac dysfunction occurs when the critical amount of myocardial structural changes is accumulated. Routine cardiac imaging studies (e.g. echocardiogram) may identify subclinical evidence of myocardial dysfunction.

There is significant interest in developing simple and reproducible methods for early detection of patients with treatment-induced myocardial damage. Available data suggest that circulating markers such as troponins could be potentially useful in early discovery of myocardial damage. Measurements of plasma troponin levels are commonly used in clinical practice in order to provide diagnostic and prognostic information in patients with myocardial ischemia. Using biochemical markers in combination with echocardiography, may offer new insight into development of myocardial damage induced by anticancer chemotherapy.

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Abbreviations: ANT – anthracyclines; cTn – cardiac troponin; cTnI – cardiac troponin I; cTnT – cardiac troponin T; DXR – doxorubicin; HDC – high dose chemotherapy; LVEDV – left ventricular end-diastolic volume; LVEF – left ventricular ejection fraction; LVESV – left ventricular end-systolic volume; SF – shortening fraction; SHR – spontaneous hypertensive rats

Troponins

Troponins are contractile and regulatory proteins responsible for the striated appearance of the muscle under the light microscopy [1]. The troponin complex regulates the Ca-mediated contractile process of striated muscle.

Gene expression is responsible for polymorphism of contractile and regulatory proteins. Differences in the structure of various types of muscles are based on distinct distribution of the regulatory and contractile proteins especially in cardiac and skeletal muscles and lead to their functional differences.

Ebashi was the first investigator, who in 1971 separated the purified form of the troponin complex into three distinct proteins by gel electrophoresis. Based on their individual functional properties, these subunit proteins were referred to as troponin T, troponin I and troponin C.

Troponin T (TnT, MW = 37 kDa) is an asymmetric protein. It includes the carboxy-terminal domain that binds the troponin complex to tropomyosin.

Troponin I (TnI, MW = 24 kDa) is a basic globular protein that inhibits interaction of actin and myosin.

Troponin C (TnC, MW = 18 kDa) is a filamental protein with two globular domains. It binds calcium and regulates activation of thin filaments during skeletal and myocardial contraction. It can bind up to four calcium ions (Fig. 1).

Troponins form the majority of myocyte's proteins and are released in the process of apoptosis. Thus it seems they may be ideal and sensitive markers used in the diagnosis of myocardial damage.

Clinically it is possible to identify only two cardiac troponins: cardiac TnI (cTnI) and cardiac TnT (cTnT). They exist in three isoforms: in the slow-twitch skeletal muscle, fast-twitch skeletal muscle and cardiac muscle isoforms. All isoforms of cTnT and cTnI are encoded by three different genes. This is the reason why they have unique amino acid composition and structure [3]. CTnI differs from the one found in skeletal muscle by an additional sequence of 31 amino acids at its N-terminal portion [1]. Antibodies specific to this N-terminal segment of cTnI are convenient and effective in distinguishing the myocardial and skeletal isoforms in immunoassays [1].

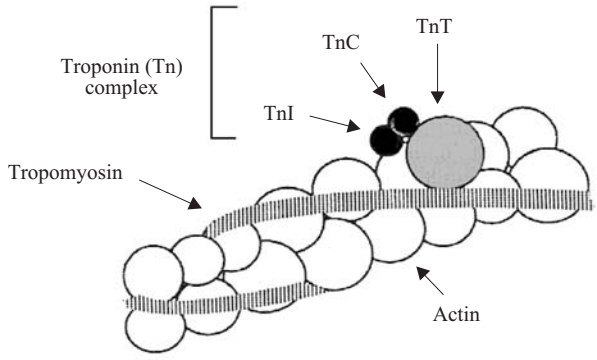

Figure 1. Structure of thin filaments (adapted from ŠPIRKOVÁ et al., 2005).

Cardiac troponins were first introduced by KATUS et al in 1989 and became standard test in laboratory diagnosis of acute myocardial infarction [4]. Progress in highly sensitive laboratory tests for estimation of structural and functional properties of cardiac troponins made them a perspective tool for the detection of minor (minimal) cardiac necrosis.

Cardiac troponin T (cTnT)

CTnT can be found in two distinct pools in human myocardium. Most of the cTnT (95%) is present in contractile filaments [4]. The rest of the cTnT (5%) is located in the cytoplasm and serves as a precursor for the synthesis of troponin complex.

In recent years new tests were developed that allow detection of cTnT released from cardiomyocytes. The absence of cross-reaction of cardiac and skeletal isoforms was crucial for clinical application of troponin laboratory assays. This is especially important in patients with chronic renal insufficiency and patients with musculoskeletal disorders. Despite no evidence of re-expression of fetal cTnT outside the heart, problematic are still elevated cTnT levels in healthy sportsmen after chronic prolonged exercise.

Ultrasensitive tests using monoclonal antibodies are able to identify unbounded cTnT that is quickly degraded in ischemic and necrotic tissues by proteolytic enzymes. Unremarkable amount of serum cTnT is in the form of ternary complex cTnT-I-C and proteolytic fragments. As sensitive as these test are, we should be aware that detection of cTnT is attenuated by heparin therapy that causes deterioration of troponin epitopes.

Today ultrasensitive assays of the second-generation and the third-generation are able to detect cTnT with 0.005 ng/ml accuracy. Such accuracy allows us to identify low levels of cTnT caused by the cardiac toxicity of anticancer therapy. However, it is questionable whether such minor cTnT elevations are due to its release from a cytosolic pool in response to reversible ischemia or whether they are a response to sustained "microinfarctions".

The release of cTnT into the serum is characterized by two peaks reflecting free cytosolic pool and cTnT bound in intracellular structures. The initial release of cTnT into the blood lasts up to 24 hours and represents the troponin T fraction not bound to myofibrils. Additionally, the process of "caplan digestion" (calcium dependent proteolytic destruction of tropomyosin complex) also contributes to the early elevation of troponin T. Late cTnT elevation is measurable approximately four days following cardiac injury.

Half-life of cTnT release into the serum is only four hours. It is associated with the continuous release of protein from the myofibrillar pool of contractile apparatus within the cells that undergo degradation [3, 4, 5].

Recent findings also suggest that cTnT could be used in stratification of the extent of myocardial injury.

Cardiac troponin I (cTnI)

Initial information about the clinical significance of cTnI dates back to the 90s. Its role was first studied in the context of ischemic coronary syndromes.

The advantage of cTnI over the cTnT lies in the fact that after the first year of life cTnI is expressed exclusively in myocardium with uniform distribution between atria and ventricles. CTnI remains below the baseline of current analytical tests in patients suffering from degenerative myopathies, in trained athletes after exhaustive exercise and even in patients with renal failure [6]. Therefore elevated serum cTnI is exclusively specific for myocardial injury.

The majority of intracellular cTnI is present in the contractile apparatus and only 3–5% is located in the free cytosolic fraction of human myocardium [1]. It was determined that 1 g of myocardium contains twice as much cTnT as it does cTnI [7]. This might be the reason why some tests are inaccurate, especially when cTnI levels are close to the lower analytical limit. It is still unclear, whether this might be the advantage of cTnT over cTnI in detection of minor necrosis.

The main disadvantage of cTnI is its presence in a complex form with cTnC (90%) in the plasma after its release from necrotic tissue. Low levels of free molecules along with their instability and high degree of proteolytic degradation over time could potentially complicate detection of cTnI in laboratory tests. The level of degradation depends on many factors including phosphorylation, oxidation and presence of autoantibodies against cTnI.

Biochemical markers of chemotherapy induced cardiac toxicity

Although anthracycline chemotherapy improved overall survival rate of patients with cancer, there is a significant risk of cardiotoxicity associated with this class of drugs [8]. Both beneficial and harmful effects of chemotherapy are linked to the diffused degeneration of myocytes and their dysfunction. In clinical oncology, early and reliable detection of even mild cardiotoxicity is important due to the predictive value of minor myocardial injury in the late onset of chemotherapy-induced cardiotoxicity.

Cardiac adverse effects caused by an administration of high doses of chemotherapy are difficult to diagnose based on their symptoms or ECG – the standard clinical methods [9]. Modern approaches such as detection of antimyosine antibodies, measurement of autonomic dysfunction or analyses of samples from endomyocardial biopsies were not helpful in the identification of subclinical and mild cardiac dysfunction induced by chemotherapy.

Therefore scientists have been trying to find an easy laboratory test that would aid in the detection of cardiac involvement after anticancer therapy. A number of new molecules have been employed to assess and/or to predict cardiac toxicity resulting from an exposure to chemotherapeutics [1]. Although many of markers have been used and are frequently incorporated into diagnostic protocols, validation studies reveal several shortcomings of the conventional markers [1]. Conventional biomarkers such as AST, ALT and CK do not appear to be abnormal in cardiotoxicity. A CK-MB fraction seems to be more sensitive. However, it increases significantly only in most serious cases of acute toxicity.

Many recent studies show effort to identify parameter able to reveal cardiotoxicity in early stages prior to the development of clinical symptoms and irreversible damage to myocardium. Cardiac troponins seem to be a great indicator of myocardial injury in this setting. Nearly absolute myocardial specificity as well as high sensitivity and capability to reflect microscopic zones of myocardial necrosis make cTn a preferred cardiac biomarker.

Cardiac troponins are released rapidly after myocardial injury in direct proportion to the extent of injury [10]. This is why researchers are focusing on cardiac specific troponins as a tool that can be used in predicting severity of cardiac damage as well as short- and long-term risks associated with cancer chemotherapy. Final recommendation regarding the prognostic value of the mentioned biomarkers cannot be made until we have gathered sufficient amount of data from a large sample group.

The application of cTnT as a biomarker of doxorubicin (DXR) cardiotoxicity was initially reported in spontaneous hypertensive rats (SHR) [1, 11, 12]. These studies showed that the magnitude of increase cTnT in serum correlated both with the total cumulative DXR dose and with the severity of cardiac lesion score (evaluated by light microscopy) [1]. Dose dependent elevations of serum cTnT in late onset of the chronic progressive cardiotoxicity following anthracycline administration have been observed also in rats, dogs and rabbits [1]. All studies show strong evidence of the high degree of concordance of results between studies done on animals and the ones observed in humans. Based on these results cardiac troponins are now considered the bridging biomarkers that can be employed in both preclinical and clinical studies monitoring drug-induced cardiac injury.

The cut-off value for cTn may be set only slightly above the “noise” level of the assay due to undetectable level of these biomarkers in the peripheral circulation under normal circumstances. Many troponin assays have excellent signal-to-noise ratio that allows them to detect even minor degrees of myocardial necrosis. Normal range of cTnT depends mainly on selected analytical method. The first generation tests did not exclude some degree of cross-reactivity between the cardiac and skeletal muscle isoforms, particularly in patients with chronic renal disease or skeletal myopathies [13]. The latest generation cTnT tests have been found 10 times more cardiospecific, and 100 times more reactive with cardiac muscle troponin T than with the skeletal one [14].

Normal values of cardiac troponins are undetectable or at lower end of the range in healthy population including children and adults regardless of their age [15, 16]. However, dif-

ferent levels of cTnI in younger and older men found by WELSH et al suggest that patient's age should have been taken into consideration when setting diagnostic cut off limits for troponins [17].

Cardiac troponins as a predictor of chemotherapy-induced cardiotoxicity in children

In European population about 1% of all malignant neoplasm arises in patients under the age of 20 [18]. There is a strong evidence of increased incidence of all neoplasms in children and adolescents over time [19]. The overall incidence of neoplasms increased by 1% in children (age group 0–14 years; increase for most types of tumors), and by 1.5% in adolescents (age group 15–19 years; notable increase was recorded for carcinomas, lymphomas, and germ-cell tumors) over the last three decades [19]. The five-year survival rate of children diagnosed with cancer by the age of 14 is 77% [20] and for adolescents is 74% [19].

While aggressive anticancer therapy in pediatric oncology is becoming more and more successful in terms of survival, more emphasis should be also placed on prevention, diagnosis and treatment of late complications and adverse effects of therapy. The most serious adverse effect of anticancer therapy is cardiomyopathy. Its incidence and severity depends on cumulative dose and other clinical factors [21].

Anthracyclines, effective cytostatic drugs, are part of many aggressive anticancer chemotherapy regimens. Tolerance of ANT is individual, so no absolute safety limits can be set for the cumulative dosage. Previously recommended dose limit of 500 mg/m^2 of ANT seems to be associated with an alarming number of abnormal cardiac findings [21].

In long-term survivors of childhood cancer, especially ALL, doxorubicin-induced cardiotoxic effects are pervasive, persistent and often progressive [22]. Early identification of patients at risk for cardiac damage after cardiotoxic therapy is important especially in children [23]. The possibility of early detection of cardiac damage during chemotherapy might enable doctors to employ strategies that can prevent and limit further myocardial damage [23].

Cardiotoxicity of cytostatics in children is very specific. Anthracycline chemotherapy in children shows usually no subclinical evidence of cardiac impairment. Cardiomyocyte loss is the general mechanism of progressive left ventricular (LV) dilation and wall thinning leading to the structural alterations in the LV [8]. Even minor loss of myocytes in children can cause serious cardiac complications in the future, because children are still growing. Growing organism lacks the potential to compensate myocardial damage in children and this is another important contributing factor for clinically manifested consequences such as heart failure, malignant ventricular tachyarrhythmia and sudden cardiac death [8, 31–35).

Chances of subsequent life threatening myocardial impairment in children are much greater than in adults [22]. Children have longer life expectancy after surviving childhood cancer. They also seem to be more susceptible to the cardiotoxic effects of ANT than adults attenuated by oncologic disease [29].

ANT therapy and chest irradiation may lead to the loss of myocytes that ultimately results in a progressive decrease in the LV mass [21]. Growing organism is not able to compensate for necrotic parts of myocardium. Thereafter inadequate LV hypertrophic response may result in increased afterload and subsequent decrease in contractility. These pathological responses lead to increased morbidity and mortality [25].

ANT cardiomyopathy may appear and progress many years after the completion of therapy [21]. One out of 20 children treated with anthracyclines develops anthracyclines-induced heart failure within 15 years after the onset of treatment [30]. Late cardiotoxicity in children is presumably due to diminished LV conctractility and an inappropriately thin LV wall, which results in elevated wall stress and progressive LV dysfunction [31].

Currently there is no reliable parameter that could with absolute sensitivity predict whether the patient will suffer from cardiac dysfunction or HF induced by chemotherapy [23]. The poor sensitivity and specificity of echocardiographic measurements in identifying subclinical structural and functional abnormalities of left ventricle in children with cancer who received doxorubicin started the search for different diagnostic approaches. Therefore, scientific research focuses more attention on new cardiospecific biomarkers of myocardial injury – cardiac troponins [32, 33].

Cardiac troponin T

Biochemical markers have not been routinely used at risk stratification of myocardial damage and in complex management of oncologic patients due to their insufficient specificity. Introduction of cardiac troponins into the routine laboratory methods evokes the question, whether cTnT is sufficiently reliable, sensitive and specific marker for detection of cardiac damage induced by chemotherapy. The main advantage of cTnT appears to be that its serum levels are undetectable in the absence of myocardial involvement [10]. Normal plasma levels of cTnT are the same in children and adults regardless of their age.

Chemotherapy induced release of cTnT is typically prolonged and continuous. It reflects chronic inflammatory myocardial changes and oxidative stress of myocytes. The 3rd generation assays are essential for reliable identification of the discrete elevations of cTnT [34]. Some studies documented elevated cTnT values before the administration of chemotherapy in ALL. Hence, children with extreme amount of leukemic blasts in the peripheral blood at baseline were more likely to have cardiac injury at diagnosis that was not related to doxorubicin therapy than those with lower values [22].

LIPSHULTZ et al examined some biochemical markers of

myocardial damage in infants to determine whether serum cTnT is able to detect any myocardial damage in children with sufficient specificity and sensitivity [10]. In three different groups of children authors found good correlation between the extent of cardiac injury and levels of cTnT. In 19 children, who underwent cardiovascular surgery for repair of congenital heart disease (positive control group), a significant linear correlation was found between the score of surgical severity, need for artificial circulation or open heart surgery and the mean levels of postoperative cTnT. In addition, increased cTnT indicated complicated postoperative sequels as well. Children who underwent non-cardiovascular surgery (17 patients, negative control group) had elevated postoperative cTnT levels only when there was preoperative cardiac involvement. LIPSHULTZ et al concluded that cTnT levels in children can be used to detect cardiac injury in a post-surgical situation [10]. In both groups preoperative elevations in cTnT identified high-risk patient with myocardial damage and also showed correlation with postoperative mortality.

The third studied group consisted of 15 children without any cardiovascular involvement, who had received doxorubicin chemotherapy at the median cumulative dose of 60 mg/m^2. CTnT levels rose in relation to the number of cycles and cumulative doses of doxorubicin. In multivariant analysis, low cTnT elevations showed significant statistical correlation with LV dilatation and LV wall thickness in the studied population with ALL. Furthermore, the study revealed the absence of cTnT elevations following non-cardiotoxic therapy as well as absence of eleveted cTnT before anthracycline therapy.

In summary, the study done by LIPSHULTZ revealed doxorubicin-associated cTnT elevations measured by serial blood concentrations as a reflection of cardiotoxic myocardial involvement. The study also supports the cTnT assays' potential in the risk stratification and prognostic forecast of patients with "minor", possibly focal myocardial diseases.

Other studies similar to LIPSHULTZ's also proved significantly superior positive as well as negative predictive value of cTnT in comparison to CK and CK-MB in detection of postoperative myocardial injury in children [15].

Recently KILICKAP et al observed elevations of cTnT that were associated with diastolic dysfunction of the left ventricle. Forty-one patients who had been scheduled to receive anthracycline-containing combination chemotherapy were included in the study. Increased cTnT levels during the anthracycline therapy were detected in 34% (14 from 41 patients). CTnT levels measured after completion of therapy were significantly higher when compared with those measured at baseline and after the first cycle of therapy [35]. Authors believe that cTnT could be a useful tool for early detection of anthracycline-induced cardiotoxicity.

Studies using some of the proven cardioprotective agents are well suited for testing the sensitivity and specificity of troponins in identification of subclinical cardiotoxicity of anticancer therapy. Dexrazoxane is a cardioprotective agent, a free-radical scavenger that may protect the heart from myocardial impairment induced by anthracycline. Formation of oxygen radicals prevents intracellular conversion of dexrazoxane to its active metal ion-binding form (ADR-925), which either removes iron from the doxorubicin-iron complex or binds free iron [36].

The main goal of other recent study by LIPSHULTZ was to determine whether dexrazoxane administration decreases doxorubicin-associated injury of cardiomyocytes. CTnT was selected in this study as biomarker for monitoring the effect of cardioprotective agent [22]. Two hundred and six children with high-risk ALL were included in the study. Patients treated with doxorubicin alone (101 children) were more likely to have elevated cTnT levels than those (105 children) who received dexrazoxane followed immediately by doxorubicin (50% vs. 21%). Dexrazoxane therapy was associated with a large and statistically significant reduction in the incidence of myocardial injury indicated by lower levels of cTnT following the therapy. These findings demonstrate the efficacy of a dexrazoxane as a cardioprotecting agent in children and the role of cTnT in monitoring of its effect [22]. Age, sex, and cumulative dose had no significant impact on cTnT levels. Correspondent findings have been demonstrated also in some animal studies [37].

Although the results of recent studies concerning the role of cTnT in early detection of myocardial damage are encouraging, so far there is no convincing evidence about its place in monitoring of cardiac toxicity after anticancer therapy [10, 11, 23, 38, 39].

KREMER et al prospectively tested the hypothesis whether cTnT is able to detect myocardial damage within 24 hours after the administration of chemotherapy [23]. The rationale for 24 hours borderline time zone came from experimental studies that had seen the earliest changes in the myocardial nuclei in myocardial specimens of rats treated with anthracyclines within 24 hours. First biochemical changes caused by oxygen free radical-related mechanisms occurred approximately 2 hours after the administration of anthracyclines. The ultrasensitive third-generation cTnT assay with a low detection threshold of 0.010 ng/ml was used in this study. The study revealed sufficient specificity (94%), but gave no convincing evidence of cTnT sensitivity (14%). Moreover statistically insufficient results (33%) were obtained about the predictive value of cTnT for left ventricle dysfunction. During the follow-up 7 months after the treatment heart failure developed in 7 out of 38 children [23].

At the present time it is being discussed whether the sampling within 24 hours after the administration of chemotherapy is too early to detect any myocardial damage. Moreover, it is unclear whether the cardiotoxic effect of anticancer therapy resulting in myocardial necrosis can be detected by elevations in cTnT in the first 24 hours after its administration [23].

Conflicting data exists about the relationship between the time of chemotherapy administration and occurrence of pathologic levels of troponins in adults [8, 40]. AUNER et al

reported a rise in the cTnT up to two weeks after the administration of chemotherapy [40].

The non-constant assessment of positive findings among comparable studies is problematic. Miscellaneous analytical methods differ often in cut off levels. For example, cTnT positive patients from LIPSHULTZ study [10] would remain undetected in FINK's work [16].

Cardiac troponin I

CARDINALE et al designed a study to identify the role of cTnI as an early marker of cardiac injury after high dose chemotherapy (HDC) [9]. The study included 204 middle age men and women (39 men, 165 women; mean age 45±10 years). All patients underwent consecutive high dose chemotherapies for aggressive malignancies resistant to the traditional chemotherapy schedules. The correlation between the highest peak of cTnI and echocardiographic changes (LVEF, LVEDV, LVESV) was evaluated by the authors during the follow-up at six and seven months after the drug administration [9].

Ultrasensitive immunoenzymatic fluorescent assay for cTnI identification was used prior, immediately after and 12, 24, 36 and 72 hours after high dose chemotherapy [9]. Normal cTnI values were found in patients with no cardiac damage or only with transient subclinical left ventricle dysfunction. Significant reduction in left ventricle ejection fraction was observed in patients with cTnI levels above a lower limit of detection (0.35 ng/ml) up to the considered cut off level (0.5 ng/ml) three months after the therapy. LVEF decrease in these patients was only transient and was followed by a recovery to baseline levels during the four- and seven-months follow-up visits. Patients with elevations of cTnI above 0.5 ng/ml suffered from more serious reduction in LVEF three months after the treatment. LVEF impairment was higher than in the previous group and was still present at the end of the follow-ups. Three patients from this group developed heart failure requiring cardiovascular treatment. They had CK-MB positivity in addition to cTnI positivity.

The data from the study validated occurrence of cardiotoxicity after high dose chemotherapeutical regimens including anthracyclines and its progressive, cumulative and dose-dependent behavior [24, 41]. The study confirmed a strong relationship between the maximal value of cTnI and maximal reduction of LVEF after HDC. The risk of developing cardiac dysfunction as revealed by cTnI positivity increased in parallel with the number of completed cycles of HDC (at baseline evaluation cTnI was negative in all patients). In addition, previous treatment with anthracyclines was more frequently associated with cTnI positivity.

Authors conclude that cTnI is an early risk and stratification biomarker for future development of significant and prolonged left ventricular dysfunction. The time course of HDC induced cardiac damage remains unclear. Further studies are needed to clarify, whether patients with a myocardial injury and proven increase of cTnI and prolonged LVEF reduction, will develop an irreversible cardiomyopathy.

Unfortunately, some of the recent data reported normal cTnI levels of patients with LV dysfunction after anthracycline chemotherapy. SOKER et al studied 31 pediatric patients with malignancies who received anthracycline containing chemotherapy at cumulative doses of 30–600 mg/m^2. Four patients (12.9%) had an LV dysfunction assessed by echocardiography. None of them had abnormal cTnI levels [42].

Similarly KOSEOGLU et al found cTnI of 22 children treated with cumulative doxorubicin doses of 120–450mg/m^2 levels within the ranges expected in healthy individuals. Despite the normal values of cTnI, echocardiography revealed impairment in cardiac function in three patients [43].

MATHEW et al started a prospective pilot study of 15 children treated by anthracycline doses ranging from 11.7 mg/kg (in patients <3 years of age) to 375 mg/m^2. All patients remained cardiac asymptomatic despite significantly lower SF and LVEF during follow-up. Moreover they did not detect any elevations of serum cTnI [44]. These findings forced the authors to reduce limitations for the upcoming study (larger samples size, longer follow-up, higher dose of chemotherapy, symptomatic patients) in order to achieve increase in cTnI levels.

SPECCHIA et al studied a group of 79 adult patients with de novo acute leukemia treated with anthracyclines. CTnI levels in seven patients increased (>0.15 ng/ml) immediately after the induction of the therapy. Four of them had elevated levels of cTnI on the 14th day and the other three on the 7th day following the induction. In five of the seven patients elevation in cTnI levels was temporary and returned to normal range. Echocardiography showed a significant reversible decrease in LVEF among patients with increased cTnI levels [45]. These results support the role of cTnI in identifying high-risk patients who may benefit from closer observation and supportive cardiac therapy.

Conclusion

Non-invasive character of troponin assessment, easy serial monitoring, and relatively low-cost tests done in outpatient setting make cardiac troponins potentially a great option for monitoring chemotherapy induced cardiac injury in comparison to techniques such as echocardiography or radionuclide scan.

Although troponins' independent predictive value seems to be reliable in its specificity, further studies are needed before cTn can be recommended as a standard diagnostic tool for detection of cardiac injury after chemotherapy. Research should also focus on a detailed understanding of pathophysiology of minor cardiac changes in the context of elevated cTn values and left ventricle systolic dysfunction.

Assessment of reversibility of myocardial injury based on serum troponin levels as well as identification of patients in

high risk for development of serious cardiovascular complications continues to be a challenge for the future studies. Close monitoring and adjustments to anticancer therapeutic strategies deserve more attention as well.

References

[1] WALLACE KB, HAUSNER E, HERMAN E, HOLT GD, MACGREGOR JT et al. Serum troponins as biomarkers of drug-induced cardiac toxicity. Toxicol Pathol 2004; 32: 106–121.

[2] ŠPIRKOVÁ Z, DAŇOVÁ K, PECHÁŇ I, PIVOVARNÍKOVÁ H, PULLMANN R. Kardiomarkery. Phonec Agency 2005: 19–32 (in Czech).

[3] COLLINSON PO, BOA FG, GAZE DC. Measurement of cardiac troponins. Ann Clin Biochem 2001; 38: 423–449.

[4] KATUS HA, REMPPIS A, SCHEFFOLD T, DIEDERICH KW, KUEBLER W et al. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. Am J Cardiol 1999; 167: 1360–1367.

[5] KRAGTEN JA, HERMENS WT, DIEIJEN VISSER MP. Cardiac troponin T release into plasma after acute myocardial infarction; only fractional recover compared with enzymes. Ann Clin Biochem 1996; 33: 314–323.

[6] ADAMS JE 3RD, BODOR GS, DAVILA-ROMAN VG, DELMEZ JA, APPLE FS et al. Cardiac troponin I – marker with hight specificity for cardiac injury. Circulation 1993; 88: 101–106.

[7] WU AHB, FENG YJ. Biochemical differences between cTnT and cTnI and their significance for diagnosis of acute coronary syndromes. Eur Heart J 1998; 19 Suppl N: N25–N29.

[8] GRENIER MA, LIPSHULTZ SE. Epidemiology of anthracycline cardiotoxicity in children and adults. Semin Oncol 1998; 25 Suppl 10: 72–85.

[9] CARDINALE D, SANDRI MT, MARTINONI A, TRICCA A, CIVELLI M et al. Left ventricular dysfunction predicted by early troponin l release after high-dose chemotherapy. J Am Coll Cardiol 2000; 36: 517–522.

[10] LIPSHULTZ SE, RIFAI N, SALLAN SE, LIPSITZ SR, DALTON V et al. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. Circulation 1997; 96: 2641–2648.

[11] HERMAN EH, ZHANG J, LIPSHULTZ SE, RIFAI N, CHADWICK D et al. Correlation between serum levels of cardiac troponin-T and the severity of the chronic cardiomyopathy induced by doxorubicin. J Clin Oncol 1999; 17: 2237–2243.

[12] HERMAN EH, LIPSHULTZ SE, RIFAI N, ZHANG J, PAPOIAN T et al. Use of cardiac troponin T levels as an indicator of doxorubicin-induced cardiotoxicity. Cancer Res 1998; 58: 195–197.

[13] MAIR J. Progress in myocardial damage detection: New biochemical markers for clinicians. Crit Rev Clin Lab Sci 1997; 34: 1–66.

[14] MULLER-BARDORFF M, HALLERMAYER K, SCHRODER A, EBERT C, BORGYA A et al. Improved troponin T ELISA specific for cardiac troponin T isoform: Assay development and analytical and clinical validation. Clin Chem 1997; 43: 458–466.

[15] IMMER FF, STOCKER F, SEILER AM, PFAMMATTER JP, PRINTZEN G, PEHEIM E. Troponin-T: improved diagnostic assessment of myocardial damage in childhood. Acta Paediatr 1997; 86: 1321–1327.

[16] FINK FM, GENSER N, FINK C, FALK M, MAIR J et al. Cardiac troponin T and creatine kinase MB mass concentrations in children receiving anthracycline chemotherapy. Med Pediatr Oncol 1995; 25: 185–189.

[17] WELSH TM, KUKES GD, SANDWEISS M. Differences of creatine kinase MB and cardiac troponin I concentrations in normal and diseased human myocardium. Ann Clin Lab Sci 2002; 32: 44–49.

[18] FERLAY J, BRAY F, PISANI P. GLOBOCAN 2000. Cancer incidence, mortality and prevalence worldwide, version 1.0. IARC Cancer Base No. 5. Lyon: IARCPress, 2001.

[19] STELIAROVA-FOUCHER E, STILLER CH, KAATSCH P, BERRINO F, COEBERGH JW et al. Geographical patterns time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study. Lancet 2004; 364: 2097–2105.

[20] US National Cancer Institute Workshop on Pediatric Oncology Late Effects of Children Cancer Networks. Backround statistics on pediatric survivorship. Niagara-on-the-Lake, Canada, June 26, 2002.

[21] PIHKALA J, SAARINEN UM, LUNDSTRÔM U, VIRTANEN K, VIRKOLA K et al. Myocardial function in children and adolescents after therapy with anthracyclines and chest irradiation. Eur J Cancer 1996; 32A: 97–103.

[22] LIPSHULTZ SE, RIFAI N, DALTON VM, LEVY DE, SILVERMAN LB et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. N Engl J Med 2004; 351: 145–153.

[23] KREMER LCM, BASTIAANSEN BAJ, OFFRINGA M, LAM J, VAN STRAALEN JP et al. Troponin T in the first 24 hours after the administration of chemotherapy and the detection of myocardial damage in children. Eur J Cancer 2002; 38: 686–689.

[24] LIPSHULTZ SE, COLAN SD, GELBER RD, PEREZ-ATAYDE AR, SALLAN SE, SANDERS SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 324: 808–815.

[25] LIPSHULTZ SE, LIPSITZ SR, MONE SM, GOORIN AM, SALLAN SE et al. Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med 1995; 332: 1738–1743.

[26] NYSOM K, COLAN SD, LIPSHULTZ SE. Late cardiotoxicity following anthracycline therapy for childhood cancer. Prog Pediatr Cardiol 1998; 8: 121–138.

[27] NYSOM K, HOLM K, LIPSITZ SR, MONE SM, COLAN SD et al. Relationship between cumulative anthracycline dose and late cardiotoxicity in childhood acute lymphoblastic leukemia. J Clin Oncol 1998: 16: 545–550.

[28] LIPSHULTZ SE. Ventricular dysfunction clinical research in infants, children and adolescents. Prog Pediatr Cardiol 2000; 12: 1–28.

[29] VON HOFF DD, ROZENCWEIG M, LAYARD M, SLAVIK M, MUGGIA FM. Daunomycin-induced cardiotoxicity in children and adults. A review of 110 cases. Am J Med 1977; 62: 200–208.

[30] KREMER LC, VAN DALEN EC, OFFRINGA M, OTTENKAMP J, VOUTE PA. Anthracycline-induced clinical heart failure in a cohort of 607 children: long-term follow-up study. J Clin Oncol 2001; 19: 191–196.

[31] LIPSHULTZ SE, COLAN SD. The use of echocardiography and Holter monitoring in the assessement of anthracycline--treated patients. In: Bricker JT, Green DM, DAngio GJ, editors. Long term complications of treatment of children and adolescents for cancer. Philadelphia, PA, Wiley-Liss, 1993: 45–62.

[32] LIPSHULTZ SE, SANDERS SP, GOORIN AM, KRISCHER JP, SALLAN SE, COLAN SD. Monitoring for anthracycline cardiotoxicity. Pediatrics 1994; 93: 433–437.

[33] LIPSHULTZ SE, SANDERS SP, GOORIN AM, KRISCHER JP, SALLAN SE, COLAN SD. The anthracycline cardiotoxicity debate. Pediatrics 1994; 94: 781–782.

[34] GAUDIN PB, HRUBAN RH, BESCHORNER WE, KASPER EK, OLSON JL et al. Myocarditis associated with doxorubicin cardiotoxicity. Am J Clin Pathol 1993; 100: 158–163.

[35] KILICKAP S, BARISTA I, AKGUL E, AYTEMIR K, AKSOYEK S et al. CTnT can be a useful marker for early detection of anthracycline cardiotoxicity. Ann Oncol 2005; 16: 798–804.

[36] SCHROEDER PE, HASINOFF BB. The doxorubicin-cardioprotective drug dexrazoxane undergoes metabolism in the rat to its metal ion-chelating form ADR-925. Cancer Chemother Pharmacol 2002; 50: 509–513.

[37] HERMAN EH, ZHANG J, RIFAI N, LIPSHULTZ SE, HASINOFF BB, CHADWICK DP et al. The use of serum levels of cardiac troponin T to compare the protective activity of dexrazoxane against doxorubicin and mitoxantrone induced cardiotoxicity. Cancer Chemother PharmacoI 2001; 48: 297–304.

[38] KAPLAN S. Biochemical markers of myocardial injury in children. Circulation 1997; 96: 2496–2497.

[39] LIPSHULTZ SE, GRENIER MA, COLAN SD. Doxorubicin-induced cardiomyopathy. N Engl J Med 1999; 340: 653–654.

[40] AUNER HW, TINCHON C, QUEHENBERGER F, LINKESCH W, STILL H. Troponins in prediction of cardiotoxic effects. Lancet 2001; 357: 808.

[41] FEENSTRA J, GROBBEE DE, REMME WJ, STRICKER BH. Drug-induced heart failure. J Am Coll Cardiol 1999; 33: 1152–1162.

[42] SOKER M, KERVANCIOGLU M. Plasma concentrations of NT-pro-BNP and cardiac troponin-I in relation to doxorubicin-induced cardiomyopathy and cardiac function in childhood malignancy. Saudi Med J 2005; 26: 1197–202.

[43] KOSEOGLU V, BERBEROGLU S, KARADEMIR S, KISMET E, YURTTUTAN N et al. Cardiac troponin I: is it a marker to detect cardiotoxicity in children treated with doxorubicin? Turk J Pediatr 2005; 47: 17–22.

[44] MATHEW P, SUAREZ W, KIP K, BAYAR E, JASTY R et al. Is there a potential role for serum cardiac troponin I as a marker for myocardial dysfunction in pediatric patients receiving anthracycline-based therapy? A pilot study. Cancer Invest 2001; 19: 352–359.

[45] SPECCHIA G, BUQUICCHIO C, PANSINI N, DI SERIO F, LISO V et al. Monitoring of cardiac function on the basis of serum troponin I levels in patients with acute leukemia treated with anthracyclines. J Lab Clin Med 2005; 145: 212–220.