Opinion Paper

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Cardiotoxic effects and myocardial injury: the search for a more precise definition of drug cardiotoxicity

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Abstract: Drug-induced cardiotoxicity is a major clinical problem; cardiotoxic drugs may induce both cardiac dysfunction and myocardial injury. Several recent studies reported that cardiac troponins measured with high-sensitivity methods (hs-cTn) can enable the early detection of myocardial injury related to chemotherapy or abuse of drugs that are potentially cardiotoxic. Several authors have some concerns about the standard definition of cardiotoxicity, in particular, regarding the early evaluation of chemotherapy cardiotoxicity in cancer patients. Several recent studies using the hs-cTn assay indicate that myocardial injury may precede by some months or years the diagnosis of heart failure (HF) based on the evaluation of left ventricular ejection fraction (LVEF). Accordingly, hs-cTn assay should considered to be a reliable laboratory test for the early detection of asymptomatic or subclinical cardiotoxic damage in patients undergoing cancer chemotherapy. In accordance with the Fourth Universal Definition of Myocardial Infarction and also taking into account the recent experimental and clinical evidences, the definition of drug-cardiotoxicity should be updated considering the early evaluation of myocardial injury by means of hs-cTn assay. It is conceivable that the combined use of hs-cTn assay and cardiac imaging techniques for the evaluation of cardiotoxicity will significantly increase both diagnostic sensitivity and specificity, and also better prevent chemotherapy-related left ventricular (LV) dysfunction and other adverse cardiac events. However, large randomized clinical trials are needed to evaluate the cost/benefit ratio of standardized protocols for the early detection of cardiotoxicity using hs-cTn assay in patients receiving chemotherapy for malignant diseases.

Keywords: cardiac troponins; cardiotoxicity; chemotherapy; high-sensitivity methods; myocardial injury.

Introduction

Drug regulatory authorities award marketing authorizations that license pharmaceutical companies to market medicinal products when there is sufficient evidence that the product has a favorable benefit-to-harm balance and especially they do not show dangerous side effects [1, 2]. The term cardiotoxicity was first used to describe the toxic effects related to cardiac function or tissue induced by the administration of local anesthetics, mercurial diuretics and digitalis in 1946 [3]. Since 1970s, the term was in particular used to describe the cardiac complications related to cancer chemotherapy [2, 3].

Drug-induced cardiotoxicity is a major clinical problem, often detected only after the introduction of the drug in clinical practice [2]. Indeed, cardiac arrhythmias, which are the most frequently drug-related cardiotoxic effects, may be not identified when safety testing is done in experimental animals and control healthy subjects (phase I of drug safety testing), but the pro-arrhythmic adverse effects of drugs may appear only when the drug is administrated to patients with underlying cardiac disease (phase II or III of drug safety testing) [2]. Accordingly, some authors have recently suggested to define “hidden cardiotoxicity” all the drug-related cardiotoxic effects detected only in the

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diseased state, such as in patients with ischaemia/reperfusion injury and/or other comorbidities leading to cardiac disease [2].

Different drugs can cause different toxic effects on cardiac function and tissue. For example, it is well known that some patients undergoing cancer chemotherapy can develop severe left ventricular (LV) systolic dysfunction [4–6]. Indeed, the most part of anticancer medications may induce direct cardiotoxicity causing cardiomyocyte injury [6, 7]. Some drugs may prolong the duration of repolarization and induce polymorphic ventricular tachycardia or impair impulse conduction [2]. These drugs can precipitate severe arrhythmias especially during ischemia and following myocardial infarction [2]. Accordingly, as a common feature, drug cardiotoxicity is more frequent in individuals/patients who already have an asymptomatic or latent cardiac disease [2].

Relationship between drug-induced cardiac dysfunction and myocardial injury

It is now well established that cardiotoxic drugs may induce both cardiac dysfunction (such as ventricular dysfunction, arrhythmias, cardiac conduction defects, ischemia, endothelial dysfunction) and myocardial injury (reversible or irreversible) [2]. In patients consuming cardiotoxic drugs, the origin of cardiac dysfunction recognizes different pathophysiological pathways: (1) modification of excitation/contraction coupling and/or intracellular calcium homeostasis and/or mitochondrial function leading to cardiomyocyte dysfunction; (2) alterations of loading conditions (preload reserve/afterload mismatch) or heart rate (force-frequency relation) and (3) alterations of the extracellular matrix composition [2].

On the other hand, myocardial injury can be reversible or irreversible [8–14] (Figure 1). Experimental evidence suggests a number of possible cardiomyocyte reversible damages in the absence of cell death, characterized by an increase in cell permeability (i.e., presence of cell wounds) or formation and release from membranous blebs or microparticles [8–11]. Irreversible cardiomyocyte damage can be due to necrosis or apoptosis [10–13]. Necrosis is an energy-independent process that results in the disintegration of cardiomyocytes, which may be exacerbated in individuals/patients consuming drugs with "hidden cardiotoxicity" [2, 8, 9]. Apoptosis is now recognized as a regulated and programmed cell death (i.e., an energy-dependent process), playing a central role in development, morphogenesis, normal cell turnover of myocardial tissue as well as in pathophysiology of cardiac diseases [8–14].

Of course, different degrees of cardiac dysfunction or myocardial injury actually coexist in individuals/patients with drug-related cardiotoxicity. Form a clinical point of view, cardiac dysfunction can be assessed by means of sign and symptoms or clinical investigations such as electrocardiography (i.e., arrhythmias) or echocardiography (i.e., ventricular dysfunction). Even using more sophisticated cardiac imaging techniques (CT scan, MRI, PET or SPECT), the detection of myocardial injury is difficult when the damaged area is small or the damage is minor. Another important clinical issue is that LV dysfunction may remain asymptomatic for a long time in patients consuming cardiotoxic drugs, but once symptomatic, the prognosis is very poor [15, 16]. The challenge is then to detect myocardial toxicity before the onset of symptomatic heart failure (HF) [15, 16]. Some recent expert documents recommended a definition of cardiotoxicity (especially in patients undergoing cancer chemotherapy) based on a 10% point

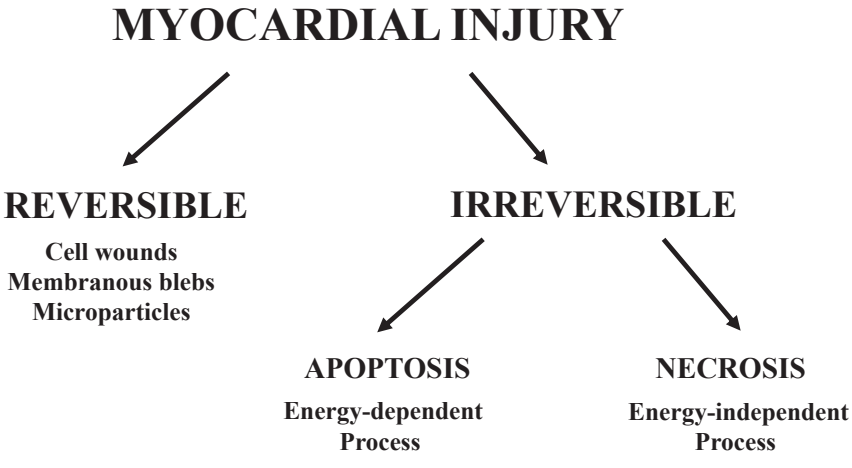

Figure 1: Mechanisms of myocardial injury (according to refs. [10] and [11]).

decrease of the left ventricular ejection fraction (LVEF) to a value <53% [5, 6, 16]. According to the international guidelines, LVEF assessment can be performed by echocardiography, cardiac nuclear imaging or MRI [4–6]. Unfortunately, this "gold standard" for cardiotoxicity in patients undergoing cancer chemotherapy is probably not sufficiently effective in the assessment of sub-clinical LV dysfunction, since it is not able to accurately evaluate myocardial injury [15–18].

Definition of myocardial injury, concerning cancer patients treated with chemotherapy agents, should be based on the *Fourth Universal Definition of Myocardial Infarction* [19]. This fundamental consensus document, endorsed by the *European Society of Cardiology* (ESC), the *American College of Cardiology* (ACC), the *American Heart Association* (AHA) and the *World Heart Federation* (WHF), states that the presence of myocardial injury should be evidenced by elevated cardiac troponin values, measured with high-sensitivity (hs-cTn) methods [19].

Analytical performance, pathophysiological characteristics, and clinical relevance of cardiac troponins measured with high-sensitivity (hs-cTn) methods

According to the most recent international guidelines, two fundamental analytical criteria must be met to establish that a method should be defined as hs-cTn: (1) the error measurement (expressed as % CV) of the cTn concentration corresponding to the 99th percentile upper reference limit (URL) value should be ≤10%; (2) measurable cTn concentrations should be obtainable at a value at, or above, the assay's LoD (limit of detection) in more than 50% of two populations of at least 300 women and men [20]. Considering that, on average, women of fertile age present significantly lower cTn levels than age-matched men, an immunoassay method should enable the reliable measurement of cTn concentrations in a large population (>600 individuals) of at least 300 apparently healthy women in order to satisfy the second criterion.

From a pathophysiological perspective, it is important to underline that current hs-cTn methods have an analytical sensitivity ranging from about 1 to 3 ng/L (Table 1) [21–27]. Recent studies reported that these LoD values correspond to the amount of cTn contained in about 5 to 8 mg of cardiomyocytes [10, 11, 28, 29]. Notably, this amount of myocardial tissue related to the cut-off value of myocardial injury (i.e., 99th percentile URL) corresponds to a myocardial mass that is too low to be detected by non-invasive cardiac imaging, including NMR or PET [10, 11, 28, 29]. Several authors suggest that the hs-cTn concentration is a reliable index of cardiomyocyte renewal [10, 11, 28–30]. According to the results reported in experimental studies on animals and humans the 99th percentile URL values of hs-cTnI and cTnT methods (ranging from 13 to 47 ng/L) (Table 1) should correspond to an average from 30 to 40 mg of cardiomyocyte renewal [10, 11, 28–30].

Several studies (including three meta-analyses) reported that hs-cTn values ≥99th percentile URL value measured in general populations [31–39] or elderly communities [40–42] are significantly associated to increased frequencies of both cardiac mortality rate and major adverse cardiac events (MACE). In particular, one study reported that even small, but progressively increasing hs-cTnI values (e.g., about 5 ng/L) can significantly increase cardiovascular risk in asymptomatic individuals in the general population [33]. Furthermore, several studies have recently reported that hs-cTn concentrations over the 99th percentile URL value, measured in well-trained athletes and apparently healthy individuals after strenuous endurance physical exercise (such as marathon and mountain bike races), are significantly correlated to high risk for MACE and cardiac mortality rate [43–46].

Thanks to the results of these studies [31–46], some authors suggested that hs-cTn assay may be a reliable laboratory test for the early detection of asymptomatic or subclinical cardiotoxic damage even in patients undergoing cancer chemotherapy [15, 17, 18, 47, 48]. Indeed, several studies have demonstrated that hs-cTn assays enable the early detection of myocardial injury in cancer patients treated with chemotherapy agents [15, 17, 18, 47–59]. In particular, two recent studies using hs-Tn methods demonstrate that a progressive increase in biomarker concentration during chemotherapy allows the identification of patients more prone to developing myocardial dysfunction and MACE [52, 53]. Furthermore, some studies demonstrated that the progressive increase of hs-cTn throughout a complete chemotherapy regimen, including several cycles of treatment, is more sensitive and accurate than the measurement of a single sample collected after only one cycle [47, 48, 57, 58]. Accordingly, cTn assay can be used for screening of patients at a high risk of cardiotoxicity from chemotherapy [17, 18, 47, 48, 58, 59]. In particular, early cardiotoxicity detection and its prompt treatment appear crucial to improve cardiac function and to avoid the progression toward symptomatic HF [17, 18, 47, 48, 58, 59].

Table 1: Analytical characteristics and distribution parameters for some hs-cTnI methods commercially available in Italy since 2016.

hs-cTnI methods	LoD, ng/L	LoQ 10%, ng/L	Median, ng/L (25th–75th percentiles)	99th percentile URL, ng/L	Number of subjects
ARCHITECT	1.3	4.7	1.8 (1.2–2.8)	18.9	1,463
ACCESS DxI	1.3	5.3	2.7 (1.9–4.0)	16.8	1,460
ADVIA CENTAUR XPT	2.2	8.4	3.3 (1.8–4.9)	46.9	1,411
hs-cTnT method					
ECLIA	3.0	8.0	4.4 (3.0–6.8)	13.1	1,600

LoD, Limit of Detection [27]. LoQ 10%, Limit of Quantitation, which is the cTn concentration measured with an error of 10% [27]. 99th percentile URL: the 99th percentile values for hs-cTnI methods were evaluated in an Italian reference population of apparently healthy individuals of both sexes (women/men ratio 0.95, age range 18–86 years, mean age 51.5 years, SD: 14.1 years) [26]. The 99th percentile for the cTnT method was evaluated as previously reported [21]. Analytical parameters and median (interquartile range) values for hs-cTnI methods were evaluated according to previous studies [23–26], those for the cTnT method were reported in previous studies [21, 22].

Clinical relevance of cardiac troponin assay in patients consuming cardiotoxic drugs

Several authors have some concerns about the imprecise definition of cardiotoxicity, especially about the best evaluation of chemotherapy cardiotoxicity in cancer patients [2, 3, 59]. Considering anthracyclines as the principal drugs involved in chemotherapy-induced cardiotoxicity, three distinct types of cardiotoxicity can be observed [59]: (1) acute, occurring after a single dose, or a single course, with the onset of symptoms within 14 days from the end of treatment; (2) early-onset chronic, the principal form of cardiotoxicity, occurring within one year, with progressive evolution toward HF and (3) late-onset chronic, developing years, possibly decades, after the end of anthracycline therapy. The last two chronic forms are considered irreversible, with a poor prognosis and a limited response to HF therapy. In this classification, the definition of cardiotoxicity is based on the occurrence of a decrease in LVEF >10% after drug administration [4–6].

However, recent evidences suggest a more complex pathophysiological scenario. The myocardial tissue, including both cardiomyocytes and other cell types (such as cardiac progenitor cells, cardiac fibroblasts, and endothelial cells), is actually considered the direct cellular target of chemotherapy cardiotoxic effect [2, 59, 60]. Accordingly, appearance and evolution of clinical symptoms and cardiac dysfunction should be considered strictly related to cardiomyocyte damage. Indeed, Cardinale et al. [59] recently suggest that anthracycline-induced cardiotoxicity is potentially a continuous phenomenon, starting with the myocardial injury at cell level, as demonstrated by the early increased in hs-Tn levels soon after cardiotoxic-drug administration. After an acute injury, if the cellular damage cannot be repaired in a short time, a chronic inflammatory response may occur [61, 62]. In this case, a chronic inflammatory response allows a pathological wound repair, with accumulation of permanent fibrotic tissue at the site of injury [61]. The final result of this dysregulated inflammatory process, which tends to progressively replace the contractile myocardial cells with fibrotic tissue, is the inability of the tissue to restore the normal function: this pathophysiological process is currently named progressive reverse myocardial remodeling [30, 61, 62]. From a clinical point of view, the use of cTn assay to identify patients with subclinical cardiotoxicity combined with early treatment with ACE-inhibitors appears to be an effective method to prevent anthracycline-related LV dysfunction and MACE [59].

Search for a more precise definition of cardiotoxicity

In the Era of precision and personalized medicine, imprecise gold-standards should not longer be used for diagnostic and prognostic evaluations [3, 63]. Advanced cancer therapies based on precision targets (using immune-mediated, biologically active small molecule, and monoclonal antibody therapies, and specific biomarkers) have progressively improved the prognosis of patients suffering of more than 200 different malignant type of cancers [3, 64]. According to data reported by National Institute of Health (NIH), in January 2019 there were about 16.9 million

cancer survivors in the United States, representing approximately 5% of the population [65]; similar good results are also reported for European Countries, and Italy shows the best health profile for patients with cancers [66]. These survivor patients are actually at high risk for a progressive evolution toward HF with a poor prognosis (mortality rate up to 60% within two years of HF diagnosis) [58, 59]. The results reported in the present article demonstrate that the early detection of myocardial injury is possible by means of a simple hs-Tn assay. Indeed, several studies [15–18, 47–60, 67] indicate that myocardial injury may precede by some months or years the diagnosis of HF carried out using the classical definition of cardiotoxicity based on LVEF reduction [4–6].

The hs-cTn assay should be considered the biochemical gold standard for myocardial injury induced by cardiotoxicity from different causes/etiologies [3, 15–17, 58, 59, 67, 68]. Several studies have demonstrated that hs-cTn assay is able to accurately detect cancer patients with subclinical cardiotoxicity [15–18, 47–59, 67]. In this way, this laboratory test, combined with an early cardioprotective treatment, should be considered to be an effective method to prevent chemotherapy-related LV dysfunction and MACE [15–18, 47–59, 67, 68].

Considering these evidences, several authors [2, 3, 58, 59, 67, 68] have previously suggested that the definition of drug-cardiotoxicity should be updated by including the early evaluation of myocardial injury by means of hs-cTn assay in accordance with the Fourth Universal Definition of Myocardial Infarction [19]. It is important to note that hs-cTn should not replace imaging techniques in the definition of cardiotoxicity; on the contrary, cardiac imaging techniques will retain their key role in providing information on anatomy, function and structure of the heart [59]. Therefore, it is conceivable that the combined use of laboratory test and cardiac imaging techniques for the evaluation of cardiotoxicity will significantly increase both diagnostic sensitivity and specificity, and also better prevent chemotherapy-related LV dysfunction and other adverse cardiac events [59]. However, large randomized clinical trials are needed in order to evaluate the cost/benefit ratio of standardized protocols for the early detection of cardiotoxicity using hs-cTn assay in patients receiving chemotherapy for malignant diseases.

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