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Troponins in heart failure

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ABSTRACT

The signs and symptoms of heart failure are frequently unspecific and correlate poorly with objective indices of cardiac function. Objective assessment of cardiac function by echocardiography or other imaging modalities also correlate poorly with symptomatic status and functional capacity. Accordingly, there is a need for circulating biomarkers that can provide incremental diagnostic and prognostic information to the existing armamentarium of tests. The introduction of more sensitive assays that allow determination of very low circulating concentrations of the myofibrillar proteins cardiac troponin I and T has not only resulted in improved diagnostic accuracy in the setting of acute coronary syndromes. The high sensitivity assays have also shown that cardiac troponins are frequently found chronically circulating in a variety of acute and chronic, cardiac and non-cardiac disease conditions, including acute heart failure and chronic symptomatic and asymptomatic left ventricular dysfunction. Cardiac troponin I and T provide may provide clinically useful prognostic information both concerning the future risk of developing heart failure in asymptomatic subjects and the risk of fatal events and hospital admissions in those with already established heart failure

This review summarizes current literature on the clinical performance and utility of cardiac troponin measurements as diagnostic and prognostic tools in patients with symptomatic heart failure, as well as in those with asymptomatic left ventricular dysfunction, and clinical phenotypes at high risk for developing heart failure, including stable coronary artery disease, left ventricular hypertrophy, and aortic stenosis.

1. Introduction

In contrast to the decline observed in the incidence and mortality rates of acute myocardial infarction during the past 40 years, the incidence of heart failure has only recently started to level off, and despite improvements in pharmacologic and non-pharmacologic therapies the hospitalization and mortality rates of severe forms remain high [1]. For instance, in the United States the prevalence has been estimated to be more than 5 million, the annual number of hospital discharges in patients with a primary diagnosis of heart failure exceeds 1 million [2] and it has been estimated that more than 3 million physician visits per year primarily can be attributed to heart failure. Accordingly, heart failure, especially among the elderly, represents a major burden on the health care system in Western countries.

The signs and symptoms of heart failure are frequently unspecific and correlate poorly with objective indices of cardiac function [3]. Accordingly, making a diagnosis exclusively based on medical history and physical examination findings can be challenging for the clinician. Findings on the electrocardiogram and chest radiograph may add valuable information in some instances, but the diagnostic accuracy of these tests in isolation is rather limited [4]. Objective assessment of cardiac function by echocardiography or other imaging modalities, may assist in the diagnostic and prognostic assessment of heart failure, but is costly and correlate poorly with symptomatic status and functional capacity. Moreover, cardiac imaging may not accurately differentiate between acute and chronic ventricular dysfunction. The limitations of clinical assessment and cardiac imaging modalities in the diagnostic and prognostic assessment of patients with ventricular dysfunction and heart failure, have led to the search for circulating biomarkers that can provide incremental diagnostic and prognostic information to the existing armamentarium of tests. One class of circulating biomarkers that holds promise as clinically useful tools in such assessment is the biomarkers of myocardial injury, and preeminent within this class, the myofibrillar proteins troponin I and T.

The introduction of more sensitive assays in clinical practice has not only resulted in improved diagnostic accuracy in the setting of acute coronary syndromes. The high sensitivity assays have also shown that cardiac troponins are frequently found chronically circulating in a variety of acute and chronic, cardiac and non-cardiac disease conditions, including acute heart failure and chronic symptomatic and asymptomatic left ventricular dysfunction [5]. Troponin elevation may be evident

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regardless of an ischemic or non-ischemic etiology, suggesting that cardiac troponin elevation is not specific for ischemic injury. Moreover, several large-scale epidemiological studies have documented that circulating cardiac troponins are detectable in large proportion of presumably healthy persons. These observations suggest that other mechanisms than ischemic injuries are operative for chronic, low-grade cardiac troponin release. Proposed underlying mechanisms involved include chronic, low-grade myocardial ischemia, necrosis, apoptosis, and autophagy [1].

This review summarizes current literature on the clinical performance and utility of cardiac troponin measurements as diagnostic and prognostic tools in patients with symptomatic heart failure (Stage C heart failure), as well as in those with asymptomatic left ventricular dysfunction, and clinical phenotypes at high risk for developing heart failure, including stable coronary artery disease, left ventricular hypertrophy, and aortic stenosis.

2. Troponin molecule/biology of troponin

A cluster of three distinct polypeptides, troponin C, troponin T, and troponin I, constitutes the troponin complex in both striated skeletal and cardiac muscle tissue. Troponin C is the calcium binding subunit, troponin T the tropomyosin-binding unit, whereas the troponin I protein modulates actin–myosin interaction by inhibiting actomyosin adenosine triphosphate activity. The troponin complex serves as a regulator of contraction via its binding to sarcomere thin filaments.

Several isoforms of troponin T and I exist, and these isoforms are differentially expressed in fetal and adult cardiomyocytes and skeletal muscle cells. Only one isoform is normally expressed in adult cardiomyocytes, and this isoform is down-regulated in adult skeletal muscle cells in parallel with specific upregulation of skeletal muscle isoforms. Thus, troponin T and I in adult cardiac and skeletal muscle tissue are genetically and antigenically distinct. In contrast, troponin C in skeletal muscle is identical to the form found in cardiac muscle cells. The adult forms of troponin I and T found in adult cardiac tissue are thus coined cardiac troponin I and cardiac troponin T.

The molecular weights of cardiac troponin I and T differ: 38 kDa for cardiac troponin T and 24 kDa for the smaller cardiac troponin I molecule. Cardiac troponin I and T are located in two pools in cardiomyocytes. More than 90% of cardiac troponin I and T are found bound to the myofibrillar apparatus, while a small percentage is found in a smaller pool unbound in the cytosol. The free pool of cardiac troponins appears to be released relatively rapidly, i.e. within the first one to two hours following myocardial injury. Clinical observations suggest that cardiac troponin I and T can be released rapidly from this unbound pool, reflected as a brief, transient increase in circulating concentrations. One example of cardiac troponin release in situations other than overt myocardial necrosis includes the transient troponin elevation observed following paroxysmal supraventricular tachycardia. In contrast, the myofibrillar-bound troponin pool is slowly and gradually released into the blood stream after cell necrosis, and cardiac troponins derived from this pool can be detected during a prolonged period, i.e. for several days, after the acute injury.

Although the processes involved in clearance of cardiac troponins are incompletely understood, the circulating half-lives of cardiac troponin I and T have been estimated to be approximately two hours [6]. Various biochemical processes may participate in modification of the structure of circulating troponins, including proteolysis, phosphorylation and oxidation [7]. Renal failure has been associated with increased levels of circulating cardiac troponins, and has commonly been ascribed to decreased renal elimination. However, several lines of evidence suggest that alternative mechanisms that involve increased release may be at least equally important. For instance, in end-stage renal failure patients, renal transplantation does not result in a significant reduction in circulating cardiac troponin concentrations.

Apart from renal failure, data from different populations, suggest that multiple factors, including gender, age and comorbidities (e.g. diabetes mellitus, hypertension and atherosclerotic disease), may affect circulating troponin values, which may be of interest for the interpretation of troponin results in patients suspected of acute HF or ACS [5].

3. Pathophysiology of myocardial ischemia

The current theory of the underlying etiology to the acute coronary syndrome (ACS) is that a plaque may rupture or erode in response to inflammation leading to local occlusive or non-occlusive thrombosis [8]. Depending on the degree of the obstruction, the clinical manifestations of ACS comprise a continuous spectrum of diagnoses that progresses from unstable angina (UA) to non-ST elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI). NSTEMI is distinguished from unstable angina by detection of elevated cardiac troponin levels.

4. Definition of myocardial infarction

Acute myocardial infarction is a condition characterized by biochemical evidence of myocardial necrosis due to ischemia. Cardiomyocyte necrosis is accompanied by a rise and fall of circulating troponin levels. The increased precision in the low analytical range of the hs-cTnT assay contributes to earlier clinical decisions [8]. The universal definition of myocardial infarction in patients presenting with symptoms of cardiac ischemia and/or changes in EKG and/or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality or identification of an intracoronary thrombus by angiography or autopsy [9], requires a rise and fall of troponin, where at least one measurement is above the 99th percentile limit [9]. No consensus has yet been obtained concerning how large such a change has to be in order to be classified as significant. Such calculations must take into account both biological variation and the analytical variation at the actual level.

The diagnosis of myocardial infarction is further subdivided into 5 clinically distinct types. Type 1 is a spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. Type 2 is myocardial infarction secondary to an ischaemic imbalance. Type 3 is myocardial infarction resulting in death when biomarker values are unavailable. Type 4a is myocardial infarction related to percutaneous coronary intervention (PCI). Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values $>5 \times$ 99th percentile URL in patients with normal baseline values. In addition, either [i] symptoms suggestive of myocardial or [ii] new ischaemic ECG changes or new LBBB, or [iii] angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolization, or [iv] imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required. Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL. The latter type is entitled type 4b. Type 5 is myocardial infarction related to coronary artery bypass grafting (CABG) in which myocardial infarction is arbitrarily defined by elevation of cardiac biomarker cardiac biomarker values $>10 \times$ 99th percentile URL in patients with normal baseline cTn values. In addition, either [i] new pathological Q waves or new LBBB, or [ii] angiographic documented new graft or new native coronary artery occlusion, or [iii] imaging evidence of new loss of viable myocardium or new regional wall motion abnormality [8].