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Use of cardiac troponins as strong markers for patients with acute coronary syndrome

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Abstract

Acute myocardial infarction (AMI) is the most important cause of cardiomyocyte necrosis. Cardiac troponin (cTn) T and I are structural proteins unique to the heart and have been used as the preferred cardiac biomarkers in the universal definition of myocardial infarction. Cardiac troponins have demonstrated nearly absolute myocardial tissue specificity and high clinical sensitivity for myocardial ischemia. The recent development of high-sensitivity cardiac troponin (hs-cTn) assays allows detection of very low levels of cTn. The hs-cTn assays have improved the diagnostic accuracy and rapid detection of myocardial infarction. Undetectable hs-cTn rules out AMI with a negative predictive value > 99% on emergency department admission. The diagnosis of acute myocardial damage requires a significant change with serial hs-cTn testing. Current consensus for rapid rule-in proposed a 20% increase within 3 to 6 hours when baseline cTn levels are elevated. In addition, relative increases > 50% above the 99th percentile upper reference limit are found to be the diagnosis of AMI, in the case of negative baseline value. Besides relative change, the absolute values of hs-cTn at emergency department presentation in patients with suspected AMI should be considered as important criteria in the differential diagnosis of the cause of cardiomyocyte damage. Cardiac troponins provide both diagnostic and prognostic information in the setting of acute coronary syndrome (ACS). Elevation of cTn in the absence of ACS should prompt an evaluation for non-thrombotic mechanism of increased cTn levels and direct management at the underlying cause.

Keyword: *acute myocardial infarction, myocardial ischemia, cardiac biomarkers, cardiac troponin, high sensitivity troponin*

บทคัดย่อ

ภาวะกล้ามเนื้อหัวใจตายเฉียบพลัน (acute myocardial infarction, AMI) คือสาเหตุที่สำคัญของการตายของกล้ามเนื้อหัวใจ โทรโปนินหัวใจ (cTn) ชนิด T และ I เป็นโปรตีนที่มีความเป็นเอกลักษณ์ในหัวใจ และนิยมใช้เป็นตัวตรวจสอบกันอย่างแพร่หลายในการตรวจภาวะกล้ามเนื้อหัวใจตาย โดย cTn มีความจำเพาะต่อกล้ามเนื้อหัวใจสูง และมีความไวสูงในการตรวจภาวะหัวใจขาดเลือด เมื่อเร็วๆนี้ได้มีการพัฒนาการตรวจหา cTn ที่มีความไวสูงซึ่งสามารถตรวจหาปริมาณ cTn ในระดับต่ำได้ วิธีการตรวจหา cTn ที่มีความไวสูง (hs-cTn assay) มีการพัฒนาในเรื่องของความถูกต้องและความไวในการตรวจภาวะกล้ามเนื้อหัวใจตาย การตรวจไม่พบระดับของ cTn ทำให้คัดแยกคนไข้ที่ไม่อยู่ในภาวะ AMI ได้ ซึ่งให้ความเชื่อถือได้มากกว่าร้อยละ 99 การวินิจฉัยคนไข้กล้ามเนื้อหัวใจตายเฉียบพลันในคนไข้แผนกฉุกเฉิน ต้องการค่าที่มีการเปลี่ยนแปลงของ cTn อย่างมีนัยสำคัญเป็นระยะๆ วิธีการที่เป็นที่ยอมรับกันในการตรวจ AMI อย่างรวดเร็วคือ ระดับ cTn ที่เพิ่มขึ้นอย่างน้อย 20% ภายใน 3 หรือ 6 ชั่วโมง เมื่อระดับ cTn สูงกว่าค่าที่ถูกกำหนดในตอนเริ่มมีอาการ ถ้าในกรณีของระดับ cTn ต่ำกว่าค่าที่กำหนดในตอนเริ่มมีอาการ การเพิ่มขึ้นมากกว่า 50% เหนือระดับ 99th เปอร์เซ็นต์ไทล์ของค่าอ้างอิงปกติก็เพียงพอที่จะวินิจฉัยคนไข้ AMI นอกจากดูการเปลี่ยนแปลงระดับ cTn แล้ว การวัดค่า cTn ที่เป็นระดับตัวเลขก็มีความสำคัญในคนไข้ในแผนกฉุกเฉินที่สงสัยว่ามี AMI ซึ่งวิธีการนี้ถูกพิจารณาว่าเป็นเกณฑ์ที่สำคัญในการแยกการวินิจฉัยสาเหตุของการบาดเจ็บกล้ามเนื้อหัวใจ cTn จึงให้ทั้งการวินิจฉัย และการทำนายกลุ่มของอาการโคโรนารีฉุกเฉิน (acute coronary syndrome, ACS) ระดับที่เพิ่มขึ้นของ cTn ในคนไข้ที่ไม่ปรากฏอาการ ACS ควรมีการพิจารณาเกี่ยวกับเรื่องของภาวะที่ไม่มีหลอดเลือดอุดตันและ จัดการโดยตรงที่สาเหตุพื้นฐาน

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1. Introduction

The recent guidelines in the third universal definition of myocardial infarction are a rise and/or fall of cardiac biomarker values combined with either clinical symptoms of ischemia, electrocardiographic changes (Thygesen et al., 2012a). Myocardial infarction (MI) is the process of myocardial cell death caused by ischemia, or the perfusion imbalance between supply and demand within the coronary arteries as a result of an acute thrombotic process (Daubert & Jeremias, 2010). Acute coronary syndrome (ACS)

refers to the group of clinical symptoms of myocardial ischemia. ACS occurs from the erosion and rupture of a fibrous cap containing a lipid-rich atherosclerotic plaque that precipitates thrombus formation within the coronary artery (Hasson, 2005).

Patients presenting with clinical symptoms of ischemia without evidence of myocardial necrosis detected by cardiac biomarkers are considered to have unstable angina (Anderson et al., 2007). Patients having positive cardiac biomarkers and presenting with ischemic symptoms, with or without electrocardiographic ST-segment depression or T wave inversion, are considered to have non-ST elevation myocardial infarction (NSTEMI). Further, patients presenting with new ST-segment elevation on the electrocardiogram (ECG) are diagnosed to ST-elevation myocardial infarction (STEMI) (Anderson et al., 2007). Myocardial infarctions (MIs) are classified into 5 types by the etiology of the ischemia (Thygesen et al., 2007). Type I MI is caused by a primary coronary event such as the spontaneous rupture of an atherosclerotic plaque or dissection within the coronary artery resulting in STEMI or NSTEMI. Type II MI associated with non-thrombotic conditions causing either increased oxygen demand or decreased oxygen demand supply such as in coronary artery spasm, coronary embolism, anemia, arrhythmia, hypertension, or hypotension, leading to myocardial ischemia. Type III MI is due to sudden unexpected cardiac death, including cardiac arrest often combined with symptoms of myocardial ischemia. Type IV MI has two subtypes; a) MI associated with percutaneous coronary intervention, b) MI associated with stent thrombosis as documented by angiography or autopsy. Type V MI is MI that associated with coronary artery bypass grafting.

The diagnosis of acute myocardial infarction (AMI) requires the rise and/or fall of cardiac biomarkers as mention above. Use of the classical cardiac biomarkers of aspartate aminotransferase (AST) lactate dehydrogenase (LDH) isozymes and creatine kinase MB (CK-MB) has been reviewed (Apple, Jesse, Newby, Wu, & Christenson, 2007; Jaffe, Babuin, & Apple, 2006; Vichaibun, 2004). These enzymes have limitations in terms of their specificity and sensitivity. Smooth muscle CK-MB may also appear in the blood with pregnancy and parturition (O'Brien et al., 2006). In addition, CK-MB also constitutes 1%-3% of the creatine kinase in skeletal muscle and is present in a small fraction in other organs such as the small bowel, uterus, prostate and diaphragm (Robert & Sobel, 1973). Among many cardiac biomarkers, cardiac troponin (cTn) has demonstrated nearly absolute myocardial tissue specific and high sensitivity for myocardial ischemia (Morrow et al., 2007).

Cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are regulatory proteins that control the calcium-mediated interaction of actin and myosin, and specific for heart muscle. Detection of cTn in peripheral blood indicates cardiomyocyte damage (Twerenbold, Jaffe, Reichlin, Reiter, & Mueller, 2012). As AMI is the most important cause of myocardial cell death, cTns are very important biomarkers for diagnosis of AMI. This review describes the role of cTn for evaluating patients with suspected AMI and give information on how to clinically apply cTn.

2. Cardiac troponin (cTn)

The troponin complex regulates the contraction of striated muscle. Troponin is composed of three different components, which are troponins C, I and T. Troponin was found to be separated into an activating factor and an inhibitory factor (Hartshorne & Mueller, 1968). Troponin C binds to calcium ion and troponin T binds to tropomyosin, thereby attaching the troponin complex to the thin filament. Troponin I binds to actin and decreases troponin C affinity for calcium, thus inhibiting actin-myosin interactions (Antman, 2002). Among three subunits (I, T and C), only cTnI and cTnT are expressed as cardiac muscle specific isoforms and are encoded by different genes in striated muscle (Parmacek & Solaro, 2004). Whereas, the genes that code for the skeletal and cardiac isoforms of troponin C are identical, thus there are no differences in structure between them. Assays that are based on high affinity antibodies and are specific for cTnT and cTnI are available.

There are three different isoforms of troponin T encoded by individual genes in cardiac muscle, fast-twitch skeletal muscle, and slow-switch skeletal muscle. There is sequence homology between cTnT and skeletal muscle troponin T with a difference of 125 amino acid residues between fast-twitch skeletal muscle and cTnT which 56.6% shows homology. There is a 120 residue difference between slow-twitch

skeletal muscle and cTnT (58.3% homology) (Gaze & Collinson, 2008). In the case of cTnI, human cTnI presents in cardiac muscle as a single isoform of 209 amino acid residues, with a molecular weight of approximately 23-24 KDa. There are three isoforms of cTnI, one is produced in cardiac muscle (cTnI), another in slow-twitch skeletal muscle, the other in fast-twitch skeletal muscle (Gaze & Collinson, 2008). The overlap in sequences between cTnI and slow-twitch skeletal muscle is approximately 40% and less for fast-twitch skeletal muscle. From the information mentioned above, thus cTnT and cTnI assays have been developed by many manufacturers for detecting cardiomyocyte damage.

3. The development of cardiac troponin assays

In previous reports, over 30% of patients with AMI do not have specific symptoms and up to 70% of them may have normal or non-diagnostic ECG recoding (Pope et al., 2000). The only use of ECG is often insufficient to diagnosis AMI. ST deviation is non-specific and is observed in other conditions such as early repolarization patterns, acute pericarditis, left ventricular hypertrophy, left bundle brunch block, hyperkalaemia and the Brugada syndrome (Bassand, Hamm, Ardissino, Boersma, & Budaj, 2007; Pope et al., 2000; Thygesen et al., 2007; Wang, Asinger, & Marriott, 2003). Thus, cardiac troponins are helpful in clinical practice in identifying patients with acute coronary syndrome.

A limitation of the earlier generations of cTn assays is that they cannot be detected during the first hours of AMI. The diagnosis of AMI may require prolonged monitoring over 6-12 hours and serial blood sampling because there often is substantial ambiguity at the time of onset of any given ischemic event (Macrae et al., 2006). The increasing morbidity and potentially mortality in AMI may occur from delaying in 'ruling in' AMI. Delaying in 'ruling out' AMI contributes to overcrowding in the emergency department (Twerenbold et al., 2012). Conventional cTn assays have been improved with respect to analytical performance. Assays with total imprecision at the 99th percentile $\leq$ 10% and measurable normal values below the 99th percentile in at least 90% of healthy individuals were classified as high-sensitive assay (Apple, 2009). Assays from several manufacturers are available for cTnI whereas, cTnT assays are still only produced by one manufacturer (Roche Diagnostics) that is clearly an advantage given the standardization issue associated with cTnI assays (Apple & Collinson, 2012).

Over the years the analytical sensitivity of cTn assays has been continuously improved and more recently a new generation of cTn assays has been introduced into clinical practice. There are several new generations of assays for cTnT since the first generation used bovine cTnT as the reference material to the fourth generation which used a fragment antigen-binding (FAB) of two cTnT-specific mouse monoclonal antibodies in a sandwich format (Giannitsis et al., 2010). The fourth generation cTnT assay is considered the standard assay for diagnosis AMI (Thygesen et al., 2012b). However, the fourth generation cTnT assay lacks adequate precision. The new high sensitive cTnT (hs-cTnT) assay is modified from the fourth generation cTnT assay (Giannitsis et al., 2010). The detection antibody was genetically re-engineered, the constant C1 region in the monoclonal mouse FAB fragment is replaced by a human IgG C1 region, leading to a mouse-human chimeric detection antibody (Giannitsis et al., 2010). This replacement was to reduce the susceptibility to interference by heterophilic antibodies. From these modifications, hs-cTnT assay were significantly improved. The limit of detection (LoD) was 0.003 ng/mL (3ng/L) and the 99th percentile cut-off point was 0.014 ng/mL (14 ng/L) as well as the coefficient of variation (CV) was 10% at 0.013 ng/mL (13 ng/L) (Giannitsis et al., 2010). The hs-cTnT assay can detect more subtle elevations indicative of cardiac injury because of lower LoD and an increased precision.

The universal definition recommends the use of a more sensitive troponin assay with a CV of 10% at the diagnostic cut-off concentration representing the 99th percentile of a reference population as mention above. The recently developed hs-cTnT assay is compatible with the criterion by having a lower CV and a lower LoD (Giannitsis et al., 2010). Aldous, Richards, Cullen, Troughton and Than (2012) reported that patients with chest pain who did not have ST segment elevation, the hs-TnT assay at a cut-off point of 99th percentile (0.014 ng/mL) was highly sensitive for the diagnosis of AMI two hours after presentation compared with the standard assay. The improvement of early diagnosis of AMI in

patients is important because of the opportunity to extend early treatment options to all patients with AMI (Reichlin et al., 2009).

The hs-TnI assay has also been improved the diagnostic ability in patients with AMI (Reichlin et al., 2009). Second generation hs-TnI assay has been used for determination of the diagnostic accuracy for AMI. The clinical sensitivity and specificity of the blood sample from patients with ischemic symptoms suggestive of ACS was 69% and 78% respectively, which improved to 94% and 81% respectively after 6 hours presentation using hs-TnI assay (Apple, Pearce, Smith, Kaczmarek, & Murakami, 2009). Keller et al. (2009) demonstrated a different hs-TnI assay and found the clinical sensitivity of 90.7% at presentation with specificity of 90.2% and positive predictive value of 87%. In addition, Reichlin et al. (2009) also demonstrated the superior diagnostic precision of multiple hs-TnT and hs-TnI assays for the detecting of AMI as compared to a standard conventional troponin assay, especially in patients presenting with symptoms onset within 3 hours. Several studies of hs-Tn assays have demonstrated a high level of accuracy for the early diagnosis of AMI including improvement of sensitivity. The hs-Tn assays became widely available and cut-offs at the 99th percentile are consistently employed.

4. Acute myocardial infarction (AMI) with hs-cTn assays and clinical application of the assays

The rapid and reliable diagnosis of AMI is very important for making decision about appropriate therapy. The hs-cTn assays allow the precise quantification of cardiomyocyte necrosis. Twerenbold et al. (2012) reported that AMI was not the only cause of myocyte necrosis, it was key to consider the absolute level as well as the change in cTn within 1-3 hours as important criteria in the differential diagnosis of the cause of cardiomyocyte necrosis (Figure 1). The higher the absolute value of hs-cTn at emergency department presentation in patients with suspected AMI leads to the higher the probability of AMI (de Filippi et al., 2010; de Lemos et al., 2010; Thygesen et al., 2010). The differential diagnosis of a small amount of myocardial injury resulting in mild elevation of cTn is broad and includes acute and chronic disorders. The cTn has been reported as a quantitative variable. Detectable levels become essential for interpretation. The larger the rise in the cTn within the first hour in the emergency department leads to the higher in the probability that is caused by AMI (Twerenbold et al., 2012). In addition, serial changes documented by a second measurement help to differentiate acute cardiac disorders (showing a rise and/or fall) from chronic cardiac disease which usually shows constant cTn levels. There is debate whether absolute or relative changes best separate acute from chronic cTn elevations, as well as AMI from other cause of cTn elevation. White (2012) described the use of a criterion of 50% based on the biological variation of another hs-Tnc assay. Reichlin et al. (2011) reported the area under the receiver operating characteristic (ROC) curve for diagnosis of AMI was significantly higher for 2 hours absolute comparison with 2 hours relative cTn changes. The ROC curve-derived cut-off value for 2 hours absolute change was 0.007 µg/L for hs-cTnT and 0.02 µg/L for hs-cTnI. From these data, absolute changes were superior to relative changes in patients with both low and elevated baseline cTn levels.

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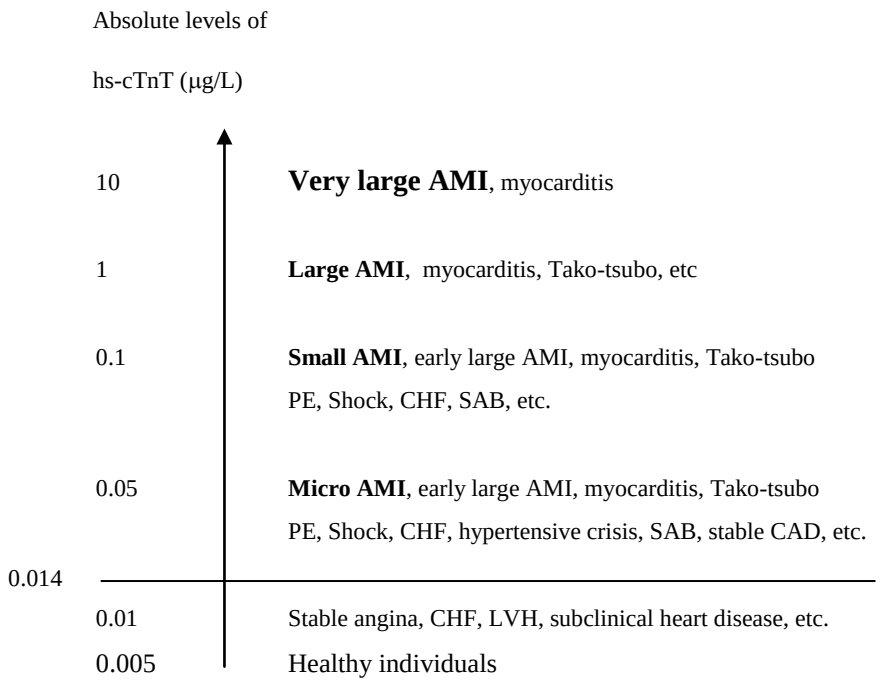

Figure 1 The differential diagnosis of hs-cTnT levels is highly dependent on the absolute level. CHF, Chronic Heart Failure; CAD, Coronary Artery Disease; LVH, Left Ventricular Hypertrophy; PE, Pulmonary Embolism; SAB, *Staphylococcus aureus* bacteremia (From: Twerenbold et al., 2012)

Guidelines recommend the use of the upper reference limit (URL) as medical decision limit even when it cannot be measured with a CV of < 10% (Jaffe, Apple, Morrow, Lindahl, & Katus, 2010). Therefore, early sensitivities must be compared by using the 99th percentile URL as a medical decision limit for standard and hs-cTn assays. Bonaca et al. (2010) reported that patients presenting with ACS, minor increases in cTn at 99th percentile URL demonstrated a 3-fold higher risk of death and recurrent myocardial infarction in short-term follow-up at 30 days as well as also in long-term follow-up, with a 2.7-fold higher risk at 12 months. There are reports on sex-specific URLs which are higher for men than women for hs-cTn assays including the already commercially available hs-cTnT and hs-cTnI assay from Roche and Abbott Diagnostics (Apple & Collinson, 2012; Apple, Ler, & Murakami, 2012; Saenger et al., 2011; Todd et al., 2007; Thygesen et al. 2012b). The use of hs-cTn assays is more important to evaluate cTn kinetics with serial testing in the clinical evaluation of chest pain patients (Hammarsten et al., 2012; Hamn et al., 2011). Blood sampling in patients with suspicion of AMI should be performed on admission and 3 hours after later. In case of 3 hours unchanged cTn level, The measurement of hs-cTn should be repeated 6 hours after admission in patients of whom the clinical suspicion of AMI is still high (Thygesen et al., 2012b). There is the use of serial sampling over a short period of time in the diagnostic approach to AMI assessment in order to overcome the limitation of decreased sensitivity in the hs-cTn assays. However, there is evidence suggesting that patients with an AMI can be reliably identified within 3 hours after admission with up to 100% sensitivity and up to 100% negative predictive value using a hs-cTn assay. As a result, observation time may be reduced for the rule-out of AMI (Filusch, Giannitsis, Katus, & Meyer, 2010; Mueller et al., 2012; Reiter et al., 2011). According to, the recommendation of using hs-cTnT for diagnosis of AMI however, it has been

suggested that some patients require at least 6 hours for a diagnosis (Hammarsten et al., 2012).

Figure 2 shows algorithm for the rapid evaluation of clinically suspected AMI with hs-cTn testing (Thygesen et al., 2012b; White, 2010). It is important to note that hs-cTn changes over a 3-6 hour period in patients presenting with subacute AMI may be < 20%. The evaluation for rapid rule in proposes a 20% increase within 3 or 6 hours when baseline cTn levels are elevated. For values below or close to the 99th percentile URL, increases above the 99th percentile URL with relative increases > 50% within 3 or 6 hours, or absolute increases for hs-cTnT of > 7 ng/L within 2 hours suggest a rising pattern and optimize the overall accuracy of AMI diagnosis (Reichlin et al., 2011; Thygesen et al., 2012b). Previous studies reported that evaluating serial changes using the hs-cTnT assay in pre-selected chest pain unit patients, suggested that increases above the 99th percentile URL with relative increases of > 250% over a 3 hours period in patients with baseline values < URL and increases > 50% with modestly increased baseline values optimize specificity for the diagnosis of AMI (Keller et al., 2011). In addition, Reichlin et al. (2012) proposed a simple algorithm that allowed a reliable rule-out and rule-in within 1 hour for the majority of these patients using baseline hs-cTnT values in combination with absolute δ-changes ($\delta = C_{max}-C_{baseline}$). However, the time interval for sampling is essential for discriminating of acute from chronic reasons for increased cTn.

The application of hs-cTn tests and the 99th percentile as the decision limit for AMI lead to a substantial increase in the detection of patients with slightly elevated cTn levels. Some groups of patients, such as elderly individuals and diabetic patients, may have increased baseline cTn concentrations because heart disease is commonly found in these patient groups (de Filippi et al., 2010; de Lemos et al., 2010). Mueller et al. (2012) suggested that it might be advisable to use a higher cut-point (about three-fold the 99th percentile URL) as a decision limit for AMI in patients with > 70-year-old. Undetectable hs-cTn ruled out ACS with a negative predictive value > 99% on emergency department admission (Hammere-Lercher et al., 2013).

5. Conditions with cTn elevation in patients not having an AMI

It is important to note that an increased hs-cTn concentration alone is not sufficient for making the diagnosis of AMI (Thygensen et al., 2012b). The elevation of hs-cTn must be interpreted in relation to the clinical presentation. An increase in cTn values can be associated with many diseases in the absence of ACS. These elevations derive from pathogenic mechanisms other than thrombotic coronary artery occlusion, which require treatment of the underlying cause rather than the administration of antithrombotic and antiplatelet agents (Jeremias, & Gibson, 2005). Elevations above the 99th percentile URL with hs-cTn assay are common in patients with structural heart disease (Table 1) including patients with stable coronary artery disease (Korosoglou et al., 2011; Ndrepepa et al., 2011). In addition, false-positive troponin elevations can occur from hemolysis and assay interference with heterophilic antibodies (Tate, 2008). However, non-specific blocking antibodies have been added to modern assays to eliminate interference resulting in preventing false-positive (Shayanfar, Bestmann, Schulthess, & Hersberger, 2008). The small increase of hs-cTn levels can be detected in a wide range of non-ischemic clinical condition, acute and chronic, cardiac and extra-cardiac, such as pericarditis, myocarditis Takotsubo cardiomyopathy, tachyarrhythmias, heart failure, pulmonary embolism, stroke and septic (Table 1) (Agewall, Giannitsis, Jernberg, & Katus, 2011; Hamn, Giannitsis, & Katus, 2002).

The cTn elevation is frequently observed in patients presenting with end-stage renal disease, even in the absence of manifestations of myocardial ischemia (Apple, Murakami, Pearce, & Herzog, 2002). However, the mechanisms of cTn elevation in patients with renal diseases are also unresolved. This may be the result of small areas of clinically silent myocardial necrosis, in addition, other causes, such as increased left ventricular mass and impaired troponin excretion have also been proposed (Antman, Grudzien, Mitchell, & Sacks, 1997; Diris et al., 2004; Ooi, Zimmerman, Graham, & Wells, 2001; Sharma et al., 2006). Elevated cTn has also been observed in patients with hypertension which is detectable in 78% of participants. This may occur from apoptosis of cardiomyocytes which play an important role in compensatory hypertrophy due to hypertension (Sato, Yamamoto, & Sawa, 2011). There is a report about patients with diabetes mellitus (DM),

the alterations in glucose metabolism which shift to fatty acid metabolism may occur during increased oxidative stress and may be an important mechanism underlying myocardial cell injury and leading to cTn elevation (Everett et al., 2001). Heart failure can lead to cTn release through both myocardial strain and myocyte death independent of myocardial ischemia. Myocardial strain is a result of biventricular volume and pressure overload, causing excessive wall tension with resultant myofibrillary damage (Horwich, Patel, MacLellan, & Fonarow, 2003). Moreover, Kusumoto et al. (2012) reported that in patients with heart failure, even in the absence of ACS, the elevation of hs-cTn levels was useful for the evaluation of heart failure severity, reflecting cardiac dysfunction evaluated by echocardiography and natriuretic peptides. The level of cTnI elevation has been shown to directly correlate with the degree of myocardial inflammation. Focal inflammatory disorders including myocarditis and immune-mediated reactions after heart transplantation have also been associated with cTn elevation (Smith, Ladenson, Mason, & Jaffe, 1997).

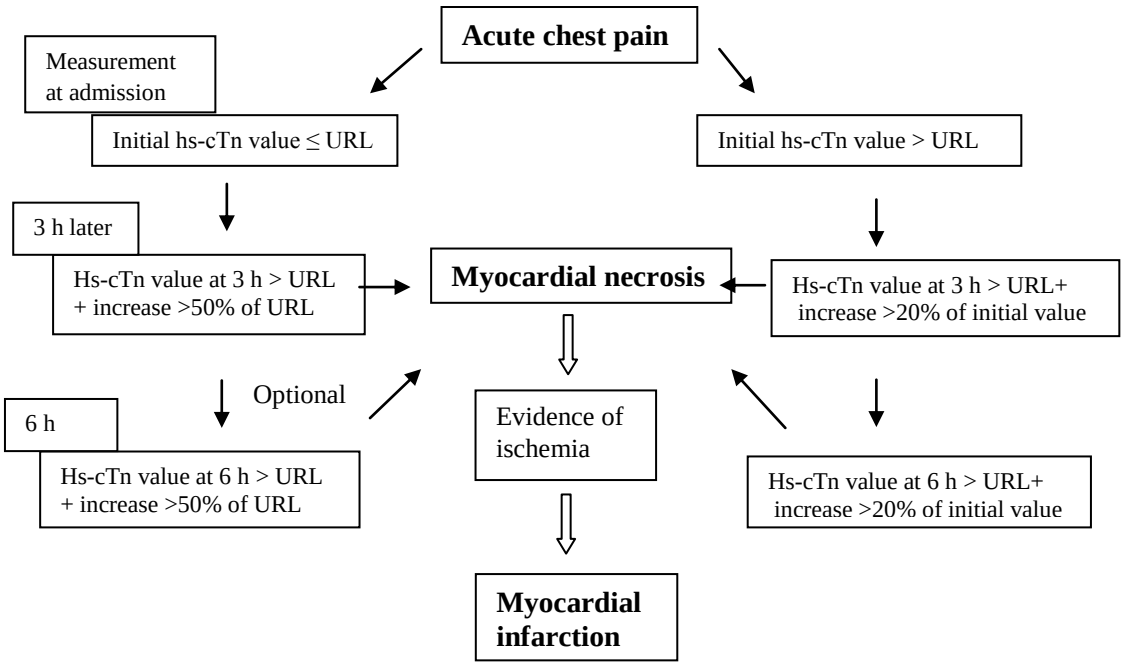

Figure 2 Algorithm for the rapid evaluation of clinically suspected AMI with hs-cTn testing. (From: Mueller, Vafaie, Biener, Giannitsis, & Katus, 2013)

Table 1 Causes of cardiac troponin elevation in the absence of ACS.

Damage related to supply/demand imbalance of myocardial ischemia
Tachy-or bradyarrhythmias
Aortic dissection and severe aortic valve disease
Cardiogenic, hypovolemic or septic shock
Hypertrophic cardiomyopathy
Severe respiratory failure
Severe anemia
Hypertension with or without LVH
Coronary embolism or vasculitis, e.g. systemic lupus erythematosus,
Kawasaki syndrome
Coronary spasm
Coronary endothelial dysfunction without significant CAD, e.g. cocaine abuse
Damage not due to myocardial ischemia
Cardiac contusion
Cardiac incision with surgery
Radiofrequency or cryoablation therapy
Pacing or defibrillator shocks
Rhabdomyolysis with cardiac involvement
Myocarditis
Cardiotoxic agents, e.g. anthracyclines, herceptin, carbon monoxide poisoning
Multifactorial causes of myocardial damage
Heart failure
Takotsubo cardiomyopathy
Severe pulmonary embolism or pulmonary hypertension
Renal failure
Severe acute neurological disease, e.g. stroke, trauma
Infiltrative disease, e.g. amyloidosis, sarcoidosis
Extreme exertion
Sepsis

ACS, acute coronary syndrome; LVH, left ventricular hypertrophy; CAD, coronary artery disease. (From: Marini, Cardillo, Caroli, Sonnino, & Biasucci, 2013)

Systemic inflammation processes, including sepsis can result in increased oxygen consumption, decreased perfusion pressure, extrinsic myocardial depression and subsequent troponin release (Ammann, Fehr, Minder, Gunter, & Bertel, 2001). As a result, myocyte damage may not be permanent, and thus cell necrosis does not occur. This observation is supported by evidence that myocardial depression during sepsis is a fully reversible process in most surviving patients (Parrillo, 1993). In addition, cTn elevation in patients with acute pulmonary embolism varies from 16% to 50% and elevated levels are associated with a significant increase in mortality (Aksay, Yamturoli, & Kiyan, 2007; Becattini, Vedovati, & Aronow, 2007; Yalamanchili et al., 2004). The detectable cTn patiens without AMI may reflect a more malignant process of accelerated cell turnover caused by exaggerated catecholamine release, increased ventricular load, increased oxygen demand or decreased supply, inflammatory process, hypoxia and subendocardial ischemia (Agewell et al., 2011). The detectable cTn can also be observed in healthy persons with extreme exertion (Shave et al., 2010). Sabatine, Morrow, de Lemos, Jarolim, and Braunwald (2009) demonstrated that the cTn within the cytosol can be released as an intact protein through increased membrane permeability, in the case of reversible injury to the myocyte without necrosis.

It is important to note that clinical assessment, serial testing, and thoughtful differentiation are required to separate AMI from other acute and chronic disorders which are also associated with low-level myocardial injury (Agewell et al., 2011). The presence of troponin elevation in a multitude of non-thrombotic disease states has been associated with increased short- and long-term mortality. Patients with elevated cTn levels, in case of 'rule-out' AMI, then a thorough diagnostic evaluation for the non-thrombotic etiology of the troponin elevation should be performed and subsequent management should be directed at treating the underlying disorders. In addition, Irfan et al. (2012) demonstrated that patients with chest pain in the absence of cardiac reason, presenting with hs-cTnT

levels > 14 ng/L were at increased risk for all-cause mortality during follow-up. This information indicates that the number of indications for testing of cTn in settings other than ACS will increase and hs-cTn measurement should always be considered for risk stratification not only in ACS but also in non-ACS cases.

6. Conclusions

AMI is the most important cause of myocardial cell death with an ongoing increase in incidence. Myocardial infarctions are classified by the etiology of the ischemia. The early detection of AMI is crucial to the preservation of cardiac function. Troponin T and troponin I are presented in cardiac and skeletal muscles, but are encoded by different genes in the two types of muscle, yielding proteins that are immunologically distinct. Both cTnT and cTnI have high sensitivity and specificity for acute coronary syndrome and are essential for the diagnosis of AMI, whereas the use of other biomarkers such as LDH and CK-MB are substantially limited due to lack of tissue specificity and sensitivity. As a result, the development of cTn assays is essential for the diagnosis of AMI. The gain in sensitivity may be particularly important in patients with a short duration from the onset of symptoms to admission. The hs-cTn assays and the use of the 99th percentile as the decision limit for AMI will lead to a substantial increase in the detection of patients with slightly elevated cTn. AMI is not the only cause of cardiomyocyte damage, the absolute level of hs-cTn assay and the changes in cTn within 3-6 hours after presentation are important criteria in the differential diagnosis of the cause of cardiomyocyte damage.

In patients with suspected AMI, the LoD of hs-assays is a useful rule-out decision limit with a negative predictive value > 99% even on emergency department admission. The diagnosis of AMI required a significant change with serial testing. At low cTn baseline concentrations (around the 99th percentile URL) the change in serial testing in order to be clinically significant requires there to be a marked (>50%) increase together with an increase above the URL. In the case of borderline increased baseline values (>URL), a minimum change of > 20% in follow-up testing is required. The hs-cTn assays provide diagnostic and prognostic information in patients with ACS. Elevated troponin levels in the absence of ACS should prompt an evaluation for a non-thrombotic mechanism of troponin increase. In addition to AMI detection, the use of hs-cTn assays allow the detection of cardiomyocyte damage in the stable phase of established cardiac disease like coronary artery disease or heart failure, or even to identify in the patients with either silent or clinically underestimated cardiac disease and therefore high risk of death.

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