Diagnostic efficacy of cardiac troponin in post-mortem examination of acute myocardial infarction

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Abstract

Major challenges for forensic experts include selection of best effective diagnostic tests in the time sensitive identification of cause of death to avoid delay in postmortem examination cases. Sudden cardiac death due to acute myocardial infarction constitutes a significant portion of the autopsies that are conducted by forensic pathologists. Lack of specificity of clinical and conventional markers causes misdiagnosis and prevents or delays in the detection. Conventional biochemical markers like creatine kinase (CK), myoglobin, and lactate dehydrogenase is no longer a best choice in the detection, because of their low specificity to cardiac injury. Recent reports indicate cardiac troponin as an extremely sensitive biochemical marker which can detect even microscopic zones of myocardial necrosis. We herein, review cardiac troponin as a biochemical marker in autopsy cases of AMI and its impact on postmortem management that will lead to guidance for early detection with quick and reliable diagnostics methods.

Keywords: Biochemical markers; acute myocardial infarction; troponins.

Introduction

AMI is the world's leading cause of morbidity and mortality[1]. Sudden cardiac death due to acute myocardial infarction constitutes a significant portion of the autopsies that are conducted by forensic pathologists[1, 2]. It is a disease with a high rate of misdiagnosis because of less sensitive conventional markers which causes unnecessary delay in the diagnosis process in postmortem examination cases[2,3]. Due to limitations of histopathological findings, it is necessary to establish diagnostic utility of different biochemical cardiac markers in biological fluids for postmortem diagnosis of MI. Since, in an estimate, infarction is not apparent on gross examination until 12-24 hrs and light microscopic (H&E) changes are not apparent before 4-6 hrs[4]. Historically, coronary artery disease assessment has been mainly binary, using WHO criteria of symptoms, electrocardiography, and biochemical markers[3].

Because of these limitations it is necessary to establish diagnostic utility of different biochemical cardiac markers in biological fluids for postmortem diagnosis of MI. Since, myocardial infarction is accompanied by the release of structural proteins and other intracellular macromolecules into the cardiac interstitium[5]. CK, myoglobin, lactate

dehydrogenase, and aspartate aminotransferase were some of the classical used biochemical markers for autopsy cases[6]. But, because of low specificity of these conventional biomarkers for cardiac injury search for more specific alternative biomarkers recently gained momentum.

Recently, the cardiac markers troponin I (cTnI) and troponin T (cTnT) have become available. Troponin I, C and T form a complex that regulates the calcium-modulated interaction of actin and myosin in striated muscle[7]. Cardiac troponin I (CTn I) is more specific marker, without any cross-reactivity and never has been found in a healthy population. Also, its sensitivity allows detection of even microinfarction and acute myocardial infarction much earlier after the onset of ischemia by using a rapid one-step assay in body fluids in autopsy cases[8-10].

Biomarkers of myocardial infarction with reference to Cardiac Troponin:

Biomarkers of myocardial infarction incorporate cardiac troponin I and T (cTnI and cTnT), CK, myoglobin, and lactate dehydrogenase. Absolute CK, lactate dehydrogenase, and aspartate aminotransferase ought to never again be utilized for the determination of MI on the grounds that they have low specificity for cardiovascular damage and more particular option biomarkers of necrosis are accessible. Myoglobin offers confinements with these markers because of its high concentration in skeletal muscle. Be that as it may, in light of its little molecular size and subsequent fast rise in the setting of myocardial necrosis, it has held esteem as an early marker of MI. In any case, this potential advantage of myoglobin may be decreased with utilization of enhanced affectability of more up to date troponin measures[11]. Albeit total CK is a sensitive marker of myocardial damage, it has poor specificity because of its high concentration in skeletal muscle. Due to its more concentration in skeletal myocytes, the MB isoenzyme of CK offers an enhanced affectability and specificity contrasted to total CK. in any case, CK-MB constitutes 1%–3% of the CK in skeletal muscle, and is exhibit in minor amounts in intestine, diaphragm, uterus, and prostate. Thusly, the specificity of CK-MB may be disabled in the setting of significant damage to these organs, particularly skeletal muscle. CK-MB subforms might likewise be utilized as an early rising indicator of MI[12] yet are not utilized today. The analysis of intense MI obliges discoveries of a common rise and/or fall of a biomarker, in conjunction with clinical proof. Since recognition of intense MI is imperative to prognosis and treatment, measurement of biomarkers of necrosis is shown in all patients with suspected AC. The creatine kinase-MB isoenzyme (CK-MB) has been a benchmark for biochemical markers, but diagnostic utility of this cardiac marker for post-mortem diagnosis of MI has not been fully established, as it is not specific for myocardium and in some cases negative predictive value obtained. Data are lacking on the new markers, yet using all of conventional biochemical marker is inappropriate and expensive.

Subsequently, forensic medicine needs more sensitive biochemical markers for the post-mortem diagnosis of acute myocardial infarction. On the premise of enhanced affectability and predominant tissue-specificity contrasted and the other accessible biomarkers of necrosis, cardiac troponin is the favored biomarker for the recognition of myocardial infarction. Rather than CK, cTnI and cTnT have isoforms that are one of a kind to heart myocytes and may be measured by assay utilizing monoclonal antibodies particular to epitopes of the cardiac form[13-15]. The advantage of cardiac troponin over different biomarkers of necrosis has been firmly established in clinical studies. Testing for cardiac troponin is associated with less false-positive results in the setting of accompanying skeletal muscle injury[15-17], furthermore gives unrivaled segregation of myocardial damage when the concentration of CK-MB is normal or minimally increased[15, 18, 19].

Additionally, the relationship between increased concentration of cardiac troponin and a higher risk of repetitive cardiac occasions in patients with typical serum concentration of CK-MB has affirmed the clinical pertinence of recognizing circulating troponin[20-22] . The aim of this review is discuss the sensitivities and specificities of cardiac troponin T (cTnT) and heart troponin I (cTnI) in serum and pericardial liquid for the post-mortem diagnosis of acute myocardial necrosis (AMI). Recently, cardiac troponin (cTnI or cTnT) has proven to be nearly absolute myocardial tissue specificity, thereby reflecting even microscopic zones of myocardial necrosis. Therefore, quick and reliable diagnostics methods for troponin detection may optimize the use of the time and resources of the autopsy pathologist and also the chances of misdiagnosis. Role of troponin in medicolegal autopsy cases and its future prospects in order for its validation and

implementation in subjects who had died from myocardial infarction will be conferred in depth.

Ischemic heart disease is the leading cause of death in industrialized countries. Sudden death as a result of cardiac damage is a common cause of acute death in forensic pathology[23-26]. Although it is not difficult to detect typical myocardial lesions using conventional pathological methods, however quantitative evaluation of the severity behind myocardial damage is not an easy task. To meet this requirement a reliable interpretation through systematic investigations is necessary which can be achieved by using a wide spectrum of pathophysiological markers. Among these, measurement of biochemical marker has become an important ancillary procedure in determining the cause and time of death[27-29]. A detail study in the distribution pattern of biochemical markers in different body fluids is of great implication in post-mortem diagnosis, since their distribution depends upon the location of tissue damage and release kinetics. Recently, application of biochemical procedures in forensic pathology is gaining momentum, because of sudden death associated with myocardial and ischemic heart disease, which is often difficult to determine morphologically[30-32]. In forensic medicine, there is an urgent need for more sensitive biochemical markers in post-mortem diagnosis of acute myocardial infarction (AMI). Estimation from conventional biochemical markers from serum can only suggests or suspect the associated lesion but it can't be confirmed[33-38]. In such situation biochemical measurement from pericardial fluid is the most important choice in biochemical tests. A comprehensive study involving a spectrum of traumatic death suggests rise in the level of troponins in blood serum and pericardial fluids from various cause of death including hyperthermia, methamphetamine abuse and carbon monoxide poisoning.

In normal clinical practice, a few regular biochemical markers are for the most part utilized for the determination of myocardial infarction (MI) all the more especially the MB isoenzyme of creatine kinase (MBCK) and myoglobin. On the other hand, the specificity of both markers is questionable, since increase in the estimation of MBCK and myoglobin might likewise happen in instances of skeletal muscle damage even without perceivable heart damage[39-41]. In the recent years, measuring cardiac troponins in serum has turned into an entrenched technique for diagnosing intense ischemic myocardial infarction and hence has to a great extent supplanted creatine kinase[42, 43]. Troponin complex comprises of 3 proteins (troponin C, I, and T), which have regulatory function in the sarcomere. Troponin C, is indistinguishable in skeletal muscle and myocardium, yet cardiovascular troponin I and T (cTnI and cTnT) are sort of not quite the same as their partners in skeletal muscle. Troponin for the most part release from injured cardiac myocytes three hours after ischemic damage, and its rise stay rose for up to a few weeks. Studies proposes that its peak concentration can be related with the degree of injury and hence measuring troponin in serum can be an important auxiliary method in examining sudden death[44-46]. In this part the essentialness of measuring heart troponin (cTn) will be talked about in connection with after death instances of intense sudden demise.

Criteria of biomarkers for diagnosis of MI

The criteria for MI suggested in these and different guidelines[42] are focused around the principle that any dependably detected myocardial infarction, if brought about via myocardial ischemia, constitutes a MI. The improvement of more sensitive and specific biomarkers of necrosis, for example, cardiac troponin, has empowered location of quantitatively much smaller area of myocardial damage[47]. Additionally, it is likely that future eras of measures for cardiac troponin will push this utmost significantly lower. All things considered, based on the total confirmation to date, the present rules reflect the predominating accord assumption[43] that any dependably detected elevation of a cardiac troponin is irregular and probably speaks to necrosis. The additional investigation is obliged to figure out if present or future generation of assays for cardiac troponin may detect release of the protein that happens amid reversible injury because of myocardial localized necrosis.

Optimal timing of sample acquisition

The ideal timing of sample acquisition for estimation of biomarkers for the diagnosis of MI gets from both properties of the accessible biomarkers and patient related components, timing and term of indications with respect to presentation and general likelihood of ACS. CK-MB starts to increase within 3–4 h after the onset of myocardial injury and tumbles to typical ranges by 48–72 h. Cardiac troponin increase with a time course like CK-MB yet can stay expanded for up to 4–7 days for cTnI and 10–14 days for cTnT.

Conversely, myoglobin concentrations begin to increase as right on time as 1 h after onset of myocyte damage and comes back to normal inside 12–24 h. In view of this kinetics, the transient ascent of the serum concentration of CK-MB and cardiac troponin regularly does not allow recognition of myocardial necrosis early (1–3 h) and does not help maximal affectability of these markers until 6 or more hours after the onset of MI[48-50]. Precise determination of the timing of symptom onset is focused around patient reporting and is frequently clinically exceptionally difficult[51]. In this manner, blood ought to be acquired from patient for testing at 6–9 h after onset of manifestation to give satisfactory clinical affectability to distinguishing MI. early testing of heart troponin or CK-MB, in combination with myoglobin, may be considered as an approach to increase early detection of infarction and to facilitate rapid initiation of treatment[52, 53]

A perfect biochemical marker for diagnosis and detection of myocardial injury ought to be display in high concentration particularly in myocardium, and ought not be introduce in different tissues, even in trace amounts or under any pathological conditions [54]. Likewise, it ought to be release quickly and totally in light of myocardial injury furthermore ought to continue in plasma for a few hours however not all that long, to give a sufficient time to helpful analysis. The ingenuity for more periods could be of great interest for routine clinical practice yet not in post-mortem diagnosis where markers ought to be of free of impedance as an after effect of post-mortem interval and from contamination caused by adjoining tissue fluids. In post-mortem examination, estimation of markers is imperative in light of the fact that customary histological routines can just suspect the myocardial lesion yet can't be secured[34, 35, 37]. Indeed in specific instances of measurable practice it is hard to diagnose AMI just from anatomic and pathological observation. In such cases wide variety of biochemical determinations in blood, cerebrospinal liquid, vitreous humor, pericardial fluid, and other body fluids can be much helpful in solving forensic related medico legal problems [27]. In such cases complementary diagnostic techniques, such as the determination of biochemical markers in cadaver fluids, take on a special importance.

Recently, cardiac troponins have picked up consideration as a specific marker of myocardial cell injury. European Society of Cardiology and the American College of Cardiology have recently recommended that these proteins ought to favored as specific marker for cardiac injury than the traditional one[55]. Measurement of cardiac troponins has turned into a standout amongst the most imperative research facility tests now days where passing can likewise be conceivable because of intense myocardial damage. The modern troponin assays are more particular for cardiac damage than ischemia injury. Indeed cases like cardiomyocyte necrosis, for example, myocarditis and cardiomyopathies, can likewise be diagnosed in light of rise in the level of serum troponin. Likewise, it has been watched that estimation of cTnT and cTnI is more exact than the routine estimation of CK-MB[56, 57]. So it has been proposed that these troponin can be utilized as a part of post-mortem examination as a qualitative diagnostic test [46]. In any case there ought to be a need of most extreme consideration when patients experiencing renal failure where abnormal amounts of cTnT may present[58]. Then again, there is a general understanding that serum cTnI is a specific marker for myocardial injury and it has been recommended that cTnI immunoreaction in autopsied hearts is a sensitive method which can employ in the diagnosis of early myocardial infarction [59, 60]. In their study on cTnT and cTnI against intense myocardial localized necrosis reasoned that relying upon their level increased from 10% to 45% inside an hour to more than 90% at 8 or more hours. Anyway its specificity starts declining gradually from 87% to 80%, inside 12 hours after the onset of chest pain for cTnT and 95% in cTnI level. Along these lines, cTnI has all the earmarks of being more perfect for the location of myocardial damage[41, 61, 62].

Recently, cardiac troponins have gained attention as a specific marker of myocardial cell injury. European Society of Cardiology and the American College of Cardiology have recently suggested that these proteins should preferred as specific marker for cardiac injury than the classical one [55]. Measurement of cardiac troponins has become one of the most important laboratory tests now days where death can also be possible due to acute myocardial damage. The modern troponin assays are more specific for cardiac damage than ischemia injury. Even cases like cardiomyocyte necrosis, such as myocarditis and cardiomyopathies, can also be diagnosed because of elevation in the level of serum troponin. Also, it has been observed that measurement of cTnT and cTnI is more accurate than the conventional measurement of CK-MB [56, 57].

So it has been suggested that these troponin can be used in autopsy as a qualitative diagnostic test [46]. But there should be a need of utmost care when patients suffering from renal failure where high levels of cTnT may present [58]. However, there is a general agreement that serum cTnI is a specific marker for myocardial injury and it has been suggested that cTnI immunoreaction in autopsied hearts is a sensitive method which can employ in the diagnosis of early myocardial infarction [59,60]. In their study on cTnT and cTnI against acute myocardial infarction concluded that depending on their level increases from 10% to 45% within a hour to more than 90% at 8 or more hours. But its specificity starts declining gradually from 87% to 80%, within 12 hours after the onset of chest pain for cTnT and 95% in cTnI level. Thus, cTnI appears to be more ideal for the detection of myocardial damage[41, 61, 62].

Recently, monoclonal antibodies against cTnI and cTnT have as of now been produced that shows almost no cross-reactivity with their respective skeletal muscle isoforms[54, 63]. Both of these marker give a prevalent specificity in a circumstance where high level of CK-MB is suspected in giving a false positive result[64]. Likewise, a few studies have obviously exhibited that cTnI and cTnT are better than other established biochemical measurement if myocardial damage must be diagnosed in patients with possible concomitant skeletal muscle damage [57]. As per[57] both markers were associated with a very nearly outright clinical affectability however the specificity was insignificantly higher for cTnI.[65] in their finding proposed a preference for cTnI in patients with chronic failure or myopathies, if myocardial damage is suspected. In an alternate careful investigation Adams et al. observed that troponin I in the venous blood especially, was specific for cardiac contusion however its specificity in the pericardium was not as different as in the venous blood[45, 66]. Hence, troponin I has depicted as having a high specificity with ischaemic myocardial injuries and in traumatic myocardial injuries compared with other class of troponin[59]. It has been also observed that during biochemical measurement from pericardial fluid, a statistically significant higher level was obtained in subjects who died from myocardial infarction compared to normal death. However in serum, only cTnI exhibit statistically significant difference with higher value in the subjects, who died from myocardial infarctions. These discrepancies aroused possibly due to their release from different sites[67-69].

Conclusion

In conclusion, based on literature and available evidences we suggest cTnI measurement as one of the useful parameter for measuring the severity of myocardial damage and thus can be implemented in medico-legal autopsy in forensic practice. We, therefore propose cTnI measurement as an essential criterion in patients who died due to sudden acute death. Thus, by using this procedure it will be possible to predict cardiac death with almost 100% accuracy.

Multimarker approach as a future detection method

Clinical studies have demonstrated that the consolidated utilization of myoglobin and a more specific marker of myocardial infarction may be helpful for the early determination of MI[70, 71]. Multimarker strategies that incorporate myoglobin have been indicated to distinguish patients with MI more quickly than laboratory based determination of a single marker[72, 73]. Advances in our understanding of the pathogenesis and results of ACS have animated improvement of new biomarkers and made the opportunity for an extended part of different biomarkers and individualization of treatment[74, 75]. Much evidence demonstrates that a multimarker method, utilizing a pathologically differing set of biomarkers, includes to biomarkers of putrefaction for danger appraisal in ACS[76]. Few studies have inspected procedures incorporating 2 or more markers notwithstanding troponin[75, 77]. Additional research assessing this and other methodologies for consolidating 2 or more pathologically differing biomarkers will clear up the suitable clinical part for such a methodology. All things considered, as new markers and treatments are found, a multimarker standard utilizing a combination of biomarkers for risk evaluation and clinical choice making can possibly enhance results for patients with ACS[76].

Conflict of interest

None declared

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