Etiology of elevated cardiac troponin levels in patients with acute respiratory disease

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SUMMARY

Title: Etiology of elevated cardiac troponin levels in patients with acute respiratory disease

Keywords: Cardiac troponin, mechanisms, myocardial injury, acute respiratory disease

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Cardiac troponins are specific biomarkers of myocardial injury. Elevated cardiac troponin has long been considered to be a specific hallmark of myocardial infarction. Increasing evidence of myocardial injury in the absence of coronary artery disease has led to the need to review the classification of myocardial injury and infarction, as non-ischemic causes have been clearly observed as being able to raise cardiac troponin levels as well. Cardiac troponin elevation is a frequent finding in patients with respiratory diseases such as pneumonia, acute respiratory distress syndrome, sepsis, acute exacerbation of chronic obstructive pulmonary disease, pulmonary hypertension and pulmonary embolism. Several different mechanisms have been proposed to explain this phenomenon including an oxygen supply and demand mismatch, inflammation - induced coronary plaque rupture and subsequent myocardial necrosis, right ventricular dysfunction, subendocardial ventricular ischemia, direct myocarditis as well as previously undiagnosed coronary artery disease. However, regardless of the underlying etiology, elevated cardiac troponin in respiratory disease is associated with increased disease severity, risk of complicated hospital stay, need for cardiac interventional procedures, as well as increased fatal outcome. The measurement of cardiac troponin poses significant usefulness in the management of severe respiratory disease and therefore should be considered as routine for patients admitted on account of acute respiratory disease. This would help in early identification of myocardial injury and categorization of more at-risk patients, in order to allow for more aggressive and targeted therapy and by doing so, improve outcomes.

Naslov: Etiologija povišenog kardijalnog troponina u bolesnika s akutnom respiratornom bolešću

Ključne riječi: kardijalni troponin, mehanizmi, ozljeda miokarda, akutna respiratorna bolest

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Sažetak

Srčani troponini specifični su biomarkeri ozljede miokarda. Povišeni srčani troponin dugo se smatrao specifičnim obilježjem infarkta miokarda. Sve više dokaza o ozljedama miokarda u odsutnosti bolesti koronarnih arterija dovelo je do potrebe za revidriranjem klasifikacije ozljeda i infarkta miokarda jer su jasno uočeni neishemijski uzroci koji također mogu povisiti razinu srčanog troponina. Povišenje srčanog troponina čest je nalaz u bolesnika s respiratornim bolestima kao što su upala pluća, sindrom akutnog respiratornog distresa, sepsa, akutno pogoršanje kronične opstruktivne plućne bolesti, plućna hipertenzija i plućna embolija. Nekoliko različitih mehanizama predloženo je za objašnjenje ovog fenomena. Oni uključuju: neusklađenost opskrbe i potražnje kisika, ruptura koronarnih plakova potaknuta upalom i posljedična nekroza miokarda, disfunkcija desne klijetke, subendokardijalna ventrikularna ishemija, izravni miokarditis kao i predhodno nedijagnosticirana bolest koronarnih arterija. Bez obzira na temeljnu etiologiju, povišeni srčani troponin u respiratornim bolestima povezan je s povećanim rizikom kompliciranog boravka u bolnici, težim oblikom bolesti, potrebom za intervencijama na koronarnim arterijama i povećanim rizikom smrtnog ishoda. Pokazano je da mjerenje srčanog troponina predstavlja značajnu korist u liječenju teških respiratornih bolesti, pa bi stoga trebalo smatrati rutinskim postupkom u bolesnika primljenih radi akutne respiratorne bolesti. Ono može pomoći u ranoj identifikaciji ozljede miokarda i kategorizaciji rizičnih bolesnika kako bi se omogućila agresivnija i ciljana terapija, a time poboljšali ishodi.

ABBREVIATIONS

CTn - Cardiac troponin

CTnI - Cardiac troponin I

CTnT - Cardiac troponin T

CRP - C-Reactive protein

BNP - Brain natriuretic peptide

ANP - Atrial natriuretic peptide

IL - Interleukin

Ck-MB - Creatinine kinase - MB

MI - Myocardial infarction

AMI - Acute myocardial infarction

CVD - Cardiovascular disease

ICU - Intensive care unit

PE- Pulmonary embolism

PCI - Percutaneous coronary intervention

PAH - Pulmonary arterial hypertension

COPD - Chronic obstructive pulmonary disease

AECOPD - Acute exacerbation of chronic obstructive pulmonary disease

ARDS - Acute respiratory distress syndrome

UDMI - Universal Definition of Myocardial Infarction

TABLE OF CONTENTS

1. INTRODUCTION

By presenting the varied etiology of elevated cardiac troponin, including causes not directly related to coronary artery disease and its complications, this review aims to constructively challenge the long-held notion of elevated cardiac troponin being a hallmark of, and therefore, the main therapeutic target for myocardial infarction.

This review seeks to demonstrate the role of cardiac troponin elevation not only in the diagnosis of ischaemic heart disease, but in particular, its significance in the prognosis of several disease conditions, with a focus on respiratory diseases. The following will be elucidated:

- Overview of cardiac troponin including proposed mechanisms of elevation and diagnostic indices
- Usefulness of cardiac troponin measurement in the diagnosis of acute coronary syndrome including risk stratification
- Differential diagnosis of elevated cardiac troponin in acute and chronic settings
- Elevated cardiac troponin in respiratory diseases with a focus on etiology and prognostic significance.

2. CARDIAC TROPONIN

2.1 OVERVIEW

Troponins are a group of regulatory proteins which are found in cardiac and skeletal muscle fibers. Together, they regulate muscular contraction through the control of calcium-mediated actin and myosin interaction. Three types (subunits) of troponin proteins are currently identified namely: troponin C (TnC), a highly conserved subunit that binds Ca2+ , troponin T (TnT), a tropomyosin-binding subunit, and troponin I (TnI), an actomyosin subunit that inhibits ATPase(1).

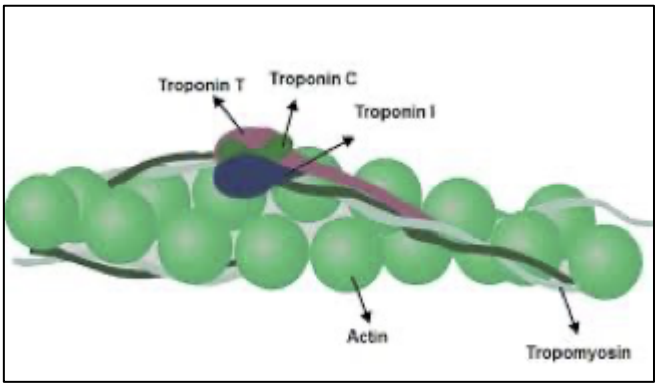

Figure 1. 3D structure of Troponin complex; The 3 subunits of troponin create a set that regulates actin- myosin interaction. According to: (2), fig 2.

Troponin is regularly distributed along the whole length of the thin filaments and with tropomyosin and actin, forms an ordered complex. When intracellular Ca2+ concentration is low, troponin, alongside tropomyosin inhibits the contractile interaction between actin and myosin and in increased intracellular Ca2+ concentrations, this inhibition is relaxed via Ca2+ /troponin binding(2).

There is no structural difference between the cardiac and skeletal isoforms of TnC because the encoding genes for them are identical. In contrast, the cardiac and skeletal subforms of troponin I and troponin TnT are distinct and they can therefore be differentiated using specially designed immunoassays. The cardiac forms of troponin,

because they are encoded by specific genes, in theory are potentially specific to the myocardium. Cardiac Troponin I has not been identified outside the myocardium and Cardiac troponin T can be found in skeletal muscle but only in small amounts although the cTnT assays in present use are not able to identify skeletal troponins(2).

Troponin is normally present in blood in minute or even undetectable levels. In the event of acute myocardial infarction and other forms of damage to cardiac muscle, there is a release and transient increase of troponin in the bloodstream. The blood troponin concentration is directly proportional to the degree of damage sustained. Troponin assays are therefore useful in detecting cardiac injury. In identifying damage to cardiac muscle, serum cTnI and cTnT measurements are more superior in terms of sensitivity and specificity(3). Elevated concentrations of cardiac troponin are now taken as the standard biochemical marker to aid the diagnosis of myocardial infarction.

2.2 SUGGESTED MECHANISMS OF ELEVATION AND KNOWN CAUSES

Elevation of cardiac troponin has been widely accepted as a biomarker of acute ischaemic injury, in particular myocardial infarction (MI). MI is defined as myocardial cell death caused by prolonged myocardial ischemia. A compromised cardiac perfusion arising from coronary atherothrombotic events is the most widely acknowledged cause of myocardial infarction and subsequent elevated cardiac troponin(2). However, several other mechanisms have now been discovered to either be a causative or contributory factor to MI. MI is also now recognized as just one out of the several types of acute myocardial injury.

According to the Universal Definition of myocardial infarction (UDMI), MI is now divided into five different subtypes and non ischemic etiology of myocardial injury is now recognised even though the differentiation in clinical emergency settings continues to be a challenge(4). Many theories have been proposed as to the

underlying mechanisms of cardiac troponin elevation in subjects with reversible myocardial ischemia and in those with myocardial injury unrelated to ischemia.

Irreversible Myocyte Necrosis

This is the most widely considered mechanism of cardiac troponin increase especially when the elevation is acute and temporary. Prolonged myocardial ischemia leads to an oxygen deficit and irreversible myocardial necrosis. A compromised blood flow to myocardial tissues, whether as a result of increased oxygen demand or rupture of a coronary artery plaque leads to myocardial ischemia, initiating a cascade of molecular and cellular events that result in necrosis(5).

A study by(6), which compared cardiomyocytes to other cell types, showed the former to be more susceptible to necrosis following triggering circumstances like the Ca2+ paradox and/or the oxygen paradox. Calcium ions leaking into the cytoplasm of cardiomyocytes cause the sarcomeres to contract and rapidly consume all the ATP, which results in rapid cardiac cell death and subsequent release of cardiac troponin together with other constituents of the cell.

Ischaemic cardiomyocytes have been found to rapidly develop intracellular oedema upon a fall in ATP levels(7). Because the dystrophin protein complex maintains the anchoring of sarcomere to the plasma membrane, the swelling does not cause a uniform cardiomyocyte enlargement but instead, the picture is that of membrane blebs formed between the points of dystrophin anchorage. Therefore, even though fragile, the cardiomyocyte membrane does not rupture until triggered by a hyposmotic or an acidic melieu(7).

Nevertheless, these injured and anoxic cardiomyocytes eventually succumb to contraction band necrosis either when forced to contract by surrounding non-ischaemic cardiac cells(8), when contraction occurs following re-oxygenation, or after acute balloon dilatation of an ischaemic ventricular chamber(9). Irreversible

myocardial injury is typically characterized by a biphasic pattern of cardiac troponin elevation.

Reversible myocardial Ischaemia

This is suggested in cases in which initial troponin appearance is followed by a rapid fall back to baseline levels within 24 hours, painting a picture of transient myofibril damage(10). This is characterised by the lack of a biphasic pattern of cTn elevation as seen in myocardial infarction.

In a report by Aw(11), two middle-aged individuals underwent a bicycle ride of 50 km. A high-sensitive assay showed both individuals to have a significant troponin elevation post exercise which fell back to near baseline concentrations within 24 hours. It was suggested that demand-based ischaemia may have led to a silent but minor type 2 AMI which, as a result of lack of symptoms, did not fulfill the criteria for diagnosis.

However, it is also argued that absence of prolonged troponin increase following onset of myocardial injury is not necessarily an evidence of reversible injury but could be explained by increased extraction of troponin from the contractile pool which has good perfusion through the area of cardiac injury.

This proposal is based on the observation by Starnberg (12) in their study that troponin complex binding to tropomyosin is not as tight as initially thought, a possible explanation for why artery reperfusion is associated with an increased washout of troponin from injured myocytes when compared with non-reperfusion. The data however, does not explain the absence of prolonged release of the non-extractable troponin (remaining 20%) if the injury is deemed to be completely irreversible.

Reversible Injury following Pulmonary embolus

Several clinical studies have demonstrated cardiac troponin elevation after acute pulmonary embolism. While the exact etiology is unknown, proposed mechanisms include direct ventricular myocardial injury from the increased pressure that results from pulmonary artery occlusion or occlusion of any of its major branches(12).This results in hypoperfusion, hypoxia, and decreased coronary perfusion.

Cardiac troponin following pulmonary embolism is usually cleared within 24 hours and is milder, possibly originating from the cardiomyocyte cytosolic troponin pool(13). This is partly because of the lower right ventricular troponin tissue content (about 20–30% for cTnT and cTnI) in comparison to the left ventricle's(15).

Apoptosis and Autophagy

Apoptosis can be defined as programmed cell death and a component of the normal cycle of tissue cells. A highly regulated process, it is initiated by cell stress or via intercellular signaling, resulting in enzyme (such as caspases) activation and cellular protein degradation(16).

The role of apoptosis in release of troponin into the bloodstream has been shown by several researchers. Weil (17) in their study on swine models induced myocardial ischemia via coronary balloon catheter insertion and inflation for 10 minutes. A histopathology using the TUNEL assay, conducted one hour after deflation and reperfusion revealed evidence of cell necrosis and apoptosis. The authors observed troponin release following reperfusion, with no evident myocardial injury(17).

Inflammation

Inflammation has been proposed as an underlying mechanism of troponin elevation, arising from observations of elevated troponin in patients who have sepsis without myocardial infarction(18), (19). It is not clear how inflammation causes a release of troponin. Suggestions of reversible myocardial ischemia have been made based on the 24 hour clearance of troponin observed in septic patients(20).

Another possible mechanism considered is reversibility due to the absence of lactic acid that is a hallmark of irreversible myocardial injury. Inflammation as an etiology has been countered by some authors who carried out studies relating to exercise-induced inflammation(21), proposing instead, an oxygen supply and demand mismatch as a cause of troponin elevation in sepsis in which there is fever, microcirculation dysfunction, respiratory failure and hypotension(22).

Myocardial stretch

In chronic heart failure, myocardial remodeling occurs which involves stretching of the cardiomyocytes. Atrial natriuretic peptide (ANP) and Brain natriuretic peptide (BNP) are consequently released from the myocardium to compensate for the decreased cardiac output associated with myocardial enlargement. Cardiac troponin is equally released and has been found to portend increased risk of adverse cardiac events in the future(23).

It has been suggested that integrins (transmembrane glycoprotein receptors which connect the intracellular and extracellular space), are released in chronic heart failure alongside other signaling molecules that together, induce myocardial stretching. In situ degradation of troponin following myocardial stretch in the absence of ischemia has also been demonstrated(24).

This mechanism is also thought to underline cardiac troponin elevation in hypertensive heart disease, Left ventricular hypertrophy(25), pulmonary disease such as pulmonary embolism and acute COPD exacerbation(26).

Stress

An adaptive response observed in pathophysiologic disease progression, stress may explain troponin elevation in patients with stress cardiomyopathy, otherwise known as Takotsubo cardiomyopathy(27). Catecholamine release in defense against stress has been found to induce myocardial damage(28). Other stress hormones such as adrenaline and noradrenaline have also been implicated. Stress induced by atrial pacing has been associated with cardiac troponin elevation in individuals with no evidence of myocardial ischemia(29).

Prolonged Exercise

Prolonged exercise as a model for stress-induced myocardial injury has been considered as a cause of troponin increase in healthy and fit individuals. Mousavi (30)in their study performed on 14 individuals after running a marathon, observed elevation in cardiac biomarkers (CK-MB, myoglobin and troponin) after the race. Enhanced imaging studies carried out 3 days afterwards showed no evident myocardial edema, indicating no true myocardial infarction(30). Other studies also support a non-ischemic cause of troponin elevation induced by exercise(31).

Drug-induced myocyte toxicity

Some chemotherapeutic agents such as doxorubicin and trastuzumab have been known to be associated with heart failure development and subsequent cardiac troponin release which is typically consistently elevated(32).

When used initially, these chemotherapeutic agents may cause reversible myocardial damage without evidence of cardiac ventricular dysfunction. Heart failure eventually ensues with time, associated with reduced drug tolerance threshold as well as efficacy.

It appears that different mechanisms which may result in cardiac troponin release exist and that these are majorly dependent on the underlying pathophysiology and physiologic circumstances.

2.3. DIAGNOSIS OF CARDIAC TROPONIN ELEVATION AND TEST INDICATIONS

Usually in normal healthy populations, troponin levels are too low to be detected by standard blood tests. Even tiny increases in the concentration of troponin are an indication of myocardial damage and may point to an underlying cardiac structural abnormality.

Cardiac troponins findings in normal, healthy adult population (33).

- Cardiac troponin T: < 0.1 ng/mL
- Cardiac troponin I: < 0.03 ng/mL

Positive cardiac troponin levels

- Troponin I : ≥ 0.4 ng/mL
- Troponin T: ≥ 0.1 ng/mL

High-sensitivity troponin T:

- < 14 ng/L for women
- < 22 ng/L for men

Several studies have demonstrated an associated higher short and mid-term mortality in subjects with troponin positive results. In troponin assays, two different reference ranges are used. An upper percentile reference limit (99th %) gives the upper limit of normal in a healthy adult population, whereas the coefficient of variation (CV) represents the percent variation in results of troponin assay which can be expected upon repeated analysis of the same sample(33).

The various commercially available troponin assays vary considerably in their sensitivity, specificity and precision. This is due to several factors: a lack of standardization, the presence of modified TnI and TnT in the serum, the use of different monoclonal antibodies directed against different troponin I epitopes, as well as variations in antibody cross-reactivity to the different detectable forms of TnI that follow its degradation(33).

The TnT assay is produced by only one manufacturer and its cutoff (99th percentile) and the 10% coefficient of variation (CV) are well established. On the other hand, as much as a 20-fold variation has been recorded in results obtained using the many commercial TnI assays available presently, each one having their own 99th percentile cutoff limits and 10% CV levels.

It is imperative therefore that clinicians are aware of the specific reference range of assays used in their practice and to note that there is no correlation between absolute values from different troponin assays.

2.4 Interpretation of Results

Cardiac troponin is a highly tissue-specific biomarker of cardiac injury. However, because it does not provide information about the etiology or mechanism of damage,

it is more useful as a disease prognosticator rather than in making an absolute diagnosis.

Regardless, significantly elevated troponin levels, particularly demonstrating a rise and fall pattern over a series of hours, strongly indicates myocardial ischaemic injury. Lower but elevated levels of troponin may indicate myocardial injury from other causes(4).

2.5 Rise and fall pattern

Using older generation assays, raised levels of troponin levels are detectable about 6 to 12 hours following myocardial injury onset, with a peak elevation observed at about 24 hours and then subsequent gradual fall over several days to weeks(34). Modern high sensitivity troponin assays are able to detect troponin elevation as early as 3-4 hours following onset of myocardial injury. As a result of this, the sensitivity of point-of-care troponin testing has increased in clinical emergency settings.

According to current guidelines, it is recommended that troponin assay is repeated 6-12 hours following initial assessment. Repeat assay should also be done up to 24 hours post onset of symptoms(34). Earlier troponin re-evaluation (at 3-4 hours) is recommended if there is a high clinical suspicion of subendocardial, non–ST-segment elevation myocardial infarction (NSTEMI), as the biomarkers may be detectable earlier with the aim of diagnosing ischemic myocardial injury as early as possible(35).

3. ROLE OF CARDIAC TROPONIN IN DIAGNOSIS OF ACUTE CORONARY SYNDROME (ACS)

3.1 Introduction

One of the most challenging and important tasks assigned to the emergency physician is making diagnosis of cardiac emergencies. The vast differentials of chest pain have to be narrowed down fast and with precision in order to administer the life-saving therapy needed.

In addition to history and physical examination, a number of important diagnostic tools are available which are useful in ascertaining the causes of chest pain. One of such tools which has become a vital aspect of cardiac workups and diagnosis is interval troponin measurement. This has revolutionized emergency medicine practice and the methods of diagnosing and treating myocardial ischemia.

Myocardial infarction (MI) is the predominant contributor to mortality in the developed world. It is defined as the irreversible death (necrosis) of cardiac muscle as a result of a prolonged deficiency of oxygen supply (ischemia). The leading cause of myocardial necrosis and infarction is the acute coronary syndromes (ACS), designated as type 1 MI(36). ACS represents a continuum of cardiac muscle ischemia that ranges from unstable angina (with no irreversible cardiac injury) to frank MI in which large areas of irreversible cardiomyocye cell death are present.

MI can be divided into the following subtypes(4):

- **ST segment elevation MI (STEMI)**

STEMI occurs when there is total and prolonged blockage of a coronary artery and by definition is an ACS accompanied with an ECG finding of ST segment elevation, and an elevation of cardiac biomarkers such as creatine kinase isoenzymes (Ck-MB), cardiac troponin T (cTnT), or cardiac troponin I (cTnI).

- **Non ST segment elevationMI(NSTEMI)**

NSTEMI occurs when there is incomplete and transient blockage of a coronary artery and by definition is an ACS unaccompanied with an ECG finding of ST segment elevation however, with an increase in cardiac biomarkers.

- **Unstable angina (UA)**

UA occurs when there is myocardial ischemia which, unlike the other acute coronary syndromes, is not severe enough to result in myocardial damage and a release of enough quantities of cardiac biomarkers to be detected. By definition, it is ACS with neither ST segment elevation nor increased cardiac biomarkers(37).

It is important to note that the evolution of the newer high sensitivity troponin assays has made this classification arguably redundant as even the mildest form of myocardial injury has been shown to result in troponin elevation now frequently more detectable.

3.2 Pathophysiology

ACS is most commonly precipitated by unstable atherosclerotic plaques within the coronary arteries (Type 1 AMI). Upon rupture of the coronary plaques, their thrombogenic contents become exposed to the circulation, resulting in platelet activation. The subsequent coagulation cascade initiation as well as other physiological effects leads to myocardial ischemia.

Type 2 MI is related to oxygen supply and demand imbalance arising from multiple factors such as coronary artery spasm, hypo/hypertension, anemia, arrhythmia, aortic valve disease, or coronary stenosis with fixed atherosclerotic lesion(36).

Even though ACS is the major cause of myocardial cell death, it is imperative to note that many other disease conditions also give rise to myocardial ischemia and as such, elevated cardiac troponin levels(36).

However, this chapter will focus on the role of elevated cardiac troponin in acute coronary syndromes as biochemical markers are a cornerstone of emergency care in patients in whom a high clinical suspicion of such is present.

3.3 Clinical Presentation

Several factors determine the clinical presentation and outcome of ACS such as: the severity and duration of coronary artery blockage, how much of the myocardium is involved, the level of oxygen demand as well as the healthy myocardium's ability to compensate(4).

The most common presentation of ACS is chest pain, often described as squeeze - like, that radiates to the left arm or jaw. This may often be associated with exertional dyspnoea, nausea from vagal stimulation and sweating from sympathetic discharge, and palpitations(36).

Not every patient will have typical symptoms however. Diabetics often do not experience chest pain, the elderly may present with altered mental status, individuals with dementia may have no memory of recent symptoms. It has also been noted that women may have atypical symptoms which further complicates accurate diagnosis in them.

Atypical presentations of ACS further highlight the usefulness of diagnostic tools, especially biochemical markers such as the cardiac-specific troponin which has now been adopted as one of the requisite criteria for the diagnosis of ACS.

3.4 Significance of raised Cardiac troponin levels in ACS

Prior to more recent developments in the diagnosis and management of ACS, the accepted criteria for diagnosing ischemic heart disease as defined by the International

Society and Federation of Cardiology and the World Health Organization (37) was a satisfaction of at least 2 of 3 criteria: clinical history, ECG findings, and temporal changes in serum enzymes. An equal consideration of 2 of the 3 criteria was needed at the time due to the wide variation in clinical presentation, the frequent presence of confounding factors on ECG, as well as the poor specificity of the then available biochemical markers (such as CK-MB and myoglobin) for myocardial injury(37).

Come the early 1990s, more cardiac-specific biomarkers (cTnT and cTnI) were discovered which brought a complete paradigm shift. With the evolution of analytically specific and sensitive cTn assays, there was a need to re-evaluate the established definitions of myocardial infarction and a joint committee of the European Society of Cardiology (ESC) and the American College of Cardiology Foundation (ACCF), convened to re-examine the definition of MI in 1999, adopted cardiac troponin as the preferred biomarker for the detection of myocardial necrosis.

It was agreed that MI is indicated if there is a maximal concentration of cTnT or cTnI exceeding the operative threshold (99th percentile of the values for a reference control) on at least a single occasion within the first 24 hours following an index clinical ischemic event(34).

As the above definition allowed a potential false positive rate of 1%, there was a further review in 2007 which was updated to add a pattern of rise and/or fall in the concentration of biomarkers (preferably cTn) (39).

Currently, the diagnosis of MI is based on the Universal definition of MI (UDMI) adopted in 2012 which defines MI as evidence of myocardial necrosis in a clinical setting that is consistent with acute myocardial ischemia(36). MI therefore can be diagnosed with the combination of clinical features and appropriate diagnostic tools such as the detection of a rise and/or fall pattern in cardiac troponin, with at least a single value exceeding the 99th percentile cutoff.

3.5 Role of cardiac troponin in Risk stratification of ACS and non-ACS causes of Myocardial injury

The heightened sensitivity (decreased thresholds of positive cTn values from 1.5 mcg/L in 1995 to 0.04 mcg/L since 2007) of new cTn technology and approaches currently being used in the evaluation of cardiac troponin rise and/or fall for making diagnosis of MI could significantly impact the management of chest pain of acute onset that presents to the emergency department(37).

Because the National Academy of Clinical Biochemistry (NACB) recommends cardiac markers to be immediately available as needed at all times and with no more than a one hour turnaround time(40), Point-of-care assays (POC) which provide rapid results and are equally more sensitive are becoming increasingly used in hospitals.

There is a prevailing concern that this may lead to increased false diagnoses of NSTEMI, as well as more false positive results in cases of raised cTn concentrations from non-cardiac causes. However, the potential benefits of POC troponin testing(37) should not be overlooked such as:

- A shortened time to positivity compared to conventional laboratory tests, which could be beneficial in reducing time to discharge in the absence of MI.
- Unnecessary patient transfers to interventional (PCI) facilities can be avoided for patients awaiting serial testing following a negative first test in the case of time-based unavailability or inaccessibility of central laboratories.

Keeping patients in order to rule out MI often places considerable burden on emergency departments and at the same time, sending patients with NSTEMI home carries a 2-fold increase in risk of mortality(41). A raised cardiac troponin level allows for risk stratification in patients who have ACS and also identifies those at high risk of having adverse cardiac events such as myocardial infarction and death for up to 6 months following the index event(42).

In a study carried out by Antman et al. in patients with ACS, a correlation was observed between the initial TnI level on admission and mortality at 6 weeks. Even though other biomarkers such as CK-MB are sensitive and specific for AMI, it had neither a predictive value for adverse cardiac events nor prognostic value(42).

In another study by Reichlin et al. (42) carried out in patients who presented with chest pain of acute onset, high sensitivity or sensitive cTn assays were combined with absolute change cut-offs to design a new method for early diagnosis or rule out of MI. The results of the study showed that 60% of the patients could be ruled out for MI after 1 hour, 17% were ruled in and the rest (23%) who remained in between the cutoffs used, needed further observation in the emergency department. Furthermore, the study showed that follow-up survival rates for the rule-out, observation, and rule-in groups were 99.8%, 98.6%, and 95.3% respectively at 30 days, and 98.1%, 89.1%, and 85.4% at 24 months, confirming the usefulness of a cTn assay-based algorithm for risk stratification(41).

3.6 Implications of "False-Positive" high sensitivity cTn (hs-cTn) results

Raised cTn levels in the absence of evident myocardial ischemia, is often regarded as a "false-positive" result. Considering that MI is just one (albeit the predominant) of the many causes of myocardial injury, this is a misleading term. Every detectable cTn elevation is an indication of myocardial injury regardless of cause and is often a pointer to subclinical or underestimated heart disease such heart failure, valvular heart disease, hypertensive heart disease, and coronary artery disease.

Cardiac troponin elevation could also arise from non-cardiac etiology. Regardless of underlying cause. Elevations of cardiac troponin generally portend a worse prognosis compared to similar patients in whom there is no cardiac troponin elevation and this even after adjustments have been made for severity of disease.

It is therefore important that non-cardiac causes of cardiac troponin elevation be considered and properly evaluated even in the presence of coronary artery disease.

4. OTHER CAUSES OF MYOCARDIAL INJURY AND STRAIN

Elevated cardiac troponin, typically transient and following a dynamic rise and/or fall pattern, is a key finding and part of diagnostic criteria for acute coronary syndrome (ACS). However, following the Fourth Universal Definition of Myocardial Infarction (UDMI), acute and chronic non-ischemic myocardial injury are now viewed as distinct clinical entities(4).

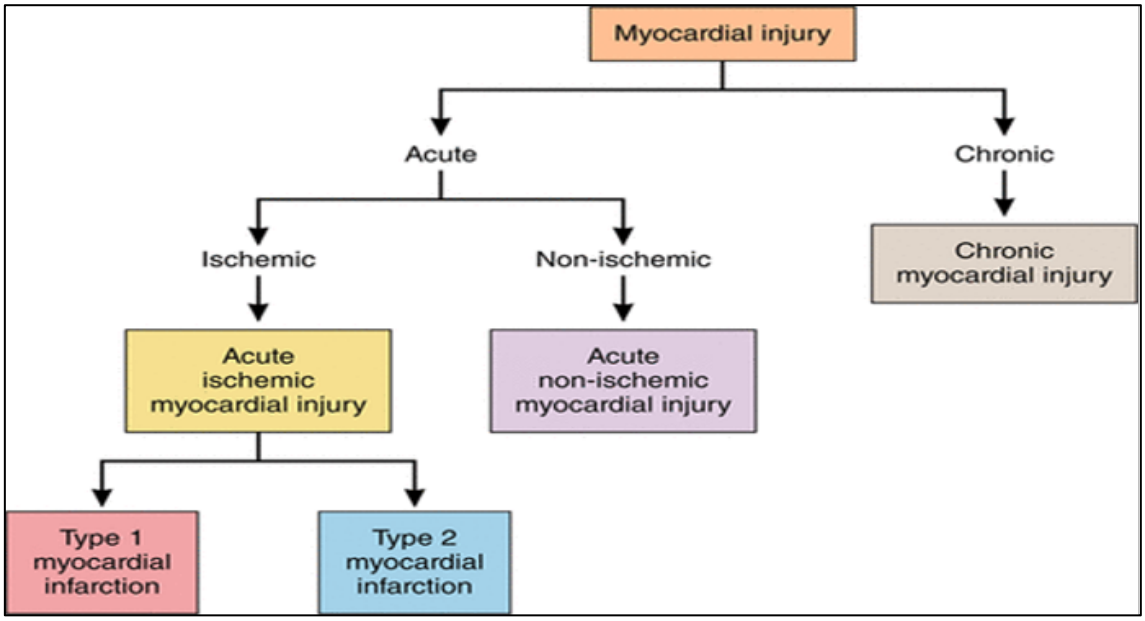

Figure 2. A Schematic representation of the causes of myocardial injury. According to: Andrew (4), fig 1.

4.1 Non-ACS causes ofAcute Myocardial Infarction

This is otherwise regarded as Type 2 AMI and can be seen in an extensive number of diseases. Relative ischaemia can occur due to imbalance in oxygen demand and supply which may in turn arise from reduced myocardial perfusion in the setting of stable coronary atherosclerosis (that is, without plaque disruption), microvascular

dysfunction, coronary artery spasm, or acute non-atherothrombotic coronary obstruction as may be seen in coronary dissection or embolism(4).

In acute aortic dissection (AAD), the layers within the aortic walls are divided, causing pain and increased oxygen demand. In AAD, Cardiac troponin concentration may be raised in as much as 18% of patients at time of presentation and portends a 3 to four-fold higher risk of a delay in diagnosis(43).

An oxygen supply and demand imbalance could also occur on the background of systemic causes such as hypotension, bradyarrhythmia, anemia, hypoxemia, or elevated cardiomyocyte oxygen demand in severe hypertension or tachyarrhythmia(4).

Tachycardia can increase oxygen demand by reducing perfusion due to the reduced diastolic time (which is when coronary blood flow occurs). A state of septic shock can equally give rise to hypoperfusion and hypoxemia, in addition to tachycardia, and raised troponin levels in these patients have been associated with poorer prognosis(44).

Hypotension can result in myocardial injury and subsequent elevated cardiac troponin in patients who are critically ill and otherwise having no concomitant cardiac disease(46). The severity of hypotension was also related to raised cardiac troponin levels and associated with worse prognosis(46).

In left ventricular hypertrophy, chronic heart failure, aortic stenosis and aortic valve disease, demand-based subendothelial ischaemia can lead to myocardial injury and raised troponin(4).

4. 2 Non Ischaemic causes of Acute Myocardial injury

Direct blunt chest wall trauma can lead to considerable damage to the ventricular muscle fibers which can subsequently cause an increase in troponin. A study carried out on 333 patients who had sustained blunt chest trauma showed raised troponin

levels in 144 (44%) of them(47). Inflammatory conditions such as myocarditis (viral, bacterial fungal, mycobacterial), pericarditis, perimyocarditis (including post-vaccination myopericarditis in children), and endocarditis are associated with raised troponin levels, thought to possibly arise from myocyte toxicity from bacterial endotoxins, pro-inflammatory cytokine (interleukins 1 and 6, tumour necrosis factor alpha) release, and microvascular thrombosis in addition to oxygen demand and supply imbalance. In patients with myocarditis, elevated cardiac troponin is useful both in the assessment of presence and severity of myocardial injury as well as in prognosis(48).

Troponin leakage can also be seen with processes not primarily associated with the heart. For instance, troponin elevation has been a recurrent finding in patients who have cerebrovascular accidents (CVA). Although CVA shares similar risk factors with cardiovascular disease, this finding has been consistent even in the absence of evident coronary artery disease. A proposed mechanism for this occurrence is a possible disruption of autonomic function following a CVA, resulting in increased catecholamine release that affects the cardiac myocytes(48).

In several studies done on CVA patients, the finding of elevated cardiac troponin has been associated with poorer outcomes(50), (51). However, such a finding is not unique and has not been confirmed by all studies(50).

4. 3 Non-Ischaemic causes of Chronic Myocardial injury

Another challenge which complicates cardiac troponin measurement for the diagnosis of AMI is myocardial injury of chronic non-ischemic etiology.

Chronically elevated cardiac troponin levels which do not demonstrate dynamic rise and/or fall patterns typical of acute MI or acute non-ischemic myocardial injury are regarded as chronic myocardial injury(4).

In patients who have chronic kidney disease associated with renal dysfunction, elevated troponin levels have been demonstrated in them greater than the 99th percentile cutoff, even in the absence of evident heart disease. Nevertheless, cardiovascular disease is highly prevalent in chronic renal failure (CRF) and is responsible for as much as 50% of mortality in CRF.

Proposed mechanisms of cardiac troponin elevation in CKD include: subclinical myocardial injury (silent ischaemia) and abnormalities of troponin catabolism and clearance in renal failure(51).

Troponin measurements and their correct interpretation is vital in CRF especially since ECG results are complicated by often concomitant electrolyte imbalance, cardiac abnormalities and drug therapy. For CRF and indeed most chronic causes of raised cardiac troponin, trends are more useful in troponin measurement to compensate for their low specificity. Even on a background of raised troponin levels, a super-imposed acute rise and fall pattern in serial testing indicates a cardiac cause(48).

Infiltrative diseases such as amyloidosis have also been found to raise troponin concentration. Cardiac troponin elevation in amyloidosis is thought to be multifactorial: microvascular ischemia, direct amyloid protein-induced cardiomyocyte toxicity as well as the mechanical effects of amyloid infiltration(52). Cases of amyloidosis with obvious involvement of the heart tend to have worse outcomes, with median survival in patients with detectable levels of cardiac troponin T and I pegged at 6 and 8 months respectively(53).

Stress cardiomyopathy, also known as Takotsubo cardiomyopathy raises cardiac troponin levels primarily via direct myocyte catecholamine toxicity. Other identified mechanisms in stress cardiomyopathy include microvascular dysfunction, coronary artery spasm and extracardiac stress leading to an oxygen demand and supply mismatch(4), although these would typically cause an acute rather than chronic troponin elevation.

Iatrogenic causes such as cardiopulmonary resuscitation, percutaneous coronary intervention, and cardioversion may lead to cardiomyocyte damage and cell membrane leakage, resulting in troponin release(55).

Other causes of chronic non-ischemic cardiac troponin elevation include drugs: chemotherapeutic agents such as trastazumab, anthracyclines, anti-HIV drugs such as reverse transcriptase inhibitors and protease inhibitors, some antimicrobial agents, and chronic diseases like Kawasaki disease and hereditary syndromes(48).

Pulmonary diseases and cardiac troponin elevation

Cardiac troponin elevation is a common finding in pulmonary diseases such pulmonary embolism, pneumonia, severe sepsis, acute respiratory distress syndrome, acute exacerbation of COPD and pulmonary hypertension which is the main focus of this review. It occurs through various proposed mechanisms and these, alongside their significance, will be discussed fully in the following chapters.

5. ELEVATION OF CARDIAC TROPONIN IN PATIENTS WITH PNEUMONIA

Introduction

The term “Pneumonia” broadly refers to any infection of the lung parenchyma, especially the terminal bronchioles and the alveoli. Classification of pneumonia can be based on etiology (bacterial, viral, fungal), on duration of symptoms (acute or chronic), on the clinical setting in which it is acquired (community-acquired and hospital-acquired) or on pattern of anatomic distribution (bronchopneumonia and lobar pneumonia).

The inciting organisms gain entry into the lung alveoli either directly through the upper respiratory tract or hematogenously. Once in the alveoli, they overwhelm the alveolar macrophages and incite an inflammatory reaction that results in the production of a fibrin-rich exudate which fills up the infected alveolar sacs together with proliferation of neutrophils. Infected alveoli stick together and are rendered airless. Thus, depending on the severity and virulence of the inciting organism, lung tissue damage ensues, leading to widespread consolidation (depending on severity), fibrosis and pulmonary edema.

5.1 Etiology of raised Cardiac troponin levels in Pneumonia

The mechanisms by which pneumonia leads to a rise in cardiac troponin levels are multiple. And some of them include:

Ventilation-perfusion (V/Q) mismatch:

The changes described above result in ventilation-perfusion mismatch in the lungs. Vital organs, including the heart, become oxygen deprived and work of breathing increases. In response, respiratory and heart rates increase. Increased heart rate in the

setting of reduced oxygen supply causes significant myocardial injury, leading to type 2 myocardial infarction.

Inflammation and Oxidative Stress:

Pneumonia has also been shown to cause an increase in systemic oxidative stress and an increase in the levels of circulating inflammatory cytokines both in the short term and the long term. These lead to an increased risk of thrombogenesis, destabilization of otherwise stable atherosclerotic plaques and possible endothelial dysfunction, predisposing the patient to myocardial ischemia and type 1 myocardial infarction(56)–(58).

Arrhythmias:

In addition to myocardial infarction, pneumonia predisposes to new/worsening cardiac arrhythmias (symptomatic bradycardia, atrial fibrillation, ventricular fibrillation, ventricular tachycardia, and cardiac arrest) as well as new/worsening heart failure as demonstrated by Corrales-Medina (58), (59). Heart failure and cardiac arrhythmias are well-known causes of relative ischemic myocardial injury and elevated troponin levels. The increase in levels of serum inflammatory cytokines(60), (61) and disturbed hemodynamic homeostasis (due to hypoxia and reduced oxygen saturations) (62) brought about by severe pneumonia has been shown to be associated with new or worsening cardiac arrhythmias both during and post-hospitalization.

Heart Failure:

A significant association has been found between community-acquired pneumonia and heart failure. Pulmonary edema, lung fibrosis and the increased work of breathing in severe pneumonia all contribute to precipitate right ventricular failure and by

extension, left ventricular dysfunction/failure. Even though in a recent study, the risk of developing heart failure was higher for older patients with pneumonia, it has been shown that even younger patients who survive an episode of pneumonia are at increased risk of developing heart failure(63).

5.2 SIGNIFICANCE OF ELEVATED TROPONIN LEVELS IN PNEUMONIA

Pneumonia in hospitalized patients is associated with myocardial injury. A recent study showed that risk factors for elevated troponin levels in patients with pneumonia include older age, severe pneumonia, prior diagnosis of ischemic heart disease, increased diastolic blood pressure at presentation and elevated creatinine levels at presentation(65).

Another study demonstrated that the incidence of myocardial infarction surges to 15% in patients with severe pneumonia(62). The risk for myocardial infarction in this group of patients is most common during the 15 days following the diagnosis of pneumonia, with the greatest risk within the first 3 days(65).

Elevated troponin levels in patients with severe pneumonia have been shown to be a marker for higher risk of mortality and poor prognosis. Aliberti et al reported that the mortality rate for patients who developed myocardial infarction following pneumonia was higher (43%) than for those who developed other cardiovascular events (21%). This mortality risk is not only seen during hospital admission but can also be seen up to 1 - year post-hospitalization(66).

These patients were shown to be at greater risk for cardiac interventions such as cardiac catheterization and percutaneous coronary interventions. It was also discovered that patients with elevated troponin levels in the setting of severe pneumonia have lengthier hospital stays than those with normal troponin levels(64).

Because of these, the authors concluded that troponin levels can be seen as an important tool in risk stratification for patients hospitalized with pneumonia and therefore recommended that troponin measurements should be considered in all patients diagnosed for pneumonia(64).

6. ELEVATION OF CARDIAC TROPONIN IN PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Introduction

Acute respiratory distress syndrome is a manifestation of severe acute lung injury which is characterized by the abrupt onset of significant hypoxemia and bilateral pulmonary inflammatory infiltrates in the absence of cardiac failure. It is a syndrome of acute respiratory failure which presents with progressive arterial hypoxemia, dyspnea, and a marked increase in the work of breathing(67).

Bachofen and Weibel first described the pathology of acute respiratory distress syndrome(68). In the first 6 days of the syndrome (acute phase), there is evidence of interstitial and alveolar edema with accumulation of inflammatory mediators such as neutrophils, macrophages, and even erythrocytes in the alveoli. There is also evidence of alveolar endothelial and epithelial injury as well as prominent hyaline membranes in the alveoli. In the subacute phase (7 – 14 days), some of the alveolar edema would have been reabsorbed and there is evidence of attempts at repair with proliferation of alveolar epithelial type II cells, infiltration of fibroblasts and some evidence of collagen deposition. In the chronic phase (after 14 days), there is evidence of resolution of acute neutrophil infiltrates with more mononuclear cells such as alveolar macrophages in the alveoli. There is also increased fibrosis with ongoing alveolar epithelial repair.

6.1 Etiology of raised Cardiac troponin levels in ARDS

Acute respiratory distress syndrome is characterized by substantial cardiovascular strain and it can precipitate elevated cardiac troponin levels through several means:

Pulmonary hypertension:

The widespread alveolar epithelial and vascular endothelial damage in ARDS results in pulmonary vascular dysfunction and is characterized by hypoxia, increase in pulmonary arterial pressure, increase in pulmonary vascular resistance and ultimately pulmonary hypertension(69), (70). Increased right ventricular afterload results from this, impeding RV pumping function. Increasing severity of pulmonary vascular dysfunction can lead to right ventricular dilatation and right ventricular failure(71). RV failure will cause left ventricular failure and a fall in right coronary circulation/perfusion and ultimately resulting in ischemia myocardial infarction.

Myocardial necrosis:

ARDS is commonly associated with sepsis and septic shock and these two pathologies are known to be associated with high levels of circulating inflammatory cytokines such as tumor necrosis factor, leukotrienes, macrophage inhibitory factor and others. It is also associated with platelet sequestration and activation. In patients who already have atherosclerotic plaques in the coronary vasculature, the circulating inflammatory mediators can cause these plaques to become destabilized and rupture leading to type 1 myocardial infarction and subsequent release of troponins into the circulation. Apart from plaque destabilization, the widespread inflammation can induce myocardial apoptosis and myocardial dysfunction(72).

Mechanical Ventilation:

ARDS has also been shown to cause marked intrapulmonary shunting which leads to worsening of existing hypoxemia. In these patients, mechanical ventilation is instituted to maintain adequate tissue oxygenation. But Webb and Tierney have demonstrated that mechanical ventilation, especially at high volumes and high pressures, causes lung injury and damage(73).

Mechanical ventilation at high volumes has been shown to pose enough risks both for the uninjured and the injured lung. In the uninjured lung, high-volume mechanical ventilation causes increased permeability of the pulmonary vasculature initiating pulmonary edema(74), (75). In the injured lung, it causes enhanced development of pulmonary edema and also causes worsening of already existing edema(76), (77).

Several theories have been proposed to explain these detrimental effects of high-volume mechanical ventilation. Older theories proposed that it causes alveolar overdistension leading to capillary stress failure and ultimately capillary endothelial and alveolar epithelial injury. Newer theories proposed that it leads to the release of pro-inflammatory cytokines such as TNF-alpha and IL-1(70), (78).

This worsening pulmonary edema that results from mechanical ventilation in the setting of acute lung injury/acute respiratory distress syndrome will initiate pulmonary hypertension which will lead to right ventricular failure and by extension, left ventricular dysfunction. The resulting tachycardia (in an attempt to increase cardiac output) and also, the increasing ventilation-perfusion mismatch, together predispose to oxygen supply-demand mismatch in myocardial tissues, leading to type 2 myocardial infarction and elevated troponin levels.

6.2 SIGNIFICANCE OF TROPONIN ELEVATION IN ARDS

Elevation of cardiac biomarkers is a common finding in patients with acute respiratory distress syndrome. Metkus et al showed that about 56% out of the 1057 ARDS patients recruited into the study had high sensitivity assay-detected troponin levels that were above the 99th percentile upper reference limit(78).

Elevated troponin levels can be used for diagnostic purposes. It proved useful in early identification and diagnosis of ARDS in children with shock(79).

Elevated troponin levels in ARDS have been associated with increased mortality and worsened outcomes in survivors. Rivara et al found that ARDS non-survivors had significantly higher cardiac Troponin levels (0.042ng/mL) than survivors (0.022ng/mL). The study also demonstrated that elevated troponin levels in ARDS was associated with a higher chance of developing tricuspid regurgitation, regional wall motion abnormalities, multiple organ failure and need for mechanical ventilation(80).

In the study by Vasile et al, results showed that cardiac troponin levels had long-term prognostic value in patients who are being managed for acute respiratory distress syndrome. For this reason, they suggested that part of the initial management of patients with respiratory conditions should also focus on identifying myocardial injury(81).

However, a systematic review and meta-analysis by Jayasimhan et al of 22 different studies even though it described an association between elevated cardiac troponin levels and higher mortality rates, failed to find this association to be statistically significant- This was possibly due to small sample sizes in most of the studies included in the meta-analysis(82).

7. ELEVATION OF CARDIAC TROPONIN IN PATIENTS WITH SEVERE SEPSIS, SEPTIC SHOCK

Introduction

Sepsis is the most frequent reason for emergency admissions in the United Kingdom, accounting for about 248, 000 of cases(83). This disease state, defined as the presence of infection along with systemic features of inflammation, is a physiological reaction to severe infection with microbes(84).

Whereas severe sepsis is described as sepsis-induced hypoperfusion of tissues or dysfunction of organs, septic shock is defined as sepsis-induced hypoperfusion that does not respond to adequate fluid resuscitation; 30mls/kg of crystalloids(22).Whatever the severity of sepsis, it is often present in critically ill patients especially in the intensive care units and often, there is an observed raised cardiac troponin level. Although this cardiac tissue biomarker is also seen in other critically ill patients where it is often associated with increased mortality, in those patients with sepsis, the results are often heterogeneous and not easy to interpret(86).

According to(87), European intensive care units have > 34% patients developing sepsis at one point in time while on admission in the intensive care unit and about 27% of these patients die on admission, with the figure rising to >50% for patients with septic shock. This chapter will try to discuss the etiology of raised cardiac troponin in patients with sepsis and the possible significance of this.

7.1 Etiology of raised troponin levels in sepsis

The prevalence of elevated cardiac troponin levels in sepsis is about 43% generally. In intensive care patients who are septic, this rises to 61%(47). The mechanism of myocyte damage leading to this in severe sepsis and septic shock is not well understood especially in the absence of a clear thrombotic acute coronary syndrome (which is the primary cause of myocardial infarction-induced troponin elevation). Nevertheless, some potential mechanisms are considered and these include:

myocardial depressive factors (inflammatory mediators, endotoxins and pro-inflammatory cytokine release), microvascular dysfunction, increased myocardial oxygen demand supply mismatch(88).

It should be noted however, that in the setting of sepsis, elevated troponin has been observed in the absence of myocardial necrosis, supported by other studies that show that myocardial hypofunction in sepsis is reversible in patients who survive(87). There is yet, no confirmed evidence of the pathophysiologic mechanisms of elevated troponin in patients who have sepsis in the intensive care unit. However, the following underlying mechanisms have been proposed:

Oxygen demand- supply mismatch:

This theory is the most prevalent explanation for sepsis-related troponin elevation. In sepsis, the metabolic requirement of the heart is raised and in order to support and maintain the functioning of the heart, blood flow to the coronary system is increased. In patients with background anaemia and subclinical coronary artery disease, this state of increased oxygen demand easily results in a mismatch in the oxygen demand and supply, leading to ischaemia and raised troponin.

It is also thought that the hypotension of sepsis results in reduced coronary perfusion pressure, leading to a decreased blood flow to the myocytes and thus, elevated troponin(19). Two studies by Cunnion (86) and Dhainaut et al. (88) challenged this theory by demonstrating that in sepsis, coronary blood flow actually is increased. However, in a recent study, the author proposed that sepsis is characterized by a generalized or focal microvascular dysfunction that leads to myocardial ischaemia and elevated troponin(92). This ischemia is not dependent on increased demand.

Also, preexisting anaemia, tachycardia, and increased myocyte oxygen demand in sepsis theoretically may exacerbate ischaemia from microvascular dysfunction. Indeed, autopsy studies have revealed the presence of contraction band necrosis in the setting

of sepsis-related troponin elevation, and this suggests also that myocardial ischaemia might be involved in the development of sepsis-associated troponin elevation(88).

Direct myocarditis:

In the absence of coronary artery disease, bacteremia leading to cytokine (IL-1β, IL-6, TNF-α) and endotoxin release, and to microvascular dysfunction, endocarditis, myocardial depression and increased myocardial cell membrane permeability, have been suggested as possible mechanisms for sepsis-related elevation of troponin. Another suggestion is the release of caspase3 in gram-negative bacterial infection, leading to myocardial depression and dilatation of the ventricles. Since TNF-α causes increased permeability of endothelial cells to macromolecules and lower molecular weight solutes, studies have proposed that a similar increase in permeability of myocyte cell membrane may be the underlying mechanism of sepsis-related troponin elevation.

Other suggested mechanisms via which TNF-α causes depression of myocardial cells and elevation of troponin include: mediation of activation of sphingomylinase, suppression of nitric oxide and calcium transient pathway, regulation of intracellular proteases, effect on protein kinases, oxygen free radicals, and transcription of cytotoxic genes(19).

Free radicals and superoxide radicals:

In the setting of sepsis, there is activation of NADPH oxidase complexes in the mitochondria which leads to the formation of free radicals. These free radicals together with leukocyte-derived superoxide radicals are believed to lead to myocardial cell damage and apoptosis(88).

Elevated filling pressures and ventricular wall stress:

It is proposed that the elevated cardiac filling pressure in the ventricles leads to cardiac muscle wall stress and subsequent activation of intracellular signaling cascade and cardiac myocardial cells damage, resulting in micro necrosis and apoptosis(95).

7. 2 Significance of elevated troponin levels in patients with sepsis:

In his review article, Hussain (89) stated that majority of patients with sepsis, severe inflammatory response syndrome (SIRS) and septic shock who died in the intensive care unit were positive for cardiac troponin by the time of death, suggesting that elevation of troponin in sepsis may be an indicator of worse prognosis.

Fernandez et al. (98) defined a slight correlation between increased troponin levels and left ventricular systolic dysfunction in patients with sepsis. In the study by Ver Elst et al. (91), this correlation was found to be stronger. They found this to be true in 78% of patients who were positive for troponin as against 2% in those who were negative as measured using trans-oesophageal echocardiography.

Troponin increase in critically ill patients with sepsis has been associated with poor prognosis and high mortality. Also, a meta-analysis done until September 2010 showed that troponin elevation in sepsis had a strong association with increased mortality. Vaile et al in 2013 carried out a study in 923 critically ill patients who had sepsis and found that 67% of those who had elevated cardiac troponin had higher 30-day mortality compared with those who had normal troponin levels.

However, a prospective cohort study done as part of the vasopressin and septic shock trial showed that raised troponin did not predict increased mortality risk. It is not clear whether raised cardiac troponin levels have no value in prognosticating sepsis outcome as the possibility is considered of divergence arising from timing and

frequency in troponin measurement. Also, stated criteria for positivity in the different studies may have contributed to the variance in obtained results(98).

Elevation of troponin in patients without coronary thrombosis is multifactorial and a frequent finding in critically ill patients with sepsis. It is possible that myocardial dysfunction is the reason for this and can explain the association of troponin with increased mortality. On the other hand, elevated troponin might be a pointer to a more acute disease occurring alongside sepsis and therefore requires thorough investigation.

8. TROPONIN ELEVATION IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE LUNG DISEASE (COPD)

Introduction

Chronic obstructive lung disease (COPD) which is characterized by an irreversible limitation of air movement in the pulmonary tree has created a huge health burden worldwide, becoming a leading cause of morbidity and mortality especially in the industrialized world and in populations with an appreciable smoking culture. According to the Global Initiative for Chronic Obstructive Lung Disease, patients with chronic obstructive lung diseases during the course of their illness may experience acute exacerbations of symptoms (AECOPD). Comorbidities occur also and include osteoporosis, depression, weight loss, anaemia, lung cancer and cardiovascular diseases(99).

Indeed, patients with COPD are more frequently admitted to hospitals on account of comorbidities especially CVD even more so than on account of the lung disease itself as the two disease entities might arise from similar predisposing factors such as age, smoking, and sedentary lifestyle(100). Myocardial infarction in patients with COPD is therefore a frequent occurrence and several documented post mortem findings point to the fact that myocardial damage is frequently undiagnosed in patients with COPD(101).

In a retrospective study of patients with AECOPD in hospitals using conventional troponin assays, elevated troponin levels were found in 18 % -70% of subjects, and was found to be an indicator of worse prognosis(102). Furthermore, using a highly sensitive assay (hs-cTnT), Hoiseth et al. found that a raised hs-cTnT in AECOPD is a vital and independent determinant of prognosis and mortality and that this effect was more prominent in patients with tachycardia(96).

The underlying mechanisms of cardiac troponin elevation in AECOPD is not yet fully understood but is believed to be due to the chronic systemic and pulmonary inflammatory processes ongoing in the course of the disease and other factor like

elevated pressure in the pulmonary circulation, coronary heart disease, hypoxemia and tachycardia.

8.1 Etiology of elevation of troponin in acute exacerbation of COPD

A number of mechanisms have been suggested to explain cardiac troponin elevation in AECOPD and they include:

Elevated pressure in the pulmonary circulation:

Many patients who suffer COPD experience increased dyspnea, sputum production, chest tightness and cough(104). These symptoms are worsened during episodes of exacerbation with bronchoconstriction and excessive mucus production leading to alveolar hypoxemia. These episodes are known as acute exacerbations of COPD (AECOPD) and are an important event in the natural course of the disease.

A compensatory increase in pulmonary vascular resistance pulmonary hypertension ensues. The resultant reduction in blood flow through the pulmonary system causes systemic hypoxemia and tachycardia and subsequent myocardial injury.

Undiagnosed coronary heart disease:

COPD is frequently associated with CAD and the highest contributor of mortality in COPD patients is cardiovascular disease(98) smoking, a common risk factor shared by COPD and CVD predisposes patients to an increased risk of ischaemic heart disease. In a retrospective study by Brekke et al. (97), carried out to determine the prevalence of previous myocardial infarction in subjects on hospital admission for COPD exacerbation, only 30% of patients who met the criteria for previous MI using the

Cardiac Infarction Injury Score (CIIS) had a diagnosis of it in their medical records. Also, coronary artery calcification, a pathognomonic feature of CAD, has been observed to be more prevalent in COPD patients compared to the general population(99).

Myocardial infarction occurring on the background of CAD, can give rise to elevated cardiac troponin. Left ventricular dysfunction has also been observed in patients with COPD(98).

Hypoxemia and tachycardia:

Progressive airflow limitation and emphysema, a characteristic of COPD, is a potent driver of alveolar hypoxia and consequent hypoxemia(100). Another factor believed to contribute to hypoxemia in COPD patients is a dysregulation of ventilatory control as patients who have chronic airflow obstruction have been observed to have blunted ventilatory responses to hypoxia(101).

AECOPD are frequently associated with a deterioration in alveolar gas exchange and hypoxemia as a ventilation perfusion (V/Q) mismatch arising in these instances therefore create an imbalance in oxygen demand and supply, leading to myocardial infarction and consequent cardiac troponin elevation.

Tachycardia, a common finding in AECOPD, results in reduced coronary perfusion due to a decrease in diastolic time. In a study by Magnus et al. (102), resting heart rate was found to be increased with increasing COPD severity ($p<0.001$). It was also observed to be associated with increased mortality from both cardiovascular as well as other causes, consistent with all COPD stages ($p<0.001$).

Chronic systemic and pulmonary inflammation:

Macnee et al. (103) noted that systemic inflammation, along with oxidative stress and hypoxia contributes to increased cardiovascular risk in patients with impaired lung

function. In the setting of chronic inflammation, atherosclerotic plaque formation is initiated by injury to the vascular wall which is enhanced by inflammation and oxidative stress(104). This is believed to be a contributor to the increased prevalence of coronary heart disease in COPD patients. In states of acute exacerbation, an otherwise stable (silent) coronary plaque may either be disrupted, leading to Type 1 MI, or may manifest as Type 2 MI due to reduced coronary perfusion in the setting of increased oxygen demand(105).

8.2 CLINICAL SIGNIFICANCE OF ELEVATED CARDIAC TROPONIN IN AECOPD

Cardiovascular disease is the most important co-morbidity in COPD patients. Cardiac troponin elevation has been found to have prognostic significance during an acute exacerbation of chronic obstructive pulmonary disease(106).

In concordance with previous studies, Saleha found a strong relationship between cardiac troponin rise and the need for ICU admissions as well as supportive ventilation amongst COPD patients. However, the duration of ventilator use and hospital stay was not found to be significant statistically. Also, Baillard et al. (107) showed elevated cardiac troponin to be a significant pointer to increased risk of mortality during AECOPD although the prospective study by Saleha did not make this finding. Two studies(95), (98) have shown raised cardiac troponins I and T to be strongly associated with higher mortality rate during follow-up periods following an acute exacerbation of COPD.

A cross-sectional study by Brekka et al. (97) listed increased breathing effort, raised left ventricular afterload due to negative intrathoracic pressure, worsening of pulmonary hypertension, hypercapnia and hypoxemia, as possible mechanisms of elevation of cardiac troponin in AECOPD, similar mechanisms to the ones reported by (98).

It follows then that cardiac injury during exacerbation of COPD may affect the outcome of the disease in these patients. In the light of this, Saleha suggested that measuring the level of cardiac troponin I during the hospital stay of patients might help to identify

the subset of patients who are at greater risk. This, according to the author, could form the basis for appropriate and more aggressive treatment with the aim of positively altering the outcome of the disease and improving the patient's chances of survival(106).

9. TROPONIN ELEVATION IN PULMONARY ARTERIAL HYPERTENSION

Introduction

Pulmonary hypertension (PAH) is defined by a diminishing luminal size and remodeling of the pulmonary vessels, resulting in ongoing rise in pulmonary vascular resistance, the result of this being right ventricular overload, right ventricular failure (RVF) and premature death(108). Mortality remains high in patients suffering from PAH in spite of improvements in the understanding of the pathophysiology of the disease as well as the rise in importance of targeted therapy in clinical practice(109).

Although protocols exist which suggest how to streamline various therapeutic methods as regards the severity of the disease(110), the grading of risk levels in the patients have continued to prove difficult and most times relies on insufficient tools such as the symptoms evaluation using the New York Heart Association (NYHA) functional classification. Thus, there is need for the use of non-invasive biomarkers of the disease as such portends invaluable potential in aiding otherwise challenging therapeutic decisions.

Previous studies have shown that the detection of cardiac troponin in the circulation is a pointer to myocardial necrosis and is diagnostic of acute myocardial infarction in the presence of signs and symptoms of ischaemia (111). Asides coronary artery disease, other diseases such as left ventricular heart failure, chronic kidney disease, sepsis, and

critical illnesses give rise to cardiac troponin elevation. Elevated cardiac troponin has also been documented in pulmonary diseases including PAH. The possible mechanisms of the rise in troponin in patients who have PAH is myocardial necrosis which results from the cascading effects of pulmonary artery vascular resistance, backflow of blood in the right ventricle, and the resultant reduction in systemic blood pressure which has detrimental effect on the coronary blood flow, leading to injury and infarction of the myocardium(112).

9.1 ETIOLOGY OF ELEVATION OF CARDIAC TROPONIN IN PULMONARY ARTERIAL HYPERTENSION

The following mechanisms have been proposed to explain the phenomenon of raised cardiac troponin in patients with pulmonary arterial hypertension:

Myocardial Ischaemia

In his study carried out in 2012, Heresi alluded that myocardial ischaemia could be an important cause of the rise in troponin levels in patients with PAH. The increase in vascular resistance, which defines pulmonary arterial hypertension, results in rise in intramural pressure in the right ventricle and this eventually leads to a reduced cardiac output and lower systemic circulatory pressures. This is a ripe situation for the occurrence of myocardial ischaemia and necrosis as the lowered blood pressure results in insufficient coronary blood flow and thus infarction, with subsequent troponin exudation from the injured myocytes as observed in a quarter of the patients who took part in this study. The study further supported this theory by showing that the participants who tested positive for troponin (had detectable concentrations of the biomarker) had more right chamber dilatation and diminished function than those who did not have detectable levels of the protein.

Increased C - reactive protein (CRP) levels

Studies have shown a positive relationship between the levels of cardiac troponin and that of the acute phase reactant, C - reactive protein in the circulation of patients with pulmonary artery hypertension(113). CRP is a known clinical marker of inflammation, with increased serum CRP concentrations regarded as a strong independent indicator of cardiovascular disease in patients who are not yet showing symptoms(114). Pro-inflammatory cytokine-mediated CRP increase results in complement activation and further release of cytokines(113). The ensuing oxidative stress predisposes to myocardial injury.

In his study however, Heresi did not find any correlation, as even an increase in the concentration of C–reactive protein in these patients by up to 1 standard deviation was not associated with death by right ventricular failure in the setting of PAH. Nonetheless, some other studies have tended to disagree with this claim Quarck et al. (115) showed that there was decreased survival in patients with pulmonary hypertension with CRP levels above the upper limit of normal (5mg/L-1). Even as discrepancies in the statistical methods used for the various studies could be the reason for these contrasting findings, the role of CRP is still being studied as regards the etiology of elevated circulating levels of cardiac troponin in patients with PAH.

Regardless of the mechanism via which elevation of cardiac troponin occurs in patients with pulmonary arterial hypertension, the detection of troponin in them certainly holds appreciable significance.

9.2 SIGNIFICANCE OF ELEVATION OF CARDIAC TROPONIN IN PULMONARY ARTERIAL HYPERTENSION

Some studies, such as a recent French study have failed to show any association between the survival of patients with severe PAH and a rise in cardiac troponin, with the authors recommending further studies (116). However, more sensitive cardiac troponin assays have shown that detectable cardiac troponin levels was associated strongly with more advanced cases of PAH, as evidenced by the presence of more functional class symptoms such as dyspnea, tachycardia, increased peripheral effusion, shorter 6 minutes walking distance, larger right atrial area, and lower HDL concentrations.

The detection of cardiac troponin using high sensitivity assays depicts a 4.7 –fold increase in risk of mortality relating to right ventricular failure or transplant. There is also only a 36-month transplant free survival of 44.1% in these troponin positive patients with PAH as against 84.7% in those with undetectable levels of cardiac troponin. Even when adjusted individually with other covariates that are known to confound the outcomes in these patients such as age, idiopathic versus associated PAH, functional class, pericardial effusion, cardiac index, creatinine, as well as CRP and HDL – C, detectable levels of cardiac troponin was still predictive of worse outcomes(112).

In essence, the measurement of cardiac troponin might be of help in early identification and treatment of patients who are suffering from pulmonary hypertension and are at risk of having myocardial infarction(117).

10. ELEVATION OF CARDIAC TROPONIN IN PATIENTS WITH PULMONARY EMBOLISM

Introduction

Pulmonary embolism (PE) is the occlusion of the pulmonary artery or any of its branches by an embolus. An embolus is an intravascular solid, liquid, or gaseous mass that gets detached from its site of origin, carried through the circulatory system by blood and gets lodged at a distant site, leading to tissue dysfunction or ischemic damage. The most commonly implicated emboli in pulmonary embolism originate from thrombi in the deep veins of the legs (deep venous thrombosis – DVT). The location of the occlusion is determined by the size of the emboli: larger emboli can block the main trunk of the pulmonary artery or straddle the pulmonary artery bifurcation whereas smaller emboli can pass into the smaller branching arteries.

10. 1 Etiology of raised troponin levels in Pulmonary Embolism

Some proposed mechanisms of cardiac troponin elevation in pulmonary embolism include:

Right Ventricular dysfunction:

When 60% or more of the pulmonary circulation is obstructed by emboli, significant functional consequences can result. This massive PE causes a sudden increase in pulmonary resistance which translates back towards the right ventricle (RV), causing an increased intraventricular pressure in order to maintain the ventricular-to-pulmonary artery gradient. This leads to further increase in pulmonary arterial pressure and resistance.

A critical point is attained where further increase in pulmonary resistance leads to significant right ventricular dilatation, septal displacement, increased right ventricular end-diastolic pressure and eventually, right ventricular failure. Resultant reduction in RV output predisposes to reduced right coronary blood flow and ischemia of the right ventricular wall(118).

Demand - based Subendocardial Ventricular Ischemia:

In addition to right ventricular failure, acute pulmonary embolism can predispose to right ventricular wall ischemia and myocardial infarction even in the presence of normal coronary perfusion. This can result in such elevated troponin levels that can cause pulmonary embolism to be misdiagnosed as myocardial infarction(119). The right ventricular wall ischemia is most noticed in the subendocardial region of the right ventricle. Hsu et al reported that the prevalence of elevated cardiac troponin levels in patients with PE is 56%(120). Palmieri et al also reported that the prevalence of elevated cardiac troponin levels in PE was 57% if a cut-off value of 0.1ng/dL was chosen(121).

Cardiac arrhythmias:

Also, pulmonary embolism has been shown to predispose to cardiac arrhythmias. The electrocardiographic findings associated with pulmonary embolism include sinus tachycardia, atrial fibrillation, atrial tachycardia, non-specific ST segment/T wave changes, T wave inversions in the right precordial leads, rightward QRS complex axis shift and other axis changes, S1Q3 or S1Q3T3 pattern, right bundle branch block(122). These are supposedly as a result of ventricular wall ischemia and myocyte damage. These arrhythmias evidently predispose to elevated circulating cardiac troponin levels.

10.2 SIGNIFICANCE OF ELEVATED CARDIAC TROPONIN LEVELS IN PULMONARY EMBOLISM

Elevated cardiac troponins in pulmonary embolism have more value in assessing for disease severity and prognosis rather than as a diagnostic tool(123), (124).

Meyer et al and Kilinc et al compared troponin levels and echocardiographic findings and came to the conclusion that elevated cardiac troponin levels in the setting of acute pulmonary embolism is a huge pointer to right ventricular dysfunction and strain(13), (125).

In their respective studies, Amorim et al and Kucher et al found that higher levels of cardiac troponins were detected in patients with massive and sub-massive pulmonary embolism as compared to patients with non-massive pulmonary embolism(133)-(135). Also, electrocardiographic findings such as right bundle branch block, T wave changes and S1Q3T3 were more frequent in PE patients with higher cardiac troponin levels than in those with normal troponin levels(136).

Some studies have also shown that elevated troponin levels can be used to identify patients who are at high risk of short-term death and adverse outcome. A systematic review and meta-analysis of 46 studies conducted by El-Menyar et al. showed that the elevated troponin levels were associated with a high risk of mortality in patients with pulmonary embolism. The meta-analysis also showed that the all-cause mortality in patients with pulmonary embolism was significantly higher in patients who developed elevated troponin levels, even in patients with low-risk pulmonary embolism(125).

It appears that the higher the levels of cardiac troponins detected in cases of acute PE, the worse the risk of death and other associated adverse events. Conversely, undetectable troponin levels were shown to be associated with higher survival rates

(irrespective of clinical risks) than those with detectable troponins(137). The prognostic value of elevated troponin levels remained the same across several studies (consistent for troponin T and troponin I levels) regardless of the specific assay used and the relative cut-off point for troponin levels used.

CONCLUSION

Cardiac troponin elevation has been sufficiently demonstrated not to be solely diagnostic of MI but rather, equally caused by a myriad of illnesses, in some cases even not directly related to the heart. This invariably presents a diagnostic challenge for the emergency physician.

The right distinction between the various causes of myocardial infarction and myocardial injury carries considerable clinical significance. By informing early decision-making regarding treatment interventions, this helps to reduce burden on emergency care staff as well as cost of healthcare from unnecessary patient transfers to interventional facilities. In addition, it has considerable prognostic significance, as evidenced by numerous studies that describe an association between elevated cardiac troponin and severity of disease as well as adverse outcomes.

In terms of respiratory diseases, the picture may be more complicated considering that cardiac complications are common in these patients, mostly owing to similar risk factors. However, results are consistent regarding the prognostic value of cardiac troponin elevation in patients with respiratory disease in whom elevated cardiac troponin is associated with increased need for cardiac interventions such as catheterization and PCI, lengthier hospital stay, as well as increased mortality risk especially if myocardial infarction occurs.

In the light of these, the usefulness of cardiac troponin in risk stratification for pulmonary diseases and indeed many other illnesses is obvious. Therefore, in addition to clinical judgment and other useful management tools, cardiac troponin

measurements should be considered in patients admitted for severe respiratory illness in order to aid early identification of myocardial injury (whether acute, chronic or acute-on-chronic) and thus, possibly improve prognosis and quality of life.

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