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Early Evaluation of Cardiac Chest Pain – Beyond History and Electrocardiograph

Ghulam Naroo and Aysha Nazir
Rashid Hospital, Dubai
United Arab Emirates

1. Overview

Acute Coronary Syndrome (ACS) represents a continuous spectrum of disease including Unstable Angina (UA), acute non-ST elevation myocardial infarction (NSTEMI), and acute ST elevation myocardial infarction (STEMI). In spite of major advances in prevention and treatment, Acute Coronary Syndrome remains a leading cause of death as well as a major cause of hospital admissions both within Europe and worldwide.[1-3]

Recent advances have allowed for early detection and disposition of patients with Acute Coronary Syndrome. The first step in the management of patients with ACS is prompt recognition. The diagnosis of ACS is largely based on the history, the electrocardiogram (ECG) and changes in cardiac biomarkers. It is a universally acknowledged fact that history remains the most essential tool in directing the need for further workup which includes serial ECGs and measurement of cardiac biomarkers.

2. Diagnostic challenges

The ECG is an important diagnostic and risk stratification tool. Most patients who have UA/NSTEMI have some ECG changes, although the ECG may be normal in 1% to 6% of patients who have NSTEMI and in approximately 4% of patients who have UA.[4]ST elevation myocardial infarction (STEMI) is diagnosed by the symptoms and the characteristic ST elevation on the ECG. The other two variants of ACS, non-ST elevation myocardial infarction and unstable angina are differentiated from each other by the presence of positive cardiac biomarker in the former and the treatment varies accordingly.[5-7]

Of the number of available markers and assays that detect myocardial necrosis, the cardiac troponins T and I and the creatinine kinase–MB (CK-MB) isoform are the most commonly used, with troponins gaining acceptance as the markers of choice in ACS. These have achieved an important role in diagnostic, prognostic, and treatment pathways by virtue of their high degree of sensitivity and specificity and their relative ease of use and interpretation. However, troponins are detectable only 6 hours after myocardial injury and are measurable for up to 2 weeks.

For a patient presenting with a suspected acute MI, the characteristics of the chest pain and the ECG findings permit initial risk stratification. The gold standard in the care of a patient

with cardiac chest pain is that an ECG and an abbreviated history and physical examination be obtained within 10 minutes of patient arrival.[8]

The early diagnosis of acute myocardial infarction (AMI) is however sometimes difficult due to: [9]

1. Equivocal electrocardiogram (ECG) changes and other conditions with ECG changes that mimic acute myocardial infarction. Atypical chest pains with many differentials confuse to make a diagnosis.
2. Acute myocardial infarction patients without ST-segment elevation.
3. Delayed liberation and detection of cardiac markers of myocardial necrosis such as troponin and creatine kinase (CK).

Cardiac troponin is frequently not detected until after 4-6 hours and in many cases, repeated measurement is needed 8-12 hours after admission. The importance of early risk stratification in the management of acute myocardial infarction is emphasized in the American Heart Association task force guidelines.[10]Risk stratification is an important objective in the evaluation of patients with ACS. The presence of positive biomarkers indicates higher risk and worse prognosis.[11]

When initiating reperfusion therapy, door-to-needle time of less than or equal to 30 minutes for initiation of fibrinolytic therapy and a door-to-balloon time of less than or equal to 90 minutes for percutaneous coronary perfusion is the standard of care.[12-14]Although, more and more hospitals are meeting this benchmark, diagnosing and excluding ACS often poses a diagnostic challenge to the clinicians.[15]A misdiagnosis may lead to considerable increase in morbidity and mortality. An ideal marker which can predict the onset of the disease, could aid in reducing the deaths due to ACS.

3. Cardiac biomarkers

Acute myocardial infarction refers to irreversible myocardial necrosis caused by an imbalance between oxygen supply and demand. In 75% cases, plaque rupture or erosion leading to thrombus formation are the causes of acute coronary syndromes. Early diagnosis and subsequent reperfusion therapies within 4 to 6 hours of onset of symptoms can salvage myocardium at risk. Therefore, optimal markers of myocardial necrosis need to be rapidly detectable in blood.

Myocardial injury causes release into the extracellular space of intracellular constituents including detectable levels of a variety of biologically active cytosolic and structural proteins such as troponin, creatine kinase, myoglobin, lactate dehydrogenase, etc.

Cardiac biomarkers have characteristic release and clearance kinetics. However, the time to presentation and comorbidities that affect clearance may confound the interpretation of biomarkers. Myoglobin is the earliest biochemical marker of myocardial cell damage, and it is detectable in blood within 1 to 2 hours of myocyte damage. Blood levels of CK-MB may be detectable in blood after 4 to 6 hours of myocardial ischemia. [16] Cardiac troponins are elevated within 4 to 12 hours of symptom onset and remain elevated for 4 to 10 days. [17]

Based on these patterns of release and clearance, a diagnostic algorithm of serial biomarker measurements has been developed. Serial sampling of multiple cardiac markers beginning at the time of presentation is recommended currently. The sensitivity of serial measurements of multiple markers nears 100%, whereas the sensitivity of a single

measurement of any biomarker at the time of presentation is poor. The recommended time between the first and second blood draw is 6 to 7 hours. [18] If cardiac marker levels are not elevated but clinical suspicion remains high, a third set of markers should be drawn at 12 to 24 hours after presentation. [19] The markers currently used in this multimarker approach are myoglobin, CKMB, and troponin.

3.1 Myoglobin

Myoglobin is a heme protein found in the cytoplasm of cardiac and skeletal muscle cells that rises most rapidly after myocardial injury but is not cardiac-specific. [16] Myoglobin levels are frequently elevated in patients who have renal failure, skeletal muscle injury, trauma, and other diseases. Myoglobin is not used in most hospital laboratories.

3.2 Creatine kinase-MB isoform

CK-MB is an enzyme present primarily in cardiac muscle and active in energy generation. CK-MB is released rapidly after myocardial injury and is more cardiac-specific than myoglobin. However, CK-MB also comprises up to 5% of skeletal muscle and can be elevated in noncardiac disease states. Before the use of troponin, CK-MB was the gold standard for the biochemical diagnosis of AMI. CK-MB is released early during AMI, and it plays an important role in defining infarct size, infarct expansion, and reinfarction.[20]

3.3 Cardiac troponins

Cardiac troponins and tropomyosin form the thin filament component of the contractile structure in striated muscle. Troponins are released into the blood stream following irreversible ischemic myocardial cell injury and remain elevated for a prolonged time. There is no clinical difference between TnT and TnI for diagnosing cardiac necrosis. There are separate cardiac and skeletal isoforms of both TnI and TnT, allowing for the development of highly cardiac-specific assays. [17, 21] Troponin assays can detect as little as 1 g of myocardial tissue necrosis, and even minute elevations in cardiac troponins have been associated with myocardial necrosis and increased rate of short- and long-term mortality. [19,22-24]

Cardiac troponins have been studied in symptomatic and asymptomatic patients who have renal dysfunction. It is important that emergency physicians include the patient's history and physical examination when considering an elevated troponin level in patients who have renal dysfunction. In patients in whom acute coronary syndrome is not suspected, renal failure may be associated with chronic elevations of TnI and TnT, without evidence of acute myocardial necrosis. However, an acute increase from baseline troponin levels may be associated with increased mortality[25, 26]

Therefore, baseline troponin levels are helpful when differentiating between acute and chronic elevations in cardiac troponins. Elevated levels of cardiac troponins in patients who have renal dysfunction may be attributable to decreased renal clearance and increased release from cytoplasm because of the loss of membrane integrity. TnT is of higher molecular weight and is more commonly present in the free, unbound form in the cytoplasm, potentially explaining why TnT is more frequently elevated than TnI. [25] A study

of asymptomatic patients who had renal failure did not show TnI levels to be elevated in this population. The previously noted false-positive TnI results in patients who have renal failure were measured during acute disease states, including sepsis or pulmonary embolism, which may independently cause elevated troponin levels. [27]

In symptomatic patients who have chest pain and renal dysfunction, elevated levels of cardiac troponin predict patients at an increased risk for adverse cardiovascular outcomes. In a study of 7033 patients who had suspected acute coronary syndromes, the elevated levels of TnT were predictive of death or myocardial infarction across the spectrum of creatinine clearance. [28]

Despite the value of cardiac troponin as a very sensitive marker for myocardial damage, elevated troponin levels do not reflect the mechanism of damage and should not be used alone to diagnose myocardial infarction. Troponin levels may be elevated in patients who have myocarditis, pericarditis, decompensated heart failure, and septic shock. The use of troponin measurements as a screening tool in patients whose conditions have a low suspicion for ACS lowers the sensitivity and positive predictive value to 47% and 19%, respectively. A high sensitive troponin could be available in future to turn out an ideal biomarker for ACS. [29]

4. Heart-type fatty acid-binding protein

Heart-type fatty acid-binding protein (h-FABP) has been researched since 1988, due to its high potential as an early marker for myocardial infarction. It bears considerable resemblance to myoglobin in terms of size, location within the cell, release and clearance kinetics. It is a relatively low molecular mass cytoplasmic protein (15 kDa) available in abundance in myocardial tissue. [30-32]It is important for myocardial homeostasis since 50 – 80% of the heart's energy is provided by lipid oxidation and h-FABP ensures intracellular transport of insoluble fatty acids. It is released from the heart during cell necrosis, it diffuses much more rapidly than troponins through the interstitial space and appears in the circulation as early as 90 minutes after the onset of symptoms, reaching its peak within 6 hours and clearing within 24 hours.

This combination of early h-FABP release after symptom onset, rapid kidney clearance from the circulation and high cardiac specificity suggests great potential for its clinical use.[30-32]Therefore,it can be derived that h-FABP may not only be of value in detecting myocardial injury in the early hours of the insult but may also be ideal for the diagnosis of reinfarctions. H-FABP has been found to be superior to troponins due to its higher sensitivity.[33, 34]A recent study showed h-FABP had a sensitivity of 75.76% and a specificity of 96.97% compared with 58.59% and 98.94% for cTnT and 68.69% and 97.54% for CK-MB in the initial 6 hours after the onset of chest pain. [35]Recent data also suggests h-FABP may provide some prognostic information which appears superior to that of troponins. [36].

4.1 h-FABP in the pre-hospital setting

There is some evidence to suggest the utility of h-FABP in the pre-hospital setting.[37]According to the literature, early assessment of H-FABP in patients presenting with chest pain improves the diagnosis of an ongoing myocardial infarction. An h-FABP self-testing kit can be helpful in the pre-hospital setting. Though an h-FABP testing kit (h-

FABP Quanta) is used for the quantitative measurement, especially in next one hour of the initial testing to see if there is a rise of titre. This kit is more useful in emergency department/CCU and ICU setting. ConformitéEuropéenne (CE) certification approving it for sale in the European Union member countries.

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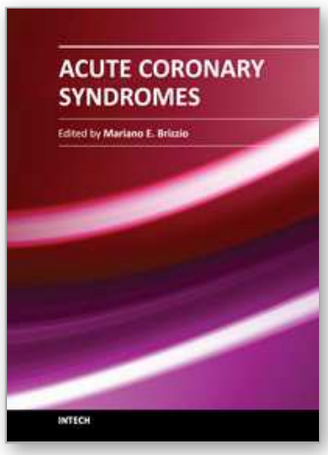

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This book has been written with the intention of providing an up-to-the minute review of acute coronary syndromes. Atherosclerotic coronary disease is still a leading cause of death within developed countries and not surprisingly, is significantly rising in others. Over the past decade the treatment of these syndromes has changed dramatically. The introduction of novel therapies has impacted the outcomes and surviving rates in such a way that the medical community need to be up to date almost on a "daily bases". It is hoped that this book will provide a timely update on acute coronary syndromes and prove to be an invaluable resource for practitioners seeking new and innovative ways to deliver the best possible care to their patients.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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