INTRODUCTION

Acute coronary syndrome encompasses a spectrum of coronary artery diseases, including unstable angina, ST-elevation myocardial infarction (STEMI; often referred to as "Q-wave myocardial infarction" and non-STEMI (NSTEMI); often referred to as "non–Q- wave myocardial infarction").

The term "acute coronary syndrome" is useful because the initial presentation and early management of unstable angina, STEMI, and NSTEMI frequently are similar.

QT dispersion represents the spatial heterogenecity of ventricular repolarization, which is defined as the dispersion of repolarization duration in simultaneously recorded leads.

QT dispersion is the difference between maximum and minimum QT interval occurring at any of the electrocardiographic leads. The underlying rationale is that the QT dispersion is likely to reflect heterogeneicities in recovery of excitability, a factor known to increase propensity for ventricular fibrillation.

QT dispersion has been proposed as a non-invasive measurement of the degree of in homogeneity in myocardial repolarization. From a practical point of view, grossly prolonged QT dispersion, perhaps ١٠٠ ms or greater, must be

interpreted simply as a sign of abnormal course of the repolarization.

QT dispersion is increased after myocardial infarction and levels are higher in patient with ventricular fibrillation, than those who did not develop ventricular fibrillation. The changes in QT dispersion are dynamic and may reflect the changing pattern of underlying ventricular recovery of ventricular excitability, which is profoundly disturbed in the earliest phase of acute infarction .The QT dispersion, might be a useful marker of cardiovascular morbidity and mortality.

The QTc dispersion, like signal averaging, can predict post myocardial infarction ventricular tachycardia inducibility. This has a clinical implication and it shed a new light on the mechanism of post myocardial infarction arrhythmogenesis.

The difference between the maximum and the minimum QT intervals to measure the QT dispersion found that increased QT dispersion may identify patient who have a high likelihood of having cardiac morbidity and mortality. Conversely, decrease QT dispersion appears to identify patients who have a very low probability of having cardiac morbidity and mortality that is why the measurement of the QT dispersion may improve the cost-effectiveness of electrophysiology testing in patients with ACS.

QT dispersion is of significant predictive value for prognosis of AMI. The QT dispersion in the surface ECG in patient with AMI prone to ventricular fibrillation may allow early identification of high risk patients soon after hospital admission.

The QT dispersion seems to be a powerful predictor of ventricular electrical instability as it can identify potential re-entry circuits for ventricular tachyarrhythmias

AIM OF THE WORK

The aim of this study is to assess the clinical value of QT dispersion and QTc dispersion in detection of myocardial injury in patients with non diagnostic initial ECG of acute coronary syndrome.

NON INVASIVE DIAGNOSTIC TOOLS FOR ACUTE CORONARY SYNDROME + RISK STRATIFICATIONS

Diagnosis of Acute Coronary Syndrome

Acute coronary syndrome encompasses a spectrum of coronary artery diseases, including unstable angina, ST-elevation myocardial infarction (STEMI; often referred to as "Q-wave myocardial infarction"), and non-STEMI (NSTEMI; often referred to as "non–Q- wave myocardial infarction"). The term "acute coronary syndrome" is useful because the initial presentation and early management of unstable angina, STEMI, and NSTEMI frequently are similar. Differentiating acute coronary syndrome from non cardiac chest pain is the primary diagnostic challenge.

The initial assessment requires a focused history (including risk factor analysis), a physical examination, an electrocardiogram (ECG) and, frequently, serum cardiac marker determinations.

Clinical Evaluation:

Symptoms of acute coronary syndrome include chest pain, referred pain, nausea, vomiting, dyspnea, diaphoresis, and lightheadedness. Some patients may present without chest pain; sudden dyspnea was the sole presenting feature in ٤ to ١٤ percent of patients with acute myocardial infarction. Pain may

be referred to either arm, the jaw, the neck, the back, or even the abdomen. Pain radiating to the shoulder, left arm, or both arms somewhat increases the likelihood of acute coronary syndrome ***(Goodacre et al., 2002)***, (likelihood ratio [LR]: (١،٦).

Typical angina is described as pain that is sub sternal, occurs on exertion, and is relieved with rest. Patients with all three of these features have a greater likelihood of having acute coronary syndrome than patients with none, one, or even two of these features. Chest pain that occurs suddenly at rest or in a young patient may suggest acute coronary vasospasm, which occurs in Prinzmetal's angina or with the use of cocaine or methamphetamine. Only about ٢ percent of patients ***(Feldman et al., 2000)*** with cocaine-associated chest pain have acute coronary syndrome.

Atypical symptoms do not necessarily rule out acute coronary syndrome ***(Cook et al., 1995)***. One study found the syndrome in ٢٢ percent of ٥٩٦ patients who presented to emergency departments with sharp or stabbing pain. However, a combination of atypical symptoms improves identification of low-risk patients. The same study demonstrated that patients presenting with sharp or stabbing pain, pleuritic pain, and positional chest pain had only a ٣ percent likelihood of having acute coronary syndrome ***(Goldberger et al., 1999).***

ECG Evaluation: will be discussed in chapter ٢.

Chemical markers of myocardial damage:

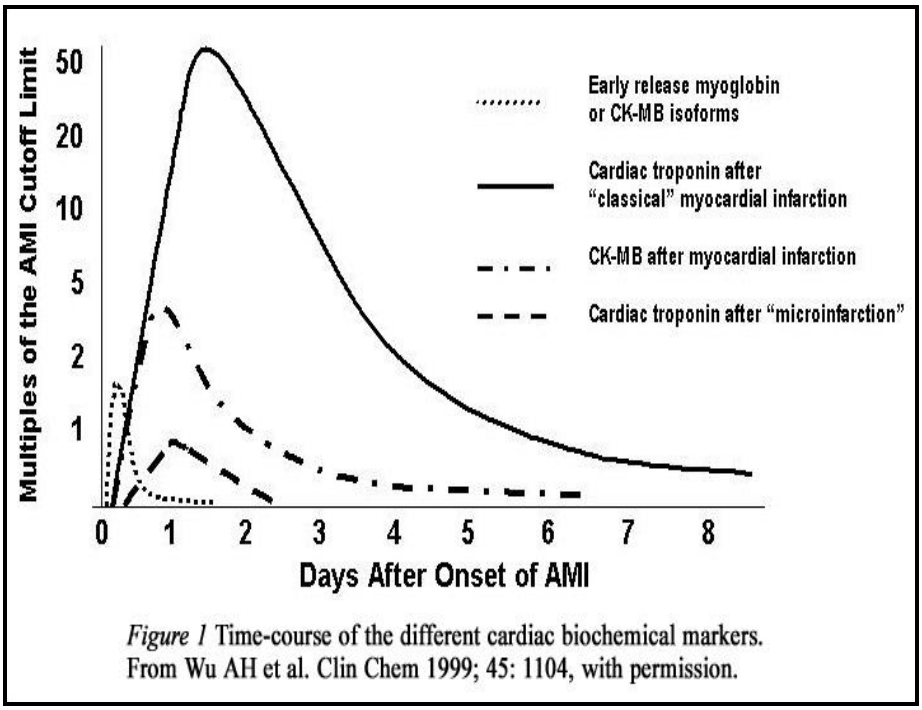

Figure 1 Time-course of the different cardiac biochemical markers.
From Wu AH et al. Clin Chem 1999; 45: 1104, with permission.

Fig. (١): Chemical markers of myocardial damage

Cardiac biomarkers are substances that are released into the blood when the heart is damaged. Measurement of these biomarkers is used to help diagnose, evaluate, and monitor patients with suspected acute coronary syndrome (ACS). The symptoms of ACS include chest pain, pressure, nausea, and/or shortness of breath. These symptoms are associated with heart attacks and angina, but they may also be seen with non-heart-related conditions. Increases in one or more cardiac biomarkers can identify patients with ACS, allowing rapid diagnosis and appropriate treatment of their condition

Cardiac troponin T or troponin I are the preferred markers of myocardial necrosis, because they are more specific and more reliable than traditional cardiac enzymes such as creatine kinas (CK) or its isoenzyme MB (CK-MB) in this setting. It is believed that any elevation of cardiac troponin T or I reflect irreversible myocardial cellular necrosis. In the setting of myocardial ischemia (chest pain, ST-segment changes) ***(AACC, 2007).***

Creatine kinase:

Creatine kinase (CK) is an enzyme that is found in striated muscle and tissues of the brain, kidney, lung, and gastrointestinal tract. This widely available marker has low sensitivity and specificity for cardiac damage. Furthermore, CK levels may be elevated in a number of non cardiac conditions, including trauma, seizures, renal insufficiency, hyperthermia, and hyperthyroidism. The serum CK level rises within three to eight hours after myocardial injury, peaks by ١٢ to ٢٤ hours, and returns to baseline within three to four days. A serum CK level may be used as a screening test to determine the need for more specific testing.

Although CK commonly was measured serially (along with CK-MB) at the time of hospital admission and six to ١٢ hours after admission, this marker largely has been replaced by cardiac troponins and CK-MB ***(Braunwald et al., 2000 and Karras et al., 2001).***

CK-MB Isoenzyme:

CK-MB is much more cardiac specific than CK alone, and is useful ***(Balk et al., 2001)*** for the early diagnosis of acute myocardial infarction. CK-MB typically is detectable in the serum four to six hours after the onset of ischemia, peaks in ١٢ to ٢٤ hours, and normalizes in two to three days.

The CK-MB mass assay is more sensitive than the CK-MB activity ***(Ann Emerg Med, 2000)*** assay. Like the CK level, the peak CK-MB level does not predict infarct size; however, it can be used to detect early reinfarction. Serial CK-MB levels commonly are obtained at admission to the emergency department and are repeated in six to ١٢ hours, depending on the assay ***(Ann Emerg Med, 2000)*** that is used.

CK-MB Subforms:

CK-MB may be further characterized into subforms (or isoforms). CK-MB٢ is found in myocardial tissue, and CK-MB١ is found in plasma ***(Puleo et al., 1989).*** The CK-MB subform assay takes about ٢٥ minutes to perform. CK-MB٢ level greater than ١ U per L in combination with a subform ratio greater than ١,٥ suggests myocardial injury ***(Puleo et al., ١٩٩٤)***. One large study involving ١,١١٠ patients with chest pain found that CK-MB subform analysis is ٩٦ percent sensitive and ٩٤ percent specific when the marker is measured

six hours after symptom onset. However, the CK-MB subform assay is not yet widely available.

This should be labeled as myocardial infarction according to the recent consensus document of the ESC and ACC ***(Davies et al., 1997).***

Troponin complex:

Is formed by three distinct structural proteins (troponin I, C, and T) and is located on the thin filament of the contractile apparatus in both skeletal and cardiac muscle regulating the calcium dependent interaction of myosin and actin. Cardiac isoforms for all three troponins are encoded by different genes and thus can be distinguished by monoclonal antibodies recognizing the distinct amino acid sequence ***(Katus et al., 1992 and Davies et al., 1997)***.

The cardiac isoforms of troponin T and I are exclusively expressed in cardiac myocytes. Accordingly, the detection of cardiac troponin T and troponin I is specific for myocardial damage, attributing these markers the role of a new gold standard ***(Jaffe et al., 2000).***

In conditions of 'false-positive' elevated CK-MB, such as skeletal muscle trauma, troponins will clarify any cardiac involvement. In patients with myocardial infarction an initial rise in troponins in peripheral blood is seen after ٣ to ٤ h due to

release from the cytosolic pool, with persistent elevation for up to ٢ weeks caused by proteolysis of the contractile apparatus. The high proportional rise of troponins, reflecting the low plasma troponin concentrations in healthy persons, allows the detection of myocardial damage in about one-third of patients presenting with acute coronary syndromes without elevated CK-MB. It is important to stress that other life threatening conditions presenting with chest pain, such as dissecting aortic aneurysm or pulmonary embolism, may also result in elevated troponin and should always be considered in the differential diagnosis ***(Lauer et al., 1997)***.

It should be appreciated that a single test for troponins on arrival of the patient in hospital is not sufficient, as in ١٠ to ١٥٪ of patients troponin deviations can be detected in subsequent h. In order to demonstrate or to exclude myocardial damage, repeated blood sampling and measurements are required ٦ to ١٢ h after admission and after any further episodes of severe chest pain. If the patient's last episode of chest pain was more than ١٢ h prior to the initial determination of troponin, a second sample may be omitted, in the absence of any other index of suspicion ***(Missov et al., 1997).***

Elevation of cardiac troponins also occurs in the setting of non-ischemic myocardial injury, e.g., myocarditis, severe congestive heart failure, pulmonary embolism, or cardio toxic chemotherapeutic agents ***(Giannitsis et al., 2000).***

This should not be labeled as false-positive test results, but rather reflect the sensitivity of the marker. True false-positive results have been documented for troponin T in the setting of skeletal myopathies or chronic renal failure and for troponin I related to interaction of the immunoassays with fibrin strands or heterophilic antibodies ***(Frankel et al., 1996, Smith et al., 1997, Laur et al., 1997 and Labugger et al., 2000)***.

Current assays have largely overcome these deficiencies, although infrequent false-positive results may still occur.

There is no fundamental difference between troponin T and troponin I testing. Differences between study results are predominantly explained by varying inclusion criteria, differences in sampling pattern and use of assays with different diagnostic cut-off. Only one manufacturer of troponin T assays is on the vehicle, while several manufacturers provide assays for troponin T.

The consensus committee's recommendations specify a diagnostic cut-off for myocardial infarction using cardiac troponins based on the ٩٩th percentile of levels among healthy controls rather than comparison to CK-MB.

Acceptable imprecision (coefficient of variation) at the ٩٩th percentile for each assay should be below ١٠٪. Each individual laboratory should regularly assess the range of reference values in their specific setting. For troponin T, cut-off

levels between ٠,٠١ and ٠,٠٣µg have been shown to be associated with adverse cardiac outcomes in acute coronary syndromes ***(FRISC II investigators, 1999 and Cannon et al., ٢٠٠١)***.

For troponin I the decision limits must be based on carefully conducted clinical studies for individual troponin I assays and should not be generalized between different troponin I assays. Slight or moderate elevations of troponins appear to carry the highest early risk in patients with acute coronary syndromes ***(Lindahl et al., 2001).***

If patients with acute coronary syndromes without ST-elevations stabilize clinically, there may be time delays before the diagnosis is confirmed and therapy is started. This may not be as critical as in ST-elevation myocardial infarction. Nevertheless, to rapidly establish the correct diagnosis relevant for prompt triage, point-of-care testing for biochemical markers may become advantageous. Point-of-care tests are assays that can be performed either directly at the bedside or at `near patient' locations such as the emergency department, chest pain evaluation centre or intensive care unit. The rationale for point-of-care testing is the potential for such tests to provide more rapid results. Point of care tests should be implemented when a central laboratory cannot consistently provide test results within ٤٥ to ٦٠ min ***(Wu et al., ١٩٩٩)***.

No special skill or prolonged training is required to read the result of these assays. Accordingly, these tests can be performed by a variety of members of the healthcare team after adequate training.

However, reading of these mostly qualitative tests is performed visually and therefore is observer dependent. A potential limitation is that visual assessment only allows a binary classification of test results without definitive information regarding the concentration of the marker in the blood. Careful reading, exactly at the assay-specific indicated time, under good illumination is essential to reduce observer misinterpretation especially in cases of marginal antibody binding. Even the faintest colouring should be read as a positive test result.

Myoglobin:

Myoglobin is a low-molecular-weight protein that is present in both cardiac and skeletal muscle. It can be detected in the serum as early as two hours after myocardial necrosis begins. Myoglobin has low cardiac specificity but high sensitivity, which makes it most useful for ruling out myocardial infarction if the level is normal in the first four to eight hours after the onset of symptoms.

Time changes in the Myoglobin value also can be extremely helpful. Combining a doubling of the baseline

Myoglobin level at two hours after symptom onset with an abnormal Myoglobin test at six hours after symptom onset increases the sensitivity to ٩٥ percent at six hours. Myoglobin should be used in conjunction with other serum markers, because its level peaks and falls rapidly in patients with ischemia ***(Marshall, 2005).***

Diagnostic imaging:

The appropriate use of diagnostic imaging in patients with acute coronary syndrome depends on proper identification of patients at intermediate risk. Patients at high risk or those with definite electrocardiographic criteria for acute MI are admitted to the hospital and undergo aggressive management, often with immediate coronary angiography and intervention. Patients at very low risk are discharged with close outpatient follow-up. Typically, patients at low risk have few or no cardiac risk factors, are stable hemodynamically and in cardiac electrical activity, are free of ongoing chest pain, and have normal electrocardiograms and serial cardiac biomarker levels ***(Wu, 2002)***.

Those patients who fall between these two extremes may be best served by imaging techniques designed to either reassign them to a low-risk group and allow for their discharge or recategorize them as being at high risk and manage their care aggressively. Graded exercise stress tests, exercise echocardiography, radionuclide myocardial perfusion imaging,