INTRODUCTION

Acute coronary syndromes (ACS) are a major cause of morbidity and mortality, accounting for up to 70% of deaths in patients with coronary artery disease. The causes of progression from an asymptomatic fibroatheromatous plaque to a vulnerable plaque which has higher risk for rupture and thrombosis, are not fully understood. Moreover, in over 60% of cases the culprit lesions responsible for an ACS are not flow-limiting on coronary angiography ***(Diego et al., 2011).***

The coronary angiogram (CAG) remains the gold-standard method for assessing coronary artery disease (CAD) ***(Hyuck and Seung, 2012).***

Multislice CT coronary angiography (MSCT) is a rapid diagnostic test that has the unique ability to noninvasively and accurately detect significant coronary artery stenosis and coronary atherosclerotic plaque Several smaller studies suggest that MSCT may be helpful to facilitate early triage in patients with acute chest pain However, the distribution of CT-angiographic findings of coronary artery disease such as plaque and stenosis and their association with ACS is not established. Such knowledge would provide the basis for the assessment of the clinical utility and the economic implications for using coronary CTA as an early triage tool ***(Udo et al., 2009).***

AIM OF THE WORK

1. To compare the coronary plaque burden in stable angina versus unstable angina as regard extent ,Type , size and anatomic distribution of plaque in all coronary segments using Multislice CT coronary angiography.

2. To determine the accuracy of Multislice CT coronary angiography in assessing the coronary plaque burden in comparison to convientional coronary angiography (CCA) in both stable and unstable angina patients.

Chapter one

BIOMARKERS

Cardiac biomarkers (CB) were first developed for assisting the diagnosis of cardiac events, especially acute myocardial infarction. The discoveries of other CB, the better understanding of cardiac disease process and the advancement in detection technology has pushed the applications of CB beyond the 'diagnosis' boundary. Not only the measurements of CB are more sensitive, the applications have now covered staging of cardiac disease, timing of cardiac events and prognostication. Further, CB has made their way to the intensive care setting where their uses are not just confined to cardiac related areas. With the better understanding of the CB properties, CB can now help detecting various acute processes such as pulmonary embolism, sepsis-related myocardial depression, acute heart failure, renal failure and acute lung injury ***(McLean and Huang, 2012).***

Blood cardiac biomarkers (CB) have become increasingly accurate for evaluating cardiac abnormalities during the past 40 years. Initially, with the focus on myocardial infarction (MI), the use of creatinine kinase-MB (CK-MB), first described in 1972, was a major step forward in the development of a highly cardiac-specific biomarker. The introduction of cardiac troponin (cTn) assays in 1989 was the next major advance, and subsequent refinement of the assays now has the definition of acute myocardial infarction (AMI) centered on it.

This progression ironically has brought considerable difficulties to the critical care physician who deals with multiorgan failure rather than the patient presenting to the emergency department with chest pain or single-organ pathology. The recent penetration of high-sensitivity (hs) cTn, replacing the fourth-generation cTn assays further compounds these diagnostic challenges ***(McLean and Huang, 2012).***

Moving beyond a sole focus on MI, the search for alternative and supplementary serum markers to assist in unravelling the presence, severity, and type of cardiac injury has been intense (Fig. 1). While cardiac ischemia/infarction is the most prevalent cause of cardiac injury with biomarker development reflecting this, the search for more meaningful biomarkers now includes CB for inflammatory processes and myocardial wall stress (as a result of pressure or volume overload) where evaluation extends beyond myocardial necrosis. The important role of C-reactive protein (CRP) as a prognostic marker is an example of the former while natriuretic peptides are now accepted as clinically useful markers of cardiac stress ***(McLean and Huang, 2012).***

Fig. (1): The development of cardiac biomarkers. ADM, adrenomedullin; BNP, B-type natriuretic peptide; CAM, cell adhesion molecule; CK-MB, creatine kinase-MB; CRP, C-reactive protein; cTn, cardiac troponin; H-FABP, human fatty-acid binding protein; HSP, heat shock protein; IL, interleukin; IMA, ischemia-modified albumin; INFγ, interferon γ; LP-LPA$_2$, lipoprotein-associated phospholipase A$_2$; PAPP, pregnancy-associated plasma protein; ROS, reactive oxygen species; sCD40L, soluble CD40 ligand ***(Blankesteijn et al., 2001).***

In the critical care setting, the challenge of confounding factors brings about interpretation difficulties. Clarity in diagnosis and/or guidance for management frequently present when the heart is the only organ affected, such as in the emergency department or cardiology ward, does not always hold in the intensive care unit (ICU) setting. Even so, an

understanding of the commonly used CB can be very helpful for cardiac evaluation of the critically ill patient ***(McLean and Huang, 2012).***

Classes of cardiac biomarkers

The search for clinically useful CB has resulted in a large number of circulating plasma substances being investigated. These can be broadly grouped temporally into three major categories: inflammatory, acute muscle injury, and cardiac stress (Fig. 2).

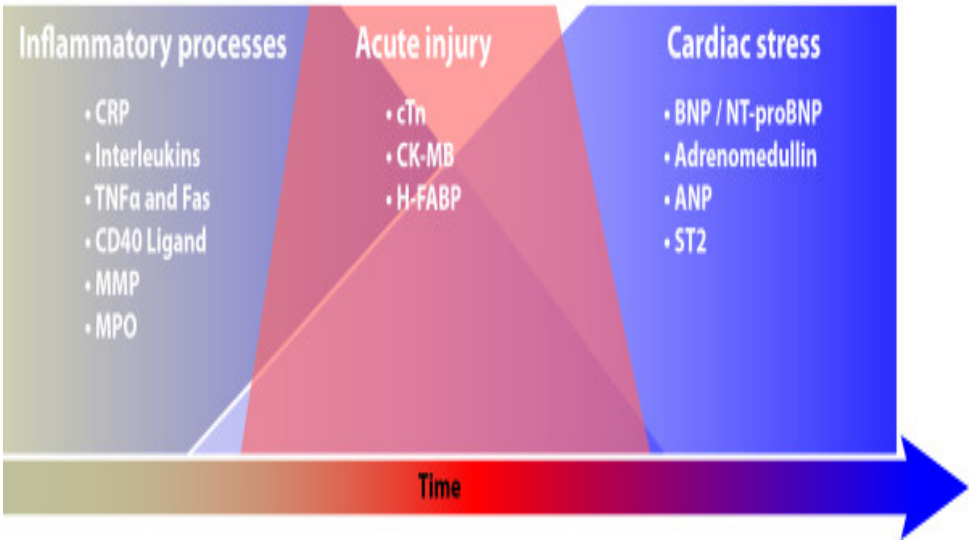

Fig. (2): Evolution of cardiac dysfunction and the associated changes in cardiac biomarkers. (see legend to Figure 1 for abbreviations) ***(McLean and Huang, 2012).***

Biomarkers for inflammatory processes

Cardiac wound healing after MI can be divided into four phases: phase 1 begins with the actual death of myocytes commencing within 6 hours and continuing for up to 4 days;

the phase 2 is that of an inflammatory response beginning 12-16 hours after onset of ischemia; phase 3 is when granulation tissue begins forming at the infarct border zone; and phase 4 consists of remodeling and repair and begins at 2-3 weeks, persisting for up to a year ***(Blankesteijn et al., 2001).***

Although a number of immune mediators, including cytokines, autoantibodies to myosin and tropomyosin, as well as interferon (IFN)-γ have been closely studied, clinically useful circulating inflammatory biomarkers to assist in the diagnosis and prognosis of AMI have yet to be established ***(McLean and Huang, 2012).***

Where an infective agent is responsible for myocardial damage, acute viral myocarditis being the prototype, once again clinically helpful inflammatory biomarkers are not available. Temporally, three phases exist when myocardial damage is due to infection: 1) myocyte destruction by the virus; 2) an innate immune response, which ultimately may cause more harm than good; and 3) possible myocardial damage, resulting in a dilated cardiomyopathy, and where once again, autoantibodies may play a role ***(Caforio et al., 2002).***

What often is overlooked is the role of inflammation in the progression of coronary artery disease (CAD), even in the absence of myocardial necrosis, and here the role of inflammatory markers hold more promise ***(Packard et al., 2008).*** Unfortunately in the critical care setting, where organs other than the heart are usually compromised, the specificity of

these markers, including tumor necrosis factor (TNF)-α, CD-40L, interleukins (IL-18, IL-6, IL-33, and IL-1a), CRP, fibrinogen, pentraxin 3, and matrix metalloproteinases, are markedly compromised. The potential of inflammatory markers is promising however, and even in apparently nonimmune settings, such as emotional stress-induced acute onset cardiomyopathy, inflammatory pathways appear to play a pivotal part ***(Wittstein et al., 2005).***

Biomarkers of myocardial injury

Cardiac troponins (cTn)

Cardiac troponin is a well established biomarker for diagnosis and prognosis of ACS. The data for troponins in ACS is robust even at minimally elevated levels. Measurement of cTnT and cTnI is now the crucial step in new diagnostic criteria for MI ***(Panteghini et al., 2004).***

cTn typically increases more than 20 times above the upper limit of the reference range in myocardial infarction as compared to creatine kinase-myocardial band (CK-MB) which usually increases 10 times above the reference range. This provides an improved signal - to - noise ratio, enabling the detection of even minor degree of necrosis with troponin. The cTn begins to elevate 3 h from the onset of chest pain in MI. Because of the continuous release, cTn elevation persists for days (cTnI: 7-10 days, cTnT: 10-14 days). This prolonged course of release with troponin is advantageous for the late diagnosis of MI, however, it limits the diagnosis of early reinfarction ***(Roy, 2010).***

Data comparing the two cTn suggest that cTnI may be slightly more sensitive. However, this may be due to different release kinetics of the two biomarkers and to different limits of detection of the currently available assays ***(Hamm, 1997).***

The evolving story of cTn to diagnose acute myocardial damage is as fascinating as it is beginning. The troponin era of enzyme immunoassay for TnT was in 1989 ***(Dolci et al., 2006).*** Evolution of these developments now has cTn as the central component of the definition of an AMI ***(Thygesen et al., 2007).*** The superior diagnostic power of cTn is demonstrated by correlation with histological findings ***(Ooi et al., 2000).*** A diagnosis of AMI is predicted on the detection of an increase or decrease of cTn, with at least one value > 99% percentile upper reference limit (URL) in patients with evidence of myocardial ischemia. This evolution extended the role of Tn from being a marker only for AMI to that of ACS and secondary myocardial damage from conditions, such as pulmonary embolus (PE), cardiac trauma, and chemotherapy-induced myocardial damage. The latest step in the evolution is the development and rapid uptake of the hs-cTn assays around the world.

Comparison of cTnT and cTnI

The cTn complex, consisting of three proteins (C, I, and T) encoded by different genes, plays a pivotal role in the modulation of calcium-dependant sarcomere contraction ***(Parmacek et al., 2004).*** cTnI and cTnT have cardio-specific isoforms not found in skeletal muscle, making for highly specific markers of myocardial damage. Both cTnI and cTnT are released from necrotic myocardium, ischemic and

nonischemic-induced, as intact proteins and degradation products ***(Hessel et al., 2008).*** Although experimental data indicates that cTn only leaks out of the cell after cell death, the finding of cTn in marathon runners and after inducible myocardial ischemia, raises the possibility of it occurring in the absence of necrosis ***(McLean and Huang, 2012).***

The cTnT assay is only available from one manufacturer, whereas cTnI assays are available from a number of vendors, rendering interpretation confusing because of the lack of standardization. It is important that the clinician has an understanding of the assay used in their institution, including analytical quality and limitations. Increasing sophistication of the assays has resulted in fewer false-negatives and false-positives; however, the presence of cTn autoantibodies in the blood or marked hemolysis can produce inaccurate results ***(McLean and Huang, 2012).***

cTn as a diagnostic marker

The central consideration in the interpretation of an elevated serum cTn is that it is a marker of myocardial damage, but on its own it does not determine the etiology of the damage. cTnT and cTnI demonstrate similar diagnostic ability in detection of myocardial damage despite analytical differences ***(Panteghini et al., 2002).*** The criteria for diagnosing an AMI are a rising or falling pattern of blood cTn levels in association with clinical features of myocardial ischemia. An international taskforce comprising of the American Heart Association/World Health Foundation/European Society of Cardiology/American College of

Cardiology Foundation (AHA/WHF/ESC/ACCF) recommends a cutoff value set at 99th percentile of URL, or the concentration at which the assay achieves a coefficient of variation of 10% if that exceeds the 99th percentile ***(Thygesen et al., 2007).*** Clinical features of AMI include classical symptoms, ECG changes, regional wall motion abnormalities, or imaging evidence of new loss of viable myocardium. In the absence of these features, an alternative cause of the cTn elevation and myocardial damage should be sought (Table 1).

Table (1): Conditions commonly associated with cTn elevations

Arrhythmias*
Aortic dissection*
Acute heart failure*
Coronary vasospasm*
Cardiomyopathy, e.g., postpartum
Coronary vasculitis, e.g., SLE, Kawasaki Syndrome* Cardiac contusion
Chemotherapy
Hypertension*
Myocarditis
Pulmonary embolus
Sepsis/septic shock
Takotsubo cardiomyopathy
Renal failure
Severe neurological disorders
Pulmonary hypertension - severe
Radiofrequency ablation*
Pericarditis
Extreme exertion

* Elevations of cTn in the absence of overt ischemic heart disease or in the patient with normal coronary arteries include those patients with myocardial ischemia from noncoronary disease, and by definition come into the MI type II classification. Certain conditions result in chronic elevations of cTn, including chronic renal failure, chronic heart failure, stable CAD, marked left ventricular wall hypertrophy, and aortic stenosis.

(McLean and Huang, 2012)

The timing of cTn elevations becomes increasingly important with the development of more sensitive assays and an understanding of the manner in which cTn is released from the damaged myocyte is helpful. An acute process involves a rise and fall with an increase occurring 2-4 hours after symptoms and remaining elevated for 7-14 days. Therefore, serial measurements, usually 3-6 hours apart are recommended ***(Wu et al., 2008).*** The less sensitive cTn assays require significant elevations, whereas the newer hs-cTn assay requires smaller ones. Biological variation may become more important at these lower levels bringing other challenges to interpreting the result ***(Wu et al., 2009).*** If the initial cTn level is not elevated, then serial measurements over 6-9 hours are necessary. If this second sample is still not elevated but clinical suspicion of an MI remains high, then a further sample at 12-24 hours should be considered. An earlier resampling at 3 hours still provides approximately 80% sensitivity in detecting AMI ***(McRae et al., 2006),*** Age seems to be a confounding factor, a study that included 1, 098 patients who underwent a single hs-cTn sample on presentation to the emergency department with symptoms suggestive of an AMI identified the best cutoff value, separating AMIs from non-AMIs, to be much higher. The hs-cTnT value for patients older than aged 70 years at 54 ng/l was nearly four times the 99^{th} percentile in AMIs, although close to the 99^{th} percentile in non AMIs. ***(Reiter et al., 2011).***

The introduction of hs-cTn, with precision sensitivity improved from the μg/l to the ng/l range, has enhanced the sensitivity and reduced the time to diagnose AMI in the acute

setting. The use of a single hs-cTnI measurement at 3 hours in patients presenting with chest pain, using a cutoff of 40 ng/l, gave a negative predictive value (NPV) of 84.1% and positive predictive value (PPV) of 86.7%; these findings predicted a 30% increase in cTn levels at 6 hours ***(Keller et al., 2009).*** The diagnostic accuracy of a number of different hs-cTn assays were found to be excellent and much superior to the standard assays ***(Reichlin et al., 2009).*** Interpretation is reliant upon the baseline level, the increase at a selected time interval (usually 6 hours), and the clinical setting. For example, whereas hs-cTnT assay has a cutoff value of 14 ng/l, a second sample at 6 hours is recommended when the value is between 14-100 ng/l to improve the specificity and PPV of the assay. A single reading above 100 ng/l is considered a high risk for ACS and warrants management accordingly. When testing for the optimal change of cTnI, Apple found a $\geq$ 30% increase from baseline (admission) level in the 4-10 hours follow-up measurements provided a sensitivity of 71% and specificity of 91% ***(Apple et al., 2009).*** Giannitsis and associates demonstrated that, compared with the 4^{th} generation cTnT, the admission hs-cTnT assay (at a cutoff of 99^{th} percentile) detected more evolving non-STEMI cases (61.5% vs. 7.7%). The detection by hs-cTnT further improved to 100% within 6 hours. The overall diagnosis of MI increased by 34.6% ***(Giannitsis et al., 2010).*** A doubling of the hs-cTnT concentration within 3 hours in the presence of a second concentration $\geq$ 99^{th} percentile is associated with a PPV of 100% and NPV of 88% ***(McLean and Huang, 2012).***

Such an approach, or a variant of it, is suitable for the development of protocols in the emergency department but unfortunately less so in the ICU where confounding issues are present.

The sedated hemodynamically unstable patient on positive pressure ventilation does not usually provide the classical symptoms of myocardial ischemia. ECG changes, often on a background of an already abnormal ECG, are nonspecific, and confounding factors, such as renal failure or heart failure, are present. Many conditions commonly found in an ICU are associated with elevated cTn levels, even in the absence of definite coronary artery pathology leading to myocardial ischemia (Table 1). Added to this is the likelihood that many MI will be a type II class as described in the international consensus guidelines (Table 2).

Table (2): Different types of myocardial infarction

Types of myocardial infarction	Clinical classification
Type 1	Spontaneous myocardial infarction related to ischemia due to primary coronary event.
Type 2	Myocardial infarction secondary to ischemia due to increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension.
Type 3	Sudden, unexpected cardiac death with symptoms and signs of cardiac ischemia. Death occurs before blood cardiac biomarkers able to be measured.
Type 4a	Myocardial infarction associated with percutaneous Intervention.
Type 4b	Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5	Myocardial infarction associated with coronary artery bypass surgery.

(McLean and Huang, 2012)

The advent of hs-cTn brings a definite improvement in diagnostic accuracy but at the expense of lower specificity, a challenge already encountered on a daily basis in the ICU with standard assays. However, this development should be seen as a positive step with the higher diagnostic accuracy, but further studies in the critically ill population are required to better define its use in this population.