CARDIAC BIOMARKERS USE AND RELEVANCE IN CRITICAL CARE

An essay

Submitted for partial fulfillment of
Master degree in intensive care

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2012

ACKNOWLEDGEMENTS

First of all my deepest gratitude and extreme thanks to Allah the Most Greatful, the Most Merciful.

I would like to express my thanks, appreciation and profound gratitude to Professor ***Dr. Mohamed Ismail Abdel-Fatah Elseady***, Professor of Anaesthesiology & Intensive Care, Faculty of Medicine, Ain Shams University, for his kind supervision, careful guidance, endless patience, great effort and continuous help throughout the course of this work.

I would like also to express my everlasting gratitude and sincere thanks to *Dr.* ***Adel Mohamed Alansary*** , Assistant Professor of Anaesthesiology & Intensive Care, Faculty of Medicine, Ain Shams University for his valuable advice, endless support, kind supervision, continuous encouragement and generous help throughout the whole work.

I wish to thank *Dr.* ***Mohamed Abdel-Salam Algendy***, Lecturer of Anaesthesiology & Intensive Care, Faculty of Medicine, Ain Shams University, for his great help, suggestions, efforts, encouragement and support helped to put this work in its final shape.

Finally, my deepest thanks and gratitude are due to my father and mother for the considerable patience they have shown and the great care they have given so as to smooth the rough edge of this work.

Wishing this work be beneficial in the medical field, I hope it will satisfy you all.

Thanks

Mohammed Elsayed Ali Ibrahim

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AIM OF THE WORK

To explain the importance of cardiac biomarkers in the critical care unit and emergency department through identifying risk-stratification and prognosis in critically ill patients.

Introduction

Introduction

The earliest blood biomarkers of cardiac injury and disease were activity-based assays to cytosolic myocardial enzymes. These included aspartate aminotransferase (AST) which was first described in 1950s, lactate dehydrogenase (LDH), and creatine kinase (CK). These enzymatic assays were found to be of most use as screening tests for ischemic myocardial necrosis brought about by acute myocardial infarction. These first-generation lacked cardiac specificity.CK isoenzymes are subsequently described in1970's.Troponin I first described as a biomarker specific for AMI in 1987 and Troponin T in 1989**.** Cardiac biomarkers are measured by immunoassay methods. National Academy of Clinical Biochemistry recommendations specify that cardiac markers should be available on an immediate basis 24 hours per day, 7 days per week Both quantitative and qualitative assays with a turnaround time of 1 hour (**Wang TJ, 2007)**.

The cardiac biomarkers that routinely used to diagnose and risk stratify patients with chest pain include cardiac troponin (I and T), CK-MB, myoglobin, and others. On the basis of improved sensitivity and superior tissue-specificity compared to the other available biomarkers of necrosis, cardiac troponin is the preferred biomarker for detection of myocardial infarction. CK-MB is an acceptable alternative

biomarker when cardiac troponin is not available. Measurement of high sensitive - CRP and B-type natriuretic peptide(BNP) or N-terminal pro-BNP(NT-proBNP) may be useful, in addition to a cardiac troponin for risk assessment in patients with a ACS. It is important to note that cardiac biomarkers are markers of all heart muscle damage, not just myocardial infarction. Other conditions that directly or indirectly lead to heart muscle injury can increase cardiac biomarkers where they predict mortality rate and prognosis outcome such as patients with acute and chronic heart failure, chronic renal failure (CRF) who are on hemodialysis , tachyarrhythmia , pulmonary embolism, Sepsis , cerebro-vascular stroke and subarachnoid hemorrhage (**Storrow ,2006)**.

The novel approach and future of cardiac biomarkers will likely be in developing earlier, more assays that may detect myocardial ischemia before complete myocardial infarction .For example, cytosolic proteins such as heart specific fatty acid binding protein (hFABP) has recently been shown to be more sensitive than troponin in myocardial infarction. One of the undergoing clinical studies shown that the measurement of ischemic modified albumin (IMA) can detect myocardial ischemia before myocardial infarction **(Niizeki T ,2007).**

Biochemical Assay of Cardiac Biomarkers

In 2001, the National Institutes of Health (NIH) working group standardized the definition of a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" and defined types of biomarkers (**Arthur J, 2001)**.

Accordingly, biomarkers can be classified as antecedent biomarkers (identifying the risk of developing an illness), screening biomarkers (screening for subclinical disease), diagnostic biomarkers (recognizing overt disease), staging biomarkers (Categorizing disease severity), or prognostic biomarkers (predicting future disease course, including recurrence and response to therapy, and monitoring efficacy of therapy) (**Arthur J, 2001)**.

A biomarker may be measured on a biosample (as a blood, urine, or tissue test), it may be a recording obtained from a person (blood pressure, Electrocardiogram (ECG), or Holter), or it may be an imaging test (echocardiogram or computed tomography (CT) scan (**Arthur J, 2001)**.

Characteristics of an Ideal Biomarker

The desirable properties of biomarkers vary with their intended use. For screening biomarkers, features such as high sensitivity, specificity, and predictive values, low costs, rapid

sustained elevation, high tissue specificity, release proportional to disease extent, and assay features conducive to point-of-care testing are critical and important **(Manolio T, 2003).**

Table 1 show: Ideal characteristics of cardiac necrosis biomarkers

•**Absolute cardiac specificity:** Biomarkers should have absolute cardio- specificity without cross - reactivity with other tissues under any physiological or pathological conditions. •**Specific for irreversible injury:** Biomarkers must differentiate reversible (ischemia) from irreversible (necrosis) injury. •**Early release**: Biomarkers should be released shortly after necrosis. Lower molecular weight biomarkers generally have faster release kinetics. Release kinetics of soluble cytoplasmic biomarkers is theoretically faster than that of structural biomarkers. •**Sensitivity:** The marker should be able to detect very minute quantities of the marker released into serum from the damaged myocardium •**High tissue sensitivity**: Biomarkers should be abundant in cardiac tissue and absent in blood under all pathological conditions except necrosis. Biomarker release should be robust. • **Predictable clearance**: Clearance kinetics should be dynamic; predictable, to allow modeling; and unaffected by comorbidities such as renal insufficiency or hepatic injury. Predictable clearance also allows detection of recurrent events such as reocclusion and assessment timing of the necrosis event. •**Complete release**: Myocyte release should be complete. Release should be in direct proportion to the extent of necrosis (infarct sizing).

Prevalence: is defined as the prior probability of the disease before the test is performed.

•**Measurable by conventional methods**: The nature of the biomarker should allow quantitative measurement by reliable, rapid, precise, and cost-effective methodology that is readily available.

Adapted from (**Arthur J, 2001)**

Defining Abnormal Biomarker Values

Defining abnormal values is a critical step before the clinical use of a biomarker. At least three potential approaches exist for defining abnormal biomarker levels. Reference limits are generated with the use of cross-sectional analyses of a reference sample and an arbitrary percentile cut point (typically the 95th or 97.5th percentile) is chosen to define abnormality. The reference range is the interval between the minimum and the maximum reference values (**LaBaer J, 2005).**

Cut points that define abnormality are typically the lower and the upper bounds of the 95% reference interval (between the lower 2.5th percentile and upper 97.5th percentile), but they may vary on the basis of the intent. The reference interval may be moved up or down according to the tradeoff between the implications (medical, ethical, social,

psychological, and economic) of false-negative and false-positive results, i.e., the consequences of missing disease, the availability and efficacy of treatment for people with abnormal values, and the costs associated with follow-up of abnormal results (**Apple FS, 2005).**

For instance, the 99th percentile value has been used to define an abnormal troponin or creatine kinase–MB value; values exceeding this limit would indicate the presence of myocardial necrosis and an acute MI. When less specific markers of myocardial necrosis are used, a higher threshold may be used; for example, if total creatine kinase is used for the diagnosis ofacute MI, a value twice the upper reference limit is recommended (**Apple FS, 2005).**

Current cardiac biomarkers include:

1- **Creatine kinase(CK)**
2- **Lactate dehydrogenase(LDH)**
3- **Troponin (Tn)**
4- **Myoglobin**
5- **Natriuretic peptides (NPs)**