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Diagnostics on acute myocardial infarction: Cardiac troponin biomarkers

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ABSTRACT

Acute myocardial infarction or myocardial infarction (MI) is a major health problem, due to diminished flow of blood to the heart, leads to higher rates of mortality and morbidity. Data from World Health Organization (WHO) accounted 30% of global death annually and expected more than 23 million die annually by 2030. This fatal effects trigger the need of appropriate biomarkers for early diagnosis, thus countermeasure can be taken. At the moment, the most specific markers for cardiac injury are cardiac troponin I (cTnI) and cardiac troponin T (cTnT) which have been considered as 'gold standard'. Due to higher specificity, determination of the level of cardiac troponins became a predominant indicator for MI. Several ways of diagnostics have been formulated, which include enzyme-linked immunosorbent assay, chemiluminescent, fluoro-immunoassays, electrical detections, surface plasmon resonance, and colorimetric protein assay. This review represents and elucidates the strategies, methods and detection levels involved in these diagnostics on cardiac superior biomarkers. The advancement, sensitivity, and limitations of each method are also discussed. In addition, it concludes with a discussion on the point-of care (POC) assay for a fast, accurate and ability of handling small sample measurement of cardiac biomarker.

Contents

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1. Introduction

James Bryan Herrick, an American physician was among the first to describe the symptoms of myocardial infarction (MI) (James, 2000). Herrick (1912) suggested, the symptoms and abnormalities of heart attacks was led by thrombosis in the coronary artery and this was not inevitable fatal. Thrombosis is obstruction of the blood flow through the circulatory system due to the formation of a blood clot inside a blood vessel. According to the pathology, MI is defined as myocardial necrosis (cell death) due to prolonged ischemia, reduction of blood supply to the heart (Thygesen et al., 2007). It is considered as the main cause of death and disability globally, and estimated 17.3 million people died in 2008, which over 80% of death take place in low- and middle-income countries. Moreover, by 2030, it is expected 23.3 million will die annually from cardiovascular disease (WHO, 2014).

Electrocardiograms (ECG) are a current method to measure and diagnose abnormal rhythms of the heart and helps to diagnose damage to the conductive tissue that carries electrical signals. However, ECG lacks sensitivity, although still remained as the recommended test to identify patients with MI (Zhang and Ning, 2012). The primary limitation of ECG is that only electrocardiographic activity at a single moment in time is represented; thus it usually needs to be done multiple times as a patient's clinical condition changes (Leisy et al., 2013). The second limitation is a subjective interpretation in the final analysis by the reading physician even though wave-pattern recognition and comparison with expected normal findings are used in ECG assessment. Thirdly, ECG is not useful for patients with non-ST segment (the contraction waves segment in the ECG representation) elevation myocardial infarction (NSTEMI), and found normal (Mahajan and Jarolim, 2011). Finally, an ECG is useful in identifying the presence of acute myocardial ischemia, a history of myocardial infarction, or the presence of a conduction defect or arrhythmia, but it is a highly unreliable test for establishing the presence of early coronary artery obstruction. To overcome these limitations and issues with ECG, the alternate strategy is the usage of potential cardiac biomarkers, which would be applicable for sensing purposes.

2. Cardiac biomarkers

Cardiac biomarkers are the indicators, which have been predominantly used in the detection of MI. The earliest documented study of MI based on biomarker has begun since 1954 (Dewar et al., 1958; Ladue and Wroblewski, 1955) focusing on glutamate oxaloacetic transaminase. It is logical to use protein quantification in a blood sample for this purpose as stated by Rosalki et al. (2004), i.e. the myocyte is the major cell in the heart, and the heart's purpose is to pump blood. When myocytes essentially cannot be regenerated due to heart cells die, then cardiac function has a high probability of being damaged. When the cell dies, the biomarker proteins (i.e. myoglobin, creatine-kinase MB, C-reactive protein and cardiac troponin are most commonly used) inside the cell will be released, with proteins in the cytoplasm leaving the cell more rapidly than the ones in membranes or fixed cell elements.

For MI, cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are regarded as more sensitive and specific than other cardiac biomarkers i.e, myoglobin and creatine-kinase MB (Jaffe and Ordonez-Llanos, 2010). Both are released from the death cell within 2–4 h and 3–4 h, respectively, after the onset of MI symptoms (Burcu Bahadır and Kemal Sezgintürk, 2015). Some results are favorable for cTnI (De Antonio et al., 2013), but the comparison was made between high sensitive cTnI with sensitive cTnT (Hetland and Dickstein, 1998). In principle, cTnT and cTnI remain in the blood stream approximately more than 10 days, reaches to peak approximately 1–2 days (Thygesen and Alpert, 2000) after myocardial injury. Because of its prolonged release in the blood, these biomarkers are useful diagnosing sub-acute myocardial infarction (Jaffe and Ordonez-Llanos, 2010). As cardiac troponin is cardiac-specific biomarker, it helped in isolating cardiac from skeletal muscle or other organs damage (McDonough and Van Eyk, 2004). In normal patients, the level of cTnI concentration is around 0.001 μg/L, but increased to 100 μg/L in MI patients (Agewall et al., 2011). Even the concentration as low as 0.01 μg/L can be related to heart failure. An increased value for cardiac troponin should be defined as a measurement exceeding the 99th percentile of a reference control group (Thygesen and Alpert, 2000). Reference values must be determined in each laboratory by studies using specific assays with appropriate quality control. Acceptable imprecision (coefficient of variation) at the 99th percentile for each assay should be defined as less than or equal to 10%. Fig. 1 shows general information regarding myocardial infarction.

In addition, there is another biomarker called troponin C (cTnC) (Takeda et al., 2003). It is originally from the 3-unit troponin complex (troponin I, T and C) along with tropomyosin, located on the actin filament. It is needed for the calcium-mediated regulation of skeletal and cardiac muscle concentration. Unfortunately, cTnC has no cardiac specificity due to the reason that cardiac isoform of troponin C is shared with slow-twitch skeletal muscles, which made it less favorable to be used as cardiac biomarker, unlike cTnI and cTnT for the diagnosis of cardiac injury.

3. Detection and quantification methods of cTnI and cTnT

In this case, biosensors can be used to detect and quantify the target molecules involved with cardiac biomarker interaction. Biosensors are integrated diagnostic devices, which merge biological or biologically-derived sensing element associated with a physicochemical transducer (Mascini and Tombelli, 2008). Generally, surface of a suitable transducer of a biosensor is immobilized with a biological receptor material (DNA, RNA or antibody), which enables conversion of biochemical signal into quantifiable electronic signal (Qureshi et al., 2012), through the mode of either electrochemical (Gomes-Filho et al., 2013; Horak et al., 2015), optical (He et al., 2013; Leung et al., 2013, 2015; Lu et al., 2014), mass change (piezoelectric/acoustic wave) (Lee et al., 2013), or magnetic (Liu et al., 2014). Compared to the conventional technique such as ECG, biosensors possess high sensitivity, high selectivity, fast analysis, reliable pretreatment and simple instrumentation (Burcu Bahadır and Kemal Sezgintürk, 2015). Different methods have been developed for cardiac troponin detection and quantification which include enzyme-linked immunosorbent assay (De Antonio et al., 2013), chemiluminescent immunoassay (Cho et al., 2009), fluoro-immunoassays (Hayes et al., 2009), electrical detections (Tuteja et al., 2014), surface