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Review

Progression in sensing cardiac troponin biomarker charge transductions on semiconducting nanomaterials

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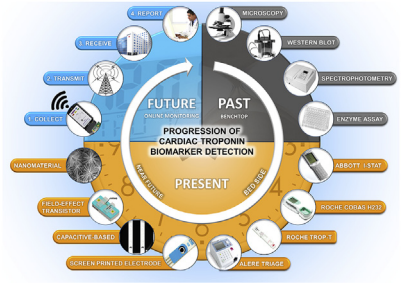
HIGHLIGHTS

- The progression of cardiac troponin detection from past to future are presented.
- Electrical label-free biosensors for cardiac troponin are discussed.
- The discussion focused on field-effect transistor-and capacitor-based devices.
- Surface functionalization, sensitivity, and innovation of devices are highlighted.
- They presented high sensitivity and specificity of real-time AMI determination.

GRAPHICAL ABSTRACT



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ABSTRACT

A real-time ability to interpret the interaction between targeted biomolecules and the surface of semiconductors (metal transducers) into readable electrical signals, without biomolecular modification involving fluorescence dyes, redox enzymes, and radioactive labels, created by label-free biosensors has been extensively researched. Field-effect transistor (FET)- and capacitor-based biosensors are among the diverse electrical charge biosensing architectures that have drawn much attention for having charge transduction; thus, enabling the early and rapid diagnosis of the appropriate cardiac biomarkers at lower concentrations. These semiconducting material-based transducers are very suitable to be integrated with portable electronic devices for future online collection, transmission, reception, analysis, and reporting. This overview elucidates and clarifies two major electrical label-free systems (FET- and capacitor-based biosensors) with cardiac troponin (cTn) biomarker-mediated charge transduction for acute myocardial infarction (AMI) diagnosis. Advances in these systems are highlighted by their progression in bridging the laboratory and industry; the foremost technologies have made the transition from benchtop to bedside and beyond.

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Contents

1. Introduction

The discovery of troponin was reported in 1963 by Setsuro Ebashi [1], and it has massively influenced the current understanding of biomarkers for cardiac muscle damage diagnostics [2]. Along with tropomyosin, the 3-unit troponin complex (troponin I, T and C) is crucial for the calcium-mediated regulation of skeletal and cardiac muscle, and is found on the actin filament [2]. Compared to other cardiac biomarkers (i.e., myoglobin (Myo), creatine kinase-MM (CK-MM), and creatine kinase-MB (CK-MB)), cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are considered to be more sensitive and specific for the detection of acute myocardial infarction (AMI) [3]. These biomarkers are convenient for diagnosing sub-AMI because of their prolonged release in the blood [4]. Theoretically, after the beginning of AMI symptoms, both cTnT and cTnI are released from the dead cells within 3–4 h and 2–4 h, respectively [5], reach their peak at approximately 1–2 d, and remain in the blood stream for more than 10 d [6]. The cTnI concentration level is approximately 1 pg/mL in normal patients, but escalates to 100 ng/mL in AMI patients [7]. Heart failure can even be associated a concentration as low as 10 pg/mL.

The determination of AMI through the discovery of cardiac troponin (cTn) as an indicator has aided doctors in decision making and helped in providing adequate treatment to the patients; thus, giving hope for more accurate and sensitive results [8]. The cardiology consensus, Joint European Society of Cardiology – American College of Cardiology Foundation – World Heart Federation [6], has named cTnI and cTnT as gold standard markers for the detection of AMI; thus, driving the growth of new devices and technologies to detect cTnI and cTnT with high sensitivity and selectivity, as a high performance system.

As illustrated in Fig. 1, in the past, enzyme-linked immunosorbent assay (ELISA), a highly sensitive assay, with a limit of detection (LOD) extending to 10 pg/mL, was the standard assay to detect cardiac biomarkers. However, this method suffers from large labour requirements and reagent consumption, especially in large-case studies. In addition, it is not suitable for quick decisions and early treatment in clinics or hospitals due to its time consuming (>6 h) methodology [9]. Moreover, significant asset investment for acquiring specific equipment is needed with this method in addition to having specially trained laboratory staff to operate it. To overcome these limitations for the detection and quantification of cTn, numerous benchtop and handheld point-of-care testing (POCT) devices have been developed to confirm the diagnosis of AMI, which is based on ELISA, fluorescent, chemiluminescent, and other technologies. Among them the Abbott I-Stat, Roche Cobas H 232 system, Roche Trop-T, and Alere Triage cardiac panel are already being commercialized. The accuracy of detection is still debatable among the practitioner society because it is not equal to that of a good lab test. In addition, most of the POCT devices require the use of a labelling method for the detection of cTn, which increases the cost and complexity of the detection device.

2. Semiconductors

To overcome the limitations and provide early detection with high accuracy for successful treatment, research on electrical label-free biosensors for biologically active materials has been growing in recent years. This is due to new techniques offering simple detection [10] and portable biosensor system fabrication possibilities for POCT. In general, electrical label-free detection involves measuring the physical properties of the chemical compound, DNA, peptide, protein, virus, or cell directly via a transducer. Electrical label-free methods utilize dielectric permittivity and conductivity to specify the existence of biochemical molecules using a suitable sensor. As a transducer, usually in semiconductor materials, the sensor converts the physical properties into a measurable signal that can be gathered by an appropriate instrument. The principle of an electrical label-free biosensor for biomolecules detection has been established using miniaturized bioelectronic devices altered with bio-affinitive agents that generate quantifiable electrical signals upon interacting with target biomolecules [11] (Fig. 2). Experimental vagueness introduced by the label effect on molecular confirmation, blocking of active binding epitopes, steric hindrance, labelling site inaccessibility, or inability to find a proper label that functions equivalently for all molecules in an experiment can be eliminated through label-free detection [12]. Furthermore, nonspecific binding can be reduced, ultimately decreasing the binding of any non-analytes and their contribution to false positive errors [13]. The use of label-free techniques avoids the need to modify biomolecules with fluorescent dyes, redox enzymes, or radioactive labels; thus, reducing costs and avoiding the need for sample pre-treatment and eventually reducing detection time and sensor fabrication complexity [14,15]. These techniques could also eliminates the need