Paper microfluidic device for early diagnosis and prognosis of acute myocardial infarction via quantitative multiplex cardiac biomarker detection

Wei Yin Lima, T. Malathi Thevarajah, Boon Tong Goh, Sook Mei Khor

Department of Chemistry, Faculty of Science, University of Malaya, 50603 Kuala Lumpur, Malaysia
Department of Pathology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia
Low Dimensional Materials Research Centre, Department of Physics, Faculty of Science, University of Malaya, 50603 Kuala Lumpur, Malaysia
University Malaya Centre for Ionic Liquids (UMCiL), University of Malaya, 50603 Kuala Lumpur, Malaysia

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ABSTRACT

The early detection of acute myocardial infarction (AMI) upon the onset of chest pain symptoms is crucial for patient survival. However, this detection is challenging, particularly without a persistent elevation of ST-segment reflected in an electrocardiogram or in blood tests. A majority of the available point-of-care testing devices allow accurate and rapid diagnosis of AMI. However, AMI diagnosis is reliable only at intermediate and later stages, with myocardial injury (> 6 h) and MI, based on the expression of specific cardiac biomarkers including troponin I or T (cTnI or cTnT), creatine kinase-MB (CK−MB), and myoglobin. Diagnosis at the early myocardial ischemia stage is not possible. To overcome this limitation, a sensitive and rapid microfluidic paper-based device (µPAD) was developed for the simultaneous detection of multiple cardiac biomarkers for the early and late diagnosis of AMI. The glycogen phosphorylase isoenzyme BB (GPBB) was detected during early (within first 4 h) ischemic myocardial injury. On the same µPAD platform, detection of prolonged elevation of levels of cTnT and CK-MB, which are only produced 6 h after the onset of chest pain in human serum, was possible. Sandwich immunoassay performed on the µPAD achieved reproducibility (RSD approximately 10% and intra-and inter-day precision (CV 10–20%, 99th percentile), as well as consistently stable test results for 28 days, with strong correlation (r² = 0.962), using the standard Siemens Centaur XPT Immunoassay system. The present findings indicate the potential of the µPAD platform as a point-of-care device for the early diagnosis and prognosis of AMI.

1. Introduction

In the clinical setting, the term acute coronary syndrome (ACS) refers to a spectrum of clinical presentation for symptoms of ischemia (inadequate blood supply to heart), such as unstable angina, non-ST elevation myocardial infarction (STEMI), and STEMI (Overbaugh, 2009). Chest pain is one of the most common complaints among patients presenting to the emergency department. The diagnosis of ACS is dependent on evidence of myocardial ischemia on an electrocardiogram (ECG) and evidence of myocardial injury by determining the levels of cardiac biochemical markers (Ryu et al., 2011). For patients with chest pain, no evidence of myocardial injury based on the levels of cardiac biomarkers in the blood is considered to present unstable angina, whereas patients presenting with positive cardiac biomarkers, with or without electrocardiographic ST-segment depression or T wave inversion, are undergoing non-STEMI due to a relatively small damage of heart muscles (Anderson et al., 2007; Bertrand et al., 2000). Furthermore, patients with ST-segment elevation on an ECG due to high damage extent of heart muscles indicate acute STEMI (Van de Werf et al., 2003) (Supplementary material Fig. S1).

In clinical trials, patients with chest pain and suspected ACS may be referred urgently to the emergency department and undergo ECG monitoring to aid in risk stratification (Lang et al., 2000). However, misinterpretation of findings on ECG accounts for 23–40% of misdiagnosed MI cases (Kontos et al., 2010). Due to ST-elevation, MI can be readily diagnosed with culprit ECG findings. However, for non-ST elevation, MI diagnoses are more challenging. Therefore, serial cardiac biomarker sampling is crucial for the diagnosis of acute MI in patients with non-diagnostic ECGs or chest discomfort symptom. Serial measurement of cardiac biomarkers of myocardial injury, such as cardiac