Current Medicinal Chemistry, 2020, *27*, 2550-2575

REVIEW ARTICLE

Electrochemical-Based Biosensors: New Diagnosis Platforms for Cardiovascular Disease

Fatemeh Yousefi[1,#], Ahmad Movahedpour[2,3,#], Zahra Shabaninejad[4,5], Younes Ghasemi[2,5,6], Shahram Rabbani[7], Ali Sobnani-Nasab[8], Soheila Mohammadi[9,10], Behzad Hajimoradi[11], Samaneh Rezaei[12], Amir Savardashtaki[2,5,*], Majid Mazoochi[13,*] and Hamed Mirzaei[14,*]

[1]Department of Biological Sciences, Faculty of Genetics, Tarbiat Modares University, Tehran, Iran; [2]Department of Medical Biotechnology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran; [3]Student research committee, Shiraz University of Medical Sciences, Shiraz, Iran; [4]Department of Biological Sciences, Faculty of Nanotechnology, Tarbiat Modares University, Tehran, Iran; [5]Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; [6]Department of Pharmaceutical Biotechnology, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran; [7]Research Center for Advanced Technologies in Cardiovascular Medicine, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran; [8]Social Determinants of Health (SDH) Research Center, Kashan University of Medical Sciences, Kashan, Iran; [9]Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran; [10]Nano Drug Delivery Research Center, Health Technology Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran; [11]Cardiology Department of Shohaday-e-Tajrish Hospital Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran; [12]Department of Medical Biotechnology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; [13]Department of Cardiology, Cardiac Electrophysiology Center, Kashan University of Medical Sciences, Kashan, Iran; [14]Research Center for Biochemistry and Nutrition in Metabolic Diseases, Institute for Basic Sciences, Kashan University of Medical Sciences, Kashan, Iran

ARTICLE HISTORY

Received: July 20, 2019
Revised: September 05, 2019
Accepted: September 12, 2019

DOI:
10.2174/0929867326666191024114207

Abstract: One of the major reasons for mortality throughout the world is cardiovascular diseases. Therefore, bio-markers of cardiovascular disease are of high importance to diagnose and manage procedure. Detecting biomarkers provided a promising procedure in developing bio-sensors. Fast, selective, portable, accurate, inexpensive, and sensitive biomarker sensing instruments will be necessary for detecting and predicting diseases. One of the cardiac biomarkers may be ordered as C-reactive proteins, lipoprotein-linked phospho-lipase, troponin I or T, myoglobin, interleukin-6, interleukin-1, tumor necrosis factor alpha, LDL and myeloperoxidase. The biomarkers are applied to anticipate cardio-vascular illnesses. Initial diagnoses of these diseases are possible by several techniques; however, they are laborious and need costly apparatus. Current researches designed various bio-sensors for resolving the respective issues. Electrochemical instruments and the proposed bio-sensors are preferred over other methods due to its inexpensiveness, mobility, reliability, repeatability. The present review comprehensively dealt with detecting biomarkers of cardiovascular disease through electro-chemical techniques.

Keywords: Cardiovascular disease, electrochemical biosensors, diagnosis, mortality, C reactive proteins, myeloperoxidase.

1. INTRODUCTION

One of the abnormalities of the heart and blood vessels, including coronary heart diseases, cerebro-vascular diseases, rheumatic heart diseases, and additional consequences are Cardio-Vascular Diseases (CVD). The World Health Organization (WHO) reported that almost 20 million (31%) mortalities in 2015 have been associated with cardio-vascular diseases in developing and developed countries worldwide [1]. Suitable diet, fatness, alcohol abuse, tobacco, anxiety, and physical inactivities are known as the common reasons for cardio-vascular disease [2]. It has been predicted that advancements in general cardio-vascular health measures decline mortalities caused by cardio-vascular diseases to 30% between 2010 and 2020 [3].

*Address correspondence to these authors at the Department of Medical Biotechnology, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran; E-mail: Dashtaki63@gmail.com; Department of Cardiology, Cardiac Electrophysiology Center, Kashan University of Medical Sciences, Kashan, Iran; E-mail: mazoochim@yhoo.com; Research Center for Biochemistry and Nutrition in Metabolic Diseases, Institute for Basic Sciences, Kashan University of Medical Sciences, Kashan, Iran; Tel: +98-31-55540022; Fax: +98-31-55540022; E-mails: mirzaei-h@kaums.ac.ir and h.mirzaei2002@gmail.com

[#]*These authors have contributed equally.*

1875-533X/20 $65.00+.00

Detecting and managing cardio-vascular diseases at the initial stages contribute significantly to the clinical diagnoses for cases with cardio-vascular diseases or those who possibly experience higher risks of cardio-vascular diseases. It should be noted that this method provides on time and survival treatment interventions and decreases the healthcare cost. Cardio-vascular disease is a major risk factor for human health. We face the increasing demands due to several causes. Hence, it is essential to develop apparatus with suitable mobility, accuracy, quickness, sensitivity, reliability, cost-effectiveness in order to detect this type of disease [4]. Today, there is enough knowledge that biomarkers identifying CVD bridge when specifying particular blood complexes (biomarkers) or changes in their concentrations determine different diseases related to cardio-vascular diseases [5].

Biomarkers could increasingly identify patients with higher risks of cardiovascular episodes and assist in making decisions on the therapeutic options [6]. Different types of biomarkers are found in the blood serum or plasma that include Heart-Type Fatty-Acid-Binding Protein (H-FABP), Creatine Kinase MM (CK-MM), creatine kinase-MB (CK-MB), myoglobin (MYO), interleukins (IL-1β, IL-6,IL-8), C-reactive protein (CRP), tumour necrosis factor alpha (TNF-α), cardiac troponins (cTnI & cTnT), NT-proBNP, and so forth [7].

A variety of methods tested detection of particular protein biomarkers for initial diagnoses and efficient therapy of stroke, cardio-vascular disease, the respective risks and inflammations [8]. Conventional methods for diagnosing cardio-vascular diseases include Liquid Chromatography (LC), enzyme-associated immunosorbent assay (ELISA), immuno-assays, and Surface Plasmon Resonance (SPR) that are on the basis of the experiments done in central laboratories, which suffer from timely procedures [4].

Moreover, bio-sensors can be categorized according to the principles of selecting analytes. Immuno-sensors that interact with antibody and antigen, and with enzyme and the target analyte, which are also known as enzymatic bio-sensors or nucleic acid-based biosensors. Each conventional (enzyme, antibody & DNA) and current components of detection contribute significantly to chemical sensors and bio-sensors, which use the intended target analyte [9]. Electrochemical immuno-sensors are dependent on the measurement of current and or voltages for detecting the bind between antibodies and antigens [10]. Each sensors have different benefits such as cost-effective, sensitive, portable, disposable, possible concurrent multi-analysis, reliable, little amount of the samples, and rapid responses. Therefore, authors paid special attention to the immuno-sensors. However, one of the problems can be regenerating the attachment sites on antibodies. This process is timely and may hurt the binding locations. Hence, it is possible that the antibody life declines. Sensitive and rapid sequence special data are provided by DNA bio-sensors [11]. In spite of the enzyme or antibody, synthesis and regeneration of DNA-based bio-sensors may be simply performed for a wide range of applications. DNA biosensors can be used to examine molecular diagnostics, pharmaco-genomics, medical diagnoses, food analyses, environmental monitoring, bio-terrorism and drug screens. The sensor are associated with various drawbacks such capability of directly transducing of the signals, preventing the image processing, statistical analyses and automating detection phases [12].

A lot of studies dealt with the techniques for developing bio-sensors, including electro-chemical (conductometry, potentiometry, amperometry), field effect transistor, piezo-electric, capacitor based bio-sensors, optic (fluorescence, luminescence, refractive indicator), or calorimetric to detect various bio-markers [13]. Electrochemical bio-sensors can be regarded a substitute for classic analyses of cardiac bio-markers [14, 15]. They have several benefits, including user-friendliness, quickness, accuracy, cost-effectiveness, and capability to multi-analyte testings [16]. It is not necessary to do costly and laborious experiments for designing biosensors techniques. Hence, the costs of providing health care services can be reduced.

Recently, nano-materials have been applied in the bio-sensors. Nano-materials possess a lot of advantages, such as conductive features, higher surface or volume, and acceptable bio-compatibility that increase their function [17]. Nano-materials presented below were combined into bio-sensors in order to detect the clinically important bio-markers. Carbon based nano-materials (*e.g.*, carbon nano-tubes (CNT), metal oxides (ZnO, CeO2, & Al2O3) metal nano-particles (Ag, Au, Pt, Cu), semi-conductors quantum dots (Cd, Se, Ge, Te), silicon / indium / gallium, graphene and so on) [18, 19]. Gold-based structures (screen-printed electrode (SPE) or nano-materials) have been viewed an important component for using in building (bio / nano) sensing due to their very good optic, electrical and mechanical features [20]. The present review comprehensively dealt with detecting biomarkers of cardiovascular disease through electrochemical techniques.

2. CARDIOVASCULAR MARKERS

Cardiovascular Diseases (CVD) are the major leading cause of death globally even in developing countries [21-23]. Hence many scientists are involved in searching for tools able to detect the early moments of CVD development. Biomarkers have an important role in the evaluation of any disease and development of drug treatments, especially in Cardiovascular Diseases (CVD). The several cardiac-specific biomarkers represent a biochemical change at heart tissue or blood level in cardiovascular diseases condition when the heart is damaged or stressed. Recent studies have reported some cardiac biomarkers that are associated with higher risk of CVD and with CVD risk factors, including troponin, Myoglobin, kinase-MB (CK-MB), C-Reactive Protein (CRP), N-terminal prohormone BNP (NT-proBNP), B-type natriuretic peptide (BNP), H-FABP, Interlukin-6 (IL-6), TNF- α and miRNAs [24-30]. Some of these biomarkers are useful in prediction of Cardiovascular Risk (CVR), while others are can be used as the late indicator of heart failure or AMI. Moreover, some cardiac biomarkers (predictive biomarkers) change in their levels adequately mirror improvement in the cardiovascular disease process when the disease is being treated, thereby reflecting an improvement in patient outcome. So, the assessment of cardiac marker elevations is helpful to make a reliable decision on a suitable treatment. Currently, several classifications exist to classify CVD biomarkers. Cardiac biomarkers can be grouped based on the pathophysiological processes which they represent, such as myocardial necrosis (*e.g*., cardiac troponin, H FABP, myoglobin, and kinase-MB (CK-MB)) inflammation (*e.g*., C-reactive protein, interleukin 6, tumor necrosis factor alpha, *etc.*) myocardial stress (*e.g*., N-terminal prohormone BNP (NT-proBNP), B-type natriuretic peptide (BNP) and microRNAs (miRNAs)) (Tables **1** and **2**). In addition to protein biomarkers, recently, genomic technology has discovered new noncoding RNA (miRNAs and LncRNAs) and molecular pathways involved in this disease. MiR-133, miR-21, miR-29 are known to play a significant role in regulation of cardiac hypertrophy, fibrosis and heart failure [27, 30-33]. A long non coding RNA, LIPCAR, is introduced as a novel biomarker of cardiac remodeling in patients with heart failure [34]. In the last years, several techniques for biomarkers detection have been reported. Many of them employ antibody-based biosensors as recognition elements whereas few techniques are based on the use of single stranded DNA or RNA oligonucleotides (aptamer) [35-38].

3. ELECTROCHEMICAL BIOSENSORS

Sensor, and in particular, bio-sensors is described as an analytical device with a biological sensor in the body that is fused with a physico-chemical transducer. Biosensors produce a continual digital electrical signal corresponding to the quantities of 1 or more analytes that are analyzed [9]. In general, they can be fabricated *via* combination of a bio-active component, which has interaction in a selective manner with the substance that should be analyzed, with a conduction system transmitting final signals. As bio-components in biosensors, nucleic acids, anti-bodies, micro-organisms, organelles, and enzyme culture may be employed like piezoelectric, acoustic, potentiometric, amperometric, thermal, and optic sensors. Additionally, as they have a greater level of specificity, their benefit is that they can measure wider ranges of concentrations directly in the coloured and turbid solutions. Yet, biosensors shelf life may be declined by the effect of environmental situations, including pH, ionic strength, and temperature [9].

It has been showed that bio-sensors in particularly, electrochemical biosensors could be employed for diagnosis a variety of biomarkers in various diseases [92]. For example, given that carcinoembryonic antigen, miR-34a, miR-24, P16 and a-fetoprotein enable to use as electrochemical biosensors in various cancers [93].

Researchers designed bio-sensors to detect CVDs bio-marker. Numerous nano-materials were applied to fabricate such bio-sensors. Nano-tubes, nano-wires, metal nano-particles and polymer based modifications have been greatly attended by the researchers because of the increased responses of analytes, higher surface areas, sensitivities, and selectivities features [94, 95]. It is of high importance to increase concentrations of cardiac bio-markers in serum due to CVD episodes and higher rate of mortality. Therefore, it is essential to detect such bio-markers quickly, reliably, and precisely. A considerable concentration of CVD bio-markers changes between pM - nM; thus, techniques for assaying them should have high sensitivity [17, 96]. Table **3** reports cut-off values of the bio-markers in the samples of serum.

3.1. Troponin

Sensitive and reliable methods for cardiac markers detection in an early development stage would have a fundamental impact on today's preventive medicine, and Cardiac troponin is one of the very early markers to increase after AMI onset [135]. Cardiac troponin I (cTnI) and T (cTnT) are globular contractile regulatory

Table 1. Various cardiac biomarkers for the diagnosis of various forms of cardiovascular diseases.

Cardiac Biomarker	CVD Indicator Type	Duration of Elevation	Initial Elevation (h)	Specificity Level	MW (kDa)	Type of Sample	References
Troponin I(cTnI)	Detection of acute myocardial infarction (AMI)	4-7 days	4-6	High	23.5	Serum	[39]
Troponin T(cTnT)	Detection of MI	10-14 days	3-4	High	37	Serum	[39]
Myoglobin	Early detection of MI	12-24 h	1-3	Low	18	Serum	[40]
Creatine kinase MB subform (CK-MB)	Early detection of MI	24-36 h	3-6	Medium	85	Serum	[41]
C-reactive protein (CRP)	Early detection of inflammation	12-24 h	4-6	High	125	Serum	[42]
N-terminal pro-B-type natriuretic peptide (NT-proBNP)	Indicator of stresses and diagnosis of heart Failure	No clinical consensus	No clinical consensus	High	8.5	Serum	[43]
B-type natriuretic peptide(BNP)	Diagnosis of heart Failure	No clinical consensus	No clinical consensus	High	3.4	Serum	[44]
Heart fatty acid binding protein (H-FABP)	Myocardial necrosis	18-30 h	2-3	Low	15	Plasma	[45]
Interlukin-6 (IL-6)	Inflammation/cardiac risk factor	No clinical consensus	No clinical consensus	No clinical consensus	21	Plasma	[46]
TNF-α	Inflammation/cardiac risk factor	No clinical consensus	No clinical consensus	No clinical consensus	17	Plasma	[47]
MiR-208	Early detection of MI	12-24 h	1-5	No clinical consensus	-	Plasma	[48, 49]
MiR-423-5p	Diagnosis of heart Failure	-	-	No clinical consensus	-	Plasma	[50]
MiR-1, miR-133a and miR-499	Early detection of MI	12-24 h	4-6	High	-	Plasma	[31, 49]
MiR-208b and -499	Sensitive markers for myocardial damage	-	12	No clinical consensus	-	Plasma	[51]
LncRNA-GAS5	A promising biomarker for CAD	No clinical consensus	No clinical consensus	No clinical consensus	-	Plasma	[52]
lncRNA H19 and LIPCAR	A novel biomarkers for CAD	No clinical consensus	No clinical consensus	No clinical consensus	-	Plasma	[53]

Table 2. Comparison of predictive biomarkers based on statistical parameters.

Cardiac Biomarker	AUC	OR	RR	HR
Troponin I(cTnI)	AIS: 0.61 [54]	CAD: 1.35 [55] AMI: 21.7 [56]	AMI: 4.2 [56]	CVD: 1.23 [57] CVD: 1.24 MI: 1.18 CHD: 1.19 HF: 1.86 AIS: 1.39 [58] ACS: 1.7 [59]
Troponin T(cTnT)	ACS: 0.98 [60] MI: 0.95 [61]	AMI: 16.7 [56]	AMI: 2.7 [56]	CVD: 1.11 MI: 0.93 CHD: 1.04 HF: 1.69 AIS: 1.22 [58]
Myoglobin	CD: 0.58 [62]	MI: 0.11 [63]	-	ACS: 1.6 [59]
Creatine kinase MB subform (CK-MB)	AIS: 0.56 [54]	MI: 2.77 [64]	MI: 1.3 [65]	ACS: 0.9 [59]
C-reactive protein (CRP)	CAD: 0.73 [66]	CHD: 1.2 [67] CHD: 1.58 [68]	CHD: 1.55 [68] AIS: 1.27 [69]	HF: 2.64 [70] MESA: 1.23 [71]
N-terminal pro-B-type natriuretic peptide (NT-proBNP)	CD: 0.83 [62] HFpEF patients aged ≥65 years: 0.761 [72]	HFpEF patients: 1.002 [72]	AIS: 4.88 [73]	MACE: 1.84 [74]
B-type natriuretic peptide(BNP)	AIS:0.73 [54] HFpEF patients aged ≥65 years: 0.89 [72]	HFpEF patients aged ≥65 years: 0.891 [72] AHF: 0.98 [75]	-	HFpEF patients: 1.5[72] MACE: 1.58 [74] CD: 1.27 [76]
Heart fatty acid binding protein (H-FABP)	AMI: 0.81 [77]	CVD: 4.21 [78]	AMI: 1.48-1.50 [79]	HF: 2.1-2.5 [80]
Interlukin-6 (IL-6)	AIS: 0.83 [73] HFpEF patients aged ≥65 years: 0.516 [72]	HFpEF patients aged <65 years: 2.069 [72]	AIS:4.09 [73]	MI: 1.53 HF: 2.28 [81] HF: 1.22 [82]
TNF-α	0.67 [72] HFpEF patients aged ≥65 years: 0.64 [72] HFpEF patients aged ≥65 years: 0.67 [72]	HFpEF patients aged ≥65 years: 0.648 [72] HFpEF patients aged <65 years: 1.584 [72]	-	HF: 1.34-2.1 [83]
MiR-208	AMI: 0.72 [84]	AMI: 69 [84]	-	-
MiR-1	AMI: 0.81 [84] AMI: 0.77 [85]	AMI: 12 [84] AHF: 1 [75]	-	-
MiR-499	CVD: 0.92 [51] MI: 0.79 [61]	AMI: 43 [84] HF: 1.7 [61]	-	CAD: 1.913 [86]

(Table 2) contd….

Cardiac Biomarker	AUC	OR	RR	HR
MiR-423-5p	HF: 0.83 [50]	AHF: 0.54 [75]	-	CS: 1.9 [87]
MiR-133a	MI and CAS: 0.918 [88] AMI: 0.932 [85] CHD: 0.597 [89]	CHD: 0.265 [89]	-	CAD: 2.35 [90]
MiR-208b	CVD: 0.94 [51] MI: 0.82 [61]	HF: 1.79 [61]	-	AMI: 5.08 [91]
LncRNA-GAS5	CAD: 0.9783 [52]	-	-	-
lncRNA H19	CAD: 0.631 [53]	CAD: 1.126 [53]	-	-
lncRNA LIPCAR	CAD: 0.722 [53]	CAD: 1.306 [53]	-	-

Abbreviations: AUC, Area Under ROC Curve; OR, Odds Ratio; RR, Risk Ratio; HR, Hazard Ratio; AIS, Patients with Acute Ischemic Stroke; CAD, Patients with Coronary Artery Disease; CHD, Patients with Coronary Heart Disease; ACS, Patients with Acute Coronary Syndrome; MESA, Multi-Ethnic Study of Atherosclerosis; CD, Patients with Chagas Diseases; MI, Myocardial Infarction; HFpEF, Heart Failure with Preserved Ejection Fraction; MACE, Major Adverse Cardiovascular Events; CS, Cardiogenic Shock Patients; AHF, Acute Heart Failure; AMI, Patients with Acute Myocardial Infarction; CVD, Patients with Cardiovascular Diseases; HF: Heart Failur; CAS, Patients with Coronary Artery Stenosis.

Table 3. The electrochemical biosensors for cardiac biomarkers.

Sensing Platform	Target	Linear Range	Limit of Detection	Refs.
Carbon nanotube/conductive polymer/antibody	cTnI	0.1-10 ng mL^{-1}	0.033 ng mL-1	[97]
Streptavidin polystyrene/ antibody	cTnI	0.1-10 ng mL^{-1}	0.2 ng mL-1	[98]
Polymer/ antibody/ alkaline phosphatase-antibody	cTnI	0.2 ng mL^{-1} - 10 µg mL^{-1}	145 pg mL-1	[99]
AuNPs/ silver NPs/ antibody	cTnI	0.1 -32 ng mL^{-1}	0.1 ng mL^{-1}	[100]
Aptamer-MoS	cTnI	10 pM-1uM	0.95 pM	[101]
didodecyldimethylammonium bromide	Myoglobin, cTnI	2.4 ng mL^{-1}, 0.03 ng mL^{-1}	-	[102]
Carboxylated CNT/ antibody	cTnT	0.1-10 ng mL^{-1}	0.033 ng mL^{-1}	[97]
Amin functionalized CNT/ antibody	cTnT	0.0025-0.5 ng mL^{-1}	0.0035 ng mL^{-1}	[103]
Silicon nanowire/ antibody	cTnT	-	1 $fgmL^{-1}$ in buffer and 30 $fgmL^{-1}$ in human serum	[104]
Poly aniline nanowire/ Antibody	Myoglobin, cTnI, CK-MB, BNP	-	100$pgmL^{-1}$, 250$fgmL^{-1}$, 150$fgmL^{-1}$, 50$fgmL^{-1}$	[105]
Silicon nanowire/ antibodies	cTnI, cTnT, CK-MM, CK-MB	-	1 $pgmL^{-1}$	[106]
MB-MWCNT	Myoglobin	0.1-3 µM	20 nM	[107]
Antibody/ Au	Myoglobin	10-650 ng mL^{-1}	2.5 ng mL^{-1}	[108]
ZnS nanocrystal/ indium-tin-oxide/ antibody	Myoglobin	1 ng mL^{1-} - 1µg mL^{-1}	-	[109]

(Table 3) contd….

Sensing Platform	Target	Linear Range	Limit of Detection	Refs.
Polymers	Myoglobin	-	-	[110]
Poly aniline nanowire/ antibody	Myoglobin, Ig G	1.4 ng/mL^{-1} - 2.5 µg/mL^{-1},-	1.4 ngmL^{-1}, 3ngmL^{-1}	[111]
Bismuth citrate/ antibody/ PbS-quantum dot	CRP	0.2-100 ng mL^{-1}	0.05 ng mL^{-1}	[112]
ZnO nanotube / antiody	CRP	10 $^{-5}$ - 1 mg L^{-1}	10 $^{-6}$ mgL^{-1}	[113]
Antibody/ ECL-antibody	CRP	1-24 µg mL $^{-1}$	-	[114]
Nano porous silica/ antibody	CRP	1 pg mL^{-1} - 1 µg mL $^{-1}$	1 pgmL^{-1}	[115]
Single strand DNA/ antibody	CRP	-	-	[116]
MWCNTs/ protein A/ HRP-antibody	CRP	-	0.5 ng mL^{-1}	[117]
Carbon nanofibers/ antibody	CRP	0.05-0.5	11 ng mL^{-1}	[118]
polymers	CRP	100 fgmL^{-1} - µgmL^{-1}	1 fgmL^{-1}	[119]
ZnO nanotube/ antibody	CRP	1×10^{-5}- 1.0 mg L^{-1}	1× 10^{-6} mg L^{-1}	[113]
Polystyrene	CRP	1 pg mL^{-1} - 1 µg mL^{-1}	1 pg mL^{-1}	[120]
Nanostructural gold/ CNT/ antibody/HRP	BNP	0.02- 100 ng mL^{-1}	6 pg mL^{-1}	[121]
AuNPs/ antibody/ phenyl alanine/ hydroquinone	BNP	0.014-15 ng mL $^{-1}$	4 pg mL $^{-1}$	[122]
Nanoporous aluminum oxide/ antibody	BNP	-	10 fg mL^{-1}	[123]
Polymer	BNP	-	50 pg mL^{-1}	[124]
AChE-labeled antibody	BNP	20-40 ng L $^{-1}$	10 ng L^{-1}	[125]
Layers of assembly films	CK-MB	-	0.25 ng mL^{-1}	[126]
DNA probes	miRNA	100aM-100pM	100aM	[127]
AuNPs/ LNA probe/ HRP	miRNA	0.01-700 pM	6fM	[128]
Three-dimensional DNA nanostructure	miRNA	10-10^{7} fM	10 aM	[129]
Probes/ esterase/ quinonimine	miRNA	0.002 - 200 nM	2 pM	[130]
Probe/ TiP-cd^{+2}/ Ru (NH3)$_6^{+3}$/ AuNPs	miRNA	1.0aM-10pM	0.76aM	[131]
Probe/ graphen oxide/ CNT/ RNA-DNA antibody/HRP-antibody	miRNA	10fM- 1nM	10fM	[132]
Antibody/ alkaline phosphatase-antibody	H-FABP	10-350ngmL^{-1}	-	[133]
Antibody/ alkaline phosphate antibody	H-FABP	4-250 ng mL-1	-	[134]

proteins that inhibit muscle contraction by blocking the interaction of actin and myosin [136]. These two proteins are unique to the heart and are sensitive and specific biomarkers of vascular events such as an acute myocardial infarction, which are released from necrotic myocardium into the blood circulation right after AMI. The initial elevation of them takes 4-6 h after the onset of ischemia and remain elevated for up to a week [137, 138].

Acute Myocardial Infarction (AMI) is one of the leading causes of death in the world [139]. Thrombus formation in the damaged coronary artery due to atherosclerosis, which results in a sudden decrease in the amount of blood and oxygen reaching the heart (ischemia), it can cause myocardial infarction [140]. So, many research groups and companies have a rapid and accurate diagnosis and prognosis of this disease. An approach for detection of cardiac injury involves

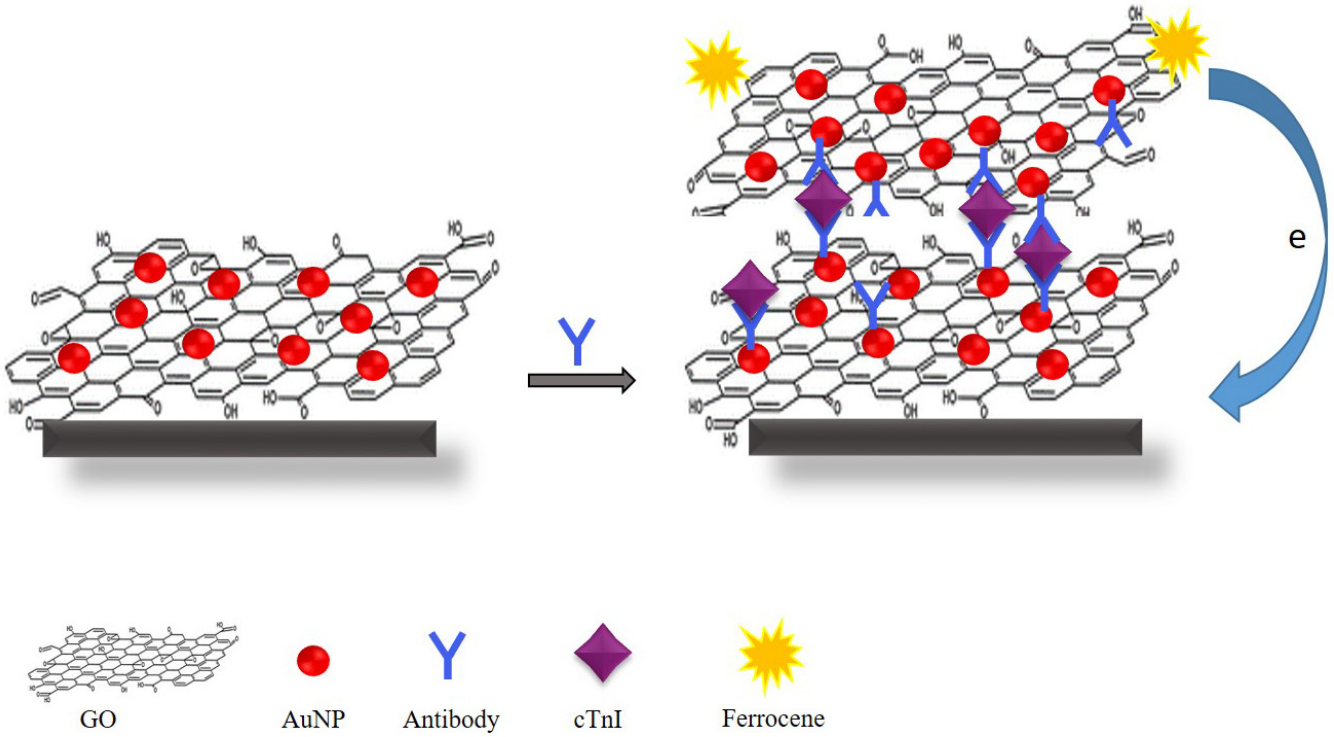

Fig. (1). Schematic of AuNPs and GO nanocomposite biosensor for detection cTnI.

measurements of Cardiac troponin in serum or plasma. Numerous studies have been carried out that the troponin C found in type 2 fibers of the skeletal muscle and the cardiac muscle; therefore, it is difficult to be used as a cardiac specific marker [141]. Unlike troponin C, cardiac troponin I is highly specific for myocardial tissue, and this type of troponin is not detectable in the blood of healthy persons compared with patients with myocardial infarction. Therefore, Troponin I is particularly useful in diagnosis of risk stratification of patients with chest pain and suspected acute coronary syndrome due to its superior specificity compared to other cardiac biomarkers [142]. In addition, the specificity and sensitivity of postmortem Troponin T for cardiac-related death, in one study, was 91% and 86%, respectively [143]. Overall, Troponin T isoforms are expressed in injured skeletal muscle and they are not detected by the diagnostic assays used in clinical practice, While Troponin I has been shown to be 100% specific for the heart [144].

Carbon nanostructure is one of the major nanomaterial that used in biosensors. Kazemi and colleagues fabricated a label-free electrochemical biosensor using porous Grapheme Oxide (GO) for cTnI detection. This biosensor could specifically detect target with 0.07 ng/mL^{-1} detection limit and linear range of 0.1 to 10 ng mL^{-1} [145]. Liu, *et al*. designed a label-free electrochemical immunosensor for cTnI detection in order to myocardial infraction early diagnosis. The Graphene Oxide (GO) and gold nanoparticles (AuNPs) were immobilized on Glassy Carbon (GC) electrode which provided a big surface area platform to load cTnI antibody and also, accelerated electron transfer. Finally, GO functionalized with ferrocene molecules, as the signal reporter, covered detection antibody. The schematic figure is illustrated in Fig. (**1**). The presented biosensor could detect 0.05 ng mL^{-1} cTnI concentration [146]. Jo *et al*. developed an aptasensor using ferrocene-modified silica nanoparticles (Fc-SiNPs) to determine TnI. In the presence of target protein, the voltammetry curve of Fc-SiNPs fell down remarkably, because the TnI bonded to aptamers blocked the electrode surface, so, the electron transfer was inhibited. In this scenario, the TnI could be detected in linear range of 1-10,000 pM and limit of detection was found to be 1.0 pM [147]. Anti-cTnI was immobilized on vertically aligned Carbon Nanofiber (CNF) for electrochemical detection of cTnI (Fig. **2**). This immunosensor demonstrated a low detection limit of about 0.2ng/ml, which is 25 times more sensitive than conventional methods [148]. Streptavidin coated AuNPs (SA-AuNPs) immobilized on electrode. Coated AuNPs with luminol, a chemilluminescence (ECL) agent, conjugated with biotin-anti-cTnI (biotin-anti-cTnI-luminol-AuNPs) bonded to SA-AuNPs. The fabricated biosensor is shown in Fig. (**3**). Changes in ECL signals during anti-cTnI and

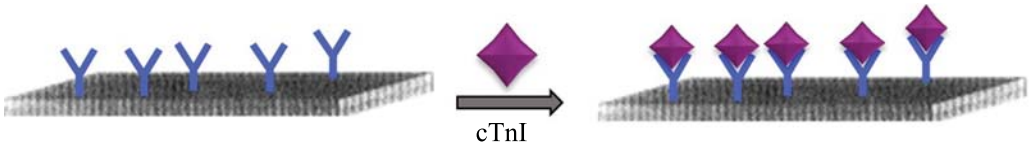

Fig. (2). Carbon nanofiber based electrochemical biosensors for cTnI.

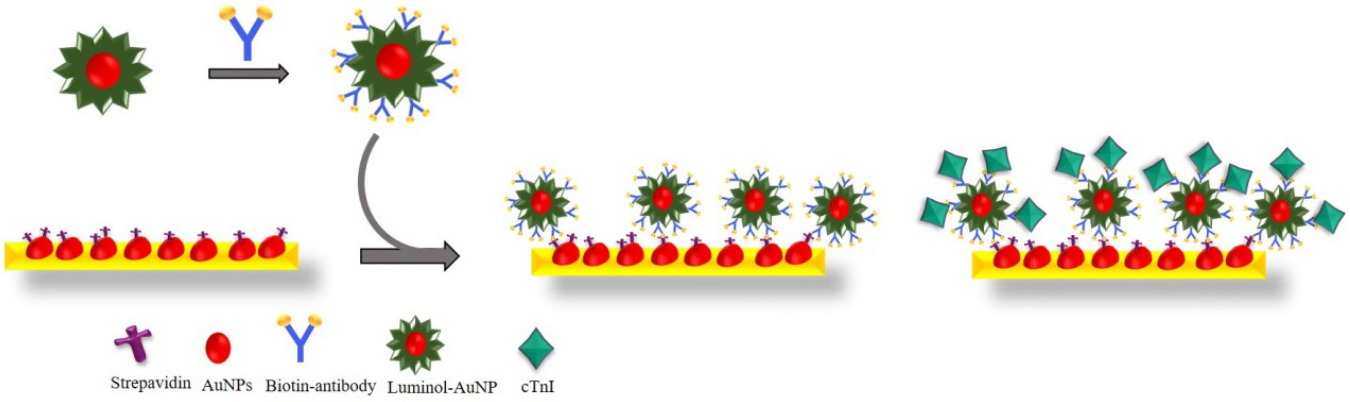

Fig. (3). immunosensor label-free for detection troponin I.

antigen reactions was used for cTnI detection in plasma samples. This nanobiosensor exhibited a detection range from 1000ng mL^{-1} to lower than 0.1 ng mL^{-1} [149].

3.2. C-reactive Protein

C-reactive protein is a long plasma half-life protein (The average plasma half-life of CRP is about 19 hours), and it is a sensitive systemic biomarker for inflammatory events and tissue damage [150]. CRP is 25KDa and it can adapt a circular form constituted by five equal subunits that Each subunit binds to two calcium ions by intermolecular noncovalent salt bridges [36, 151]. It is Produced and secreted mainly by liver in response to interleukin-6 (IL-6) and either IL-1 or tumor necrosis factor-alpha. High levels of this protein are related with a large clinical state of diseases such as: inflammation both acute and chronic, cardiovascular diseases and bacterial infections (1000-fold over baseline) [152-155]. Research and developments in this area have proved that CRP can predict mortality and cardiovascular events, such as myocardial infarction (MI) and stroke [28, 156, 157]. More recently, CRP has been used as a general marker for Inflammation contributes to all phases of atherosclerosis, from fatty streak initiation to Cardiovascular Disease (CVD) events [158, 159]. Also, plasma CRP concentration increases following MI that was first reported in 1982 [160]. Subsequent large studies have shown that post-infarct CRP concentrations are significantly associated with increased incidence of cardiac complications such as cardiac death and heart failure [24]. To data, Measurement of C-reactive protein may be useful for risk assessment in patients with coronary heart disease. Clinical reference ranges for CRP assay are described as ≤1 $\mu g \cdot mL^{-1}$ for low risk, 1-3 $\mu g \cdot mL^{-1}$ for medium risk and ≥3 $\mu g \cdot mL^{-1}$ for high risk [161]. In healthy normal subjects, CRP is a trace plasma protein (<5 mg/L) and its concentration tends to increase slightly with age [162].

Gupta and colleagues provided an electrochemical CRP biosensor. The immobilized anti-CRP on carbon nanofiber was used as biosensing platform. The sensor had detection limit about 11 ng mL^{-1} with a desirable specificity [163]. In another research a highly sensitive biosensor for CRP in serum was reported. The anti-CRP immobilized on standard polycrystalline gold electrodes. The limit of detection was found to be 176 pM and the linearity with log CRP concentration was in the range of 0.5-50 nM. This biosensor showed very ideal selectivity and regeneration after assay without loss of sensitivity [164]. The interaction between anti-CRP immobilized on electrode and CRP was investigated using electrochemical techniques. This methods could effectively probe CRP concentration in a wide range, from 1.15×10^{-5} to 1.15 mg L^{-1} [165]. Wang *et al*. provided an electrochemical aptasensor for CRP detection. Firstly, silica microspheres functionalized with AuNPs, provided large surface area for immobilizing anti-CRP and Zn^{2+} as signal molecules (silica-

AuNPs- anti-CRP- Zn^{2+}). CRP-aptamer were immobilized on AuNPs modified electrode (AuNPs-aptamer electrode). The fabricated biosensor scheme is illustrated in Fig. (**4**). In the presence of CRP, a sandwich structure was formed and Zn^{2+} reductive peak was recorded clearly. This apatasensor showed linearity in the range from 0.005 ng mL^{-1} to 125 ng mL^{-1} and detection limit as low as 0.0017 ng mL^{-1} of CRP concentration [166]. Liu and colleagues introduced Metal-Organic Frameworks (MOFs) as signal probes. They presented a electrochemical immunoassay using Au-MOFs for C-reactive detection [167]. MOFs are component consist of metal ions or clusters bonded by organic bridging ligands to form one, two, or three dimensional structures [168, 169].

3.3. Myoglobin

Myoglobin (Myo) is an intracellular O2 binding hemoprotein in heart and skeletal muscle. Cardiac myoglobin is one of the very early markers to increase after AMI onset and it was introduced as the first nonenzymatic protein used for AMI diagnosis [170]. Myoglobin has some value characterize including the small size of the molecule (17.8 kDa), facilitating quick release into blood (as early as 1-3 h upon AMI onset), and reaching the maximum between 6 and 12 h after the first symptoms of muscle damage [40]. So, its high sensitivity and high predictive value makes myoglobin a valuable early screening test for AMI [171]. Because of myoglobin rise and fall more rapidly, this marker continues to be used in certain clinical scenarios such as reinfarction, infarct extension and early onset chest pain. Isakov *et al*. demonstrated that Serum myoglobin levels were elevated in 178 patients with acute myocardial infarction compared to the normal control cases. Their data showed that serum myoglobin is a reliable measure of myocardial necrosis and appears to be related to infarct size [172]. Thielmann *et al*. showed that

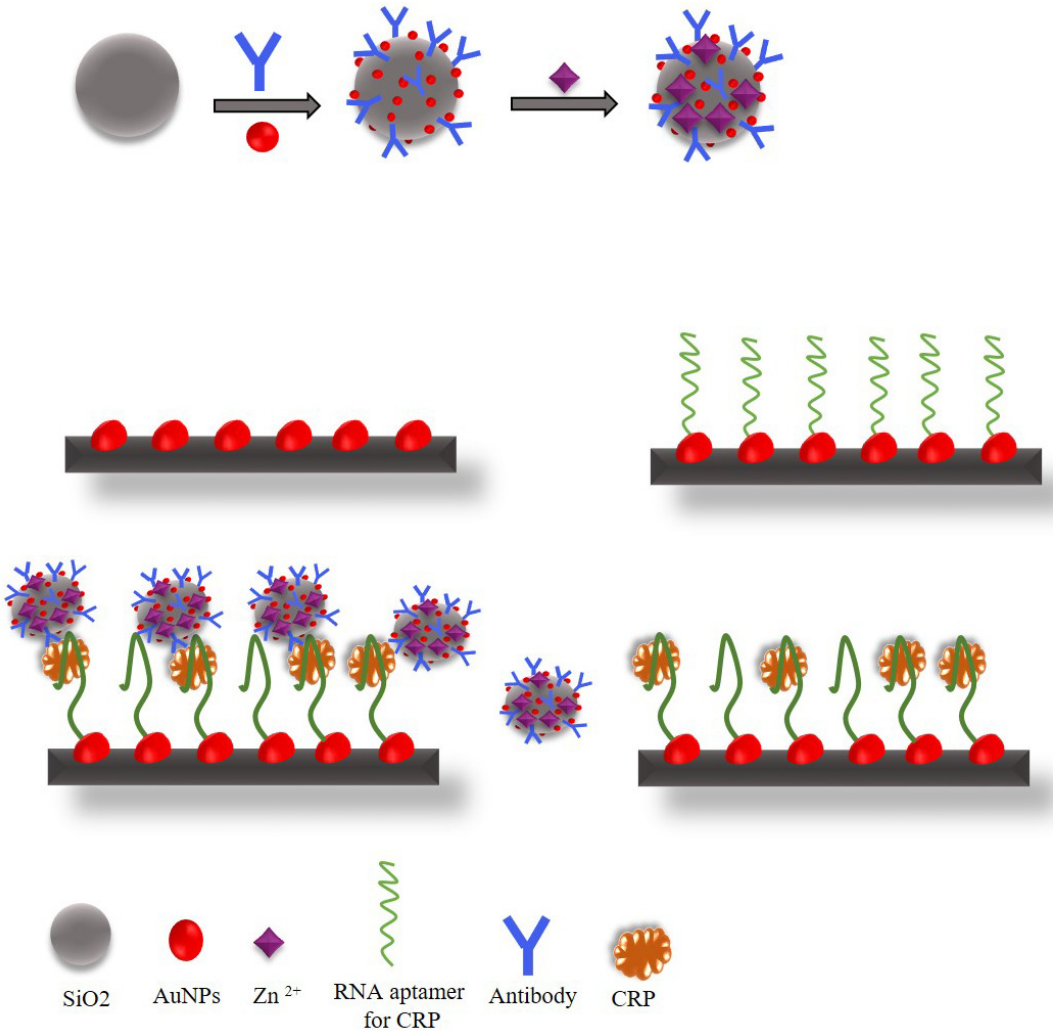

Fig. (4). Aptasensor based on electrochemical detection of C-reactive.

the Myoglobin levels have a higher difference at 12 h after aortic unclamping as compared to troponin I at the same time point. So, this protein is introduced as an earlier marker for myocardial ischemia than troponin I [29]. whereas it has cross-activity with skeletal muscle injury[173] and somewhat lower sensitivity and specificity, this marker of myocardial ischemia might be useful in addition to troponin I as an early warning sign of myocardial diseases.

For direct electrochemically detection, myoglobin was immobilized on AuNPs and Multi Wall Carbon Nanotubes (MWCNTs) [174]. Cobalt nanoparticles (CoNPs) on carbon ionic liquid electrode was used as a myoglobin electrochemical sensing platform [175]. Ruan, *et al*. applied a sensing approach based on graphene, ionic liquid and chitosan composite for the myoglobin immobilization. The high conductivity of ionic liquid and graphene, large surface to volume ration of graphene, and chitosan biocompatibility increased myoglobin absorption and direct electron transfer between protein and electrode [176].

Pur *et al*. fabricated an ECL based for early detection of myoglobin. Aptamer was used for specifically detection of globin in serum and urine samples. The linearity of biosensor was in the range of 0.05 to 25 nM myoglobin concentration, with detection limit of 12pM [177]. Black phosphorus, also known as phosphorene, is a two-dimensional nanostructure which is very much like graphite in terms of similarity in black and flaky form, electrical conductivity and having sheets of linked atoms [178]. In this structure each atom bonds covalently with three neighboring atoms to give a honeycomb structure [147]. An electrochemical based approach using aptamer-functionalized black phosphorus was reported to detect myoglobin. Black phosphorus with aptamers provided a biosensing platform with improved selectivity and sensitivity compared to conventional detection methods. The presented sensor has detection limit of 0.524 pg mL^{-1} with a dynamic response range from 1pg mL^{-1} to 16μg mL^{-1} for serum myoglobin [179]. Moreira *et al*. used polymers for electrochemically myoglobin detection with 2.25 μg mL^{-1} [180].

3.4. Creatine Kinase-MB

Creatine kinase (CK) is a key enzyme of cellular energetics with a number of isoenzymes consists of CK-MM, CK-MB, CK-BB and mitochondrial-CK. Each subunit of the dimeric CK is expressed in a tissue-specific manner that is regulated by a distinct gene [181]. CK-MB is found predominately in the human myocardium; with concentration ranges from 5 to 30% of the total CK activity of the heart [182]. Voss *et al*. demonstrated, in 1995, that the tissue distribution of CK-MB in normal and diseased human heart tissue showed a 30% increase in CK MB in diseased left ventricles and a 35% increase in diseased right ventricles compared to normal myocardium [183]. A recent report which is studied in the acute LAD occlusion showed that myocardial CK-MB globally increased 3-fold at 5 h after occlusion [184]. This study confirmed Ingwall's earlier report which represented, in normal hearts obtained from young, that the CK-MB composition was found to be < 2% [185]. Moreover, the CK-MB content of skeletal muscle in patients with Duchenne's muscular dystrophy was found to be part of a dynamic process influenced by numerous cellular events [186]. In conclusion, CK-MB is not 100% specific for the heart so; increased serum CK-MB concentrations must be evaluated cautiously and taken in context with clinical findings.

CK-MB plays a phosphor-transferase role in creatin, so, the phosphate presence is necessary [187, 188]. Phosphorylated creatine (Pcrea), an electroactive compound, was immobilized on Au electrode and electrochemical spectroscopy methods were applied to follow the chemical modifications in the electrode. CK-MB in solution consumed the Pcrea and caused a significant change in electrical response (Fig. **5**). The limit of detection was 0.11 μg mL^{-1} and performed specific in presence of bovine serum albumin (BSA), TnI and myoglobin [189].

Lee *et al*. fabricated biosensor base on single site-specific Polyaniline (PANI) nanowire with monoclonal antibodies which could detect cardiac biomarker. In this scenario, cTnI, BNP, myoglobin and CK-MB could be simultaneously detect in 250 fg mL^{-1}, 50 fg mL^{-1}, 100 pg mL^{-1} and 50 fg mL^{-1} concentrations, respectively [105]. Prakash and colleagues reported another multiplexed electrochemical immunosensor that simultaneously detected cardiac markers including cTnI, myoglobin and CK-MB. MWCNTs embedded epoxy-based negative photoresist (SU-8) were functionalized with specific antibody. Using these hybrids caused overcoming their respective shortcomings, MWCNTs minimal functional groups and low conductivity for SU-8. The linear range for cTnI, myoglobin and CK-MB were found to be 0.1-10 ng mL^{-1}, 1-50 ng mL^{-1} and 10-10,000 ng mL^{-1}, respectively [190].

3.5. B-type Natriuretic Peptide

B-type Natriuretic Peptide (BNP) is a cardiac neurohormone initially identified in the brain. Multiple

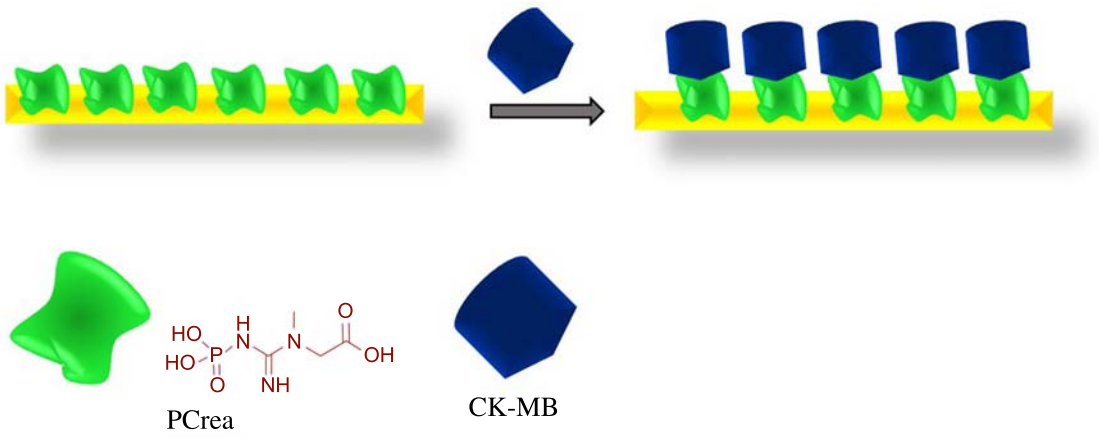

Fig. (5). Simple electrochemical biosensor for detection creatine kinase using PCrea.

studies have identified that this protein has secreted from the heart, particularly the ventricles as a response to heart failure with the progression of clinical symptoms, and then its levels go down when heart failure is stable. [191, 192]. The pre-prohormone BNP (proBNP) cleaved to biologically active 32-aminoacid BNP and non-biologically active 76-aminoacid N-terminal pro-BNP (NT-proBNP) [193]. Recent studies have shown that the concentration of BNP and NTproBNP are increased in a variety of cardiovascular conditions, permitting their use in diagnosis [194]. Clerico and colleagues revealed that serum BNP was potentially useful tools as a novel biomarker for discriminating between normal subjects and patients with different degrees of heart failure. Data showed that protein Levels of B-type natriuretic peptide were significantly elevated in patients with left ventricular dysfunction in their serum samples when compared with normal controls [192]. According to results of the clinical studies performed by Maisel, rapid measurement of B-type natriuretic peptide is useful in establishing or excluding the diagnosis of congestive heart failure in patients with acute dyspnea [26].

Several other novel biomarkers are also being explored as potential heart failure biomarkers, such as NT-proBNP [25], H-FABP [195], Interlukin-6 (IL-6) [196], TNF-α [197], Myeloperoxidase (MPO) [198]; however, some of these are yet to be fully investigated in larger, non-selected samples for their association with incident heart failure.

Simple, acute and reliable evaluation of blood BNP level is of importance for diagnose and distinguish heart failure patients from other dyspnea ones [199]. Electrochemical techniques combined with signal amplifiers seem to be appropriate for gain this purpose [200].

Matsuura *et al*. presented an electrochemical enzyme assay to determine BNP. Anti-BNP functionalized with acetylcholinesterase (AChE) undergone with BNP as target; so the immunological reaction occurred. Further, BNP-AuNPs were added into solution and bonded to unreacted AChE-anti-BNP; in this way they removed from solution [201]. AChE is a very highly active cholinesterase which catalyzes breakdown of acetylcholine and some other choline esters [202, 203]. Eventually, the AChE activity evaluated based on thiol-production chemisorption on an Ag electrode. Finally, AChE reaction caused thiocholine chemisorption which resulted in improved sensitivity for BNP. In this platform 20-200 pg mL^{-1} of BNP concentration could be determined [201]. Recently, Hartati, *et al*. developed immunosensor with the streptoavidin/biotin based on electrochemical techniques. Biotinylated anti-BNP as capture antibody decorated on steptoavidin-modified electrode. In the presence of BNP, the immunological reaction occurred between BNP protein and capture antibody. An anti-BNP conjugated with horseradish peroxidase (HRP), as the secondary antibody, and 3,3,5,5'-tetramethybezidine dihydrochloride (TMB) were used to measure the peak current. The schematic procedure of this sensing platform is shown in Fig. (**6**). The detection limit of 3.3 ng mL^{-1} and a linear detection range from 0.001 to 100 ng mL^{-1} were recorded for BNP concentration [204].

Recently, Shanmugam *et al*. reported multianalyte device for simultaneous detection of cTNI, troponin and BNP. Due to high isoelectric point of pH9.5, ZnO NPs facilitated electron transfer. The antibodies spe-

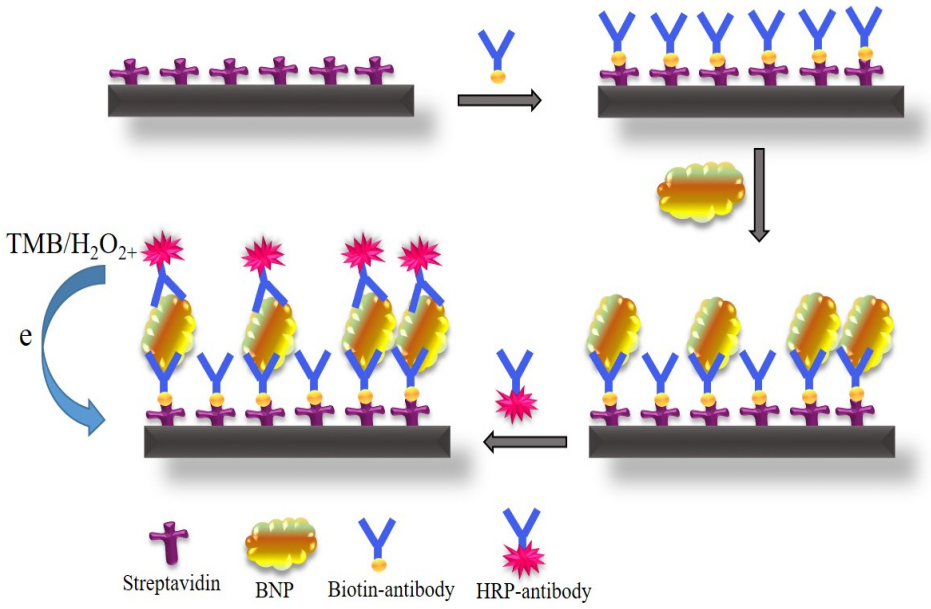

Fig. (6). Immunosensor detection of BNP cardiac biomarker using HRP enzyme.

cific for each biomarker were immobilized on ZnO NPs. In this scenario, dynamic range from 1 pg mL to 100 ng mL^{-1} and limit of detection at 1pg mL^{-1} were obtained for three biomarkers in human serum samples [205].

3.6. Noncoding RNA

Advanced genomics technologies have revealed noncoding regulatory RNAs representing supernatural diversity in size, structure, and molecular function [206]. The levels of individual ncRNA and specific ncRNA signatures are linked to the diagnosis and prognosis for diseases. Recently, increasing evidence suggests that noncoding RNAs have a putative role in the pathophysiology of cardiovascular disease [207, 208]. Noncoding RNAs can be divided into small (<200 nt) noncoding RNAs and long noncoding RNAs (lncRNAs) [206]. Among the small noncoding RNAs, micro RNAs have been studied extensively in cardiovascular diseases. Several studies showed the associations of microRNA to cardiac hypertrophy and cardiac fibrosis, and make them an attractive biomarker to guide future heart failure therapy [209, 210]. They can act as a player in regulation of cardiac fibrosis *e.g.* microRNA-29 [30] microRNA-21 [32], hypertrophy (*e.g.* microRNA-133) [31], and heart failure [33]. One study has even found that several cardiac microRNAs are detectable in blood early after myocardial infarction. Wang *et al.* showed that elevated cardiac-specific miR-208a in human plasma may be a novel biomarker for early detection of myocardial injury. Their result showed that miR-208a was undetectable in non-AMI patients, but it was easily detected in 90.9% AMI patients and in 100% AMI patients within 4 h of the onset of symptoms [48].

In addition, long noncoding RNAs [211] have since also been evaluated by several investigators in relation to the pathological process of a variety of cardiovascular diseases, including AMI [212], Heart Failure (HF) [34], and congenital heart disease [181]. Kumarswamy *et al*. provide evidence that late circulating levels of the lncRNA named LIPCAR, are associated with adverse outcomes after myocardial infarction and in chronic heart failure [34]. However, at the present time, studies about circulating noncoding RNA as a clinical biomarker of AMI is still in its infancy, and measurement of both microRNAs and long noncoding RNAs to established heart failure biomarkers, and their stability and reliability in diagnosing AMI still requires further exploration.

Electrochemical biosensors have the potentials to meet a suitable devise for miRNA detection because of their simplicity, low cost and sensitivity [213]. In this section we propose, specific and promising examples of electrochemical platform for miRNA detection.

Wu *et al*. proposed a miRNA biosensor based on hybridization chain reaction and catalyzed hairpin assembly. They used four label-free hairpin probes named H1 to H4 decorated on AuNPs-graphene nanohybrid film. Firstly, the H1, as the capture probe, was opened in the presence of target miRNA. Hybridization H1 with H2 resulted in getting free the

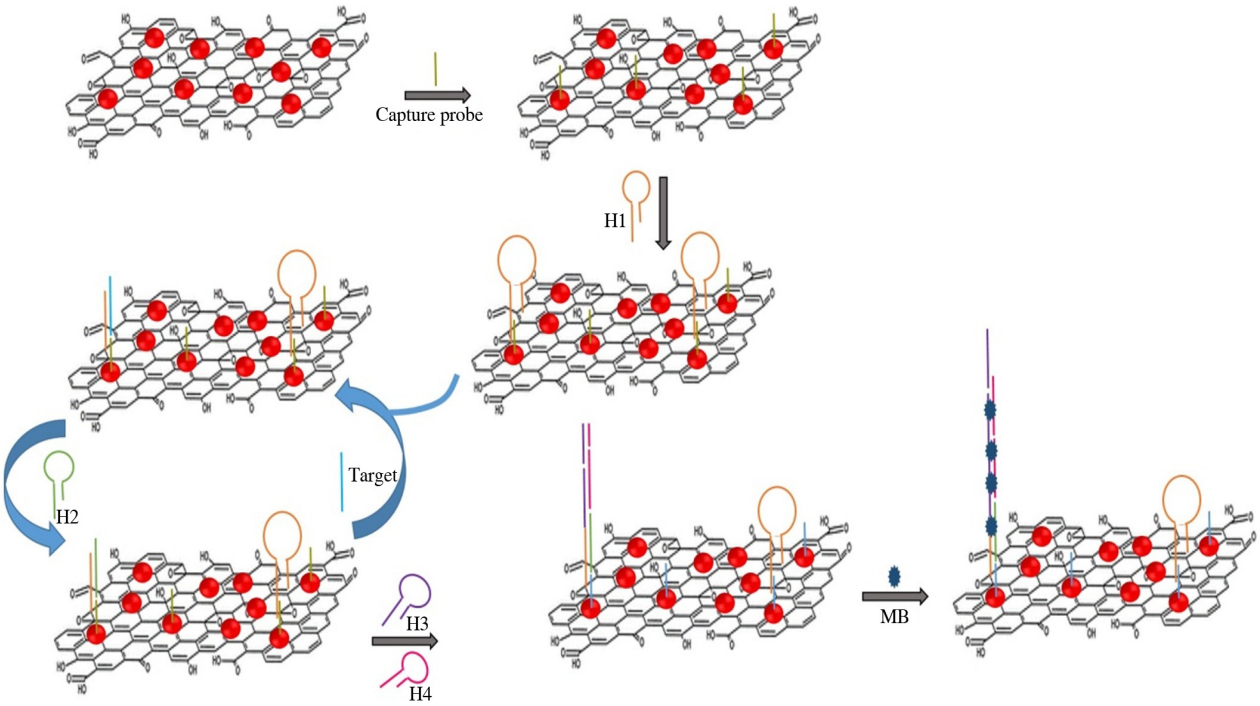

Fig. (7). Electrochemical biosensor based on Go functionalized AuNPs for dual amplification miRNA detection.

H1 with H2 resulted in getting free the target miRNA. The released miRNA rehydride with reaming H1 probe. After target recycling process, the H1-H2 hybrids was exposed with H2 stem which served as HCR initiator. Finally, Methylene Blue (MB), is an electrochemical indicator, intercalated into double strand DNAs to amplify electrochemical signals. The Fig. (**7**) illustrated this sensing platform. The linearity ranged from 10fM to 1nM [214]. An electrochemical genosensor based on inosin-modified capture probe was presented for miRNA detection. Due to probe-target miRNA hybridization the inosin was oxide to guanine which caused an electrical signal [215]. In a miRNA electrochemical biosensor, the morpholino capture probe immobilized on Indium Tin Oxide (ITO)-functionalize electrode [216]. Morpholino oligomers are DNA base attached to methylenemorphone rings *via* phosphodiester bonds. It is worth notice that they have neutral charge and are resistance to enzyme degradation [217, 218]. Hybridization of target miRNA and probe converted the neutral surface to anionic, due to hybridized miRNA strand. Then, HRP enzyme embedded in polymers added to sensing platform. The electrochemical signals were produced in the presence of H_2O_2. The linearity miRNA concentration ranged from 5.0 fM to 2.0 fM and the detection limit was found to be 2.0 fM [216].

CONCLUSION

Valuable insights can be available for the clinicians through cardiac bio-markers, which assist them diagnosing, prognosing, and deciding on the patients' therapeutic options in order to provide immediate remedies while seeing myocardial infarction symptoms. There are a growing papers studying the cardiac bio-markers detection. Numerous techniques have been proposed for analyzing and detecting *via* optical, chemiluminescence, radio-immunoassay, and enzyme associated immuno-sorbent assay techniques. However, they suffer from a lot of challenges, including long-term usage, costly devices, and pre-treatment procedures. In spite of the above techniques, electro-chemical procedures enjoy interesting characteristics, such as rapidness, mobility, inexpensiveness, reliability, accuracy, and so forth. The present review aims at summarizing current researches conducted on detecting CVD biomarkers through electro-chemical techniques. It was found that SWV, EIS and DPV are greatly attracted due to detecting cardiac bio-markers. In general, EIS technique was applied to characterize the morphologies of sensors in order to demonstrate various substances over the sensor surface. Optimization of DPV and SWV techniques have been done for sensitively detecting of cardio-vascular bio-markers.

Moreover, the study presents nano-particles with the widespread application in making bio-marker bio-sensors. With regard to the review of the publications, gold- and carbon-based nano-particles are frequently used to detect cardiac bio-markers. Nano-materials are largely attracted due to integrating into bio-sensor apparatus, because detecting sensitiveness and values of detection limit may be improved by such nanomaterials. Thus, simple synthesizing and integrating into each sensor are their advantages.

Future researches should detect cardio-vascular biomarkers at the clinic because of the convenient procurement process to measure and rapid use through blood or additional biological specimens obtained from the participants. Biomarkers can help management decisions, fast and precise diagnoses, and risks stratifications. They contribute invaluably to the provision of efficient healthcare and minimize healthcare charges. They also may predict numerous cardio-vascular diseases. Currently, authors paid increasingly attention to the application of the lab-on a chip bio-sensors, which are called mobile sensing, on the basis of smart phone and micro-fluidic instruments. Such instruments enjoy influential imaging and computation abilities for gaining rapid data achievement and reporting. These characteristics are of high importance to the personnel and participants. Lab-on a chip sensor will be employed in the cardiac illnesses and diagnoses of disease in the future.

LIST OF ABBREVIATIONS

AChE = Acetylcholinesterase

AMI = Acute Myocardial Infarction

AuNPs = Gold Nanoparticles

BNP = B-Type Natriuretic Peptide

BSA = Bovine Serum Albumin

CK = Creatine Kinase

CK-MB = Creatine Kinase-MB

CK-MM = Creatine Kinase MM

CNF = Carbon Nanofiber

CNT = Carbon Nano Tubes

CoNP = Cobalt Nanoparticles

CRP = C-Reactive Protein

cTn = Cardiac Troponin

cTnI = Cardiac Troponin I

cTnT = Cardiac Troponin T

CVD = Cardiovascular Diseases

CVR = Cardiovascular Risk

DNA = Deoxyribonucleic Acid

DPV = Differential Pulse Voltammetry

ECL = Enhanced Chemilluminescence

EIS = Electrochemical Impedance Spectroscopy

ELISA = Enzyme-Associated Immuno-Sorbent Assay

Fc-SiNPs = Ferrocene-Modified Silica Nanoparticles

GC = Glassy Carbon

GO = Graphene Oxide

H1 = Hairpin Probe 1

H2 = Hairpin Probe 2

H3 = Hairpin Probe 3

H4 = Hairpin Probe 4

HFABP = Heart Type Fatty Acid Binding Protein

HRP = Horseradish Peroxidase

IL = interleukin

ITO = Indium Tin Oxide

LAD = Left Anterior Descending Coronary Artery

LC = Liquid Chromatography

LDL = Low-Density Lipoprotein

LIPCAR = Long Non-Coding Cardiac Associated RNA

LncRNA = Long Non-Coding RNA

MB = Methylene Blue

MI = Myocardial Infarction

MiR = MicroRNA

miRNA = microRNA

MOF = Metal-Organic Framework

MPO = Myeloperoxidase

MWCNT = Multi Wall Carbon Nanotube

MYO = Myoglobin

ncRNA = Noncoding RNA

NT-proBNP = N-Terminal Pro b-Type Natriuretic Peptide

PANI = Polyaniline

Pcrea = Phosphorylated Creatine

Pro-BNP = Pre-Prohormone b-Type Natriuretic Peptide

RNA = Ribonucleic Acid

SA-AuNPs = Streptavidin Coated AuNPs

SPE = Screen Printed Electrode

SPR = Surface Plasmon Resonance

SWV = Square Wave Voltammetry

TMB = Tetramethylbenzidine Dihydrochloride

TNF-α = Tumor Necrosis Factor Alpha

WHO = World Health Organization

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Pagidipati, N.J.; Gaziano, T.A. Estimating deaths from cardiovascular disease: a review of global methodologies of mortality measurement. *Circulation,* **2013**, *127*(6), 749-756. http://dx.doi.org/10.1161/CIRCULATIONAHA.112.128413 PMID: 23401116

[2] Altintas, Z.; Fakanya, W.M.; Tothill, I.E. Cardiovascular disease detection using bio-sensing techniques. *Talanta,* **2014**, *128*, 177-186. http://dx.doi.org/10.1016/j.talanta.2014.04.060 PMID: 25059146

[3] Benjamin, E.J.; Muntner, P.; Alonso, A.; Bittencourt, M.S.; Callaway, C.W.; Carson, A.P.; Chamberlain, A.M.; Chang, A.R.; Cheng, S.; Das, S.R.; Delling, F.N.; Djousse, L.; Elkind, M.S.V.; Ferguson, J.F.; Fornage, M.; Jordan, L.C.; Khan, S.S.; Kissela, B.M.; Knutson, K.L.; Kwan, T.W.; Lackland, D.T.; Lewis, T.T.; Lichtman, J.H.; Longenecker, C.T.; Loop, M.S.; Lutsey, P.L.; Martin, S.S.; Matsushita, K.; Moran, A.E.; Mussolino, M.E.; O'Flaherty, M.; Pandey, A.; Perak, A.M.; Rosamond, W.D.; Roth, G.A.; Sampson, U.K.A.; Satou, G.M.; Schroeder, E.B.; Shah, S.H.; Spartano, N.L.; Stokes, A.; Tirschwell, D.L.; Tsao, C.W.; Turakhia, M.P.; VanWagner, L.B.; Wilkins, J.T.; Wong, S.S.; Virani, S.S. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation,* **2019**, *139*(10), e56-e528. http://dx.doi.org/10.1161/CIR.0000000000000659 PMID: 30700139

[4] Qureshi, A.; Gurbuz, Y.; Niazi, J.H. Biosensors for cardiac biomarkers detection: A review. *Sens. Actuators B Chem.,* **2012**, *171*, 62-76. http://dx.doi.org/10.1016/j.snb.2012.05.077

[5] Rezaei, B.; Ghani, M.; Shoushtari, A.M.; Rabiee, M. Electrochemical biosensors based on nanofibres for cardiac biomarker detection: A comprehensive review. *Biosens. Bioelectron.,* **2016**, *78*, 513-523. http://dx.doi.org/10.1016/j.bios.2015.11.083 PMID: 26657595

[6] Dadu, R.T.; Nambi, V.; Ballantyne, C.M. Developing and assessing cardiovascular biomarkers. *Transl. Res.,* **2012**, *159*(4), 265-276. http://dx.doi.org/10.1016/j.trsl.2012.01.003 PMID: 22424430

[7] Aydin, S.; Ugur, K.; Aydin, S.; Sahin, İ.; Yardim, M. Biomarkers in acute myocardial infarction: current perspectives. *Vasc. Health Risk Manag.,* **2019**, *15*, 1-10. http://dx.doi.org/10.2147/VHRM.S166157 PMID: 30697054

[8] Ray, S.; Reddy, P.J.; Choudhary, S.; Raghu, D.; Srivastava, S. Emerging nanoproteomics approaches for disease biomarker detection: a current perspective. *J. Proteomics,* **2011**, *74*(12), 2660-2681. http://dx.doi.org/10.1016/j.jprot.2011.04.027 PMID: 21596164

[9] Justino, C.I.; Duarte, A.C.; Rocha-Santos, T.A. Critical overview on the application of sensors and biosensors for clinical analysis. *Trends Analyt. Chem.,* **2016**, *85*, 36-60. http://dx.doi.org/10.1016/j.trac.2016.04.004

[10] Burcu Bahadır, E.; Kemal Sezgintürk, M. Applications of electrochemical immunosensors for early clinical diagnostics. *Talanta,* **2015**, *132*, 162-174. http://dx.doi.org/10.1016/j.talanta.2014.08.063 PMID: 25476294

[11] Hahn, S.; Mergenthaler, S.; Zimmermann, B.; Holzgreve, W. Nucleic acid based biosensors: the desires of the user. *Bioelectrochemistry,* **2005**, *67*(2), 151-154. http://dx.doi.org/10.1016/j.bioelechem.2004.07.006 PMID: 16019267

[12] Katagiri, F.; Glazebrook, J. *Overview of mRNA expression profiling using DNA microarrays,* **2009**. http://dx.doi.org/10.1002/0471142727.mb2204s85

[13] Fathil, M.F.; Md Arshad, M.K.; Gopinath, S.C.; Hashim, U.; Adzhri, R.; Ayub, R.M.; Ruslinda, A.R.; Nuzaihan M N, M.; Azman, A.H.; Zaki, M.; Tang, T.H. Diagnostics on acute myocardial infarction: Cardiac troponin biomarkers. *Biosens. Bioelectron.,* **2015**, *70*, 209-220. http://dx.doi.org/10.1016/j.bios.2015.03.037 PMID: 25841117

[14] Szunerits, S.; Mishyn, V.; Grabowska, I.; Boukherroub, R. Electrochemical cardiovascular platforms: Current state of the art and beyond. *Biosens. Bioelectron.,* **2019**, *131*, 287-298. http://dx.doi.org/10.1016/j.bios.2019.02.010 PMID: 30851492

[15] Hu, X.; Guiseppi-Elie, A.; Dinu, C.Z. Biomolecular interfaces based on self-assembly and self-recognition form biosensors capable of recording molecular binding and release. *Nanoscale,* **2019**, *11*(11), 4987-4998. http://dx.doi.org/10.1039/C8NR10090J PMID: 30839012

[16] de Ávila, B.E.F. Multiplexed Determination of Amino-Terminal Pro-B-Type Natriuretic Peptide and C-Reactive Protein Cardiac Biomarkers in Human Serum at a Disposable Electrochemical Magnetoimmunosensor. *Electroanalysis,* **2014**, *26*(2), 254-261. http://dx.doi.org/10.1002/elan.201300479

[17] Hasanzadeh, M.; Shadjou, N. Electrochemical nanobiosensing in whole blood: Recent advances. *Trends Analyt. Chem.,* **2016**, *80*, 167-176. http://dx.doi.org/10.1016/j.trac.2015.07.018

[18] Justino, C.I. Strategies for enhancing the analytical performance of nanomaterial-based sensors. *Trends Analyt. Chem.,* **2013**, *47*, 27-36. http://dx.doi.org/10.1016/j.trac.2013.02.004

[19] Ronkainen, N.J.; Okon, S.L. Nanomaterial-Based Electrochemical Immunosensors for Clinically Significant Biomarkers. *Materials (Basel),* **2014**, *7*(6), 4669-4709. http://dx.doi.org/10.3390/ma7064669 PMID: 28788700

[20] Mozalev, A.; Baccar, H.; Abdelghani, A. Preparation and biosensing performance of porous-alumina-assisted gold nanostructures on substrates. *Procedia Eng.,* **2016**, *168*, 1188-1191. http://dx.doi.org/10.1016/j.proeng.2016.11.404

[21] Lozano, R.; Naghavi, M.; Foreman, K.; Lim, S.; Shibuya, K.; Aboyans, V.; Abraham, J.; Adair, T.; Aggarwal, R.; Ahn, S.Y.; Alvarado, M.; Anderson, H.R.; Anderson, L.M.; Andrews, K.G.; Atkinson, C.; Baddour, L.M.; Barker-Collo, S.; Bartels, D.H.; Bell, M.L.; Benjamin, E.J.; Bennett, D.; Bhalla, K.; Bikbov, B.; Bin Abdulhak, A.; Birbeck, G.; Blyth, F.; Bolliger, I.; Boufous, S.; Bucello, C.; Burch, M.; Burney, P.; Carapetis, J.; Chen, H.; Chou, D.; Chugh, S.S.; Coffeng, L.E.; Colan, S.D.; Colquhoun, S.; Colson, K.E.; Condon, J.; Connor, M.D.; Cooper, L.T.; Corriere, M.; Cortinovis, M.; de Vaccaro, K.C.; Couser, W.; Cowie, B.C.; Criqui, M.H.; Cross, M.; Dabhadkar, K.C.; Dahodwala, N.; De Leo, D.; Degenhardt, L.; Delossantos, A.; Denenberg, J.; Des Jarlais, D.C.; Dharmaratne, S.D.; Dorsey, E.R.; Driscoll, T.; Duber, H.; Ebel, B.; Erwin, P.J.; Espindola, P.; Ezzati, M.; Feigin, V.; Flaxman, A.D.; Forouzanfar, M.H.; Fowkes, F.G.; Franklin, R.; Fransen, M.; Freeman, M.K.; Gabriel, S.E.; Gakidou, E.; Gaspari, F.; Gillum, R.F.; Gonzalez-Medina, D.; Halasa, Y.A.; Haring, D.; Harrison, J.E.; Havmoeller, R.; Hay, R.J.; Hoen, B.; Hotez, P.J.; Hoy, D.; Jacobsen, K.H.; James, S.L.; Jasrasaria, R.; Jayaraman, S.; Johns, N.; Karthikeyan, G.; Kassebaum, N.; Keren, A.; Khoo, J.P.; Knowlton, L.M.; Kobusingye, O.; Koranteng, A.; Krishnamurthi, R.; Lipnick, M.; Lipshultz, S.E.; Ohno, S.L.; Mabweijano, J.; MacIntyre, M.F.; Mallinger, L.; March, L.; Marks, G.B.; Marks, R.; Matsumori, A.; Matzopoulos, R.; Mayosi, B.M.; McAnulty, J.H.; McDermott, M.M.; McGrath, J.; Mensah, G.A.; Merriman, T.R.; Michaud, C.; Miller, M.; Miller, T.R.; Mock, C.; Mocumbi, A.O.; Mokdad, A.A.; Moran, A.; Mulholland, K.; Nair, M.N.; Naldi, L.; Narayan, K.M.; Nasseri, K.; Norman, P.; O'Donnell, M.; Omer, S.B.; Ortblad, K.; Osborne, R.; Ozgediz, D.; Pahari, B.; Pandian, J.D.; Rivero, A.P.; Padilla, R.P.; Perez-Ruiz, F.; Perico, N.; Phillips, D.; Pierce, K.; Pope, C.A., III; Porrini, E.; Pourmalek, F.; Raju, M.; Ranganathan, D.; Rehm, J.T.; Rein, D.B.; Remuzzi, G.; Rivara, F.P.; Roberts, T.; De León, F.R.; Rosenfeld, L.C.; Rushton, L.; Sacco, R.L.; Salomon, J.A.; Sampson, U.; Sanman, E.; Schwebel, D.C.; Segui-Gomez, M.; Shepard, D.S.; Singh, D.; Singleton, J.; Sliwa, K.; Smith, E.; Steer, A.; Taylor, J.A.; Thomas, B.; Tleyjeh, I.M.; Towbin, J.A.; Truelsen, T.; Undurraga, E.A.; Venketasubramanian, N.; Vijayakumar, L.; Vos, T.; Wagner, G.R.; Wang, M.; Wang, W.; Watt, K.; Weinstock, M.A.; Weintraub, R.; Wilkinson, J.D.; Woolf, A.D.; Wulf, S.; Yeh, P.H.; Yip, P.; Zabetian, A.; Zheng, Z.J.; Lopez, A.D.; Murray, C.J.; AlMazroa, M.A.; Memish, Z.A. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet,* **2012**, *380*(9859), 2095-2128. http://dx.doi.org/10.1016/S0140-6736(12)61728-0 PMID: 23245604

[22] Nichols, M.; Townsend, N.; Scarborough, P.; Rayner, M. Cardiovascular disease in Europe: epidemiological update. *Eur. Heart J.,* **2013**, *34*(39), 3028-3034. http://dx.doi.org/10.1093/eurheartj/eht356 PMID: 24014390

[23] Nichols, M.; Townsend, N.; Scarborough, P.; Rayner, M. Cardiovascular disease in Europe 2014: epidemiological update. *Eur. Heart J.,* **2014**, *35*(42), 2950-2959. http://dx.doi.org/10.1093/eurheartj/ehu299 PMID: 25139896

[24] Casas, J.P.; Shah, T.; Hingorani, A.D.; Danesh, J.; Pepys, M.B. C-reactive protein and coronary heart disease: a critical review. *J. Intern. Med.,* **2008**, *264*(4), 295-314. http://dx.doi.org/10.1111/j.1365-2796.2008.02015.x PMID: 18823504

[25] Januzzi, J.L.; van Kimmenade, R.; Lainchbury, J.; Bayes-Genis, A.; Ordonez-Llanos, J.; Santalo-Bel, M.; Pinto, Y.M.; Richards, M. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *Eur. Heart J.,* **2006**, *27*(3), 330-337. http://dx.doi.org/10.1093/eurheartj/ehi631 PMID: 16293638

[26] Maisel, A.S.; Krishnaswamy, P.; Nowak, R.M.; McCord, J.; Hollander, J.E.; Duc, P.; Omland, T.; Storrow, A.B.; Abraham, W.T.; Wu, A.H.; Clopton, P.; Steg, P.G.; Westheim, A.; Knudsen, C.W.; Perez, A.; Kazanegra, R.; Herrmann, H.C.; McCullough, P.A. Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N. Engl. J. Med.,* **2002**, *347*(3), 161-167. http://dx.doi.org/10.1056/NEJMoa020233 PMID: 12124404

[27] Melman, Y.F.; Shah, R.; Das, S. MicroRNAs in heart failure: is the picture becoming less miRky? *Circ Heart Fail,* **2014**, *7*(1), 203-214. http://dx.doi.org/10.1161/CIRCHEARTFAILURE.113.000266 PMID: 24449811

[28] Nagai, T.; Anzai, T.; Kaneko, H.; Mano, Y.; Anzai, A.; Maekawa, Y.; Takahashi, T.; Meguro, T.; Yoshikawa, T.; Fukuda, K. C-reactive protein overexpression exacerbates pressure overload-induced cardiac remodeling through enhanced inflammatory response. *Hypertension,* **2011**, *57*(2), 208-215. http://dx.doi.org/10.1161/HYPERTENSIONAHA.110.158915 PMID: 21220701

[29] Thielmann, M.; Massoudy, P.; Marggraf, G.; Knipp, S.; Schmermund, A.; Piotrowski, J.; Erbel, R.; Jakob, H. Role of troponin I, myoglobin, and creatine kinase for the detection of early graft failure following coronary artery bypass grafting. *Eur. J. Cardiothorac. Surg.,* **2004**, *26*(1), 102-109. http://dx.doi.org/10.1016/j.ejcts.2004.03.015 PMID: 15200987

[30] van Rooij, E.; Sutherland, L.B.; Thatcher, J.E.; DiMaio, J.M.; Naseem, R.H.; Marshall, W.S.; Hill, J.A.; Olson, E.N.

Dysregulation of microRNAs after myocardial infarction reveals a role of miR-29 in cardiac fibrosis. *Proc. Natl. Acad. Sci. USA,* **2008**, *105*(35), 13027-13032. http://dx.doi.org/10.1073/pnas.0805038105 PMID: 18723672

[31] Carè, A.; Catalucci, D.; Felicetti, F.; Bonci, D.; Addario, A.; Gallo, P.; Bang, M.L.; Segnalini, P.; Gu, Y.; Dalton, N.D.; Elia, L.; Latronico, M.V.; Høydal, M.; Autore, C.; Russo, M.A.; Dorn, G.W., II; Ellingsen, O.; Ruiz-Lozano, P.; Peterson, K.L.; Croce, C.M.; Peschle, C.; Condorelli, G. MicroRNA-133 controls cardiac hypertrophy. *Nat. Med.,* **2007**, *13*(5), 613-618. http://dx.doi.org/10.1038/nm1582 PMID: 17468766

[32] Thum, T.; Gross, C.; Fiedler, J.; Fischer, T.; Kissler, S.; Bussen, M.; Galuppo, P.; Just, S.; Rottbauer, W.; Frantz, S.; Castoldi, M.; Soutschek, J.; Koteliansky, V.; Rosenwald, A.; Basson, M.A.; Licht, J.D.; Pena, J.T.; Rouhanifard, S.H.; Muckenthaler, M.U.; Tuschl, T.; Martin, G.R.; Bauersachs, J.; Engelhardt, S. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. *Nature,* **2008**, *456*(7224), 980-984. http://dx.doi.org/10.1038/nature07511 PMID: 19043405

[33] Tijsen, A.J.; Pinto, Y.M.; Creemers, E.E. Non-cardiomyocyte microRNAs in heart failure. *Cardiovasc. Res.,* **2012**, *93*(4), 573-582. http://dx.doi.org/10.1093/cvr/cvr344 PMID: 22180601

[34] Kumarswamy, R.; Bauters, C.; Volkmann, I.; Maury, F.; Fetisch, J.; Holzmann, A.; Lemesle, G.; de Groote, P.; Pinet, F.; Thum, T. Circulating long noncoding RNA, LIPCAR, predicts survival in patients with heart failure. *Circ. Res.,* **2014**, *114*(10), 1569-1575. http://dx.doi.org/10.1161/CIRCRESAHA.114.303915 PMID: 24663402

[35] Bini, A.; Centi, S.; Tombelli, S.; Minunni, M.; Mascini, M. Development of an optical RNA-based aptasensor for C-reactive protein. *Anal. Bioanal. Chem.,* **2008**, *390*(4), 1077-1086. http://dx.doi.org/10.1007/s00216-007-1736-7 PMID: 18066708

[36] Centi, S. Detection of C Reactive Protein (CRP) in Serum by an Electrochemical Aptamer-Based Sandwich Assay. Electroanalysis. *An International Journal Devoted to Fundamental and Practical Aspects of Electroanalysis,* **2009**, *21*(11), 1309-1315.

[37] Lin, S.; Lee, C.K.; Lin, Y.H.; Lee, S.Y.; Sheu, B.C.; Tsai, J.C.; Hsu, S.M. Homopolyvalent antibody-antigen interaction kinetic studies with use of a dual-polarization interferometric biosensor. *Biosens. Bioelectron.,* **2006**, *22*(5), 715-721. http://dx.doi.org/10.1016/j.bios.2006.02.011 PMID: 16569500

[38] Piccoli, J.; Hein, R.; El-Sagheer, A.H.; Brown, T.; Cilli, E.M.; Bueno, P.R.; Davis, J.J. Redox capacitive assaying of C-reactive protein at a peptide supported aptamer interface. *Anal. Chem.,* **2018**, *90*(5), 3005-3008. http://dx.doi.org/10.1021/acs.analchem.7b05374 PMID: 29411973

[39] Adams, J.E., III; Abendschein, D.R.; Jaffe, A.S. Biochemical markers of myocardial injury. Is MB creatine kinase the choice for the 1990s? *Circulation,* **1993**, *88*(2), 750-763. http://dx.doi.org/10.1161/01.CIR.88.2.750 PMID: 8339435

[40] Sallach, S.M.; Nowak, R.; Hudson, M.P.; Tokarski, G.; Khoury, N.; Tomlanovich, M.C.; Jacobsen, G.; de Lemos, J.A.; McCord, J. A change in serum myoglobin to detect acute myocardial infarction in patients with normal troponin I levels. *Am. J. Cardiol.,* **2004**, *94*(7), 864-867. http://dx.doi.org/10.1016/j.amjcard.2004.06.019 PMID: 15464666

[41] Freeman, A.P.; Fatches, K.R.; Carter, I.W.; Cloonan, M.J.; Wilcken, D.E. Comparison of serum myoglobin and creatine kinase MB isoenzyme in early diagnosis of acute myocardial infarction. *Br. Heart J.,* **1981**, *45*(4), 389-392. http://dx.doi.org/10.1136/hrt.45.4.389 PMID: 7225253

[42] Kushner, I.; Broder, M.L.; Karp, D. Control of the acute phase response. Serum C-reactive protein kinetics after acute myocardial infarction. *J. Clin. Invest.,* **1978**, *61*(2), 235-242. http://dx.doi.org/10.1172/JCI108932 PMID: 621273

[43] Luchner, A.; Hengstenberg, C.; Löwel, H.; Trawinski, J.; Baumann, M.; Riegger, G.A.; Schunkert, H.; Holmer, S. N-terminal pro-brain natriuretic peptide after myocardial infarction: a marker of cardio-renal function. *Hypertension,* **2002**, *39*(1), 99-104. http://dx.doi.org/10.1161/hy0102.100537 PMID: 11799086

[44] Dorobantu, M.; Fruntelata, A.G.; Scafa-Udriste, A.; Tautu, O.F. B-type natriuretic peptide (BNP) and left ventricular (LV) function in patients with ST-segment elevation myocardial infarction (STEMI). *Maedica (Buchar.),* **2010**, *5*(4), 243-249. PMID: 21977165

[45] Kleine, A.H. *Release of heart fatty acid-binding protein into plasma after acute myocardial infarction in man.Lipid Metabolism in the Healthy and Disease Heart*; Springer, **1992**, pp. 155-162.

[46] Patterson, C.C.; Smith, A.E.; Yarnell, J.W.; Rumley, A.; Ben-Shlomo, Y.; Lowe, G.D. The associations of interleukin-6 (IL-6) and downstream inflammatory markers with risk of cardiovascular disease: the Caerphilly Study. *Atherosclerosis,* **2010**, *209*(2), 551-557. http://dx.doi.org/10.1016/j.atherosclerosis.2009.09.030 PMID: 19836021

[47] Subirana, I.; Fitó, M.; Diaz, O.; Vila, J.; Francés, A.; Delpon, E.; Sanchis, J.; Elosua, R.; Muñoz-Aguayo, D.; Dégano, I.R.; Marrugat, J. Prediction of coronary disease incidence by biomarkers of inflammation, oxidation, and metabolism. *Sci. Rep.,* **2018**, *8*(1), 3191. http://dx.doi.org/10.1038/s41598-018-21482-y PMID: 29453342

[48] Wang, G-K.; Zhu, J.Q.; Zhang, J.T.; Li, Q.; Li, Y.; He, J.; Qin, Y.W.; Jing, Q. Circulating microRNA: a novel potential biomarker for early diagnosis of acute myocardial infarction in humans. *Eur. Heart J.,* **2010**, *31*(6), 659-666. http://dx.doi.org/10.1093/eurheartj/ehq013 PMID: 20159880

[49] Gidlöf, O.; Andersson, P.; van der Pals, J.; Götberg, M.; Erlinge, D. Cardiospecific microRNA plasma levels correlate with troponin and cardiac function in patients with ST elevation myocardial infarction, are selectively dependent on renal elimination, and can be detected in urine samples. *Cardiology,* **2011**, *118*(4), 217-226. http://dx.doi.org/10.1159/000328869 PMID: 21701171

[50] Goldraich, L.A.; Martinelli, N.C.; Matte, U.; Cohen, C.; Andrades, M.; Pimentel, M.; Biolo, A.; Clausell, N.; Rohde, L.E. Transcoronary gradient of plasma microRNA 423-5p in heart failure: evidence of altered myocardial expression. *Biomarkers,* **2014**, *19*(2), 135-141. http://dx.doi.org/10.3109/1354750X.2013.870605 PMID: 24506564

[51] Corsten, M.F.; Dennert, R.; Jochems, S.; Kuznetsova, T.; Devaux, Y.; Hofstra, L.; Wagner, D.R.; Staessen, J.A.;

Heymans, S.; Schroen, B. Circulating MicroRNA-208b and MicroRNA-499 reflect myocardial damage in cardiovascular disease. *Circ Cardiovasc Genet,* **2010**, *3*(6), 499-506. http://dx.doi.org/10.1161/CIRCGENETICS.110.957415 PMID: 20921333

[52] Yin, Q.; Wu, A.; Liu, M. Plasma long non-coding RNA (lncRNA) GAS5 is a new biomarker for coronary artery disease. *Med. Sci. Monit.,* **2017**, *23*, 6042-6048. http://dx.doi.org/10.12659/MSM.907118 PMID: 29267258

[53] Zhang, Z.; Gao, W.; Long, Q.Q.; Zhang, J.; Li, Y.F.; Liu, D.C.; Yan, J.J.; Yang, Z.J.; Wang, L.S. Increased plasma levels of lncRNA H19 and LIPCAR are associated with increased risk of coronary artery disease in a Chinese population. *Sci. Rep.,* **2017**, *7*(1), 7491. http://dx.doi.org/10.1038/s41598-017-07611-z PMID: 28790415

[54] Park, S.K. The Usefulness of Cardiac Biomarker in Patients with Acute Ischemic Stroke. *J. Korean Neurol. Assoc.,* **2015**, *33*(3), 173-177. http://dx.doi.org/10.17340/jkna.2015.3.6

[55] Adamson, P.D.; Hunter, A.; Madsen, D.M.; Shah, A.S.V.; McAllister, D.A.; Pawade, T.A.; Williams, M.C.; Berry, C.; Boon, N.A.; Flather, M.; Forbes, J.; McLean, S.; Roditi, G.; Timmis, A.D.; van Beek, E.J.R.; Dweck, M.R.; Mickley, H.; Mills, N.L.; Newby, D.E. High-sensitivity cardiac troponin I and the diagnosis of coronary artery disease in patients with suspected angina pectoris. *Circ. Cardiovasc. Qual. Outcomes,* **2018**, *11*(2), e004227. http://dx.doi.org/10.1161/CIRCOUTCOMES.117.004227 PMID: 29444926

[56] Olatidoye, A.G.; Wu, A.H.; Feng, Y.J.; Waters, D. Prognostic role of troponin T versus troponin I in unstable angina pectoris for cardiac events with meta-analysis comparing published studies. *Am. J. Cardiol.,* **1998**, *81*(12), 1405-1410. http://dx.doi.org/10.1016/S0002-9149(98)00200-8 PMID: 9645888

[57] Blankenberg, S.; Salomaa, V.; Makarova, N.; Ojeda, F.; Wild, P.; Lackner, K.J.; Jørgensen, T.; Thorand, B.; Peters, A.; Nauck, M.; Petersmann, A.; Vartiainen, E.; Veronesi, G.; Brambilla, P.; Costanzo, S.; Iacoviello, L.; Linden, G.; Yarnell, J.; Patterson, C.C.; Everett, B.M.; Ridker, P.M.; Kontto, J.; Schnabel, R.B.; Koenig, W.; Kee, F.; Zeller, T.; Kuulasmaa, K. BiomarCaRE Investigators. Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium. *Eur. Heart J.,* **2016**, *37*(30), 2428-2437. http://dx.doi.org/10.1093/eurheartj/ehw172 PMID: 27174290

[58] Welsh, P.; Preiss, D.; Hayward, C.; Shah, A.S.V.; McAllister, D.; Briggs, A.; Boachie, C.; McConnachie, A.; Padmanabhan, S.; Welsh, C.; Woodward, M.; Campbell, A.; Porteous, D.; Mills, N.L.; Sattar, N. Cardiac Troponin T and Troponin I in the General Population. *Circulation,* **2019**, *139*(24), 2754-2764. http://dx.doi.org/10.1161/CIRCULATIONAHA.118.038529 PMID: 31014085

[59] Jaffery, Z.; Nowak, R.; Khoury, N.; Tokarski, G.; Lanfear, D.E.; Jacobsen, G.; McCord, J. Myoglobin and troponin I elevation predict 5-year mortality in patients with undifferentiated chest pain in the emergency department. *Am. Heart J.,* **2008**, *156*(5), 939-945. http://dx.doi.org/10.1016/j.ahj.2008.06.020 PMID: 19061710

[60] Ryu, D-R.; Park, J.T.; Chung, J.H.; Song, E.M.; Roh, S.H.; Lee, J.M.; An, H.R.; Yu, M.; Pyun, W.B.; Shin, G.J.; Kim, S.J.; Kang, D.H.; Choi, K.B. A more appropriate cardiac troponin T level that can predict outcomes in end-stage renal disease patients with acute coronary syndrome. *Yonsei Med. J.,* **2011**, *52*(4), 595-602. http://dx.doi.org/10.3349/ymj.2011.52.4.595 PMID: 21623601

[61] Gidlöf, O.; Smith, J.G.; Miyazu, K.; Gilje, P.; Spencer, A.; Blomquist, S.; Erlinge, D. Circulating cardio-enriched microRNAs are associated with long-term prognosis following myocardial infarction. *BMC Cardiovasc. Disord.,* **2013**, *13*(1), 12. http://dx.doi.org/10.1186/1471-2261-13-12 PMID: 23448306

[62] Keating, S.M.; Deng, X.; Fernandes, F.; Cunha-Neto, E.; Ribeiro, A.L.; Adesina, B.; Beyer, A.I.; Contestable, P.; Custer, B.; Busch, M.P.; Sabino, E.C. NHLBI Retrovirus Epidemiology Donor Study-II (REDS-II), International Component. Inflammatory and cardiac biomarkers are differentially expressed in clinical stages of Chagas disease. *Int. J. Cardiol.,* **2015**, *199*, 451-459. http://dx.doi.org/10.1016/j.ijcard.2015.07.040 PMID: 26277551

[63] Srinivas, V.S.; Cannon, C.P.; Gibson, C.M.; Antman, E.M.; Greenberg, M.A.; Tanasijevic, M.J.; Murphy, S.; de Lemos, J.A.; Sokol, S.; Braunwald, E.; Mueller, H.S. Myoglobin levels at 12 hours identify patients at low risk for 30-day mortality after thrombolysis in acute myocardial infarction: a Thrombolysis in Myocardial Infarction 10B substudy. *Am. Heart J.,* **2001**, *142*(1), 29-36. http://dx.doi.org/10.1067/mhj.2001.116068 PMID: 11431653

[64] Landesberg, G.; Shatz, V.; Akopnik, I.; Wolf, Y.G.; Mayer, M.; Berlatzky, Y.; Weissman, C.; Mosseri, M. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J. Am. Coll. Cardiol.,* **2003**, *42*(9), 1547-1554. http://dx.doi.org/10.1016/j.jacc.2003.05.001 PMID: 14607436

[65] Abdelmeguid, A.E.; Topol, E.J.; Whitlow, P.L.; Sapp, S.K.; Ellis, S.G. Significance of mild transient release of creatine kinase-MB fraction after percutaneous coronary interventions. *Circulation,* **1996**, *94*(7), 1528-1536. http://dx.doi.org/10.1161/01.CIR.94.7.1528 PMID: 8840840

[66] Ndrepepa, G.; Braun, S.; Tada, T.; King, L.; Cassese, S.; Fusaro, M.; Keta, D.; Kastrati, A.; Schmidt, R. Comparative prognostic value of C-reactive protein & fibrinogen in patients with coronary artery disease. *Indian J. Med. Res.,* **2014**, *140*(3), 392-400. PMID: 25366207

[67] van der Meer, I.M.; de Maat, M.P.; Kiliaan, A.J.; van der Kuip, D.A.; Hofman, A.; Witteman, J.C. The value of C-reactive protein in cardiovascular risk prediction: the Rotterdam Study. *Arch. Intern. Med.,* **2003**, *163*(11), 1323-1328. http://dx.doi.org/10.1001/archinte.163.11.1323 PMID: 12796068

[68] Anand, S.S.; Yusuf, S. C-reactive protein is a bystander of cardiovascular disease. *Eur. Heart J.,* **2010**, *31*(17), 2092-2096. http://dx.doi.org/10.1093/eurheartj/ehq242 PMID: 20675658

[69] Kaptoge, S.; Di Angelantonio, E.; Lowe, G.; Pepys, M.B.; Thompson, S.G.; Collins, R.; Danesh, J. Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an in-

dividual participant meta-analysis. *Lancet,* **2010**, *375*(9709), 132-140. http://dx.doi.org/10.1016/S0140-6736(09)61717-7 PMID: 20031199

[70] Kardys, I.; Knetsch, A.M.; Bleumink, G.S.; Deckers, J.W.; Hofman, A.; Stricker, B.H.; Witteman, J.C. C-reactive protein and risk of heart failure. The Rotterdam Study. *Am. Heart J.,* **2006**, *152*(3), 514-520. http://dx.doi.org/10.1016/j.ahj.2006.02.023 PMID: 16923423

[71] Fonseca, F.A.H.; Izar, M.C.O. High-sensitivity C-reactive protein and cardiovascular disease across countries and ethnicities. *Clinics (São Paulo),* **2016**, *71*(4), 235-242. http://dx.doi.org/10.6061/clinics/2016(04)11 PMID: 27166776

[72] Mavrea, A.M.; Dragomir, T.; Bordejevic, D.A.; Tomescu, M.C.; Ancusa, O.; Marincu, I. Causes and predictors of hospital readmissions in patients older than 65 years hospitalized for heart failure with preserved left ventricular ejection fraction in western Romania. *Clin. Interv. Aging,* **2015**, *10*, 979-990. PMID: 26124651

[73] Dieplinger, B.; Bocksrucker, C.; Egger, M.; Eggers, C.; Haltmayer, M.; Mueller, T. Prognostic value of inflammatory and cardiovascular biomarkers for prediction of 90-day all-cause mortality after acute ischemic stroke—results from the Linz Stroke Unit Study. *Clin. Chem.,* **2017**, *63*(6), 1101-1109. http://dx.doi.org/10.1373/clinchem.2016.269969 PMID: 28348074

[74] Mishra, R.K.; Beatty, A.L.; Jaganath, R.; Regan, M.; Wu, A.H.; Whooley, M.A. B-type natriuretic peptides for the prediction of cardiovascular events in patients with stable coronary heart disease: the Heart and Soul Study. *J. Am. Heart Assoc.,* **2014**, *3*(4), e000907. http://dx.doi.org/10.1161/JAHA.114.000907 PMID: 25053234

[75] Seronde, M-F.; Vausort, M.; Gayat, E.; Goretti, E.; Ng, L.L.; Squire, I.B.; Vodovar, N.; Sadoune, M.; Samuel, J.L.; Thum, T.; Solal, A.C.; Laribi, S.; Plaisance, P.; Wagner, D.R.; Mebazaa, A.; Devaux, Y. GREAT network. Circulating microRNAs and outcome in patients with acute heart failure. *PLoS One,* **2015**, *10*(11), e0142237. http://dx.doi.org/10.1371/journal.pone.0142237 PMID: 26580972

[76] Kotecha, D.; Flather, M.D.; Atar, D.; Collins, P.; Pepper, J.; Jenkins, E.; Reid, C.M.; Eccleston, D. Alternative Risk Markers in Coronary Artery Disease (ARM-CAD) Study. B-type natriuretic peptide trumps other prognostic markers in patients assessed for coronary disease. *BMC Med.,* **2019**, *17*(1), 72. http://dx.doi.org/10.1186/s12916-019-1306-9 PMID: 30943979

[77] Jacobs, L. Annals express: Rapidly rule out acute myocardial infarction by combining copeptin and HFABP with cardiac troponin. *Ann. Clin. Biochem.,* **2015**. http://dx.doi.org/10.1177/0004563215578189

[78] Beysel, S.; Kizilgul, M.; Ozbek, M.; Caliskan, M.; Kan, S.; Apaydin, M.; Ozcelik, O.; Cakal, E. Heart-type fatty acid binding protein levels in elderly diabetics without known cardiovascular disease. *Clin. Interv. Aging,* **2017**, *12*, 2063-2068. http://dx.doi.org/10.2147/CIA.S137247 PMID: 29255351

[79] Cubranic, Z.; Madzar, Z.; Matijevic, S.; Dvornik, S.; Fisic, E.; Tomulic, V.; Kunisek, J.; Laskarin, G.; Kardum, I.; Zaputovic, L. Diagnostic accuracy of heart fatty acid binding protein (H-FABP) and glycogen phosphorylase isoenzyme BB (GPBB) in diagnosis of acute myocardial infarction in patients with acute coronary syndrome. *Biochem. Med. (Zagreb),* **2012**, *22*(2), 225-236. http://dx.doi.org/10.11613/BM.2012.025 PMID: 22838188

[80] Hoffmann, U.; Espeter, F.; Weiß, C.; Ahmad-Nejad, P.; Lang, S.; Brueckmann, M.; Akin, I.; Neumaier, M.; Borggrefe, M.; Behnes, M. Ischemic biomarker heart-type fatty acid binding protein (hFABP) in acute heart failure - diagnostic and prognostic insights compared to NT-proBNP and troponin I. *BMC Cardiovasc. Disord.,* **2015**, *15*(1), 50. http://dx.doi.org/10.1186/s12872-015-0026-0 PMID: 26072112

[81] Held, C.; White, H.D.; Stewart, R.A.H.; Budaj, A.; Cannon, C.P.; Hochman, J.S.; Koenig, W.; Siegbahn, A.; Steg, P.G.; Soffer, J.; Weaver, W.D.; Östlund, O.; Wallentin, L. STABILITY Investigators. Inflammatory biomarkers interleukin-6 and C-reactive protein and outcomes in stable coronary heart disease: experiences from the STABILITY (stabilization of atherosclerotic plaque by initiation of darapladib therapy) trial. *J. Am. Heart Assoc.,* **2017**, *6*(10)e005077 http://dx.doi.org/10.1161/JAHA.116.005077 PMID: 29066452

[82] Fanola, C.L.; Morrow, D.A.; Cannon, C.P.; Jarolim, P.; Lukas, M.A.; Bode, C.; Hochman, J.S.; Goodrich, E.L.; Braunwald, E.; O'Donoghue, M.L. Interleukin-6 and the risk of adverse outcomes in patients after an acute coronary syndrome: observations from the SOLID-TIMI 52 (stabilization of plaque using darapladib—thrombolysis in myocardial infarction 52) trial. *J. Am. Heart Assoc.,* **2017**, *6*(10), e005637. http://dx.doi.org/10.1161/JAHA.117.005637 PMID: 29066436

[83] Dunlay, S.M.; Weston, S.A.; Redfield, M.M.; Killian, J.M.; Roger, V.L. Tumor necrosis factor-α and mortality in heart failure: a community study. *Circulation,* **2008**, *118*(6), 625-631. http://dx.doi.org/10.1161/CIRCULATIONAHA.107.759191 PMID: 18645056

[84] Liu, X.; Fan, Z.; Zhao, T.; Cao, W.; Zhang, L.; Li, H.; Xie, Q.; Tian, Y.; Wang, B. Plasma miR-1, miR-208, miR-499 as potential predictive biomarkers for acute myocardial infarction: An independent study of Han population. *Exp. Gerontol.,* **2015**, *72*, 230-238. http://dx.doi.org/10.1016/j.exger.2015.10.011 PMID: 26526403

[85] Kuwabara, Y.; Ono, K.; Horie, T.; Nishi, H.; Nagao, K.; Kinoshita, M.; Watanabe, S.; Baba, O.; Kojima, Y.; Shizuta, S.; Imai, M.; Tamura, T.; Kita, T.; Kimura, T. Increased microRNA-1 and microRNA-133a levels in serum of patients with cardiovascular disease indicate myocardial damage. *Circ Cardiovasc Genet,* **2011**, *4*(4), 446-454. http://dx.doi.org/10.1161/CIRCGENETICS.110.958975 PMID: 21642241

[86] Li, Q.; Chen, L.; Chen, D.; Wu, X.; Chen, M. Influence of microRNA-related polymorphisms on clinical outcomes in coronary artery disease. *Am. J. Transl. Res.,* **2015**, *7*(2), 393-400. PMID: 25901206

[87] Jäntti, T.; Segersvärd, H.; Tolppanen, H.; Tarvasmäki, T.; Lassus, J.; Devaux, Y.; Vausort, M.; Pulkki, K.; Sionis, A.; Bayes-Genis, A.; Tikkanen, I.; Lakkisto, P.; Harjola, V.P. Circulating levels of microRNA 423-5p are associated with

90 day mortality in cardiogenic shock. *ESC Heart Fail.,* **2019**, *6*(1), 98-102. http://dx.doi.org/10.1002/ehf2.12377 PMID: 30472788

[88] Wang, F.; Long, G.; Zhao, C.; Li, H.; Chaugai, S.; Wang, Y.; Chen, C.; Wang, D.W. Plasma microRNA-133a is a new marker for both acute myocardial infarction and underlying coronary artery stenosis. *J. Transl. Med.,* **2013**, *11*(1), 222. http://dx.doi.org/10.1186/1479-5876-11-222 PMID: 24053180

[89] Zhu, L. The correlations of circulating microRNA-133a with the risk and severity of coronary heart disease. *Int. J. Clin. Exp. Med.,* **2017**, *10*(1), 972-978.

[90] Kim, J.S.; Pak, K.; Goh, T.S.; Jeong, D.C.; Han, M.E.; Kim, J.; Oh, S.O.; Kim, C.D.; Kim, Y.H. Prognostic Value of MicroRNAs in Coronary Artery Diseases: A Meta-Analysis. *Yonsei Med. J.,* **2018**, *59*(4), 495-500. http://dx.doi.org/10.3349/ymj.2018.59.4.495 PMID: 29749132

[91] Alavi-Moghaddam, M.; Chehrazi, M.; Alipoor, S.D.; Mohammadi, M.; Baratloo, A.; Mahjoub, M.P.; Movasaghi, M.; Garssen, J.; Adcock, I.M.; Mortaz, E. A Preliminary Study of microRNA-208b after Acute Myocardial Infarction: Impact on 6-Month Survival. *Dis. Markers,* **2018**, *2018*2410451 http://dx.doi.org/10.1155/2018/2410451 PMID: 29977411

[92] Shabaninejad, Z.; Yousefi, F.; Movahedpour, A.; Ghasemi, Y.; Dokanehiifard, S.; Rezaei, S.; Aryan, R.; Savardashtaki, A.; Mirzaei, H. Electrochemical-based biosensors for microRNA detection: Nanotechnology comes into view. *Anal. Biochem.,* **2019**, *581*113349 http://dx.doi.org/10.1016/j.ab.2019.113349 PMID: 31254490

[93] Roointan, A.; Ahmad Mir, T.; Ibrahim Wani, S.; Mati-Ur-Rehman, ; Hussain, K.K.; Ahmed, B.; Abrahim, S.; Savardashtaki, A.; Gandomani, G.; Gandomani, M.; Chinnappan, R.; Akhtar, M.H. Early detection of lung cancer biomarkers through biosensor technology: A review. *J. Pharm. Biomed. Anal.,* **2019**, *164*, 93-103. http://dx.doi.org/10.1016/j.jpba.2018.10.017 PMID: 30366148

[94] Ozkan, S.A. *Electroanalytical methods in pharmaceutical analysis and their validation*; HNB Publishing, **2012**.

[95] Justino, C.I.; Rocha-Santos, T.A.; Duarte, A.C. Advances in point-of-care technologies with biosensors based on carbon nanotubes. *Trends Analyt. Chem.,* **2013**, *45*, 24-36. http://dx.doi.org/10.1016/j.trac.2012.12.012

[96] Bakirhan, N.K.; Ozcelikay, G.; Ozkan, S.A. Recent progress on the sensitive detection of cardiovascular disease markers by electrochemical-based biosensors. *J. Pharm. Biomed. Anal.,* **2018**, *159*, 406-424. http://dx.doi.org/10.1016/j.jpba.2018.07.021 PMID: 30036704

[97] Gomes-Filho, S. A carbon nanotube-based electrochemical immunosensor for cardiac troponin T. *Microchem. J.,* **2013**, *109*, 10-15. http://dx.doi.org/10.1016/j.microc.2012.05.033

[98] Silva, B.V.; Cavalcanti, I.T.; Mattos, A.B.; Moura, P.; Sotomayor, Mdel.P.; Dutra, R.F. Disposable immunosensor for human cardiac troponin T based on streptavidin-microsphere modified screen-printed electrode. *Biosens. Bioelectron.,* **2010**, *26*(3), 1062-1067. http://dx.doi.org/10.1016/j.bios.2010.08.051 PMID: 20863683

[99] Abdorahim, M. Nanomaterials-based electrochemical immunosensors for cardiac troponin recognition: An illustrated review. *Trends Analyt. Chem.,* **2016**, *82*, 337-347. http://dx.doi.org/10.1016/j.trac.2016.06.015

[100] Shumkov, A.A. Gold and silver nanoparticles for electrochemical detection of cardiac troponin I based on stripping voltammetry. *Bionanoscience,* **2013**, *3*(2), 216-222. http://dx.doi.org/10.1007/s12668-013-0090-9

[101] Qiao, X.; Li, K.; Xu, J.; Cheng, N.; Sheng, Q.; Cao, W.; Yue, T.; Zheng, J. Novel electrochemical sensing platform for ultrasensitive detection of cardiac troponin I based on aptamer-MoS_2 nanoconjugates. *Biosens. Bioelectron.,* **2018**, *113*, 142-147. http://dx.doi.org/10.1016/j.bios.2018.05.003 PMID: 29754053

[102] Suprun, E.V.; Saveliev, A.A.; Evtugyn, G.A.; Lisitsa, A.V.; Bulko, T.V.; Shumyantseva, V.V.; Archakov, A.I. Electrochemical approach for acute myocardial infarction diagnosis based on direct antibodies-free analysis of human blood plasma. *Biosens. Bioelectron.,* **2012**, *33*(1), 158-164. http://dx.doi.org/10.1016/j.bios.2011.12.045 PMID: 22310155

[103] Silva, B.V.; Cavalcanti, I.T.; Silva, M.M.; Dutra, R.F. A carbon nanotube screen-printed electrode for label-free detection of the human cardiac troponin T. *Talanta,* **2013**, *117*, 431-437. http://dx.doi.org/10.1016/j.talanta.2013.08.059 PMID: 24209364

[104] Chua, J.H.; Chee, R.E.; Agarwal, A.; Wong, S.M.; Zhang, G.J. Label-free electrical detection of cardiac biomarker with complementary metal-oxide semiconductor-compatible silicon nanowire sensor arrays. *Anal. Chem.,* **2009**, *81*(15), 6266-6271. http://dx.doi.org/10.1021/ac901157x PMID: 20337397

[105] Lee, I.; Luo, X.; Huang, J.; Cui, X.T.; Yun, M. Detection of cardiac biomarkers using single polyaniline nanowire-based conductometric biosensors. *Biosensors (Basel),* **2012**, *2*(2), 205-220. http://dx.doi.org/10.3390/bios2020205 PMID: 25585711

[106] Zhang, G-J.; Luo, Z.H.; Huang, M.J.; Ang, J.J.; Kang, T.G.; Ji, H. An integrated chip for rapid, sensitive, and multiplexed detection of cardiac biomarkers from fingerprick blood. *Biosens. Bioelectron.,* **2011**, *28*(1), 459-463. http://dx.doi.org/10.1016/j.bios.2011.07.007 PMID: 21807497

[107] Pakapongpan, S.; Palangsuntikul, R.; Surareungchai, W. Electrochemical sensors for hemoglobin and myoglobin detection based on methylene blue-multiwalled carbon nanotubes nanohybrid-modified glassy carbon electrode. *Electrochim. Acta,* **2011**, *56*(19), 6831-6836. http://dx.doi.org/10.1016/j.electacta.2011.05.089

[108] Sharma, V. Electrochemical impedance immunosensor for the detection of cardiac biomarker Myogobin (Mb) in aqueous solution. *Thin Solid Films,* **2010**, *519*(3), 1167-1170. http://dx.doi.org/10.1016/j.tsf.2010.08.063

[109] Mishra, S.K.; Kumar, D.; Biradar, A.M.; Rajesh, Electrochemical impedance spectroscopy characterization of mercaptopropionic acid capped ZnS nanocrystal based bioelectrode for the detection of the cardiac biomarker--myoglobin. *Bioelectrochemistry,* **2012**, *88*, 118-126. http://dx.doi.org/10.1016/j.bioelechem.2012.07.006 PMID: 22922532

[110] Moreira, F.T. Surface imprinting approach on screen printed electrodes coated with carboxylated PVC for myoglobin detection with electrochemical transduction. *Procedia Eng.,* **2012**, *47*, 865-868.

http://dx.doi.org/10.1016/j.proeng.2012.09.284

[111] Lee, I.; Luo, X.; Cui, X.T.; Yun, M. Highly sensitive single polyaniline nanowire biosensor for the detection of immunoglobulin G and myoglobin. *Biosens. Bioelectron.,* **2011**, *26*(7), 3297-3302. http://dx.doi.org/10.1016/j.bios.2011.01.001 PMID: 21269820

[112] Kokkinos, C.; Prodromidis, M.; Economou, A.; Petrou, P.; Kakabakos, S. Disposable integrated bismuth citrate-modified screen-printed immunosensor for ultrasensitive quantum dot-based electrochemical assay of C-reactive protein in human serum. *Anal. Chim. Acta,* **2015**, *886*, 29-36. http://dx.doi.org/10.1016/j.aca.2015.05.035 PMID: 26320633

[113] Ibupoto, Z.H. Development of a disposable potentiometric antibody immobilized ZnO nanotubes based sensor for the detection of C-reactive protein. *Sens. Actuators B Chem.,* **2012**, *166*, 809-814. http://dx.doi.org/10.1016/j.snb.2012.03.083

[114] Miao, W.; Bard, A.J. Electrogenerated chemiluminescence. 72. Determination of immobilized DNA and C-reactive protein on Au(111) electrodes using tris(2,2′-bipyridyl)-ruthenium(II) labels. *Anal. Chem.,* **2003**, *75*(21), 5825-5834. http://dx.doi.org/10.1021/ac034596v PMID: 14588023

[115] Lin, K-C.; Kunduru, V.; Bothara, M.; Rege, K.; Prasad, S.; Ramakrishna, B.L. Biogenic nanoporous silica-based sensor for enhanced electrochemical detection of cardiovascular biomarkers proteins. *Biosens. Bioelectron.,* **2010**, *25*(10), 2336-2342. http://dx.doi.org/10.1016/j.bios.2010.03.032 PMID: 20417087

[116] Songjaroen, T. Label-free detection of C-reactive protein using an electrochemical DNA immunoassay. *Sens. Biosensing Res.,* **2016**, *8*, 14-19. http://dx.doi.org/10.1016/j.sbsr.2016.03.003

[117] Buch, M.; Rishpon, J. An Electrochemical Immunosensor for C-Reactive Protein Based on Multi-Walled Carbon Nanotube-Modified Electrodes. Electroanalysis. *An International Journal Devoted to Fundamental and Practical Aspects of Electroanalysis,* **2008**, *20*(23), 2592-2594.

[118] Gupta, R.K.; Meyyappan, M.; Koehne, J.E. Vertically aligned carbon nanofiber nanoelectrode arrays: electrochemical *etc*hing and electrode reusability. *RSC Advances,* **2014**, *4*(43), 22642-22650. http://dx.doi.org/10.1039/c4ra01779j PMID: 25089188

[119] Anwar, R.M. Highly sensitive conductive polymer nanofibers for applications in cardiac biomarker detection. *Adv. Sci. Eng. Med.,* **2013**, *5*(7), 633-640. http://dx.doi.org/10.1166/asem.2013.1297

[120] Kunduru, V.; Bothara, M.; Grosch, J.; Sengupta, S.; Patra, P.K.; Prasad, S. Nanostructured surfaces for enhanced protein detection toward clinical diagnostics. *Nanomedicine (Lond.),* **2010**, *6*(5), 642-650. http://dx.doi.org/10.1016/j.nano.2010.03.002 PMID: 20353834

[121] Zhuo, Y.; Yi, W.J.; Lian, W.B.; Yuan, R.; Chai, Y.Q.; Chen, A.; Hu, C.M. Ultrasensitive electrochemical strategy for NT-proBNP detection with gold nanochains and horseradish peroxidase complex amplification. *Biosens. Bioelectron.,* **2011**, *26*(5), 2188-2193. http://dx.doi.org/10.1016/j.bios.2010.09.033 PMID: 20952179

[122] Serafín, V.; Torrente-Rodríguez, R.M.; González-Cortés, A.; García de Frutos, P.; Sabaté, M.; Campuzano, S.; Yáñez-Sedeño, P.; Pingarrón, J.M. An electrochemical immunosensor for brain natriuretic peptide prepared with screen-printed carbon electrodes nanostructured with gold nanoparticles grafted through aryl diazonium salt chemistry. *Talanta,* **2018**, *179*, 131-138. http://dx.doi.org/10.1016/j.talanta.2017.10.063 PMID: 29310212

[123] Panneer Selvam, A.; Prasad, S. Nanosensor electrical immunoassay for quantitative detection of NT-pro brain natriuretic peptide. *Future Cardiol.,* **2013**, *9*(1), 137-147. http://dx.doi.org/10.2217/fca.12.76 PMID: 23259480

[124] Liu, P. High yield two-dimensional (2-D) polyaniline layer and its application in detection of B-type natriuretic peptide in human serum. *Sens. Actuators B Chem.,* **2016**, *230*, 184-190. http://dx.doi.org/10.1016/j.snb.2016.02.051

[125] Matsuura, H.; Sato, Y.; Niwa, O.; Mizutani, F. Electrochemical enzyme immunoassay of a peptide hormone at picomolar levels. *Anal. Chem.,* **2005**, *77*(13), 4235-4240. http://dx.doi.org/10.1021/ac040190m PMID: 15987132

[126] Kim, J. Rapid prototyping of multifunctional microfluidic cartridges for electrochemical biosensing platforms. *Sens. Actuators B Chem.,* **2014**, *202*, 60-66. http://dx.doi.org/10.1016/j.snb.2014.05.009

[127] Hong, C-Y.; Chen, X.; Liu, T.; Li, J.; Yang, H.H.; Chen, J.H.; Chen, G.N. Ultrasensitive electrochemical detection of cancer-associated circulating microRNA in serum samples based on DNA concatamers. *Biosens. Bioelectron.,* **2013**, *50*, 132-136. http://dx.doi.org/10.1016/j.bios.2013.06.040 PMID: 23850778

[128] Yin, H.; Zhou, Y.; Chen, C.; Zhu, L.; Ai, S. An electrochemical signal 'off-on' sensing platform for microRNA detection. *Analyst (Lond.),* **2012**, *137*(6), 1389-1395. http://dx.doi.org/10.1039/c2an16098f PMID: 22311172

[129] Wen, Y.; Liu, G.; Pei, H.; Li, L.; Xu, Q.; Liang, W.; Li, Y.; Xu, L.; Ren, S.; Fan, C. DNA nanostructure-based ultrasensitive electrochemical microRNA biosensor. *Methods,* **2013**, *64*(3), 276-282. http://dx.doi.org/10.1016/j.ymeth.2013.07.035 PMID: 23911620

[130] Pöhlmann, C.; Sprinzl, M. Electrochemical detection of microRNAs *via* gap hybridization assay. *Anal. Chem.,* **2010**, *82*(11), 4434-4440. http://dx.doi.org/10.1021/ac100186p PMID: 20433153

[131] Cheng, F-F.; He, T.T.; Miao, H.T.; Shi, J.J.; Jiang, L.P.; Zhu, J.J. Electron transfer mediated electrochemical biosensor for microRNAs detection based on metal ion functionalized titanium phosphate nanospheres at attomole level. *ACS Appl. Mater. Interfaces,* **2015**, *7*(4), 2979-2985. http://dx.doi.org/10.1021/am508690x PMID: 25588109

[132] Tran, H.V.; Piro, B.; Reisberg, S.; Huy Nguyen, L.; Dung Nguyen, T.; Duc, H.T.; Pham, M.C. An electrochemical ELISA-like immunosensor for miRNAs detection based on screen-printed gold electrodes modified with reduced graphene oxide and carbon nanotubes. *Biosens. Bioelectron.,* **2014**, *62*, 25-30. http://dx.doi.org/10.1016/j.bios.2014.06.014 PMID: 24973539

[133] Schreiber, A.; Feldbrügge, R.; Key, G.; Glatz, J.F.; Spener, F. An immunosensor based on disposable electrodes for rapid estimation of fatty acid-binding protein, an early marker of myocardial infarction. *Biosens. Bioelectron.,* **1997**, *12*(11), 1131-1137. http://dx.doi.org/10.1016/S0956-5663(97)00003-1 PMID: 9451800

[134] O'Regan, T.M.; Pravda, M.; O'Sullivan, C.K.; Guilbault, G.G. Development of a disposable immunosensor for the detection of human heart fatty-acid binding protein in human whole blood using screen-printed carbon electrodes. *Talanta,* **2002**, *57*(3), 501-510. http://dx.doi.org/10.1016/S0039-9140(02)00047-4 PMID: 18968649

[135] Hasić, S.; Kiseljaković, E.; Jadrić, R.; Radovanović, J.; Winterhalter-Jadrić, M. Cardiac troponin I: the gold standard in acute myocardial infarction diagnosis. *Bosn. J. Basic Med. Sci.,* **2003**, *3*(3), 41-44. http://dx.doi.org/10.17305/bjbms.2003.3527 PMID: 16232149

[136] Cheng, Y.; Regnier, M. Cardiac troponin structure-function and the influence of hypertrophic cardiomyopathy associated mutations on modulation of contractility. *Arch. Biochem. Biophys.,* **2016**, *601*, 11-21. http://dx.doi.org/10.1016/j.abb.2016.02.004 PMID: 26851561

[137] Davies, K.R.; Gelb, A.W.; Manninen, P.H.; Boughner, D.R.; Bisnaire, D. Cardiac function in aneurysmal subarachnoid haemorrhage: a study of electrocardiographic and echocardiographic abnormalities. *Br. J. Anaesth.,* **1991**, *67*(1), 58-63. http://dx.doi.org/10.1093/bja/67.1.58 PMID: 1859761

[138] Korff, S.; Katus, H.A.; Giannitsis, E. Differential diagnosis of elevated troponins. *Heart,* **2006**, *92*(7), 987-993. http://dx.doi.org/10.1136/hrt.2005.071282 PMID: 16775113

[139] Moran, A.E.; Tzong, K.Y.; Forouzanfar, M.H.; Rothy, G.A.; Mensah, G.A.; Ezzati, M.; Murray, C.J.; Naghavi, M. Variations in ischemic heart disease burden by age, country, and income: the Global Burden of Diseases, Injuries, and Risk Factors 2010 study. *Glob. Heart,* **2014**, *9*(1), 91-99. http://dx.doi.org/10.1016/j.gheart.2013.12.007 PMID: 24977114

[140] Thygesen, K.; Alpert, J.S.; White, H.D. Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J. Am. Coll. Cardiol.,* **2007**, *50*(22), 2173-2195. http://dx.doi.org/10.1016/j.jacc.2007.09.011 PMID: 18036459

[141] Song, W-J.; Van Keuren, M.L.; Drabkin, H.A.; Cypser, J.R.; Gemmill, R.M.; Kurnit, D.M. Assignment of the human slow twitch skeletal muscle/cardiac troponin C gene (TNNC1) to human chromosome 3p21.3-->3p14.3 using somatic cell hybrids. *Cytogenet. Cell Genet.,* **1996**, *75*(1), 36-37. http://dx.doi.org/10.1159/000134453 PMID: 8995486

[142] Ravkilde, J. Risk stratification in acute coronary syndrome using cardiac troponin I. *Clin. Chem.,* **2000**, *46*(4), 443-444. http://dx.doi.org/10.1093/clinchem/46.4.443 PMID: 10759466

[143] Cina, S.J.; Brown, D.K.; Smialek, J.E.; Collins, K.A. A rapid postmortem cardiac troponin T assay: laboratory evidence of sudden cardiac death. *Am. J. Forensic Med. Pathol.,* **2001**, *22*(2), 173-176. http://dx.doi.org/10.1097/00000433-200106000-00012 PMID: 11394753

[144] Stelzle, D.; Shah, A.S.V.; Anand, A.; Strachan, F.E.; Chapman, A.R.; Denvir, M.A.; Mills, N.L.; McAllister, D.A. High-sensitivity cardiac troponin I and risk of heart failure in patients with suspected acute coronary syndrome: a cohort study. *Eur. Heart J. Qual. Care Clin. Outcomes,* **2018**, *4*(1), 36-42. http://dx.doi.org/10.1093/ehjqcco/qcx022 PMID: 29045610

[145] Kazemi, S.H.; Ghodsi, E.; Abdollahi, S.; Nadri, S. Porous graphene oxide nanostructure as an excellent scaffold for label-free electrochemical biosensor: Detection of cardiac troponin I. *Mater. Sci. Eng. C,* **2016**, *69*, 447-452. http://dx.doi.org/10.1016/j.msec.2016.07.005 PMID: 27612734

[146] Liu, G.; Qi, M.; Zhang, Y.; Cao, C.; Goldys, E.M. Nanocomposites of gold nanoparticles and graphene oxide towards an stable label-free electrochemical immunosensor for detection of cardiac marker troponin-I. *Anal. Chim. Acta,* **2016**, *909*, 1-8. http://dx.doi.org/10.1016/j.aca.2015.12.023 PMID: 26851079

[147] Jo, H.; Gu, H.; Jeon, W.; Youn, H.; Her, J.; Kim, S.K.; Lee, J.; Shin, J.H.; Ban, C. Electrochemical aptasensor of cardiac troponin I for the early diagnosis of acute myocardial infarction. *Anal. Chem.,* **2015**, *87*(19), 9869-9875. http://dx.doi.org/10.1021/acs.analchem.5b02312 PMID: 26352249

[148] Periyakaruppan, A.; Gandhiraman, R.P.; Meyyappan, M.; Koehne, J.E. Label-free detection of cardiac troponin-I using carbon nanofiber based nanoelectrode arrays. *Anal. Chem.,* **2013**, *85*(8), 3858-3863. http://dx.doi.org/10.1021/ac302801z PMID: 23384128

[149] Li, F.; Yu, Y.; Cui, H.; Yang, D.; Bian, Z. Label-free electrochemiluminescence immunosensor for cardiac troponin I using luminol functionalized gold nanoparticles as a sensing platform. *Analyst (Lond.),* **2013**, *138*(6), 1844-1850. http://dx.doi.org/10.1039/c3an36805j PMID: 23377497

[150] Ramadan, M.A. Acta Crystallographica Section D In: *The three-dimensional structure of calcium-depleted human C-reactive protein from perfectly twinned crystals*; , **2002**; 58, pp. 6-2. http://dx.doi.org/10.1107/S0907444902005693

[151] Ledue, T.B.; Rifai, N. Preanalytic and analytic sources of variations in C-reactive protein measurement: implications for cardiovascular disease risk assessment. *Clin. Chem.,* **2003**, *49*(8), 1258-1271. http://dx.doi.org/10.1373/49.8.1258 PMID: 12881440

[152] Blake, G.J.; Ridker, P.M. Inflammatory bio-markers and cardiovascular risk prediction. *J. Intern. Med.,* **2002**, *252*(4), 283-294. http://dx.doi.org/10.1046/j.1365-2796.2002.01019.x PMID: 12366601

[153] Lee, S-S. High-sensitivity C-reactive protein as an associate of clinical subsets and organ damage in systemic lupus erythematosus. In: *Seminars in arthritis and rheumatism*; Elsevier, **2008**. http://dx.doi.org/10.1016/j.semarthrit.2007.09.005

[154] Libby, P.; Ridker, P.M.; Maseri, A. Inflammation and atherosclerosis. *Circulation,* **2002**, *105*(9), 1135-1143. http://dx.doi.org/10.1161/hc0902.104353 PMID: 11877368

[155] Pagana, K.D.; Pagana, T.J. *Mosby's Manual of Diagnostic and Laboratory Tests-E-Book*; Elsevier Health Sciences, **2017**.

[156] Cao, J.J.; Thach, C.; Manolio, T.A.; Psaty, B.M.; Kuller, L.H.; Chaves, P.H.; Polak, J.F.; Sutton-Tyrrell, K.; Herrington, D.M.; Price, T.R.; Cushman, M. C-reactive protein, carotid intima-media thickness, and incidence of ischemic stroke in the elderly: the Cardiovascular Health Study. *Circulation,* **2003**, *108*(2), 166-170. http://dx.doi.org/10.1161/01.CIR.0000079160.07364.6A PMID: 12821545

[157] Ridker, P.M.; Glynn, R.J.; Hennekens, C.H. C-reactive protein adds to the predictive value of total and HDL cho-

lesterol in determining risk of first myocardial infarction. *Circulation,* **1998**, *97*(20), 2007-2011. http://dx.doi.org/10.1161/01.CIR.97.20.2007 PMID: 9610529

[158] Yasojima, K.; Schwab, C.; McGeer, E.G.; McGeer, P.L. Generation of C-reactive protein and complement components in atherosclerotic plaques. *Am. J. Pathol.,* **2001**, *158*(3), 1039-1051. http://dx.doi.org/10.1016/S0002-9440(10)64051-5 PMID: 11238052

[159] Williams, T.N.; Zhang, C.X.; Game, B.A.; He, L.; Huang, Y. C-reactive protein stimulates MMP-1 expression in U937 histiocytes through Fc[γ]RII and extracellular signal-regulated kinase pathway: an implication of CRP involvement in plaque destabilization. *Arterioscler. Thromb. Vasc. Biol.,* **2004**, *24*(1), 61-66. http://dx.doi.org/10.1161/01.ATV.0000104014.24367.16 PMID: 14592848

[160] de Beer, F.C.; Hind, C.R.; Fox, K.M.; Allan, R.M.; Maseri, A.; Pepys, M.B. Measurement of serum C-reactive protein concentration in myocardial ischaemia and infarction. *Br. Heart J.,* **1982**, *47*(3), 239-243. http://dx.doi.org/10.1136/hrt.47.3.239 PMID: 7059401

[161] Morrow, D.A.; Cannon, C.P.; Jesse, R.L.; Newby, L.K.; Ravkilde, J.; Storrow, A.B.; Wu, A.H.; Christenson, R.H. National Academy of Clinical Biochemistry. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Circulation,* **2007**, *115*(13), e356-e375. PMID: 17384331

[162] Burtis, C.A.; Ashwood, E.R.; Bruns, D.E. *Tietz textbook of clinical chemistry and molecular diagnostics-e-book*; Elsevier Health Sciences, **2012**.

[163] Gupta, R.K.; Periyakaruppan, A.; Meyyappan, M.; Koehne, J.E. Label-free detection of C-reactive protein using a carbon nanofiber based biosensor. *Biosens. Bioelectron.,* **2014**, *59*, 112-119. http://dx.doi.org/10.1016/j.bios.2014.03.027 PMID: 24709327

[164] Bryan, T.; Luo, X.; Bueno, P.R.; Davis, J.J. An optimised electrochemical biosensor for the label-free detection of C-reactive protein in blood. *Biosens. Bioelectron.,* **2013**, *39*(1), 94-98. http://dx.doi.org/10.1016/j.bios.2012.06.051 PMID: 22809521

[165] Hennessey, H.; Afara, N.; Omanovic, S.; Padjen, A.L. Electrochemical investigations of the interaction of C-reactive protein (CRP) with a CRP antibody chemically immobilized on a gold surface. *Anal. Chim. Acta,* **2009**, *643*(1-2), 45-53. http://dx.doi.org/10.1016/j.aca.2009.04.009 PMID: 19446062

[166] Wang, J.; Guo, J.; Zhang, J.; Zhang, W.; Zhang, Y. RNA aptamer-based electrochemical aptasensor for C-reactive protein detection using functionalized silica microspheres as immunoprobes. *Biosens. Bioelectron.,* **2017**, *95*, 100-105. http://dx.doi.org/10.1016/j.bios.2017.04.014 PMID: 28431362

[167] Liu, T-Z.; Hu, R.; Zhang, X.; Zhang, K.L.; Liu, Y.; Zhang, X.B.; Bai, R.Y.; Li, D.; Yang, Y.H. Metal-organic framework nanomaterials as novel signal probes for electron transfer mediated ultrasensitive electrochemical immunoassay. *Anal. Chem.,* **2016**, *88*(24), 12516-12523. http://dx.doi.org/10.1021/acs.analchem.6b04191 PMID: 28193012

[168] Hamon, L.; Llewellyn, P.L.; Devic, T.; Ghoufi, A.; Clet, G.; Guillerm, V.; Pirngruber, G.D.; Maurin, G.; Serre, C.; Driver, G.; van Beek, W.; Jolimaître, E.; Vimont, A.; Daturi, M.; Férey, G. Co-adsorption and separation of CO2-CH4 mixtures in the highly flexible MIL-53(Cr) MOF. *J. Am. Chem. Soc.,* **2009**, *131*(47), 17490-17499. http://dx.doi.org/10.1021/ja907556q PMID: 19904944

[169] Zhao, M.; Deng, K.; He, L.; Liu, Y.; Li, G.; Zhao, H.; Tang, Z. Core-shell palladium nanoparticle@metal-organic frameworks as multifunctional catalysts for cascade reactions. *J. Am. Chem. Soc.,* **2014**, *136*(5), 1738-1741. http://dx.doi.org/10.1021/ja411468e PMID: 24437922

[170] Nassar, A-E.F. Electrochemical properties of myoglobin embedded in Langmuir-Blodgett and cast films of synthetic lipids. *J. Chem. Soc., Faraday Trans.,* **1995**, *91*(12), 1775-1782. http://dx.doi.org/10.1039/FT9959101775

[171] McDonnell, B.; Hearty, S.; Leonard, P.; O'Kennedy, R. Cardiac biomarkers and the case for point-of-care testing. *Clin. Biochem.,* **2009**, *42*(7-8), 549-561. http://dx.doi.org/10.1016/j.clinbiochem.2009.01.019 PMID: 19318022

[172] Isakov, A.; Shapira, I.; Burke, M.; Almog, C. Serum myoglobin levels in patients with ischemic myocardial insult. *Arch. Intern. Med.,* **1988**, *148*(8), 1762-1765. http://dx.doi.org/10.1001/archinte.1988.00380080054016 PMID: 3401097

[173] Bhayana, V.; Gougoulias, T.; Cohoe, S.; Henderson, A.R. Discordance between results for serum troponin T and troponin I in renal disease. *Clin. Chem.,* **1995**, *41*(2), 312-317. http://dx.doi.org/10.1093/clinchem/41.2.312 PMID: 7874786

[174] Cao, W. Direct electrochemistry and electrocatalysis of myoglobin immobilized on gold nanoparticles/carbon nanotubes nanohybrid film. Electroanalysis. *An International Journal Devoted to Fundamental and Practical Aspects of Electroanalysis,* **2008**, *20*(17), 1925-1931.

[175] Sun, W. Electrodeposition of Co nanoparticles on the carbon ionic liquid electrode as a platform for myoglobin electrochemical biosensor. *J. Phys. Chem. C,* **2009**, *113*(26), 11294-11300. http://dx.doi.org/10.1021/jp8114594

[176] Ruan, C. Electrochemical myoglobin biosensor based on graphene-ionic liquid-chitosan bionanocomposites: Direct electrochemistry and electrocatalysis. *Electrochim. Acta,* **2012**, *64*, 183-189. http://dx.doi.org/10.1016/j.electacta.2012.01.005

[177] Pur, M.R.K. Highly sensitive label-free electrochemiluminescence aptasensor for early detection of myoglobin, a biomarker for myocardial infarction. *Mikrochim. Acta,* **2017**, *184*(9), 3529-3537. http://dx.doi.org/10.1007/s00604-017-2385-y

[178] Yasue, H.; Yoshimura, M.; Sumida, H.; Kikuta, K.; Kugiyama, K.; Jougasaki, M.; Ogawa, H.; Okumura, K.; Mukoyama, M.; Nakao, K. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation,* **1994**, *90*(1), 195-203. http://dx.doi.org/10.1161/01.CIR.90.1.195 PMID: 8025996

[179] Kumar, V.; Brent, J.R.; Shorie, M.; Kaur, H.; Chadha, G.; Thomas, A.G.; Lewis, E.A.; Rooney, A.P.; Nguyen, L.; Zhong, X.L.; Burke, M.G.; Haigh, S.J.; Walton, A.; McNaughter, P.D.; Tedstone, A.A.; Savjani, N.; Muryn, C.A.; O'Brien, P.; Ganguli, A.K.; Lewis, D.J.; Sabherwal,

P. Nanostructured aptamer-functionalized black phosphorus sensing platform for label-free detection of myoglobin, a cardiovascular disease biomarker. *ACS Appl. Mater. Interfaces,* **2016**, *8*(35), 22860-22868. http://dx.doi.org/10.1021/acsami.6b06488 PMID: 27508925

[180] Moreira, F.T. Electrochemical biosensor based on biomimetic material for myoglobin detection. *Electrochim. Acta,* **2013**, *107*, 481-487. http://dx.doi.org/10.1016/j.electacta.2013.06.061

[181] Schlattner, U.; Klaus, A.; Ramirez Rios, S.; Guzun, R.; Kay, L.; Tokarska-Schlattner, M. Cellular compartmentation of energy metabolism: creatine kinase microcompartments and recruitment of B-type creatine kinase to specific subcellular sites. *Amino Acids,* **2016**, *48*(8), 1751-1774. http://dx.doi.org/10.1007/s00726-016-2267-3 PMID: 27318991

[182] Lang, H.; Würzburg, U. Creatine kinase, an enzyme of many forms. *Clin. Chem.,* **1982**, *28*(7), 1439-1447. http://dx.doi.org/10.1093/clinchem/28.7.1439 PMID: 7044614

[183] Voss, E.M.; Sharkey, S.W.; Gernert, A.E.; Murakami, M.M.; Johnston, R.B.; Hsieh, C.C.; Apple, F.S. Human and canine cardiac troponin T and creatine kinase-MB distribution in normal and diseased myocardium. Infarct sizing using serum profiles. *Arch. Pathol. Lab. Med.,* **1995**, *119*(9), 799-806. PMID: 7668937

[184] Sharkey, S.W.; Elsperger, K.J.; Murakami, M.; Apple, F.S. Canine myocardial creatine kinase isoenzyme response to coronary artery occlusion. *Am. J. Physiol.,* **1989**, *256*(2 Pt 2), H508-H514. PMID: 2916683

[185] Ingwall, J.S.; Kramer, M.F.; Fifer, M.A.; Lorell, B.H.; Shemin, R.; Grossman, W.; Allen, P.D. The creatine kinase system in normal and diseased human myocardium. *N. Engl. J. Med.,* **1985**, *313*(17), 1050-1054. http://dx.doi.org/10.1056/NEJM198510243131704 PMID: 2931604

[186] Silverman, L.; Mendell, J.; Gruemer, H. creatine-kinase isoenzymes in muscular-dystrophy In: *Clinical Chemistry; amer assoc clinical chemistry*; 2101 l street nw: suite 202, washington, dc, **1974**.

[187] Neumeier, D.; Hofstetter, R. Radioimmunoassay for subunit B in isoenzymes CK-MB and CK-BB of creatine phosphokinase. *Clin. Chim. Acta,* **1977**, *79*(1), 107-113. http://dx.doi.org/10.1016/0009-8981(77)90467-3 PMID: 890944

[188] Kanemitsu, F.; Okigaki, T. Creatine kinase MB isoforms for early diagnosis and monitoring of acute myocardial infarction. *Clin. Chim. Acta,* **1992**, *206*(3), 191-199. http://dx.doi.org/10.1016/0009-8981(92)90088-8 PMID: 1606705

[189] Moreira, F.T.; Dutra, R.A.; Noronha, J.P.; Sales, M.G. Novel sensory surface for creatine kinase electrochemical detection. *Biosens. Bioelectron.,* **2014**, *56*, 217-222. http://dx.doi.org/10.1016/j.bios.2013.12.052 PMID: 24508544

[190] Prakash, M.D. Electrochemical Detection of Cardiac Biomarkers Utilizing Electrospun Multiwalled Carbon Nanotubes Embedded SU-8 Nanofibers. *Electroanalysis,* **2017**, *29*(2), 380-386. http://dx.doi.org/10.1002/elan.201501163

[191] Cheng, V.; Kazanagra, R.; Garcia, A.; Lenert, L.; Krishnaswamy, P.; Gardetto, N.; Clopton, P.; Maisel, A. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J. Am. Coll. Cardiol.,* **2001**, *37*(2), 386-391. http://dx.doi.org/10.1016/S0735-1097(00)01157-8 PMID: 11216951

[192] Clerico, A.; Iervasi, G.; Del Chicca, M.G.; Emdin, M.; Maffei, S.; Nannipieri, M.; Sabatino, L.; Forini, F.; Manfredi, C.; Donato, L. Circulating levels of cardiac natriuretic peptides (ANP and BNP) measured by highly sensitive and specific immunoradiometric assays in normal subjects and in patients with different degrees of heart failure. *J. Endocrinol. Invest.,* **1998**, *21*(3), 170-179. http://dx.doi.org/10.1007/BF03347297 PMID: 9591213

[193] Mair, J.; Hammerer-Lercher, A.; Puschendorf, B. The impact of cardiac natriuretic peptide determination on the diagnosis and management of heart failure. *Clin. Chem. Lab. Med.,* **2001**, *39*(7), 571-588. http://dx.doi.org/10.1515/CCLM.2001.093 PMID: 11522102

[194] Markham, D.W.; de Lemos, J.A. *Screening for cardiovascular disease using B-type natriuretic peptides: detecting an imbalance of the four humours*; Oxford University Press, **2005**.

[195] Okamoto, F.; Sohmiya, K.; Ohkaru, Y.; Kawamura, K.; Asayama, K.; Kimura, H.; Nishimura, S.; Ishii, H.; Sunahara, N.; Tanaka, T. Human heart-type cytoplasmic fatty acid-binding protein (H-FABP) for the diagnosis of acute myocardial infarction. Clinical evaluation of H-FABP in comparison with myoglobin and creatine kinase isoenzyme MB. *Clin. Chem. Lab. Med.,* **2000**, *38*(3), 231-238. http://dx.doi.org/10.1515/CCLM.2000.034 PMID: 10905760

[196] Wollert, K.C.; Drexler, H. The role of interleukin-6 in the failing heart. *Heart Fail. Rev.,* **2001**, *6*(2), 95-103. http://dx.doi.org/10.1023/A:1011401825680 PMID: 11309528

[197] Conraads, V.M.; Denollet, J.; De Clerck, L.S.; Stevens, W.J.; Bridts, C.; Vrints, C.J. Type D personality is associated with increased levels of tumour necrosis factor (TNF)-α and TNF-α receptors in chronic heart failure. *Int. J. Cardiol.,* **2006**, *113*(1), 34-38. http://dx.doi.org/10.1016/j.ijcard.2005.10.013 PMID: 16325284

[198] Tang, W.H.; Brennan, M.L.; Philip, K.; Tong, W.; Mann, S.; Van Lente, F.; Hazen, S.L. Plasma myeloperoxidase levels in patients with chronic heart failure. *Am. J. Cardiol.,* **2006**, *98*(6), 796-799. http://dx.doi.org/10.1016/j.amjcard.2006.04.018 PMID: 16950188

[199] McCullough, P.A.; Hollander, J.E.; Nowak, R.M.; Storrow, A.B.; Duc, P.; Omland, T.; McCord, J.; Herrmann, H.C.; Steg, P.G.; Westheim, A.; Knudsen, C.W.; Abraham, W.T.; Lamba, S.; Wu, A.H.; Perez, A.; Clopton, P.; Krishnaswamy, P.; Kazanegra, R.; Maisel, A.S. BNP Multinational Study Investigators. Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. *Acad. Emerg. Med.,* **2003**, *10*(3), 198-204. http://dx.doi.org/10.1197/aemj.10.3.198 PMID: 12615582

[200] Pedrero, M.; Campuzano, S.; Pingarrón, J.M. Electrochemical biosensors for the determination of cardiovascular markers: A review. *Electroanalysis,* **2014**, *26*(6), 1132-1153. http://dx.doi.org/10.1002/elan.201300597

[201] Matsuura, H. Surface electrochemical enzyme immunoassay for the highly sensitive measurement of B-type natriure-

ric peptide. *Sens. Actuators B Chem.,* **2005**, *108*(1-2), 603-607.
http://dx.doi.org/10.1016/j.snb.2004.11.042

[202] Rosenberry, T.L. Acetylcholinesterase. *Adv. Enzymol. Relat. Areas Mol. Biol.,* **1975**, *43*, 103-218.
http://dx.doi.org/10.1002/9780470122884.ch3 PMID: 891

[203] Soreq, H.; Seidman, S. Acetylcholinesterase--new roles for an old actor. *Nat. Rev. Neurosci.,* **2001**, *2*(4), 294-302.
http://dx.doi.org/10.1038/35067589 PMID: 11283752

[204] Hartati, Y.W. B-Type Natriuretic Peptide (BNP) Detection Using Electrochemical Immunosensor Based On Sandwich ELISA With Horseradish Peroxidase-Tetramethylbenzidine System *Procedia technology,* **2017**, *27*, 149-150.
https://doi.org/10.1016/j.protcy.2017.04.065

[205] Shanmugam, N.R.; Muthukumar, S.; Tanak, A.S.; Prasad, S. Multiplexed electrochemical detection of three cardiac biomarkers cTnI, cTnT and BNP using nanostructured ZnO-sensing platform. *Future Cardiol.,* **2018**, *14*(2), 131-141.
http://dx.doi.org/10.2217/fca-2017-0074 PMID: 29388803

[206] Hombach, S.; Kretz, M. *Non-coding RNAs: classification, biology and functioning.Non-coding RNAs in Colorectal Cancer*; Springer, **2016**, pp. 3-17.
http://dx.doi.org/10.1007/978-3-319-42059-2-1

[207] Gangwar, R.S.; Rajagopalan, S.; Natarajan, R.; Deiuliis, J.A. Noncoding RNAs in cardiovascular disease: pathological relevance and emerging role as biomarkers and therapeutics. *Am. J. Hypertens.,* **2018**, *31*(2), 150-165.
http://dx.doi.org/10.1093/ajh/hpx197 PMID: 29186297

[208] Poller, W.; Dimmeler, S.; Heymans, S.; Zeller, T.; Haas, J.; Karakas, M.; Leistner, D.M.; Jakob, P.; Nakagawa, S.; Blankenberg, S.; Engelhardt, S.; Thum, T.; Weber, C.; Meder, B.; Hajjar, R.; Landmesser, U. Non-coding RNAs in cardiovascular diseases: diagnostic and therapeutic perspectives. *Eur. Heart J.,* **2018**, *39*(29), 2704-2716.
http://dx.doi.org/10.1093/eurheartj/ehx165 PMID: 28430919

[209] Creemers, E.E.; Tijsen, A.J.; Pinto, Y.M. Circulating microRNAs: novel biomarkers and extracellular communicators in cardiovascular disease? *Circ. Res.,* **2012**, *110*(3), 483-495.
http://dx.doi.org/10.1161/CIRCRESAHA.111.247452 PMID: 22302755

[210] van Rooij, E.; Olson, E.N. MicroRNA therapeutics for cardiovascular disease: opportunities and obstacles. *Nat. Rev. Drug Discov.,* **2012**, *11*(11), 860-872.
http://dx.doi.org/10.1038/nrd3864 PMID: 23080337

[211] Mercer, T.R.; Dinger, M.E.; Mattick, J.S. Long non-coding RNAs: insights into functions. *Nat. Rev. Genet.,* **2009**, *10*(3), 155-159.
http://dx.doi.org/10.1038/nrg2521 PMID: 19188922

[212] Yan, Y. Circulating long noncoding RNA UCA1 as a novel biomarker of acute myocardial infarction. *BioMed research international,* **2016**, *2016*
http://dx.doi.org/10.1155/2016/8079372

[213] Peng, Y.; Jiang, J.; Yu, R. A sensitive electrochemical biosensor for microRNA detection based on streptavidin-gold nanoparticles and enzymatic amplification. *Anal. Methods,* **2014**, *6*(9), 2889-2893.
http://dx.doi.org/10.1039/C4AY00033A

[214] Wu, X. Dual signal amplification strategy for enzyme-free electrochemical detection of microRNAs. *Sens. Actuators B Chem.,* **2014**, *203*, 296-302.
http://dx.doi.org/10.1016/j.snb.2014.06.131

[215] Lusi, E.A.; Passamano, M.; Guarascio, P.; Scarpa, A.; Schiavo, L. Innovative electrochemical approach for an early detection of microRNAs. *Anal. Chem.,* **2009**, *81*(7), 2819-2822.
http://dx.doi.org/10.1021/ac8026788 PMID: 19331434

[216] Gao, Z.; Deng, H.; Shen, W.; Ren, Y. A label-free biosensor for electrochemical detection of femtomolar microRNAs. *Anal. Chem.,* **2013**, *85*(3), 1624-1630.
http://dx.doi.org/10.1021/ac302883c PMID: 23323518

[217] Hudziak, R.M.; Barofsky, E.; Barofsky, D.F.; Weller, D.L.; Huang, S.B.; Weller, D.D. Resistance of morpholino phosphorodiamidate oligomers to enzymatic degradation. *Antisense Nucleic Acid Drug Dev.,* **1996**, *6*(4), 267-272.
http://dx.doi.org/10.1089/oli.1.1996.6.267 PMID: 9012862

[218] Kim, J. *A Novel Zebrafish Model for Assessing In Vivo Delivery of Morpholino Oligomers.Exon Skipping and Inclusion Therapies*; Springer, **2018**, pp. 293-306.
http://dx.doi.org/10.1007/978-1-4939-8651-4-18