Acute Myocardial Infarction Biosensor: A Review From Bottom Up☆

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Abstract: Acute myocardial infarction (AMI) is a cardiovascular disease that is produced due to a deficiency of oxygen generating irreversible damage in the heart muscle. In diagnosis, electrocardiogram (ECG) investigation has been the main method but is insufficient, so approaches like the measurement of biomarkers levels in plasma or saliva have become one of the most commonly applied strategies for prognosis of AMI, as some of them are specifically related to a heart attack. Many tests are carrying on to determine biological markers changes, but usually, they present disadvantages related to time consumption and laborious work. To overcome the issues, researchers around the world have been developing different ways to enhance detection through the use of biosensors. These diagnostic devices have a biological sensing element associated to a physicochemical transducer that can be made from different materials and configurations giving place to different kinds of detection: Electrical/Electrochemical, Optical and Mechanical. In this review, the authors presents relevant investigations related to the most important biomarkers and biosensors used for their detection having in mind the nanotechnology participation in the process through the application of

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nanostructures as a good choice for device configuration. (Curr Probl Cardiol 2021;46:100739.)

1. Introduction

Cardiovascular diseases are the main cause of death in the world.[177,187] According to a report presented by the Global Burden of Disease Study, in 2017 these diseases were responsible for 31.8% of all deaths worldwide and at least half of all cardiovascular deaths were caused by ischemic heart diseases (IHD).[187] As the main cause of death among IHD around the world, being part of the acute coronary syndrome (ACS) and representing high impact in morbidity and cost to society, there is a need to develop stra tegies to detect in time any signs of acute myocardial infarction (AMI, [Fig 1]).[18,36,53,163] During AMI, the myocardium suddenly experiments a reduction or stoppage of blood flow, which results in necrosis of the cardiac muscle and therefore the presence of a heart attack.[4,8] Normally, an AMI patient presents chest pain, weakness, sweating, nausea, vomiting, and sometimes loss of consciousness.[180]

AMI can be caused by a number of factors like arterial embolism and thrombosis[54] and is produced due to a deficiency of oxygen (increase demand or insufficient supply) that generates irreversible damage to the heart muscle, making the patient susceptible to other complications like arrhythmias, embolies, and aneurysms.[180,220] Due to thrombolysis is heavily related with AMI, the most susceptible people to acquire it are the ones that present diabetes mellitus, hypertensive lack of control, previous heart attack and people of 75 years old.[139] Also, Premature AMI

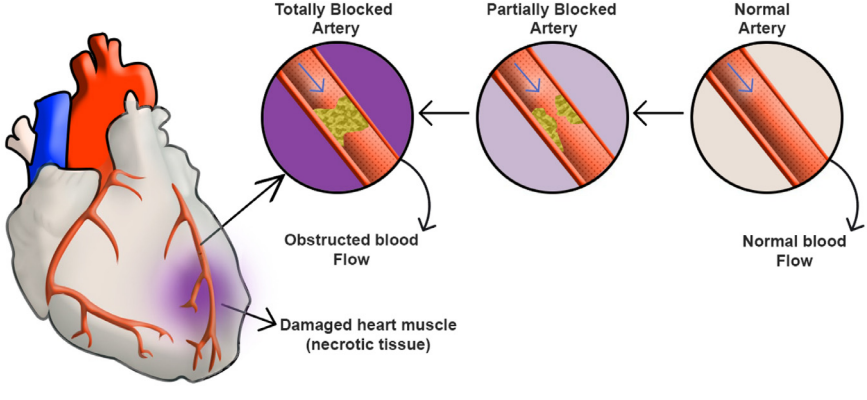

Fig. 1. AMI scheme showing a heart with tissue damage due to blocked artery. Elaborated from.[56,230]

List of Abbreviations

ACS	acute coronary syndrome
AMI	acute myocardial infarction
CL	chemiluminescence
CK	creatine kinase
CK-BB	creatine phosphokinase brain band
CK-MB	creatine phosphokinase myocardial band
CK-MM	creatine phosphokinase skeletal muscle
CMOS	complementary metal - oxide - semiconductor
CNFs	carbon nanofibers
CNTs	carbon nanotubes
cTn	cardiac troponins
CRP	C-reactive protein
ECG	electrocardiogram
ECL	electroluminescence
ED	emergency department
ELISA	enzyme-linked immunosorbent assay
FET	field-effect transistors
FOBs	Fiber-optic biosensors
FRET	Fluorescence resonance energy transfer
Gal-3	galectin -3
H-FABP	heart-type fatty acid binding protein
IHD	ischemic heart diseases
MYO	myoglobin

presents a differential risk profile guided by intensive cigarette consumption.[233] There are various types of AMI, like[180]:

1. Type 1: Spontaneous infarction presenting ischemia due to a previous coronary event like plaque erosion and/or plaque rupture (ST or no-ST elevation infarction).[180]
2. Type 2: Also with ischemia but related to oxygen (Increase demand or decrease supply), embolism, arrhythmia and hyper or hypotension.[180]
3. Type 3: Suddenly infarct with cardiac death occurring before test can be made or at the time of cardiac biomarkers appear in the blood.[180]

4. Type 4: Infarction related to percutaneous coronary interventions divided in 2: associated with the intervention itself and with stent thrombosis.[180]
5. Type 5: Infarction related to coronary artery bypass grafting.[180]

The adverse outcomes of the condition can be diminished with an acute diagnosis, treatment and division of patients according to their predictions.[36] Treatment of the condition is usually guided by a primary angioplasty, a procedure that helps to restore coronary flow by open clogged heart arteries using a balloon catheter inserted in the blocked blood vessel.[49,259] The process can be made on patients with signs of a huge infarction ($\geq$ 15 mm cumulative ST segment elevation and/or $\geq$ 7/12 leads of electrocardiogram with $\geq$ 1 mm ST segment deviation) and a negative evaluation for thrombolytic treatment; patients that can or can not participate in the thrombolytic treatment presenting 2 or more risks (more than 70 years, heart rate more than 100 beats/min, systolic blood pressure less than 100 mm Hg, previous infarction, previous coronary artery bypass grafting and diabetes); patients that can or can not participate in the thrombolytic treatment presenting 1 or none risks but with signs of huge infarction.[259]

Diagnosis has various tools: physical examination, electrocardiogram (ECG), biomarkers, and imaging.[78] It can be improved or more likely to be successful with an early treatment (less than 6 hours previous symptoms), improving survival rate, due to myocardial necrosis is irreversible and 85% heart damage progresses in the first 2 hours after the onset of a heart attack.[98,220] Usually, this condition is related to specific symptoms: changes in levels of cardiac markers like creatine phosphokinase myocardial band) (CK-MB) and enzyme levels of cardiac troponins (cTn) as troponin T (TnT) and troponin I (TnI).[18,215]

In recent years, electrocardiographic investigation has been the main method for establishing MI diagnosis, but only 57% of AMI patients reveal ECG changes, so clinical evaluations combined with the use of an ECG are insufficient to diagnose AMI in most patients with ACS in emergency department (ED).[151,209,217] Due to this, the measurement of the levels of biomarkers in plasma (blood assays) is one of the most commonly applied strategies for prognosis of AMI, as some of them are specifically related to a heart attack (Fig 2).[174] Also, biological markers are useful in ED to stratify patients in high or low risk in order to discharge the ones that are not in danger, making ED care cost effective.[69] A well, early diagnosis of ACS by biomarkers diminishes complications and long term recurrence of symptoms in patients admitted in ED[53]

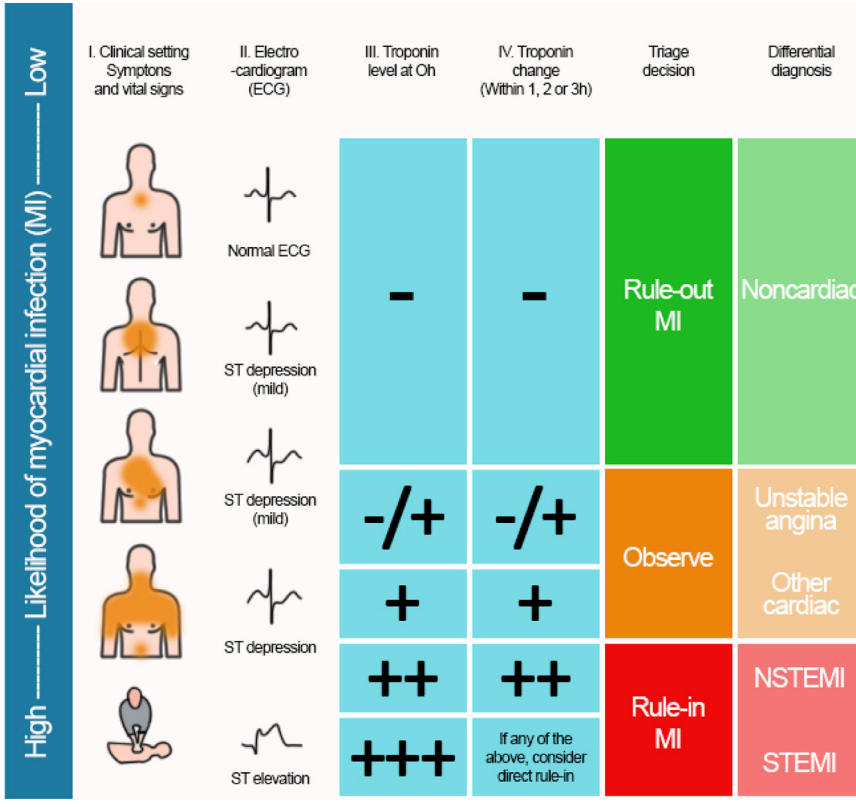

Fig. 2. Patient assessment with suspected ACS. CPR, cardiopulmonary resuscitation; NSTEMI, non-ST-segment myocardial infarction; STEMI, ST-segment elevation myocardial infarction. Elaborated from.[217]

Many tests are carrying on to determine the changes in a biomarker level. Usually, testing presents disadvantages related to time consumption and laborious work, like in the case of enzyme-linked immunosorbent assay (ELISA), fluorescence and surface plasma resonance (SPR) [1,6]. Related to time, The American Heart Association has dictated a turnaround time of 60 minutes and a preferred time of 30 min since sample collection to results reporting, being difficult to achieve in laboratory tests.[35,126] Besides, The National Academy of clinical biochemistry has recommended testing in conjunction of an early biomarker (reaction in the first 6 hours) with a AMI specific biomarker increasing in the blood between 6 and 9 hours.[234] In other way, due to concentration level of biomarkers are in the range of pM to nM, detection methods have to be very sensitive.[167]

Point of care (POC) platforms are a good choice for fast and multiple detection, despite its lack of sensitivity and specificity that is present in

laboratories.[126] Due to the above, researchers around the world have been developing different ways to enhance detection through the use of biosensors as a way to create a link between POC and central laboratory.[126]

Biomarkers as early diagnosis tool

A biological marker is a substance that can be found in tissues and fluids of the body and they indicate a particular disease, as their levels change in comparison when the individual is healthy.[16]

Biomarkers have to present ideally various characteristics, including:[39,167]

- High clinical sensitivity and specificity to predict risk
- Quick release for early diagnosis
- Capability to remain elevated for a reasonable time to allow a suitable diagnostic window
- Ability to be assayed quantitatively wit cost and time-efficiency.

Any biomarker has been found to satisfy all these characteristics, so the simultaneous quantification of different biomarkers would be of great interest, allowing clinicians to diagnose heart issues quickly and/or accurately design a patient care strategy.[167] Some of the biomarkers that have been used to prevent morbidity and mortality in life due to AMI are listed on the next mental map.

Regardless of the hard work of researchers around the world, markers diagnostic of myocardial conditions remains one of the most challenging approaches, due to not all markers used have a high concentration in the myocardium, present a rapid release in the blood stream at the time of ischemia or persist in blood enough time to allow a diagnostic path.[53,186] As an example, the Figure 4 shows heart-related problem based on cardiac troponin concentration, where as the biomarker level increases, the condition worsens (Table 1).

CK-MB

Creatine kinase (CK) is an enzyme expressed in large quantities in muscle tissues.[36] CK has 3 isoenzymes: CK-MM (creatine phosphokinase skeletal muscle), CK-BB (creatine phosphokinase brain band) and CK-MB.[153] CK-BB is present in brain tissue, CK-MM exist in skeletal tissue, while CK-MB (very low in blood, almost undetectable) is specific to myocardial cells but it is also establish in skeletal muscle (present in cardiac muscle in 25%-30% and in skeletal muscle in 1%; Fig 3).[53,69,153]

Table 1. Biomarkers response in AMI

Biomarker	Indicator	Cut-off Levels (ng/ml$_{-1}$)	Specificity	Initial elevation (h)	Peak (h)	Return to normal (h)	Reference
Tns	Tissue necrosis and Tissue ischemia Early detection of AMI	TnI: 0.01-0.1 TnT:0.05-0.1	High	6-9	12-48	96-240	[177]
CK-MB	Tissue necrosis Early detection of AMI	10	Medium	4-8	18-24	24-48	[153,177]
MYO	Tissue necrosis Early detection of AMI	70-200	Low	0.5-10	12	24-36	[53,103,132,177]
NT-proBNP	Heart failure Detection of AMI	0.25-2	High	24-48	NCC	NCC	[30,177]
Copeptin	Heart failure Long - Term Detection of AMI	>4.45	Low	0-1	3	12-36	[199,221]
CRP	Inflammation (Plaque rupture) Cardiac risk factor	$<10^3$ Low risk 1-3$\times10^3$ Middle risk 3-15$\times10^3$ High risk	Medium	8-12	12-24	480-720	[159,167,177,250]
Gal-3	Inflammation (Plaque rupture) Myocardial injury - Fibrosis	NCC	Low	NCC	NCC	NCC	[119]
Fibrinogen	Inflammation (Plaque rupture) Acute detection	3.58$\times10^6$ Low risk 3.58-4.20$\times10^6$ Middle risk >4.20$\times^6$ High risk	NCC	NCC	NCC	NCC	[177]
SAA	Inflammation (Plaque rupture)	NCC but increase	NCC	4-6	NCC	NCC	[37,137,138]
H-FABP	Tissue ischemia Early detection of AMI	10	Low	0.5	6-8	24	[102,153,167]
Irisin	Tissue ischemia	NCC but decrease	Low	48	NCC	72	[17]

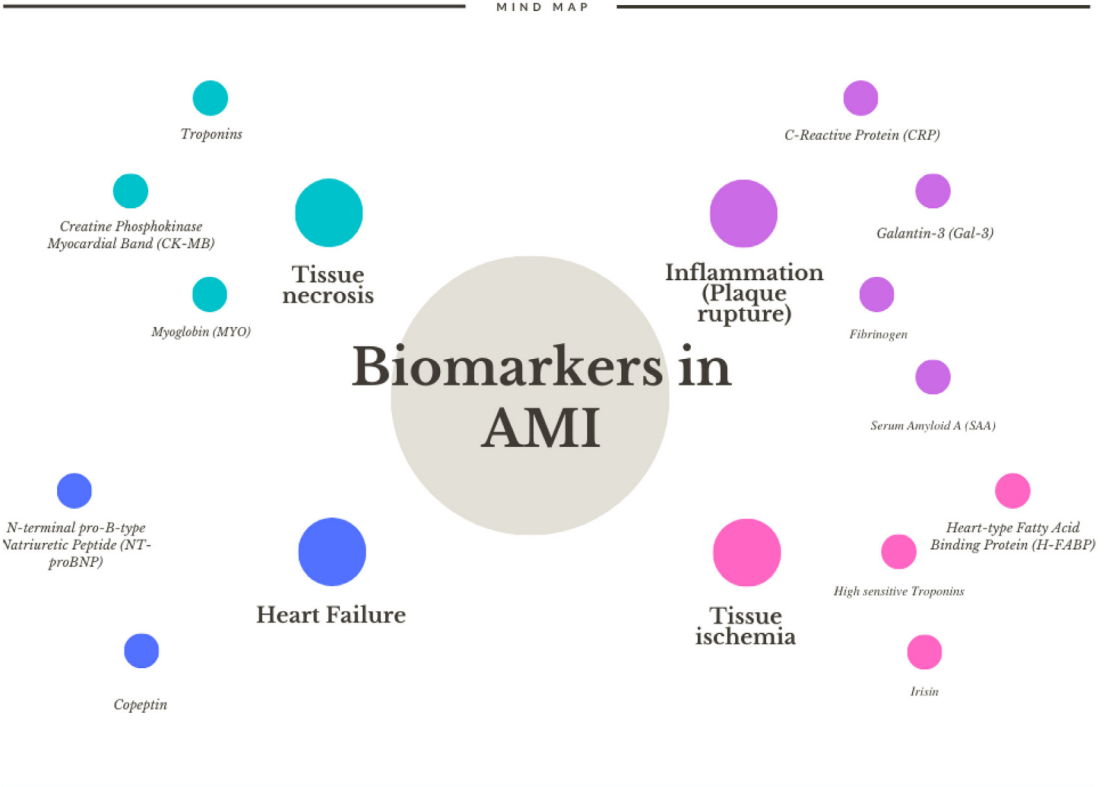

Fig. 3. Biomarkers implicated in myocardial Infarction processes divided according to their specialization. Elaborated from[16,39,59,95,189].

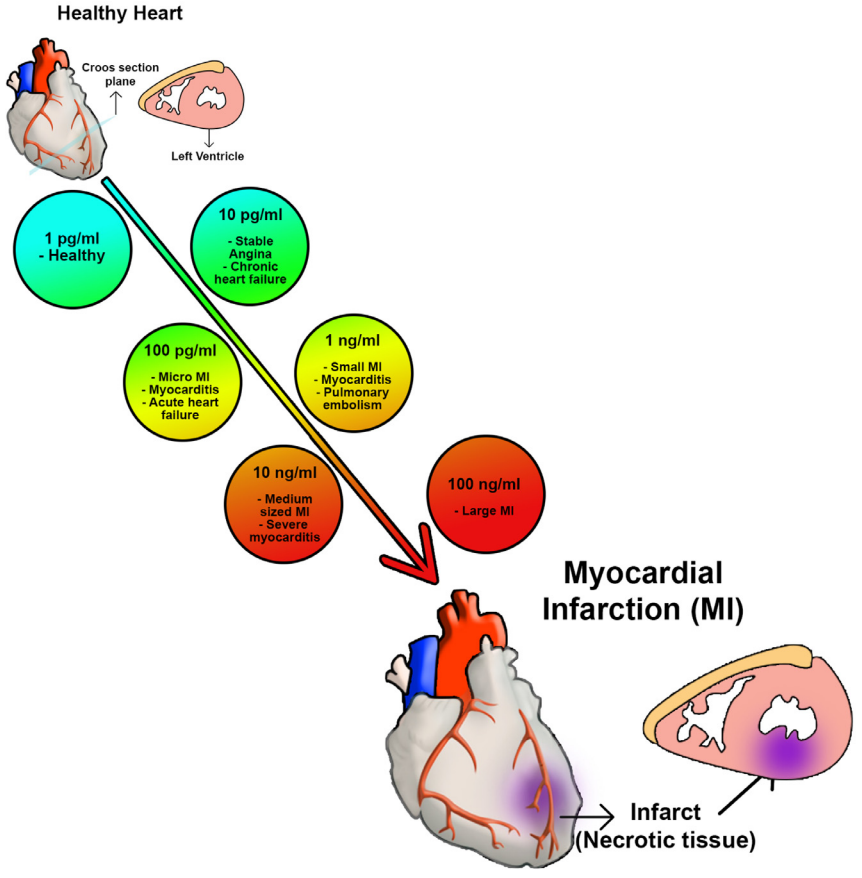

Fig. 4. Heart damage related to AMI as a function of troponin concentration. Elaborated from.[3]

CK-MB has been present since the last century inside the strategies of AMI prognosis. This enzyme levels increase with cell damage of myocardial tissue, becoming detectable between 4 and 8 hours from the appearance of chest pain, rising at 18-24 hours and returning to normal value within 24-48 hours.[153] Inhibitors, interference from other enzymes or drugs used in the tests can influence the CK-MB activity, but its evaluation for AMI provides reliable and exact diagnosis in acute stage.[53,260]

In 1982 Denmark researchers evaluated the performance of the enzyme related to AMI in 321 male patients, where they found that a semiquantitative expression of the extent of myocardial necrosis was possible to be determined in vivo.[74] In the 90s studies focused on early diagnosis of patients admitted in ED and the unity of coronary care presenting symptoms of chest pain, finding that the use of techniques that

involves the enzyme can help to identify AMI with rapid diagnostic characterization even without a previous ECG.[50,71] In more recent times, works has been reported to be center on CK-MB evaluations compared with other agents like myoglobin (MYO), TnI and plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) to see if their estimation together as a conjunct can help with acute diagnosis of AMI. That is the case of the work presented by Fan et al. where it was determined that the detection of these four agents can contribute to the early diagnosis of the condition and lower the mortality of AMI in acute stage.[65] Wang et al. also evaluated CK-MB, MYO and TnI finding similar results that indicates the success of the enzymes strategies in prognosis for AMI.[227] In the same way, heart-type fatty acid binding protein (H-FABP) has been study and compare to CK-MB, TnI and MYO by Pyati et al. showing satisfactory results for all marker as important values for diagnosis by using Immunoturbidimetric method for H-FABP measure, Chemiluminescence immunoassay for MYO and TnI measure and Immunoinhibition method for CK-MB.[176]

Cardiac Troponins (TnI, TnT)

While CK-MB has been widely used in the past, cTn, proteins of the cardiac myofibrillar apparatus, has shown to be present in most of the cases of infarction specially 24 hours after, as it is 100% cardiac tissue specific.[64,69] However, they have a disadvantage since they do not become elevated during the initial hours of AMI.[16] Tns levels raised between 6 and 9 hours after symptoms appear, so the sensitivity is around 39%−43% in the first 3 hours for a patient admitted in ED.[130] Levels have its peak at 12-48 hours after onset of symptoms and remains elevated for 4-10 days.[69] Specifically, cardiac TnI levels in normal serum are below 0.6 ng/mL. When it reaches to 0.7-1.4 ng/mL, minor myocardial injury can be concluded, while evident myocardial necrotic damage should be considered when cTnI concentration elevates over 1.5 ng/mL.[32]

It is important to mention that despite troponins raise consistent to AMI symptoms, also elevate its levels in presence of other cardiac diseases like myocarditis or shock.[69] In this case, the interpretation plays a relevant role according to clinical context.[69] As well, patients need a repeat troponin test 6-12 hours after the initial evaluation to irreproachable rule out AMI.[69]

Recent studies have been focused on high-sensitivity cardiac TnI. High sensitivity assays detect troponin in a precisely way at an acute time with a negative predictive value for AMI exclusion $> 95\%$ that can rise near

100% if tests are repeated 3 hours later.[69] Boeddinghaus et al. evaluated the enzymes by 4 methods that predict the existence of AMI, making measures in patients at presentation and after 1 hour of symptoms appeared (limit of detection, single cutoff, 1 hour algorithm and 0-1 hour algorithm). Results showed that all methods had the same effectiveness and safety, despite single cutoff should not be applied in early presenters.[31] For their part, Pickering et al. applied only the limit of detection strategy to rapid rule-out AMI using a nonischemic ECG in patients with chest pain, corroborating the success of the enzyme for the process.[171]

H-FABP

H-FABP (also called mammary-derived growth inhibitor[183]) is a soluble protein of 12-15 kDa formed by 132 amino acids, being one of the most abundant in the heart in the cardiomyocytes (5% -15 % of the total cytosolic protein pool)[15,76,176] This protein is not totally cardiac specific, because is present in other tissues but in lower concentrations (brain, kidney, skeletal tissue, adrenal gland, and mammary gland tissues, as well as in blastocysts)[15,176,183] and It is involved in fatty acids intracellular transportation for oxidation in the mitochondria.[176]

H-FABP is being considered more and more for its capacity to distinguish between one patient and another with and without ischemic heart conditions, despite is restricted to clinical research due to an nonexistence method for its measurement in a fast and easy way.[36,176] H-FABP is sensitive for early diagnosis of AMI and has been investigated as a useful tool in estimations of patients that arrives in the ED with chest pain with an increased concentration as early as 30 minutes after myocardial injury, peaking at 6−8 hours and returning to baseline at 24 hours.[102,153] In tests the protein presents a negative predictive value of 82%.[39] Vupputuri et al. reported that the performance of H-FABP is superior to TnI and CB-MK during the initial stage (3-6 hours) in patients evaluated.[212,226] As a conclusion they referred to a conjunction between H-FABP and TnI as an early and late marker respectively for and ideal coverage of AMI diagnostic.[226] Contrary to this, Navarro et al. affirmed that when H-FABP acts like a sole biomarker is not superior to high sensitive TnT, so they realized a dual strategy with both markers where the results in 360 patients reduced hospital admissions in 42% by detecting successfully AMI.[154]

In recent studies researches have been comparing H-FABP with other biomarkers besides TnI. That is the case of a study guided in Bratislava where 60 patients where evaluated for early diagnosis of ACS using H-

FABP, TnI, galectin-3 (Gal-3) and CK-MB, finding great results for the 3 first between 2 and 4 hours since admission.[15]

MYO

MYO is a small globular hemoprotein present in cardiac myocytes and skeletal muscle with a molecular weight of 16.8 kDa.[18,69,73] It is part of the globin family being formed by a porphyrin ring (with a central ferrous iron molecule) and a single polypeptide chain of 154 amino acids.[73]

This protein is released quickly to follow muscle injury and is the primary marker of AMI (secreted from the kidneys within 24 hours) due to its low molecular weight and can be present in the bloodstream if exists muscle damage (change in cell membrane permeability).[18,160] MYO has no specificity but increases its levels around 30 minutes after the symptoms onset and it remains elevated between 6 and 10 hours in all patients, picking at the 12th hour, returning to normal stage after 1-1.5 days.[53,103,132] Despite all of that, the negative predictive value for AMI is only 89%.[53] MYO also appear in the urine when it reaches levels above 0.5-1.5 mg/dL.[73]

In recent years MYO has been displaced for high sensitive cardiac troponins, so is not really needed for early diagnosis of AMI.[8] Despite of that, MYO is present in studies for combined detection of the condition, where next to CK-MB, TnI and NT-proBNP has improve results in diagnosis and has shown a positive correlation with CK-MB, reasons why its still important in lower mortality of AMI in acute phase.[65,227]

In other research, MYO has been discarded as a renal marker for long-term prediction for patients after AMI studies in 569 subjects in 6 years.[19]

NT-proBNP

NT-proBNP is a neurohormone (neuretic peptide) synthesized in atrial or ventricular myocardium.[87] Neuretic peptides as cardiac biomarkers released from cardiac myocytes in response to ventricular wall stress, ischemia or infarction have shown prognostic value related to AMI.[57,87,106] The increasing of this marker levels is related with short and long term risk of death and heart failure.[9] Also, NT-proBNP values increases during the first 24-48 hours in AMI, another reason to be considered good for diagnosis.[30]

NT-proBNP improves the performance of high sensitive TnT for early detection of infarct as has been demonstrated in various studies due to the peptide levels are higher for AMI than in another chest pain

condition,[77,213] but acts so much better in long term predictions to identify higher risk patients over time because neuretic peptides can change significantly over time.[106,150] As well, NT-proBNP is useful to determine an specific type of AMI, being type 1 related to coronary artery thrombus (low myocardial blood flow accompanied with myocyte necrosis) while type 2 is not related with coronary artery disease (disproportion between myocardial oxygen supply and demand resulting in myocardial injury with necrosis).[70,162]

In other studies, NT-proBNP has been studied along with other markers besides the cardiac ones. Kasap et al. evaluated the performance of the peptide and other markers like C-reactive protein (CRP), finding good outcomes for diagnosis of AMI according to the serum levels in a population of 100 patients with the condition and 40 in a healthy state.[87]

CRP

CRP is an acute-phase nonspecific biomarker of the pentraxin protein family that has five equal polypeptide chains in a pentameric structure and is sensitized by the liver in response to interleukin-6 and other cells as adipocytes.[5] CRP presents systemic inflammation that elevates in patients that suffers myocardial infarction and is also associated with the incidence of other cardiovascular events.[27,159,216] CRP monitoring is the best way to prevent future clinical events due to coronary factors like myocardial infarction.[5,179]

According to studies reported in literature, levels of this protein increase during the first 8-12 hours since the appearance of symptoms for AMI (normal level in healthy person: less than 1 mg/dl) and return to baseline 3-4 weeks later.[159,250] In this case, marker levels are related to infarct size and are reduced by acute reperfusion.[250] Also, the increase is associated in short term to death after AMI, while long term analysis is poorly studied.[173,250]

CRP has been widely studied and in its high sensitive form is related to cardiovascular events specifically in women, where can act as a significant predictor of risk.[184,231] In the same way, CRP is useful as a predictor of heart failure in cases of previous AMI, thus helps to decrease mortality index during the following of symptoms in treated patients.[28]

Ziakas et al. affirmed that CRP evaluated against fibrinogen and interleukin-6 shows better results for prognosis in-hospital and follow-up for patients with AMI receiving thrombolysis.[258] Also, in recent works Alkouri et al. presented results in which CRP levels are acute in prognosis identifying appropriate candidates for evaluation and anti-inflammatory

therapies as a mode of prevention for AMI.[7] In the same way, Wang et al. evaluated CRP and TnI before and after AMI, finding that both levels post event can help to elucidate the performance and efficacy of treatment.[228]

Fibrinogen

Since the 50's Fibrinogen, an acute phase reactant, a large and soluble glycoprotein of the coagulation system synthesized by hepatocytes (normal circulating levels of 1.5 to 4 mg/ml and 340 kDa), has been studied as a risk factor for AMI.[21,33,134,144] Fibrinogen is the third most abundant of plasma proteins and is formed by 3 polypeptides: Aα–, Bβ– and γ-chains.[33] Its synthesis is guided by IL-6 and other proinflammatory cytokines[33] This protein is related in several mechanisms like platelet aggregation, cell injury and plasma viscosity, which are associated with the appearance of thrombi driven to thrombosis, the major determinant for cardiovascular diseases like myocardial ischemia, stroke, peripherial vascular disease, abdominal aortic aneurysm and pulmonary embolism.[33,134,142]

Various studies in patients has shown the increase of this marker up to 800 mg per 100 cc in AMI patients.[129] Works has reported the increase levels related to a bad prognosis during hospitalization and ischemic heart disease specific for patients with angina and AMI.[2,223] Also, there is evidenced of fibrinogen as an important value for risk division and aggressive reduction of infarct size in patients previously submitted to angioplasty.[55] More recent studies has evaluated fibrinogen in healthy and AMI people, finding that the marker is a valuable screening tool to identify individuals with latent risk of suffer AMI despite researches have demonstrated the poor efficacy of the marker for long term predictions.[194,240,243]

Fibrinogen has been related to more traditional factors like obesity, which increase the risk for cardiovascular diseases.[5] It has been reported that reduction of body mass index as a result of a healthy diet, has helped decrease fibrinogen levels.[58]

SAA

Serum Amyloid A (SAA) is a very sensitive acute phase protein, a neuroendocrine marker, with reactivity and sensitivity response similar to CRP, despite studies have shown that SAA responds differently than CRP in inflammatory diseases.[88,135,193,236] SAA is synthesized by hepatocytes of the liver trough cytokines like interleukin-1, interleukin-6 and

Tumor Necrosis Factor-α.[90,135,191] It is secreted from activated macrophages, vascular smooth muscle cells, endothelial cells and salivary gland cells.[5,85] This last thing, makes SAA affordable for use as a noninvasive activity marker.[85]

SAA has high density lipoproteins and its metabolic process is quick.[48,138] In normal plasma, is present in trace amounts but its serum levels increased few hours (4-6 hours) in presence of tissue injury and inflammation.[37,137,138]

It is shown that SAA is an useful predictor for AMI, as has been demonstrated by Katayama et al. evaluating SAA levels in 433 AMI subjects.[89] Also, SAA seems to be an independent predictor of AMI for admitted patients in ED presenting chest pain, despite predicts a poor outcome in patients with unstable angina.[127,193]

Gal-3

Galactins involve 15 lectins that are divided in 3 groups: prototype, chimera and tandem, being Gal-3 the only one in the chimera group.[60] Gal-3 is a glycoprotein with 26 kDa, which is secreted by activated cardiac macrophages that can act as an independent predictor for mortality in myocardial infarction.[15] This protein resides in both nucleus and cytoplasm of different cells (endothelial cells, epithelial cells, activated microglia, inflammatory cells like macrophages) and also in the extracellular space (tissues like spleen, stomach, colon, liver, kidney, heart, uterus, ovary, and pancreas) and related to patients with acute and chronic heart failure has been shown good results in short term prognosis.[29,131,244]

Specifically, in patients with atherosclerotic based problems like myocardial infarction, Gal-3 have limited use in the long term prognostication for which its use is questionable.[123] Various studies have focused on Gal-3 levels in AMI patients[141,198,210,219,233] finding that elevated levels of the protein are associated with ischemic heart disease and with AMI depending on prior treatment (different medicines and procedures) of the condition. For example, Bivona et al. demonstrated that despite Gal-3 levels boosts during the first hour since admission of AMI patients in ED, yet there is a lack of elucidation for the protein as biomarker for AMI.[29]

In recent works, has been demonstrated that Gal-3 is valuable for predicting myocardial injury during the early stage of AMI due to changes in presence of inflammation or fibrosis, but the secretion kinetics of its plasma during the event is still disputable.[119,218] Stanojevic et al. evaluated again this protein in AMI patients and found that when the patient is involve in a high risk group, suffering for example atrial fibrillation or

arrhythmia, Gal-3 levels increase behaving like an ideal target for treating AMI patients that are under high risk groups.[202]

Additional biomarkers

Other biomarkers like copeptin and irisin are also being studied.[18] Copeptin is a marker of stress secreted from the neurohypophysis in equimolar quantities with arginine vasopressin after the synthesis in the hypothalamus.[149,152,168] It rises quickly in AMI (0-1 hour) after symptoms appear and decrease to normal levels within 12-36 hours in early presenters[199]) despite not being cardiac specific. As a single variable presents poor accuracy to diagnose or exclude the condition,[152] due to its changes in serum occurs under various conditions besides AMI (respiratory tract infection, sepsis and stroke).[181]

As cTn are the most accurate standard biomarkers, its combination with copeptin may facilitate the diagnostic evaluation of AMI.[181] The dual strategy (recommended by the European Society of Cardiology (ESC)[78]) could avoid the delay in ruling out AMI, diminishing the anxiety of the tested patient and the missed used of resources in ED.[152] This combination can achieve a negative predictive value of 99.7%.[39] For example, Jeong et al. investigated the performance of copeptin, CK-MB and TnI alone and in combination for 271 patients with chest pain, finding that the dual strategy of TnI/copeptin improves AMI prognostic in patients with early-onset chest pain in an ED configuration.[84] In similar studies, Stallone et al. and Morawiec et al. evaluated the combination of copeptin with high-sensitivity cTn. In the first case, 2000 patients with around 2 hours of symptoms onset were assessed by the dual strategy showing that copeptin did not increase accuracy in diagnostic.[201] In the second research, copeptin acted as an independent predictor in mortality for all patients tested and its mixture with high sensitivity TnT did not show any improvement for exclusion in ACS conditions.[147]

On the other hand, irisin is a thermogenic uncoupling protein that can also be clinically effective for early diagnosis. This protein is expressed in other organs besides cardiac muscle like kidneys and liver.[16] In humans, it can be extracted from both blood and saliva.[16] Related to AMI, irisin levels decrease during the first 48 hours where symptoms appear and then returns to a normal state after 72 hours.[17]

Various studies have shown results where the concentration of irisin can be taken to account in prognosis of AMI. That is the case of a research of Hsieh et al. where they measured serum irisin concentrations using ELISA and found that said concentration was elevated in post-ST

elevation myocardial infarction patients with increased risk for adverse cardiovascular events.[80] In the same way Anastasilakis et al. investigated levels of irisin at the time of AMI, having results of lower irisin in comparison with control samples.[10] In other work, El-Mottaleb et al. evaluated the therapeutic response of irisin as agent in cardiovascular diseases. This study aimed to calculate the level of the protein in infarction with or without heart failure and its possible relation with cardiac markers, finding an inconclusive result towards the use of irisin in prognosis of AMI due to its unknown sensitivity and specificity.[62]

Biosensors in AMI detection

Biosensors are integrated diagnostic devices with a biological sensing element associated to a physicochemical transducer that can be made from different materials and configurations.[136] They can be classified in 2: Bioreceptor or transducer type (Fig 5).[225] A bioreceptor is a molecular specie like an antibody, a protein and an enzyme or a biological system such as cells, tissues and even complete organisms, that uses a biochemical agent for recognition and its responsible for adhered the analyte to the sensor for the measurement.[225] Bioreceptor recognition can be classify in:[20,182,224]

- Antibody - Antigen interactions (Immunosensors or affinity sensors): the detection of the target analyte (antigen) is a result of the specific binding with the specific region of the antibody attached to the surface of the transducer. Due to the large binding between the antibody and the antigen, this sensors are usually for a single use (disposable).
- Nucleic acid - DNA interactions.
- Enzymes interaction: An enzyme e catalyses the conversion of analyte to product.
- Cellular structure - Cells interactions.
- Synthetic bioreceptor interactions.

In other way, transducer type biosensors are divided in:[203,224]

- Optical measurements.
- Electrochemical measurements.
- Mechanical measurements.

Usually, a biosensor that utilize a microchip based transducer is also called biochip, which is a conjunction of biosensors individually

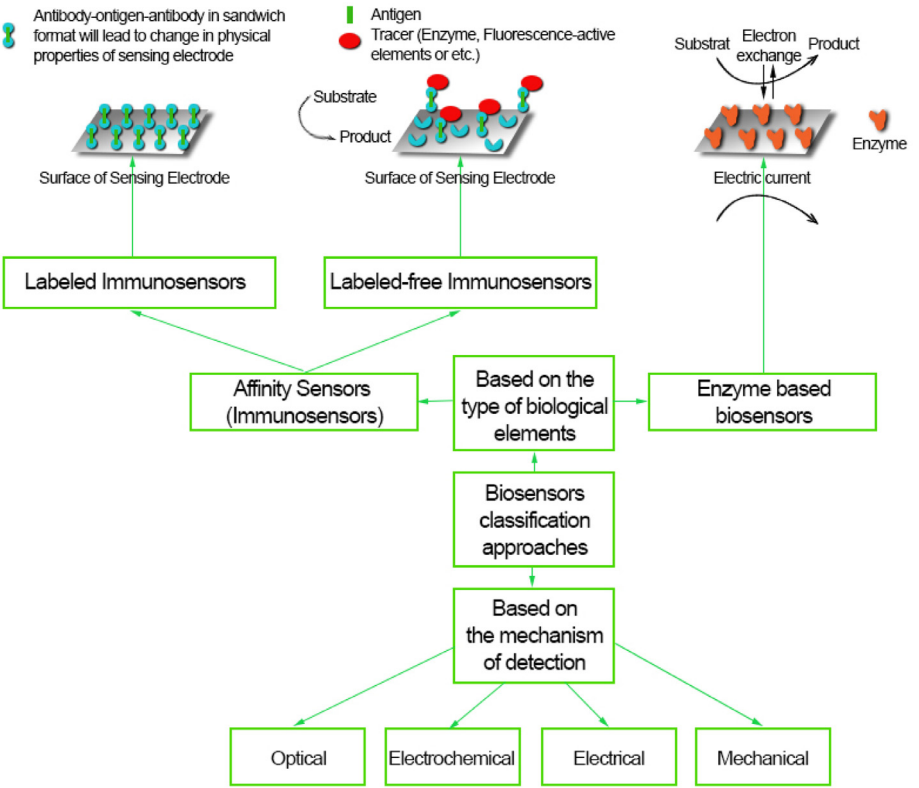

Fig. 5. Biosensor types. Elaborated from.[182]

monitored that are used for multianalysis of analytes.[203,224] It is important to mention that environmental conditions (pH or temperature) can decrease the life of the biosensor.[20]

First biosensors were catalytic elements that combined enzymes with transducer (can be electrochemical, optical, thermometric, piezoelectric and magnetic) in order to convert a biological signal into an electronic one.[136] With the apparition of affinity biosensors, researchers studied the use of a variety of biological elements like antibodies, receptors or nucleic acids.[136] In that case, affinity is given by the immobilized molecule.[136] Since that, sensing performance have been improved, leading to a technological development that anticipates an annual turnover of 22.68 billion of dollars by 2020.[146] Figure 6 Shows general classification of biosensors where the different biological elements and transducers are present.

In general, biosensors market faces several challenges related to biomarkers detection, such as: ultrasensitivity (detection at very low concentrations), selectivity (discriminate between an specific biomarker and other molecules present in a biological fluid), low noise in signal readout, low cost and detection limit, minimal sample volume, monitoring at long term and quick and sharp detection.[45]

The use of nanostructured materials (at least 1 dimensions below 100 nm, different properties form the bulk, surface properties predominant) have been encourage in biosensors fabrication due to sensitivity improvement, possibility of nano-biosensors, requirements of small amounts of sample for detection, better molecular attachment (large surface-area-to-volume ratios) and maximization of the activity and the lifetime of the immobilized molecules (comparable sizes of the nanomaterials and biological molecules).[67,110,161,182] Between the group, nanoparticles, nanotubes, nanowires and nano-patterned surfaces have been utilized as electrodes in biosensing applications (Fig 7).[182]

Electrical detection

Actually, the use of electrical detection is encourage due to its low cost, easy miniaturization and the fact that it can be used for non specialized people.[67,167] To sense small chemical and biological elements through electrical detection, the use of nanostructures (nanowires, nanoribbons, nanobelts, carbon nanotubes, nanoparticles among others) is beneficial owing to the similar size between sensor and target.[67] However, the results obtained by this technology can be affected by PH values and different charges of the molecules due to the conductance measurement of the nanostructure.[113]

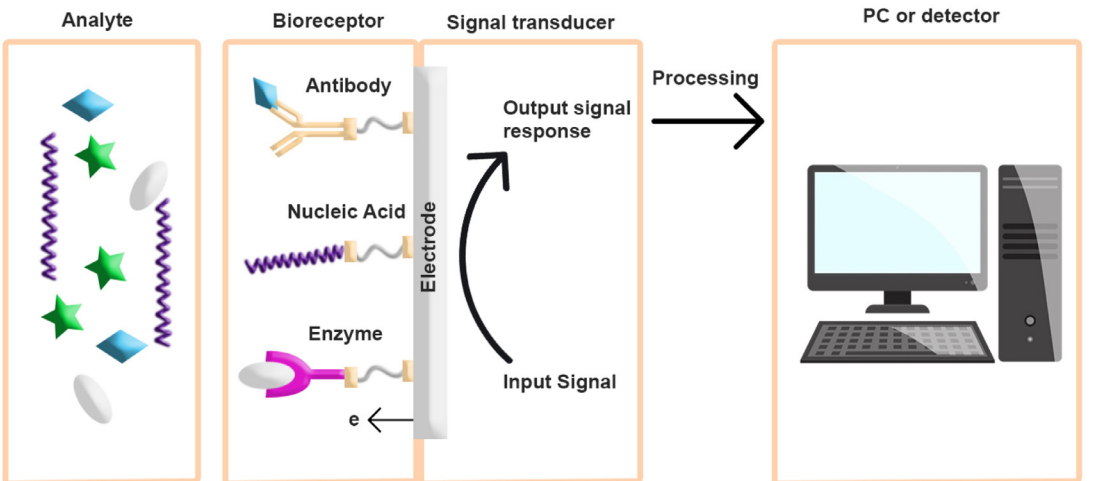

Fig. 6. General configuration of a biosensor. Elaborated from.[136,192]

Type	Nanoparticles		Nanofibers			Nanolayers
	Nanospheres	Nanoclusters	Nanofibers	Nanowires and Nanorods	Nanotubes	Thin films and Nanoplates
View						

Fig. 7. Families of nanostructured materials. Elaborated from.[182]

Nanostructure metal-oxides materials (NMOs) have received attention as transducer due to its nontoxic morphology, biocompatibility, large surface area, catalytic properties and absorption capability (origins appropriate biomolecules immobilization) that allows the enhancement of the sensing characteristic.[197,200,241] In the fabrication of an efficient biosensor, the selection of the proper NMOs for immobilization of the bioreceptor is crucial.[12] Usually, NMOs binds with the biomolecules by physical adsorption (weak interactions like Van der Waals and electrostatic forces) or covalent binding.[12] In general, the use of this materials improves sensitivity and limit of detection in the biosensor, besides its simple and inexpensive fabrication process.[12]

Nanowire based field-effect transistors (FET) are commonly use in biosensor designs because it has sensitivity, label free, real time, and multifunctional biosensing.[105] In FET devices, charge biomolecules in buffer solution bind with their counterparts immobilized on the biosensor surface, inducing changes of carrier concentrations and thus, regulating the electrical transport of the device.[105] Many materials have been integrated in FET type biosensors, basically various semiconductors like silicon (Si) nanowires,[6] Tin dioxide (SnO_2) nanowires[205] and indium oxide (In_2O_3) nanowires.[81] Si nanowires have received special attention due to its biocompatibility and remarkable electrical properties.[42,52] Besides, FET Si nanowires can be made by using complementary metal-oxide semiconductor (CMOS) processes, which allows a low cost production.[109] Although this kind of sensors have good sensitivity, remaining problems related to scattering of transistors operating in liquid atmosphere are still present during sensing experiments.[79] To solve the above, the use of gate insulator layer is highly encourage because it acts as a sensing surface in the liquid - gated FET sensor.[164,232] In this field, Kutovyi et al., proposed a liquid-gated Si nanowire FET biosensor for TnI detection by using noise spectroscopy as a characterization technique for biosensor performance evaluation and as an analytical method that permits label free sensing.[109] Low frequency noise spectroscopy allows to enhance the sensor surface and the electrical behavior of the transistor.[109,204] In the same way, Fathil et al., presented a zinc oxide (ZnO) FET biosensor for TnI detection fabricated via photolithography with an extra gate, resulting in high sensitivity detection with a limit of 1.6 fg/mL.[68]

Especially, FET has been used for troponin detection as shown in Kim et al., where honeycomb nanowires was used to produced a FET Si biosensor with high sensitivity and label free for TnI detection, resulting in a detection limit of 5 pg/mL.[99] In this case, the honeycomb structure

provides major electrical performance and large surface area compare with conventional nanowires.[100,185]

In addition, Chua et al. proposed a silicon nanowire array platform used for real time troponin T detection by electrical measurement supported on the conductance changes of the individual nanowires.[47] Based on the same kind of platform, Zhang et al. developed a multi detection device for various biomarkers like CK-MB and TnT until 100 pg/L in untreated blood serum.[253] In more recent studies, Lee et al. used a novel material, polyaniline, to produce a nanowire through electrochemical deposition growth technique with multi detection purpose applied to cardiac biomarkers TnI and MYO among others, achieving low detections like 250 pg/L, 100 ng/L, 150 pg/L, and 50 pg/L for TnI, MYO, CK-MB, and BNP.[114]

FET nanobelts are found in literature too. Cheng et al. developed detection of TnI using SnO_2 FET nanobelt along with a microfluidic configuration, with a sensitivity detection of 2 ng/L accompanied with speed and portability.[43] Usually, nanobelts are produced via catalyst free physical vapor growth, allowing to have good crystal properties and biocompatibility.[165]

Si nanoribbons are also used, fabricated by top - down methods that results complicated because the process needs oxidation, photolithography, and wet etching. To avoid that, researchers are using shadow mask fabrication method to produce semiconducting metal-oxide-based biosensors, where the process is at room temperature performed without the use of a cleanroom and besides is cost effective, reliable, and photolithography free.[126] In_2O_3 is present in FET nanoribbons too, allowing to have real time, quick responsive and label free biosensors that are ideally for first blood sample analysis.[11,40,97,116,117,126]

Carbon nanotubes (CNTs) are utilized due to their structure, physical and chemical properties (conductance, stiffness, and possibilities to be functionalize).[249] Due to the speed of electron transfer, a CNT electrode can have high sensitivity with low limits of detection, thus decreasing the response time.[82,112] Besides, CNTs can formed a nanostructure surface that allows the immobilization of a higher amount of biomolecules thanks to the increase of the electroactive area.[72] Gomes-Filho et al. developed an immunosensor based on CNTs mixed with a polymer film for TnT detection with a low detection limit of 0.033 ng/L despite of some instabilities in the response due to the deposition and assembly of the CNTs on the polymer film.[72] To solve the problem, Silva et al. proposed an amine functionalized CNTs merged into the ink printing used to produce screen printed electrode (SPE), obtaining better limit of detection at 0.0035 ng/L.[196]

Carbon nanofibers (CNFs), especially vertical aligned ones, where each fiber acts as a nanoelectrode has been utilized to fabricate biosensors

with success.[13,38,104,170,195] Owing to the biocompatibility, conductivity and option for easy surface modification, nanoelectrode arrays based on vertical aligned CNFs and fabricated by plasma enhanced chemical vapor deposition, can be used as a biosensor platform.[75] Under this alignment, Gupta et al., fabricated a nanoelectrode array based on vertically aligned CNFs for CRP detection using cyclic voltammetry and electrochemical impedance spectroscopy to obtain a detection limit of 11 ng/mL.[75]

FET biosensors can also present electrical double layer and a high electron mobility transistor to improve assay sensitivity by its unique electrical, chemical and thermal qualities.[251] Under this statement, Sarangadharan et al., proposed a FET biosensor using electrical double layer with AlGaN/GaN high electron mobility transistor for TnI detection without sample processing steps, resulting in a detection range of 0.006-148 ng/mL.[190]

Electrochemical detection

Label free electrochemical detection is consider a sustainable, inexpensive and short response time method for biomarker analysis.[188] Electrochemical detection presents high sensitivity, selectivity and low cost (no need of expensive equipment for signal transduction since electron-transfer process directly generates an electronic signal).[22–25,92,94,145] Electrochemical biosensors are build usually in potentiometric, capacitive, and amperometric mode.[182] Amperometric biosensors are most common due to its simplicity in use and its potential capacities.[182] One of the most important issues of the technique is the immobilization of the recognition elements in the transducer surface, which can be made with the help of gels, polymeric membranes, conductive salts, etc.[133,222]

The electrochemical immunosensors have based on current and/or voltage measurements to detect binding between antigen-antibody.[20] Carbon nanostructures have shown good properties for electrochemical detection of biomarkers, specially graphene nanostructures show superior electrical and electrochemical behavior along with its huge surface area.[175,188] Kazemi et al., proposed a label free electrochemical biosensor for TnI detection with porous graphene oxide as substrate, resulting in a detection limit of 0.07 ng/mL.[93]

Electrochemical nanobiosensors modified with gold nanoparticles show promising results in biomarkers detection through the use of antibodies, in a process of 30 minutes.[209] Also, electrochemical aptasensing is useful for detection.[156,177] Negahdary et al., presented an aptamer based biosensor for TnI detection, with a gold electrode used as a

transducer, obtaining a range of detection between 0.03 and 2 ng/mL when evaluating 89 human samples.[155]

The use of imprinting technology in biorecognition agents mixed with the SPE method seems to be beneficial for disposables and low cost medical devices such as biosensors.[148] In this case, Moreira et al., proposed a disposable biosensor for MYO detection with a reusable molecularly imprinted polymer assembled on a polymeric layer of carboxylated poly (vinyl chloride)(PVC COOH) to obtain a plastic antibody resulting in a limit of detection of 2.25 μg/mL.[148]

Application of covalent organic frameworks in electrochemical biosensors have taken importance due to its large surface area, low density, thermal stability and exceptional electrical, porous and mechanical properties.[238,254] Zhang et al., probed the use of a novel sandwich type sensor for TnI detection, enhancing signal trough fabrication based in titanium dioxide nanoparticles mixed with polypyrrole and gold (TiO2-PPy-Au) as a substrate material and toluidine blue-gold covalent organic frameworks (TB-Au-COFs) as nanoprobe, resulting in a limit of detection of 0.17 pg/mL.[254] In this case, TB (an aromatic heterocyclic dye) acts as a viable redox probe due to its high conductivity and stability and PPy (a conductive polymer) served as a conductivity improver.[120,169]

2D Hexagonal boron nitride nanosheets are suitable for sensing applications due to its surface area and conductivity and it is possible to reduce their size transforming them into quantum dots.[14,96] Yola et al., probed the above by presenting an imprinted electrochemical biosensor based on boron nitride quantum dots for TnI detection, obtaining a limit of detection of 0.0005 ng/mL.[247]

Otherwise, the use of DNA in electrochemical biosensor structure could be beneficial, as demonstrated by Lee et al., when employing this kind of improvement with an Au nanospike for highly sensitive TnI detection.[115]

Optical detection

Optical biosensors depends on polarization or frequency of the input light that is related to the biological process and are classified in calorimetric, fluorescence, luminescence (chemiluminescence and electroluminescence) and SPR biosensors.[1] In fluorescence or luminescence categories, the biological target is highlighted with fluorescent tags or dyes, which is complicated and time consuming.[66,252] In other way, calorimetric measurement is directly observable and thus better but its sensitivity is lower.[1]

For calorimetry assays different elements have been developed like silicon chips, glass surfaces and gold electrodes. Wen-YaWu et al. developed a calorimetric biosensor for TnI detection based on Poly(dimethyl siloxane) PDMS-gold nanoparticles (Au NPs) composite film with silver inclusions.[237]

In luminescence field, Fang Li et al., proposed the use of luminol functionalized gold nanoparticles (luminol-Au NPs) as a sensitive label - free electroluminescence (ECL) immunosensor for TnI detection, where the ECL intensity was depending on the TnI level.[118] For chemiluminescence, Zhao et al., presented an immunosensing biochip for multiple detection in blood of some cardiac biomarkers such as TnI, CK-MB and MYO, using a nitrocellulose filter membrane for antibody immobilization, resulting in a fast and efficient detection.[256] In the same way, Yang et al., demonstrated the use of an electrogenerated chemiluminescence (CL) biosensor for multiple and individual detection of TnI, TnT, and MYO, using aptamers as capture probes, ruthenium complex (Ru1)-labeled streptavidin as CL signal probe and photomultiplier tube and charged coupled device as detectors.[245] In the photomultiplier tube model, the limit of detection was 0.30 ng/mL, 31 pg/mL, 0.79 pg/mL for TnT, MYO, and TnI, respectively.[245]

For SPR sensing, there is a need of a metal film deposited on a glass prism and biorecognition elements with proteins, antibodies, DNA and other immobilized agents on the sensor surface.[157] In this case, when the biorecognition element reacts with the specific antigen, the refractive index experiments a change in form of light variation.[63] Fireman Dutra et al., proposed a covalently immobilized antibody for TnT detection, deposited on gold surface through a self-assembled monolayer of thiols with cysteamine-coupling chemistry, allowing a repetitive measurement with cost saving.[61] in the same way, Liu et al., immobilized a TnT antibody trough self-assembled monolayer applied to a homogeneous mixture of oligo(ethylene glycol)(OEG-terminated alkanethiolated and mercaptohexadecanoic acid) on Au by SPR, allowing a detection in the first 2 minutes after injection with a detection range varying from 50 μg/mL to 100 ng/mL.[125] Also Pawula et al., demonstrated that the use of this kind of SPR biosensor build trough self-assembled monolayer can obtain an specific, rapid and sensitive detection of TnT in a concentration range of 25-1000 ng/mL in direct assays.[166]

H-FABP detection have been analyzed by SPR biosensors.[86] Kunz et al., proposed an optical immunosensor based on SPR for label free detection of H-FABP, presenting a sensitive range between 0.2 and 2 μg/mL which is not applicable for detection of micro-necrosis.[108]

Long-range surface plasmon-polaritons are known as surface plasmon waves which propagation takes place along a metal stripe surrounded by dielectric elements of similar refractive index.[26] The length of propagation for long-range surface plasmon-polaritons can be in the order of centimeters, while normal plasmon polaritons normally used in SPR are limited to 80 μm, making the long-range surface plasmon-polaritons more suitable for sensing applications.[107] According to this, Krupin and Beriniri proposed a SPR based long-range surface plasmon-polaritons biosensor for label free detection of TnI, obtaining limits of detection of 430 pg/mL for the direct assay and 28 pg/mL for the sandwich assay.[107]

Other optical biosensors for detections have been proposed as in the case of optomagnetic technology based on nanoparticles for troponin detection.[1] For example, Bruls et al., proposed TnI detection via actuated magnetic nanoparticles.[34]

Despite of the advantages (high sensitivity, specificity, simplicity among others) in fluorescence methods, there are many limitations related with high costs, labeling and use of dyes with low light stability.[41] In spite of its low photostability, solubility in water and narrow excitation spectra, different fluorescent nanomaterials have been recently employed as dyes, such as quantum dots and noble metal nanoclusters.[41] Due to the above it is necessary to search for new fluorophores like fluorescent carbon dots, a quasispherical nanoparticles with 10 nm or less in size with high water dispersibility and stable fluorescence intensity.[51,248] Under this statements, Chen et al., proposed a biosensor based on carbon dots for MYO detection with detection limit of 20 pg/mL.[41]

Fluorescence resonance energy transfer (FRET), a traduction method that explains the transfer of energy between light and sensitive molecules (donor and receptor molecules have to be very close from each other) is the based for other optical biosensors that are categorized in 2 types: intermolecular (also called bimolecular) and intramolecular (also called unimolecular).[158] In this case, superposition is needed between the absorption spectrum of the receptor and the fluorescence emission spectrum of the donor.[158] As a precedent, Stringer et al., proposed a FRET biosensor with quantum dots in donor position and organic dyes as receptors for detection of TnI.[206] In the same area, Pierce et al., proposed a FRET immunosensor for subcutaneous implantation in order to provide early warning of a heart attack via cardiac troponins detection, thus reducing false positives.[172]

Fiber-optic biosensors (FOBs) are being studied too as a label free biosensors. However, most results in this field have shown low sensitivity in sensing.[44,124,207] Due to the above, Zhou et al., developed an optical

microfiber coupler biosensor label free and with high reproducibility for TnI detection, obtaining a detection limit of 2 fg/mL.[257] Also, in literature has been reported the use of FOBs based on the concept of total internal reflection fluorescence, where the incident light propagating in the fiber core is totally reflected and the remaining shadow layer of electromagnetic field can be used to produce the evanescent wave excitation of fluorescence by the excite fluorophores of absorbing species.[46] In this case, the intensity of the signal of a FOB depends on the quantity of the absorbed fluorophores by the analyte.[46]

Mechanical detection

Micro Electro Mechanical Systems presents new tools for biomedical (enzymatic) analysis by implementing micro mechanical biosensors (transducers) that usually use cantilevers that has the ability to convert a chemical signal into a mechanical motion.[83] In this kind of biosensors, detection is taking place when the enzyme sticks to the antibody on the surface of the cantilever, creating a difference in surface stress and thus a deflection as a result of the chemical reaction produced by them.[83] Jeetender et al., probed this approach by proposing a mechanical biosensor for troponin detection.[83]

Other detection types

Photonic crystal approach with open optical microcavity offers easy functionalization of the sensing surface, easy designed and engineered for functioning in any optical wavelength.[252] In this case, Zhang et al., demonstrated the performance of a photonic crystal based biosensor integrated with a microfluidic system for MYO detection with a detection limit of 70 ng/mL, which generates viability for its use as a POC monitoring device.[252]

Colorimetric technique has great potential for POC testing due to the cost effective, fast and easy performance.[229] Detection of biomarkers at low concentration is an important challenge in colorimetric POC biosensors (medium to lower picomolar) and to solve the issue, the use of surface enhanced Raman scattering is beneficial in order to obtain detection in ultra low levels.[122] According to this, Lim et al., presented a surface enhanced Raman scattering based microfluidic paper device (μPAD)) for cardiac biomarkers detection such as TnT and CK-MB, obtaining 1 and 10 pg/mL as the limit of detection, respectively.[121]

Zhang et al., proposed a colorimetric method for MYO detection based on the aggregation of gold nanoparticles (AuNPs) fulfilling with the advantages mentioned but without obtaining a low limit of detection.[255] On the other hand, Wang et al., demonstrated that the use of the colorimetric technique mixed with DNAzyme functionalized AuNPs for MYO detection improved detection in a concentration as low as 2.5 nM.[229]

Peptide based approaches for biosensors have been investigated too, due to peptides can be easily synthesized and manipulated to improve target specificity and affinity.[242] Peptides from phage display are one of the most promising for biosensing applications.[235,242] It has been reported that electrochemical biosensors based on peptides maintain promise for point on care diagnostics, presenting high sensitivity, simplicity, efficiency, velocity, and portability.[101,242]

Impedimetric method allows to have biosensors with direct monitoring between antibody and antigen.[140] Also, being label free biosensors, do not present the necessity of biochemical reagents, thus making the process easier.[140] With the objective of improve the sensitivity of this kind of sensors, Miao et al., proposed a thin layer impedimetric biosensor between 2 layers of conducting glass for FABP detection using physical absorption for the immobilization of antibodies, resulting in a concentration limit of 200 mg/mL.[140]

Nanofluidics has become adequate for rapid and label free biomolecule sensing.[246] Specially, nanofluidic diode biosensor enhances the robustness and detection sensitivity of the device.[246] Due to this, Yeasmin et al., proposed a nanofluidic diode biosensor with an asymmetric nanoslit for electrical and label free detection of TnT, where results showed a great reproducibility of the sensing performance.[246]

Origin of the sample for detection

The human body presents a variety of fluids like blood, saliva, urine, tears, sweat and cerebrospinal fluid, all containing several proteins that are useful for monitoring health and prevent diseases.[128] Most studies of AMI biomarkers have centered their efforts in plasma (blood) samples, revealing high significance in myocardial injury, stress, inflammation, and stretch.[178] Nowadays, the use of human saliva samples have been encourage in AMI diagnosis due to its noninvasive and economical origin.[178] Saliva is a fluid with the function of maintain oral health, lubrication and binding, composed by salivary and nonsalivary agents, that is to say, proteins synthesized from blood or in the salivary glands (parotid, submandibular, sublingual, and minor salivary glands).[91,128,214,239]

Whole saliva is composed mainly by water and other elements like bacterial and exfoliated cells, electrolytes, glycoproteins, enzymes, antibacterial compounds, sugars, lipids, hormones, peptides and minimum amounts of gingival crevicular fluid found in the gingival crevice surrounding the teeth.[111,128,178]

Besides the benefits mentioned, a salivary proteome should be very practical in order to determine a heart condition.[178] Having in mind that around 27% of saliva proteins are similar to plasma proteins, the studies based on proteins found in both will be very useful to predict AMI progression and give treatment for patients in ED.[128] Various studies have demonstrated the relation between some salivary biomarkers and AMI condition as shown in Figure 8.

Whole saliva can be collected by drooling, spitting or swabbing into a tube, which states minimal risk for healthcare professionals and patients[178] Referent to collection, salivary tests presents challenges to beat according to stability and quality of the sample.[178] First, some proteins suffer degradation in saliva so the peptides observed can be varied.[178] In this case, some researchers have shown that degradation is related to the biological states of the human body, age, gender, and immunity.[208,211] On the other hand, older age is also important in this field due

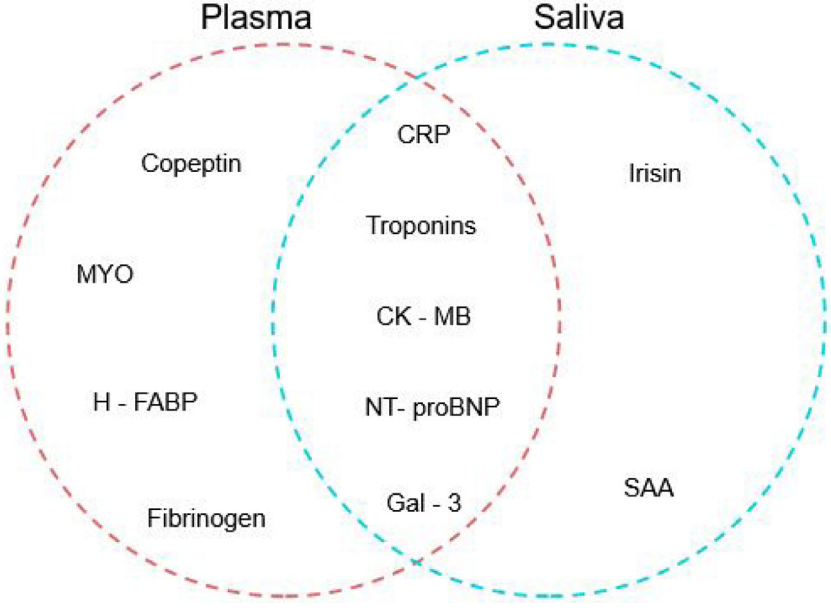

Fig. 8. Sample for detection: Salivary and plasma biomarkers. Elaborated from.[65,119,143,178,194]

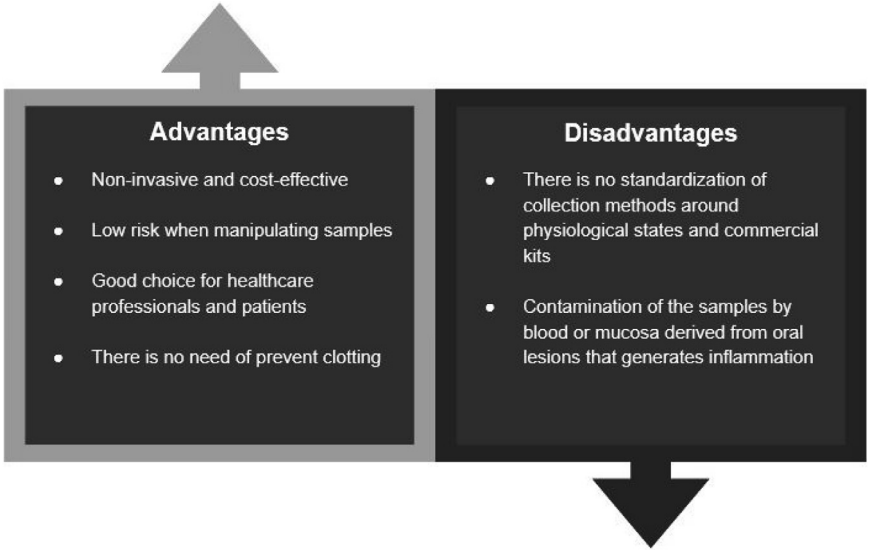

Fig. 9. Advantages and disadvantages of saliva as based for biomarkers detection in AMI prognosis. Elaborated from.[178]

to some people suffer from dry mouth as a consequence of their conditions, which limits the amount of sample collected and also the results.[178]

In Figure 9 are listed some of the advantages and disadvantages of saliva samples for AMI diagnosis.

Despite of the advances, none of the salivary biomarkers listed have shown any signs for AMI onset prediction, so the future aim is to provide an early and acute diagnosis through the use of this markers in order to increase the survival rate of cardiovascular patients compared of those evaluated by plasma.[178]

Authors Contribution

J. A. Reyes-Retana: Writing - Review and Editing, Supervision, Project administration. L. C. Duque-Ossa: Conceptualization, Methodology, Investigation, Writing - Original Draft.

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