THE RELEVANCE OF CLINICAL PATHOLOGY LABORATORIES IN THE MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION: A REVIEW

A IMPORTÂNCIA DO LABORATÓRIO DE PATOLOGIA CLÍNICA NA AVALIAÇÃO DO ENFARTE AGUDO DO MIOCÁRDIO: UMA REVISÃO **PT**

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LA IMPORTANCIA DEL LABORATORIO EN LA EVALUACIÓN DEL INFARTO AGUDO DE MIOCARDIO: UNA REVISIÓN **ES**

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ABSTRACT

Acute myocardial infarction (AMI) impairs the myocardium ability to pump blood. If this condition is not reversed in time, it will compromise the entire cardiovascular system, which in turn can lead to the collapse of all other physiological systems. Therefore, for the rapid and correct management of this condition the role played by the clinical pathology laboratory (CPL) is crucial due to its rapid response in the quantification of cardiac biomarkers. Through the measurements realized in CPL, it is possible to not only diagnose myocardial injury but also evaluate the injury size, establish a prognostic, or estimate the risk of re-infarction. Currently, the data provided by CPL to the clinician is increasingly accurate and robust, which is only possible due to the evolution that has been made in this field during the last three decades. Therefore, the major objective of this review is to emphasize the relevance that CPL has in the management of AMI patients.

Keywords: *Acute myocardial infarction; Clinical Laboratory Techniques; Biomarkers; Heart Function Tests; Troponin.*

RESUMO

O Enfarte agudo do miocárdio (EAM) é uma condição que é caracterizada pela incapacidade do miocárdio em bombear sangue de forma adequada. Se não for revertida atempadamente comprometerá todo o sistema cardiovascular que, por sua vez, pode levar ao colapso de todos os outros sistemas fisiológicos. Portanto, para uma avaliação correta e rápida desta condição é fundamental o papel desempenhado pelo Laboratório de Patologia Clínica (LPC), através da rápida resposta na quantificação dos biomarcadores cardíacos. Através das quantificações realizadas no LPC é possível não apenas diagnosticar uma lesão no miocárdio, mas também avaliar a sua extensão, estabelecer um prognóstico ou estimar o risco de ocorrência de um novo enfarte. Atualmente, os dados fornecidos pelo LPC ao clínico são incrivelmente robustos e sensíveis, o que apenas é possível devido à evolução que tem existido nesta área nas últimas três décadas. Assim, o grande objetivo desta revisão é salientar a relevância que o LPC tem na gestão de pacientes com suspeita de EAM.

Palavras-chave: *enfarte agudo do miocárdio, Técnicas de Laboratório Clínico; Biomarcadores; Testes de Função Cardíaca; troponina.*

RESUMEN

El infarto agudo de miocardio (IAM) afecta la capacidad del miocardio para bombear sangre. Si esta condición no se revierte inmediatamente comprometerá todo el sistema cardiovascular lo que a su vez puede conducir al colapso de todos los demás sistemas fisiológicos. Para la correcta y rápida valoración de esta patología es fundamental el servicio prestado por el laboratorio clínico (LC), lo que solo es posible por su rápida respuesta en la cuantificación de biomarcadores cardíacos. Debido a las mediciones realizadas en LC es posible no solo diagnosticar la lesión miocárdica sino también evaluar el tamaño de la lesión, establecer un pronóstico o estimar el riesgo de un nuevo infarto. Actualmente, los datos que proporciona el LC al clínico son cada vez más

robustos y sensibles, lo que solo fue posible gracias a la evolución que se ha hecho en este campo en las últimas tres décadas. Por lo tanto, el principal objetivo de esta revisión es enfatizar la relevancia que tiene el LC en la gestión de pacientes con sospecha de IAM.

Palabras clave: *infarto agudo de miocardio; Técnicas de Laboratorio Clínico; Biomarcadores; Pruebas de Función Cardíaca; troponina.*

INTRODUCTION

Cardiovascular diseases (CVDs) are the number one cause of death worldwide, taking an estimated 17.9 million lives each year (WHO., 2018). Despite CVDs are a group of several disorders that affect the heart and blood vessels there is one condition that stands out to all others that is the ischemic heart disease with approximately 9.5 million deaths per year (WHO., 2018). This clinical condition is an acute coronary syndrome (ACS) caused by the inefficient blood supply to myocardium due to narrowed coronary arteries, which then results on cardiac malfunction (Thygesen, Alpert, Jaffe, Chaitman, & Bax, 2018). Although several etiologies could cause this disorder, the most common initiating mechanism is a rupture or erosion of a vulnerable atherosclerotic coronary plaque, resulting in the exposure of circulating blood to a highly thrombogenic core in the plaque (Anderson & Morrow, 2017). The reduction of blood flow or the total blockade of coronary arteries leads to myocardial ischemia, which reduces the heart muscle's ability to pump blood or to abnormal heart rhythm, an devastating event that is known as heart attack or AMI (Thygesen et al., 2018).

Upon the admission to the emergency department, the diagnosis of AMI is made based on the identification of a triad of events, which include the symptoms, the biochemical markers, and the electrocardiogram findings (Anderson & Morrow, 2017). To AMI be diagnosed of those three set of events, two must be present (Anderson & Morrow, 2017). The most commonly reported symptom is chest pain which could be accompanied by an association of other non-specific symptoms that include fatigue, dyspnea, epigastric, or upper extremity diffuse discomfort, which may not occur equally in all patients (Thygesen et al., 2012). AMI may also induce atypical symptoms such as palpitation or cardiac arrest, or even occur without symptoms (Thygesen et al., 2018; Thygesen et al., 2012). The latest clinical criteria to diagnose AMI (2018) denotes the presence of acute myocardial injury in the setting of evidence of acute myocardial ischemia (Thygesen et al., 2018). In this sense, in a clinical environment the myocardial ischemia is present when the patient shows some of the above mentioned symptoms or is detected based on specific alterations on the electrocardiogram (ECG), which are characterized by the elevation of the ST-segment (Anderson & Morrow, 2017). On the other hand, the myocardial injury is detected by the elevation of cardiac troponins (cTn) above the 99th percentile being this quantified on the CPL (Thygesen et al., 2018). Interestingly, there can also be an AMI without ECG alterations, called non-Q AMI, being the role of CPL especially relevant because the diagnosis is made through patient symptoms and the evaluation of cardiac biomarkers (Anderson & Morrow, 2017).

The rapid and correct assessment of AMI is crucial to determine the patients outcome (Thygesen et al., 2018). For example, previous observational prospective cohort studies reported a high degree of uncertainty when patients present at the emergency department with breathlessness (Kelly et al., 2017; Laribi et al., 2019). Chronic obstructive airway disease and ACS coexist in approximately 30% of patients, making the diagnosis difficult (Kelly et al., 2017; Laribi et al., 2019). Through the CPL it is possible to provide results of the several cardiac biomarkers in less than one hour. Additionally, the physiological changes often precede clinical deterioration leading to a need for better monitoring patients receiving treatment, which could be made through the blood biomarkers (McCullough et al., 2002). In the specific case of AMI the pathophysiological mechanism lead to the death of cardiomyocytes, leading to the release of their content into the circulatory system (Aydin, Ugur, Aydin, Sahin, & Yardim, 2019). Historically, the laboratorial response has been characterized by the quantification of proteins or enzymes with specific isoforms present in these type of cells (Mythili & Malathi, 2015).

Therefore, the major objective of this narrative review is to highlight the progressive role of CPL on the correct and rapid assessment of myocardial injury and consequent management of AMI.

METHODOLOGICAL PROCEDURES

This is a narrative review, and the literature search was conducted on the PubMed database, combining the term "Acute myocardial infarction" with the terms "laboratory", "Cardiac biomarkers", "cardiac troponins", "myoglobin", "creatine kinase", "Brain natriuretic peptide", "N-terminal fragment", "new biomarkers", "High-sensitive C-reactive protein", "soluble ST2", "Myeloperoxidase" and "Heart-type fatty acid binding protein" using the boolean "AND". Only english language articles that have been peer-reviewed were selected. The two authors conducted the literature search and screened the abstracts and the full text of the studies independently. Were excluded all those articles that were not considered relevant to the major objective of this review, as well as letters to the editor and conference presentations.

3. CLINICAL PATHOLOGY LABORATORY VS. ACUTE MYOCARDIAL INFARCTION

Over the last decades the importance of CPL in medicine has increased, and currently among the variables that influence medical decisions, laboratory assays are considered to be the most important and commonly used (Ngo, Gandhi, & Miller, 2017). This phenomenon is associated to the identification of high specific and sensitive biomarkers but also to the development of technology that made them, accurate, cheaper and faster (Ngo et al., 2017; Sturgeon, Hill, Hortin, & Thompson, 2010). The biomarkers accuracy provide concrete and precise information in relation to the general health status of the individual or of a specific physiological system (Sturgeon et al., 2010). An example of this evolution is precisely the assessment of cardiac function, and specifically the diagnosis of AMI in which the laboratory response over the past decades has been fundamental to the clinical definition of this condition or in the way that cardiac function has been assessed. Not forgetting that all these laboratory data must be combined and interpreted with other cardiological tests, such as the ECG or the echocardiogram to a robust assessment of this vital function (Thygesen et al., 2018).

In the 1970s, the laboratorial biomarker detection of myocardial injury was based on the elevation of serum levels of several enzymes, such as, aspartate transaminase (AST), lactate dehydrogenase (LDH), and creatine kinase (CK)(WHO, 1979). However, due to their low specificity for the detection of cardiac muscle injury had little value in the diagnosis of AMI. The role of CPL would progressively change over the years due to the development of laboratory immunoassays in the 1980s and to the identification of the first cardiac biomarker, the Creatine kinase-MB (CK-MB). Until the late 90s the elevation of CK-MB was considered the gold-standard laboratorial test to detect myocardial injury (Braunwald et al., 2002). Then, in 2007 after the introduction of the laboratorial quantification of cTn there was a need to create a Universal definition of myocardial infarction (Thygesen et al., 2007). A consensus guideline from both European Society of Cardiology (ESC) and the American College of Cardiology (ACC) emphasized the importance of sensitive serological biomarkers in the detection of myocardial injury, and added cTn to CK-MB as the gold-standard laboratory tests (Thygesen et al., 2007). However, the clinical definition of AMI did not remain stagnant and recently (2018) it was readjusted again (Thygesen et al., 2018). A new consensus guideline from the ESC and the ACC defined has laboratorial criteria for the detection of myocardial injury the elevation of cTn (Thygesen et al., 2018). The great novelty of the latest guideline was the

CK-MB withdrawal as a gold-standard (Thygesen et al., 2018). This alteration was associated to the fact that it is a less specific biomarker but fundamentally due to the introduction of high-sensitive assays for the detection of cTn (Thygesen et al., 2018). Once again, the evolution of CPL and its methodologies was fundamental for the contemporary definition of AMI.

3.1 THE GOLD STANDARD - CARDIAC TROPONINS

The troponin complex is part of the regulatory apparatus of the myocyte, and is involved in the Ca^{2+}-mediated muscle contraction (both skeletal and cardiac muscles) that is exerted via conformational changes of the individual components (Bodor, 2016; Thygesen et al., 2012). This complex is constituted by 3 subunits, the calcium binding troponin C (TnC), the inhibitory troponin I (TnI), and the tropomyosin binding troponin T (TnT) (Bodor, 2016; Thygesen et al., 2012). Interestingly, both TnT and TnI subunits have distinct isoforms for each muscle type, hence there are specific cardiac isoforms, the cTnT and cTnI, respectively (Bodor, 2016; Thygesen et al., 2012). The success of cTn in the laboratorial detection of myocardial injury is associated to the ability to generate specific monoclonal antibodies against both cTnT and cTnI, which allows the use of immunoassays to perform their quantification (Ahmed & Hazen, 2017). Over the latest years the sensitivity of these assays has progressively increased, from the first generation cTn assays by decreasing diagnostic cut-offs from 0.5 μg/L to 0.01 μg/L, and nowadays with the high-sensitivity cTn (hs-cTn) immunoassays with a limit of quantification down to as low as 0.001 μg/L (Ahmed & Hazen, 2017). Usually the two cardiac-specific isoforms are quantified together in the same assay, however, it is also possible to measure them individually (Ahmed & Hazen, 2017).

cTn are released within two hours of symptoms onset, peak at 12 hours, and remain elevated for the next 5-14 days (table 1) (Ahmed & Hazen, 2017; Thygesen et al., 2018). They are considered the most tissue-specific biomarkers to evaluate myocardial injury, and according to the latest guideline from ESC and ACC when cTn are increased above the 99th percentile upper reference limit a diagnosis of myocardial injury should be made (figure 1) (Thygesen et al., 2018). When this injury is caused by myocardial ischemia (confirmed by ECG) or there is a presence of symptoms the patient is diagnosed with an AMI (Thygesen et al., 2018).

It is also important to note that although elevated cTn values indicate an injury in myocardial cells, there is also the possibility that these elevations can be induced by other conditions (non-pathological and/or pathological) that can lead to the release of these structural proteins from the myocardium into bloodstream, as is the case of normal turnover of myocardial cells, apoptosis, cellular release of cTn degradation products, increased cellular wall permeability, hypertensive emergency, stroke, sepsis, chronic kidney disease, heart failure (Thygesen et al., 2018). Unfortunately, laboratory quantification of cTn does not distinguish what is behind this elevation, but through other tests the CPL can play a fundamental role in differential diagnosis.

3.2 EVALUATION OF MYOCARDIAL INJURY WITH THE NON-GOLD-STANDARD CARDIAC BIOMARKERS

The role of CPL on AMI extends beyond the detection of myocardial injury by measuring cTn, there are also other cardiac biomarkers available on CPL that due to their characteristics have predictive or prognostic value to help the clinician to evaluate properly the cardiac function and make the differential diagnosis, the evaluation of the risk of re-infarction, or the follow-up of the patients. Such as, CK-MB, Myoglobin, Brain natriuretic peptide (BNP), and N-terminal fragment (NT-proBNP) (Figure 1).

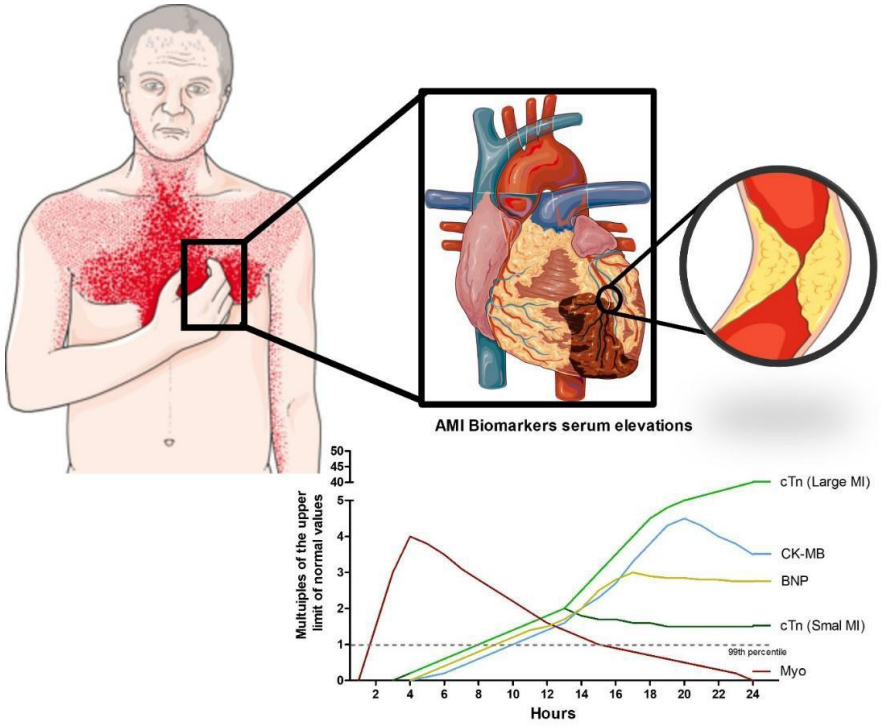

FIGURE 1: REPRESENTATIVE IMAGE OF THE ONSET OF AN ACUTE MYOCARDIAL INFARCTION WITH THE OCCLUSION OF THE CORONARY ARTERIES AND THE CORRESPONDENT CARDIAC BIOMARKER ELEVATIONS IN THE FIRST 24 HOURS AFTER THE INJURY. ABBREVIATIONS: AMI: ACUTE MYOCARDIAL INFARCTION; BRAIN NATRIURETIC PEPTIDE (BNP); CARDIAC TROPONINS (CTN); CREATINE KINASE-MB (CK-MB); MYOCARDIAL INJURY; MYOGLOBIN (MYO). IMAGE ADAPTED FROM THE FREE ONLINE DATABASE "SMART SERVIER".

3.2.1. CREATINE KINASE-MB

CK is an enzyme that is present in the cytosol of cells, and participates in the energy production process catalyzing the reversible transformation of creatine and ATP to creatine phosphate and ADP (Aydin et al., 2019). The CK enzyme is a dimer constituted by two monomers (CK-M and CK-B) and can be found in 3 isoforms, the CK-MM (muscle type), the CK-BB (brain type), and the CK-MB (heart type), being this isoform highly expressed on cardiac muscle (Aydin et al., 2019; Bodor, 2016; Young et al., 1997). Initially the measurements of cardiac enzymes were made through activity-based assays, however with the development of monoclonal antibodies specific for CK-MB in the 1980s the firsts immunoassays were developed (Bodor, 2016). In fact, CK-MB was the first cardiac biomarker measured trough immunoassays and this evolution allowed the laboratory to provide the necessary analytical specificity and sensitivity to detect the release of CK-MB after injury (Bodor, 2016), being considered the gold-standard laboratory test to detect myocardial injury for decades (Thygesen et al., 2018).

After ischemia, CK-MB is rapidly released to bloodstream and could be detected on serum, approximately 3 hours after symptoms onset (Jurlander, Clemmensen, Wagner, & Grande, 2000; Young et al., 1997), rises to twice the normal values within 6 hours, peaks within 12 to 24 hours and returns to basal levels approximately after 48 to 72 hours (table 1) (Jurlander et al., 2000). CK-MB measurements have an approximately 90% sensitivity for detection of myocardial injury 6 hours after symptom onset, but the sensitivity goes down to approximately 35-50% when used sooner (Jurlander et al., 2000; Young et al., 1997).

This biomarker can also play an important role on the evaluation of the risk of re-infarction, infarct size and expansion based on serial measurement (Ahmed & Hazen, 2017; Antman et al., 2000).

Although CK-MB is highly expressed in cardiomyocytes, there are other tissues where it is also expressed but in small amounts, as is the case of tongue, diaphragm, uterus, prostate and skeletal muscle, therefore any injury or inflammation in this tissues could result in CK-MB's release into bloodstream (Kiranmayi, Bhavani, & Tagore, 2015; Vassiliadis, Barascuk, Didangelos, & Karsdal, 2012). On the other hand, CK-MB activity has been also described to increase in certain patients with ischemic stroke, subarachnoid hemorrhage and head trauma in absence of any clinically evidence of AMI (Kiranmayi et al., 2015). To increase the specificity of CK-MB to distinguish the elevations induced by myocardial injury from the elevations secondary to other conditions, the measurement of CK-MB as a percentage of total CK has been proposed (Vassiliadis et al., 2012). However, the World Health Organization international diagnostic criteria, and several other professional societies recommend the use of absolute CK-MB based on one or two consecutive measurements (Thygesen et al., 2018). Despite the high-sensitivity assays to measure cTn have largely replaced the use of CK-MB on the detection of myocardial injury, if they are not available the CK-MB still remains an alternative marker (Vassiliadis et al., 2012).

3.2.2. MYOGLOBIN

Myoglobin (Myo) is a globular heme-protein located on the cytoplasm of both cardiac and skeletal muscle cells, where its main function is to store and supply oxygen (Wittenberg, 2003). The relatively low molecular weight (16.7 kDa) and its location inside the cell contributes to its rapid release into the bloodstream after a muscle cell injury (Morrow et al., 2007; Vassiliadis et al., 2012). Indeed, after myocardial injury Myo is the earliest cardiac biomarker detected in serum, approximately 30 minutes to 2 hours after injury it is possible to detect Myo elevations, reaches the peak within 4 hours after symptoms onset, and return to basal levels within 24 hours (table 1) due to rapid renal clearance (Morrow et al., 2007; Vassiliadis et al., 2012). Like CK-MB, Myo was also introduced in CPL in the early 1980s (Gibler et al., 1987), and its measurements over the decades have been optimized until the last generation immunoassays (Aydin et al., 2019).

However, when compared with the other two cardiac biomarkers discussed above, Myo is less tissue-specific and sensitive on the detection of cardiac muscle injury. Since both cardiac and skeletal myocytes share 100% homology on the expression of Myo, therefore when there is a skeletal muscle injury its serum levels also increase (Ahmed & Hazen, 2017). Additionally, due to its renal clearance, on patients suffering from renal insufficiency the serum levels of Myo are usually above the reference values (Vassiliadis et al., 2012). Similarly, to what happened with CK-MB, over the latest years the role of Myo in the assessment of AMI has decreased and the reason is the same (Ahmed & Hazen, 2017). However it can be an useful tool to detect re-infarction and on the evaluation of injury size when serum levels of cTn are still elevated (Braunwald et al., 2002; Moe & Wong, 2010).

3.2.3. BRAIN NATRIURETIC PEPTIDE AND N-TERMINAL FRAGMENT

Brain natriuretic peptide (BNP) and its inactive cleavage product N-terminal fragment (NT-proBNP) are polypeptide cardiac neurohormones that are released from the cardiac cells to bloodstream in response do hemodynamic stress (Fu, Ping, Wang, & Luo, 2018). Both BNP and NT-proBNP are secreted in membrane granules of cardiac ventricles when left ventricle function is insufficient and cardiac wall is stretched due to transmural pressure or volume overload (Fu et al., 2018; Vassiliadis et al., 2012). BNP production in normal healthy people is minimal, and an increase of BNP and NT-proBNP serum levels occur in the setting of higher filling pressures in patients with cardiac dysfunction (Ahmed & Hazen, 2017), on AMI this rise is detectable after 4 hours of symptoms onset, peaks at 16 hours and returns to basal levels after 7 days (table 1) (Fu et al., 2018; Morita et al., 1993).

It was introduced in CPL in the 2000 (Chien, Chen, & Kao, 2006; Doust, Glasziou, Pietrzak, & Dobson, 2004), and their serum levels correlate with the severity of symptoms, being a powerful predictor of death and major adverse cardiovascular events in patients with AMI (Ahmed & Hazen, 2017; Vassiliadis et al., 2012). On the other hand, BNP serum levels can increase in several conditions, such as renal failure, pulmonary hypertension, primary aldosteronism, cirrhosis, and thyroid disease, what may limit its value in the assessment of cardiac function (Loria, Dato, Graziani, & Biasucci, 2008; Vassiliadis et al., 2012). Currently these biomarkers are routinely assessed on CPL, being NT-proBNP used on the prognosis of patients with ACS (Raizada et al., 2007), and the BNP assay for risk stratification (Shapiro, Chen, Burnett, & Redfield, 2003).

Biomarker	Serem elevation	Peak	Basal levels	Type
cTn	2h	12h	5-14d	Gold-standard
CK-MB	3-6h	12-24h	2-3d	Infarct size Risk of re-infarction
Myo	30min-2h	4h	24h	Infarct size Risk of re-infarction
BNP and NT-proBNP	4h	16h	7d	Predictor of death and major adverse cardiovascular events

TABLE 1: BIOLOGICAL VARIATIONS OF AMI BIOMARKERS AFTER MYOCARDIAL INJURY AND THEIR CLINICAL SIGNIFICANCE. ABBREVIATIONS: HOUR (H), MINUTE (MIN), DAY (D).

3.2.4. HIGH-SENSITIVE C-REACTIVE PROTEIN

C-reactive protein (CRP) is an acute phase protein secreted by the hepatocytes during inflammatory stimulus, and its physiological role is to bind and signal cells that are dead or are dying, as well as some pathogens, to be eliminated (Mythili & Malathi, 2015). Classically it is classified as an inflammatory biomarker, however it was correlated with plaque vulnerability, angina, AMI, coronary vasospasm, and left ventricular dysfunction (Ahmed & Hazen, 2017; Mythili & Malathi, 2015).

CRP started to be measured on the CPL in the 90s, and the earlier methods were not sufficiently sensitive to measure serum levels within the normal range (Helal et al., 2012; Knight, 2015). However, with the development of CPL quantification methods there are high-sensitivity assays for CRP (hs-CRP), which allows the measurement or the detection of mild elevations, even within the normal range (Helal et al., 2012; Knight, 2015). Whereas the traditional CRP assays measure the range between 10 to 1,000 mg/L, the hs-CRP methods are able to quantify values on the range from 0.5 to 10 mg/L (Knight, 2015), and can be used as prognostic indicator on ACS, in which CRP levels were associated with poor outcome (de Winter et al., 1999; Mythili & Malathi, 2015), or as an risk indicator of cardiovascular disease (hs-CRP <1 mg/L low risk; 1 to 3 mg/L average risk; >3 mg/L high risk) (Knight, 2015). However, it is also important to note that in laboratorial routine cannot be used in the diagnosis of AMI (Mythili & Malathi, 2015), due to its lack of specificity and sensitivity since its values increase rapidly in response to trauma, inflammation, and infection (Ahmed & Hazen, 2017).

3.3. THE NEW ERA IN THE ASSESSMENT OF AMI

Taking into account what was previously mentioned, it is clear that there is a correlation between the evolution of CPL methodologies and equipment's, and the relevance that it has gained over the past decades in the patient diagnosis, treatment, management, and follow-up. It is also clear that this evolution is a continuous process, and that simultaneously efforts are being made not only technically and methodologically, but also on the identification of new biomarkers. Historically, the research has essentially focused on proteins that have specific cardiac isoforms and on the inflammatory biomarkers that correlate with cardiac injury (Bodor, 2016). Over the recent years, the researcher's objective has remained the same, however, no major progress has been made in the identification of new AMI biomarkers (Aydin et al., 2019; Bodor, 2016). Across the most relevant biomarkers that were identified as potential candidates most of them are related to the inflammation and the vulnerability of atherosclerotic plaques and are described as risk and/or prognostic biomarkers as is the case of the soluble ST2 or Myeloperoxidase (MPO). Perhaps the only exception to these inflammatory markers is a protein found in cardiomyocytes, the Heart-type fatty acid binding protein (H-FABP).

3.3.1. HEART-TYPE FATTY ACID BINDING PROTEIN

H-FABP is a cytosolic low molecular protein (15 kDa) present in the cardiac tissues that is responsible for the transport of long-chain fatty acids from the plasma membrane to the sites of β-oxidation in mitochondria and peroxisomes, and to the endoplasmic reticulum for lipid synthesis (Aydin et al., 2019; Mythili & Malathi, 2015). H-FABP have also the ability to protect cardiomyocytes against long-chain fatty acids, which are localized at high concentrations, especially during ischemia (Aydin et al., 2019). This protein is released from cardiomyocytes to bloodstream following an ischemic episode, and its levels begin to rise within 30 min after myocardial injury (Table 2), peaks at 6-8 hours, and returns to basal levels within approximately 24 hours (Aydin et al., 2019).

H-FABP is considered 20 times more specific for cardiac muscle than Myo (Ahmed & Hazen, 2017; Aydin et al., 2019), and there are observations indicating that when measured along with cTn have a negative predictive value of 98% for the diagnosis of AMI (McMahon et al., 2012). Furthermore, the rapid return to basal levels offers a potential application in patients with suspected re-infarction, instead of CK-MB (Pelsers, Hermens, & Glatz, 2005). In addition, to its diagnostic potential H-FABP can also be used as a predictive biomarker of mortality following AMI (Mythili & Malathi, 2015). When compared to the other potential ACS biomarkers, probably at this point H-FABP is the best candidate to be included in the laboratory routine (Pelsers et al., 2005).

3.3.2. MYELOPEROXIDASE

MPO is a metalloproteinase produced by the polymorphonuclear leukocytes and macrophages that catalyzes the production of reactive oxygen species which are important for the development of atheromas and plaque ruptures (Mythili & Malathi, 2015). It is classified as an inflammatory marker (Mythili & Malathi, 2015; Omran, Zahran, Kadry, Belal, & Emran, 2018), but MPO serum levels also increase on ACS, especially on AMI (Omran et al., 2018). This association was made based on the role that MPO represent in all stages of the atherosclerotic process and its rapid increase in bloodstream after myocardial injury, raising the hypothesis that it could be a potential early diagnostic biomarker (Omran et al., 2018).

It was reported that within 2h of symptoms onset (table 2) the diagnostic performance of MPO is markedly improved with a negative predictive value of 95.6% and a sensitivity of 95.8% when compared to the negative predictive value of 73.3% and a sensitivity of 50.0% for c-TnI (Rudolph et al., 2011). Suggesting that MPO could emerge as an useful biomarker to rule out AMI on early stages. On the other hand, in contrast to its high negative predictive value MPO have a low specificity (61.1%) and positive predictive value (62.1%)(Rudolph et al., 2011). Due to this lack of specificity MPO has not yet achieved the cardiac biomarker

status, however there is a report that have suggested that if MPO is used in association with CK-MB and cTn early after the symptoms onset it is possible to correctly discriminate 91% of the AMI patients with a specificity of 76% (Omran et al., 2018). Furthermore, there are also studies that indicate that MPO can be used as a predictive marker for future cardiovascular adverse events, death, reinfarction, and the need for coronary revascularization (Ahmed & Hazen, 2017; Baldus et al., 2003).

3.3.3. SOLUBLE ST2

ST2 is a member of the superfamily of interleukin-1 receptors, and exists as a transmembranar (sT2L) or as a soluble (sST2) receptor (Ahmed & Hazen, 2017; Aleksova et al., 2019). The overexpression of sST2 is associated with inflammation and immune response, but also with myocardial stress or injury (Aleksova et al., 2019). It was demonstrated that on patients with myocardial infarction the sST2 serum levels starts to rise 3 hours after the symptom's onset (table 2) and peaks at 12 hours after which there is a slight decrease (Shimpo et al., 2004). Despite this association with AMI, it was reported that sST2 has a sensitivity of 77.4% and a specificity of 89.7% for AMI which is insufficient to be considered a diagnostic biomarker (Zhang, Zhang, Mi, & Liu, 2013). However, it was reported that sST2 has an independent predictive value for either in chronic heart failure (it predicts patients outcome beyond NT-proBNP and hs-cTn) (Emdin et al., 2018), or in acute heart failure like AMI (Ahmed & Hazen, 2017; Aimo et al., 2017; Aleksova et al., 2019). Indeed, different clinical trials have demonstrated the prognostic significance of sST2 either on short-term (30 days)(Shimpo et al., 2004) or long term (6 months)(Zhang et al., 2013) after myocardial infarction. Being reported that higher early levels of sST2 were correlated with worst outcome, the risk of re-infarction and mortality (Zhang et al., 2013). Therefore, sST2 represents a clinically relevant biomarker reflecting pathophysiological processes and contributing to predictive information on the management of AMI.

Biomarker	Serem elevation	Type
H-FABP	39min	Risk of re-infaction Predictive biomaker of mortality
MPO	- 2h of symptooms onset	predicative marker of reinfraction, mortality and the need for coronary revascularization
Soluble ST2	3h	Prognostic marker

TABLE 2: BIOLOGICAL VARIATIONS OF THE POTENTIAL AMI BIOMARKERS AFTER MYOCARDIAL INJURY AND THEIR CLINICAL SIGNIFICANCE. ABBREVIATIONS: HOUR (H), MINUTE (MIN).

4. DISCUSSION AND CONCLUSION

The correct assessment of AMI is crucial to save patients and depends on both clinical and laboratory findings, including ECG and biomarkers for cardiomyocyte injury (Thygesen et al., 2018). Over the last decades it was clear that the evolution of CPL was crucial to provide to the clinician more concrete and accurate data so that he can proceed to the correct diagnosis, treatment, management, and follow-up of AMI patients, thus reducing the error associated to the clinical decision making.

To achieve this status, it was fundamental the successive improvements in laboratory technologies and methodologies, like the development of the first immunoassays and then with their optimization to the high-sensitivity assays for the detection and quantification of small elevations of specific biomarkers, or the identification of increasingly tissue-selective and specific biomarkers. These two factors combined shortened the time between the admission of patients on the emergency department with suspected AMI and the laboratorial response to accurately detect and diagnose AMI (Aydin et al., 2019). Currently, it is possible to provide the quantification of all cardiac biomarkers assessed in the laboratory routine in less than one hour. Being unanimous that the most significant advance that was made in the assessment of AMI was the development of hs-cTn immunoassays.

Although currently hs-cTn are considered the gold-standard analyte for detection of myocardial injury (Thygesen et al., 2018) we cannot forget the role that other analytes have played in the latest decades or what they can contribute under certain circumstances to the management of AMI. An example of this is the CK-MB, which for decades was considered the best biomarker to diagnose myocardial injury (Bodor, 2016). CK-MB only lost this role because more specific and sensitive tests emerged, however it remains a very important biomarker to evaluate the risk of re-infarction and infarct size (Bodor, 2016). Another cardiac marker that could be used to evaluate the risk of re-infarction is Myo. Despite its low specificity for the detection on myocardial injury its rapid renal clearance made it the ideal marker to detect the re-infarction or the evaluation of injury size when serum levels of cTn are still elevated (Vassiliadis et al., 2012). The latest cardiac biomarkers that arrive to laboratory were the BNP, NT-proBNP and Hi-CRP, all of them have a low sensitivity for the detection of myocardial injury, but they are powerful predictor of outcome, major adverse cardiovascular events and death in patients diagnosed with AMI (Ahmed & Hazen, 2017; Vassiliadis et al., 2012).

The research conducted over the latest years on the pursuit of the identification of an AMI biomarker focused essentially on proteins that have specific cardiomyocyte isoforms and on the inflammatory biomarkers that correlate with cardiac injury and to the atherosclerotic process. These efforts resulted in the identification of several interesting markers, such as H-FABP (Aydin et al., 2019). A protein that is released from cardiomyocytes to bloodstream after an ischemic period, and currently is probably the strongest candidate reach the laboratory routine and help on AMI diagnosis (Aydin et al., 2019). In addition, MPO and sST2 were also referenced, the first is seen as a biomarker with a high negative predictive value which could be used to exclude AMI diagnosis and the second has a better prognostic value than what is currently used NT-pro-BNP (Rudolph et al., 2011; Shimpo et al., 2004).

Furthermore, the research on the assessment of AMI pursuing the ideal biomarker to evaluate myocardial injury continue. The researchers are attempting to identify a marker that have a highly sensitive and specific value to detect a small degree of myocardial injury that unmistakably exclude damage to other muscles. Ideally, should also give information regarding the infarct size, prognosis, distinguish between reversible and irreversible damage, and show the result of reperfusion therapy. Until then, it is essential that these studies continue to be developed.

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