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Myocardial necrosis markers in myocardial ischemia reperfusion (MI/R) injury: a review

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Abstract
Myocardial ischemia/reperfusion injury is one of the main causes of morbidity and mortality in the world. This injury is experienced by patients suffering from cardiovascular diseases such as coronary heart diseases and subsequently undergoing reperfusion treatments in order to manage the conditions. Ischemia can be especially detrimental to the heart due to its high energy demand. Several cellular alterations have been observed upon the onset of ischemia. The danger created by cardiac ischemia is somewhat paradoxical in that a return of blood to the tissue, termed reperfusion, can result in further damage. The serum markers of myocardial injury are used to help in establishing the diagnosis of myocardial infarction. Use of various biochemical markers, including lactate dehydrogenase (LDH), creatine kinase (CK) total enzyme activity, CK-MB activity, Myoglobin, CK-MB mass, cardiac troponin I (cTnI), and cardiac troponin T (cTnT) have been investigated for noninvasive assessment of reperfusion. It is hoped that further studies will help refine the clinical use of new biomarkers like high-sensitivity cardiac troponin (hs-cTn) immunoassays in myocardial injury.

Keywords: Myocardial ischemia-reperfusion, creatine kinase, troponin, myoglobin, lactate dehydrogenase, aspartate amino transferase

SCHEDULE

I. Overview of the Myocardial Ischemia Reperfusion Injury

Myocardial ischemia reperfusion (MI/R) injury has multiple confluent pathways, including reactive oxygen species (ROS), ion channels, inflammation and endothelial dysfunction [1]. It occurs during the treatments such as, thrombolysis and percutan transluminal coronary angioplasty (PTCA). After myocardial ischemia essential nutrients decreases and metabolic wastes increases. Reflow of blood to an ischemic area must be provided in a short time to increase the rescued tissues. Beside this beneficial effect of reflow, it leads to some damages. Morphological changes, enzyme washout and ventricular arrhythmias happen during the restoration of blood [2]. Some clinical studies had been done to prevent these impacts of reperfusion with some antioxidant agents such as melatonin [3], caffeic acid phenethyl ester (CAPE) [4], and aminoguanidine (AG) [5] (Figure 1).

ROS are accepted as the main cause of ischemia reperfusion (I/R) injury. These oxygen species are highly reactive and quickly overwhelm the cell's free radical scavenging system. This triggers loss of cellular function by reactions with proteins, lipids and nucleic acids. Superoxide dismutase (SOD), catalase (CAT), glutation peroxidase (GSH-Px) and some other enzymes reacts with ROS and prevents the harmful effects of them [6, 7].

The loss of membrane phospholipids plays an important role in the development of I/R injury. Melatonin is a well-known antioxidant and free radical scavenger. Melatonin also reduces the intracellular calcium (Ca^{+2}) overloading and inhibit lipid peroxidation [8]. We investigated the protective effects of melatonin on MI/R-induced oxidative changes. GSH levels, an antioxidant, which are influenced by oxidative stress, and malondialdehyde (MDA) levels, which is an index of lipid peroxidation, were measured. MDA levels were significantly higher, but GSH levels were lower in I/R group than in the control group. Melatonin significantly reduced the MDA values and increased GSH levels. This indicates that melatonin improves antioxidant capacity of the heart and attenuates

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the degree of lipid peroxidation after I/R [9]. As we mentioned above, I/R is accompanied by a significant increase in MDA production and decrease in GSH content in heart. Administration of CAPE reduced MDA production and prevented the depletion of GSH content. These beneficial changes in these biochemical parameters are also associated with parallel changes in histopathological appearance. These findings reveal us I/R is associated with overproduction of oxygen radicals or insufficient antioxidant and CAPE exhibit cardioprotective effects probably by the radical scavenging and antioxidant activities [10,11].

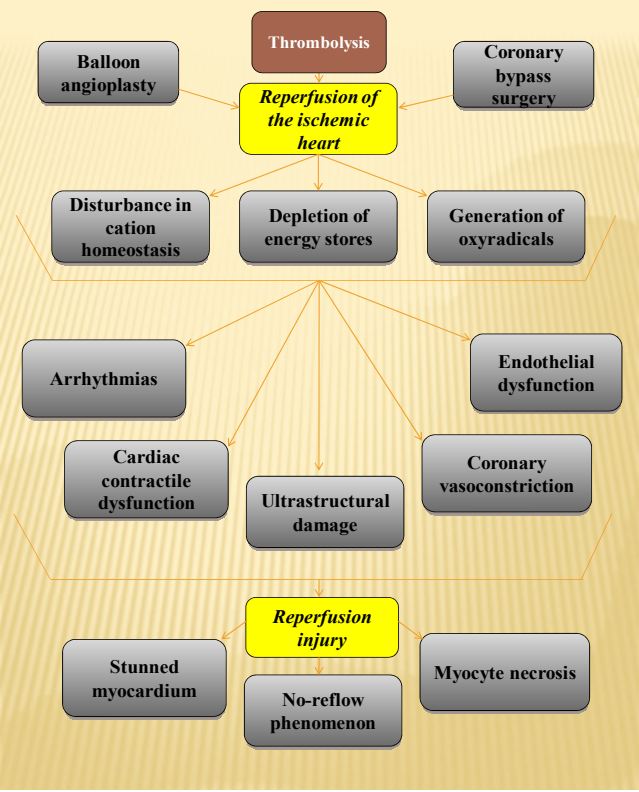

Figure 1. Algorithm of The Myocardial Ischemia Reperfusion Injury

MI/R is accompanied by induction of inducible nitric oxide synthase (iNOS) that leads to increase in production of nitric oxide (NO). Increase in production of NO is together with myocardial injury [12]. In our previous study [13], we investigated the effects of aminoguanidine (AG), iNOS inhibitor, on the percentage of infarct size in rats. AG administration elevated mean arterial blood pressure, statistically reduced the myocardial infarct size and infarct risk zone. In conclusion our study revealed that AG shows a reduction in NO's side effect in I/R injury.

ROS, produced in the myocardium during reperfusion, change the membrane permeability of potassium, Ca^{+2} and sodium ion channels. The activity of these ion pumps decreases. In physiological conditions, Ca^{+2} is tolerated with storing or throwing out. Because of energy deficiency during ischemia, Ca^{+2} accumulates in the cell and causes toxic effects. That is, the depression in the Ca^{+2} regulatory mechanism by results in intracellular Ca^{+2} overload and cell death [14,15].

The mechanism of I/R injury complicated with the activation of polymorphonuclear neutrophils (PMNs) [16,17]. This cascade of injury to be inflammatory and involve interactions between circulating PMNs and the coronary endothelium [18].

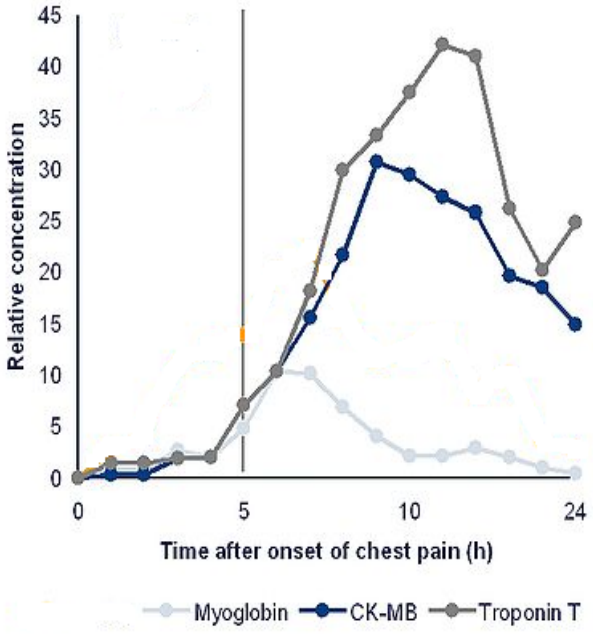

Figure 2. Comparison of cardiac marker in the first hours after chestpain onset and the relative concentration [66].

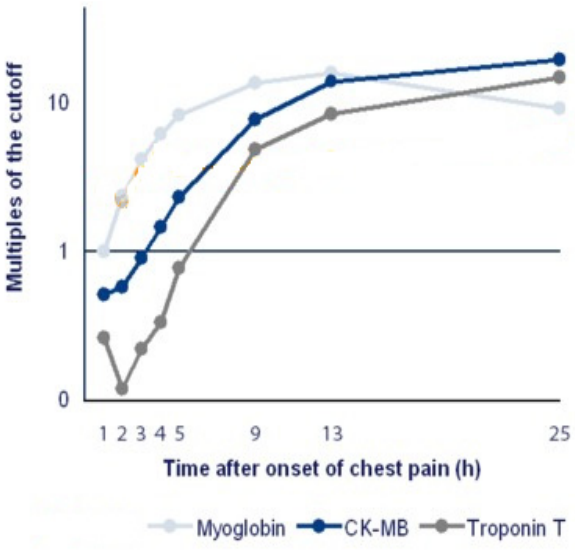

Figure 3. Comparison of cardiac marker in the first hours after chestpain onset and the multiples of the cutoff [66].

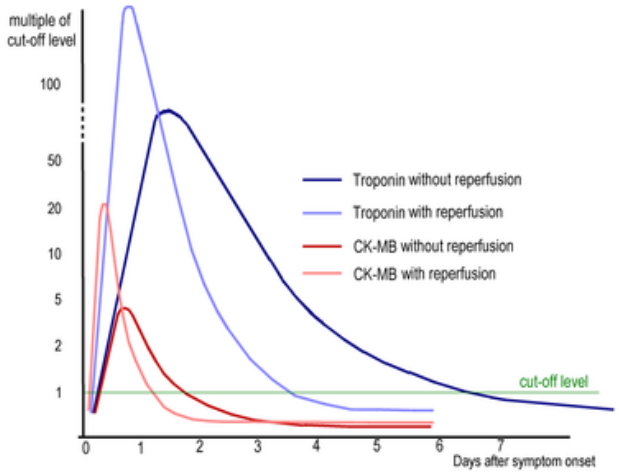

Figure 4. Kinetics of cardiac markers in myocardial infarction with or without reperfusion treatment [66].

Table 1. Characteristics of AMI biomarkers [32].

Biomarker	Kinetics			Sensitivity for myocyte necrosis	Specificity for myocyte necrosis
	First detection, hours	Maximum value, hours	Return to normal values, days		
AST	3-4	15-28	5	++	+
LDH	5-10	60-144	12	++	+
CK total enzyme activity	3-9	10-20	3	++	+
CK-MB activity	3-8	10-20	3	++	++
Myoglobin	1-3	4-7	1-1.5	+++	+
CK-MB mass	3-12	12-18	2-3	+++	+++
cTnI	3-7	10-20	10	++++	++++
cTnT	3-8	15-120	14	++++	++++

Characteristics of True Biochemical Marker

1. It should be myocardial tissue specific (It should be absent in non-myocardial tissues).
2. It should be released in the blood soon after the MI (Sensitivity).
3. It should be detected in blood while injury can be prevented/reversible
4. It should be remained high blood concentration level
5. It could determine prognosis.
6. Its cost should be cheaper and analysis period should be shorter than the others [22].

Creatine Kinase

The enzyme CK is responsible for transferring a phosphate group from ATP to creatine [23]. All cytoplasmic CK is composed of M and/or B subunits that associated to form CK-MM, CK-MB and CK-BB isoenzymes. "Total CK" refers to the cumulative activity of the MM, MB and BB enzymes in patient samples. CK-MM is dominant in both skeletal and myocardial muscle. In patients, have myocardial disease, the CK-MB isoenzyme comprises %20 of the total CK in this tissue [24]. So CK-MB is an important cytoplasmic enzyme in the evaluation of coronary problems. In normal individuals' percentage of CK-MB is lower than in patients. However still, CK-MB is not a biological cardiac specific marker.

The rising and falling CK-MB in serial measurements are pathognomic for the diagnosis of MI [25]. CK-MB begins to rise within 3-4 h after the onset of myocardial injury. It reaches a suitable level 8-12 h after the onset of symptoms and falls to normal ranges by 48-72 h. A short time to peak CK or CK-MB concentration has been proposed as an indicator of reperfusion [26,27].

Tanasijevic et al. measured CK-MB in 442 patients exposed thrombolytic therapy [28]. They compared the enzyme values before and after treatment. The pathency in the infarct related artery is graded by angiography according to the thrombolysis in M/I (TIMI) criteria, in which TIMI 0 no perfusion past the occlusion; TIMI 1 is penetration past the occlusion without perfusion; TIMI 2 is partial perfusion past the occlusion; and TIMI 3 is complete perfusion. Before treatment, CK-MB value in "TIMI Grades 0-1" group is bigger than "TIMI Grade 2-3" group. After treatment, in the blood was taken at 60 minutes, it is identified that the enzyme value in both groups is higher than according to the first value [29].

II. Biochemical Markers

Myocardial I/R is accompanied by the release of structural proteins, enzymes and other intracellular molecules into the cardiac interstitium. Reperfusion especially leads to a rapid release of these enzymes, possibly as a result of a "washout" effect [19,20]. This enzyme washout is useful clinically as a noninvasive marker for successful coronary recanalisation [21].

Biochemical markers of myocardial necrosis include creatine kinase (CK), cardiac troponin T and I, myoglobin (Mb), lactate dehydrogenase (LDH), aspartate amino transferase (AST) and some others (Table 1). We will mention about these enzymes in the remainder of this section.

In another study, Zhu et al. measured CK-MB level in rats. In I/R group, CK-MB reached a peak value approximately in 3 h and remained elevated for 2 days [30].

Xing et al. aimed to evaluate CK-MB mass for the early diagnosis of the infarct related artery pathency (RAR) after thrombolysis in their study. They enrolled the average maximal values of CK-MB mass and CK-MB activity appeared at 9.2 h and 9.4 h in the group with continuous reperfusion. In non-reperfusion group CK-MB mass peaked at 20.4 h and CK-MB activity at 21.2 h. The peak value of CK-MB mass was significantly higher in the continuous reperfusion group than in non-reperfusion group [31]. In conclusion they stated that CK-MB mass can be used as an indicator of RAR after thrombolysis.

In Danese and Montagnana's review, CK-MB mass measurement has the advantage to be more stable than the enzyme activity after storage and appears to be more sensitive, by increasing in plasma and serum more rapidly than CK or CK-MB activity. However, it is not sufficiently rapid when compared to myoglobin in the early diagnosis of acute myocardial infarction (AMI), mostly in the first 6 hours after symptom onset. As for the enzymatic activity, the mass value of CK-MB also increases in many conditions other than AMI [32].

Troponin Isoforms

Troponin isoforms are the most sensitive and specific marker for myocardial damage. Because it has increased specificity compared with CK-MB. Troponin is a superior marker for myocardial injury. The troponins are components of the regulatory complex located on the thin filament of the contactile apparatus of the myocyte. There are three types of troponins: troponin C (TnC), Troponin I (TnI) and Troponin T (TnT). They have different structure and function. Three of them are essential components of the contractile complex of both skeletal and myocardial striated muscle. TnT functions to bind the troponin complex to the tropomyosin strand; TnI functions to inhibit the activity of actomyosin ATPase; and TnC serves to bind four Ca^{+2} ions, thus regulating contraction [33-35].

In these proteins TnT and TnI have high cardiac specifity. Although TnT and TnI are structural proteins, the reports suggested that a "cytosolic" pool of these. Proteins were released into the circulation after cell injury [36]. They will be increased in blood for many days following AMI, cardiac TnT (cTnT) more markedly than cardiac TnI (cTnI). Data indicate that TnI is a specific marker in cases involving skeletal muscle injury and renal failure. Increased TnT is related to both cytosolic and structural damage, so in patients with high level of TnT, it is known that myocardial damage is seen [37].

In Licka et al.'s study, TnT concentration was investigated in reperfused and nonreperfused patients. Group 1 (non-reperfusion group) was including 14 patients (in 10 patients, no recanalisation was attempted and in an additional 4 patients recanalisation was not successful.). Group 2 (reperfusion group) was including 23 patients (Coronary recanalisation was achieved by intravenous thrombolysis, by Percutaneous Transluminal Coronary Angioplasty, or by both procedures.). Either reperfusion or non-reperfusion group, TnT serum concentrations increased after the onset of the symptoms at about 3.5 h and reached a peak value, approximately in 15 hours, since skeletal TnT is < 1%, the specifity and sensitivity of TnT were about 96% and 100%, respectively. Additionally, the biphasic curve of TnT concentration is observed in the study, as we mentioned above (in reperfusion group) [41].

In another study Katus et al., in 50% of 388 patients with chest pain, 3 h after the beginning of the problems, demonstrated that, serum TnT levels started to increase, and in all patients it remained elevated, more than 130 hours in blood [34].

Rempiss et al. investigated the relation between TnT level measurements in the first hours and reperfusion success in patients treated with thrombolytic agents. This study showed that, cTnT measurements during the first two days after the onset of AMI can be used to assess the early success of thrombolytic therapy. They identified serum TnT concentration have biphasic curve, in patients applied in early 5.8 after onset of the symptoms and was provided reperfusion with successful thrombolytic therapy. They demonstrated that the administration thrombolytic therapy is effective in providing the reperfusion [42].

cTnT is used in current therapies in the diagnosis of AMI, to identify thrombolytic treatment is successful or not, in the prognosis of patients with angioplasty and coronary by-pass [38]. The reperfusion dependent early increase in serum cTnT concentration was detectable until 38 hours after the onset of pain and on average reached a peak value at 14 hours. TnT serum concentrations show a biphasic curve with one peak on the first day resulting from a release of the cytosolic TnT pool and a second "plateau" phase 3-4 days after the beginning of chest pain resulting from intra myocardial degradation. A second peak of TnT seems to be almost uneffected by early coronary reperfusion [39,40].

cTnI assay showed high specificity for cardiac injury even in the presence of acute muscle disease, chronic muscle disease, chronic renal failure, and after marathon running [35]. Cummins showed that serum cTnI was elevated within 4 to 6 hours in patients with AMI, reached a mean peak level of 112 ng/mL (range, 20–550 ng/mL) at 18 hours, and remained above normal value for up to 8 days following myocardial injury [43].

Nowadays, high-sensitivity cardiac troponin (hs-cTn) assays are considered the biomarkers of choice in the early diagnosis of AMI being able to detect cTn release at an

earlier time point than the previous generations of cTn assays, especially in patients with a recent onset of chest pain [32]. Most patients with an AMI, can be reliably identified within 3 h after admission, with nearly 100% sensitivity and 100% NPV using a hs-cTn assay, which indicates that observation time in the emergency department may be reduced for rule out of AMI. However, in patients with 3 h values unchanged, but in whom pre-test likelihood of AMI is high, additional subsequent sampling (e.g., at 2 or 3 h) may still be advisable [44].

Myoglobin

Myoglobin is the primary oxygen-carrying pigment of muscle tissue. It is an intramyocardial protein that is released into the systemic circulation and rapidly cleared via the kidneys after myocardial injury [45, 46]. Its molecular weight is lighter than the others (CK-MB isoforms, cTnT, cTnI). Mb has some advantages and disadvantages. Advantages; high sensitivity and negative predictive value and useful for early detection of MI and reperfusion. Disadvantages; low specifity in presence of skeletal muscle injury and renal insufficiency and rapid clearance after necrosis. Because of this disadvantage, Mb is used less than the other markers [47].

Some studies indicate Mb concentration–time curve in humans and animals, and the rate of rise of Mb is both sensitive and specific as an indicator of successful coronary artery occlusion and reperfusion have been well defined. Mb concentration begins to rise as early as 1 h after onset of myocyte damage and returns to normal within 12-24 h [48,49].

I will mention widely about Spangenthal et al.'s study, as associated with using Mb in reperfusion. Eighteen chronically instrumented dogs were made hypotensive by being bled with a femoral artery catheter in to a reservoir adjusted to maintain a constant mean arterial pressure of 50 mm Hg for 8 hours. After the first hour of hypotension, each dog was studied under different protocols: group 1, 2 hours of mid–left anterior descending artery (LAD) occlusion followed by 5 hours of unlimited reperfusion; group 2, 7 hours of mid-LAD occlusion without reperfusion; or group 3, 7 additional hours of hypotension alone. Systemic lactate extractions demonstrated a shift to anaerobic metabolism in skeletal muscle and confirmed that shock was established in all animals. Regional arteriovenous Mb differences in group 1 animals demonstrated release of large amounts of Mb from reperfused myocardium; in contrast, smaller amounts of Mb were released both from skeletal muscle rendered ischemic by hypotension and from myocardium rendered ischemic by coronary occlusion without reperfusion. In group 1 dogs, arterial Mb rose rapidly immediately after reperfusion, with peak Mb occurring 108±24 minutes (mean±SEM) after vessel reopening. In group 2 and group 3 dogs, arterial Mb rose more slowly, such that peak Mb was not reached within 8 hours in 11 of 12 animals [50].

Spangenthal et al.'s study differs from other myoglobin-related reperfusion studies. Because it indicates that, Mb kinetics allows early identification of coronary reperfusion after myocardial injury even in the presence of significant systemic hypotension. There is a difference between hypotensive and normotensive samples. Time to peak Mb after reperfusion is longer in hypotensive animals (108±24 minutes) than in normotensive animals (25±2 minutes). However, the rate of rise in Mb concentration after reperfusion is not significantly different in the hypotensive animals of the present study (slope, 51±16 ng $\cdot$ mL^{-1} $\cdot$ min^{-1}) than in earlier normotensive animals (slope, 70±13 ng $\cdot$ mL^{-1} $\cdot$ min^{-1}, P>.50) [50].

Direct monitoring of myoglobin efflux during ischemia and reperfusion has been limited because of inherent sample collection problems in the ischemic region. Recently, the cardiac dialysis technique offered a powerful method for monitoring myocardial interstitial levels of low-molecular-weight compounds in the cardiac ischemic region. In Kitagawa et al.'s study, they implanted a dialysis probe in the left ventricular free wall in anesthetized rabbits. The main coronary artery was occluded for 60 or 120 min. They examined the effects of myocardial ischemia and reperfusion on myocardial interstitial myoglobin levels. They saw that, interstitial myoglobin increased within 15 min of ischemia and continued to increase during 120 min of ischemia, whereas blood myoglobin increased at 45 min of ischemia. At 60 min of ischemia, reperfusion markedly accelerated interstitial myoglobin release. The interstitial myoglobin level was fivefold higher at 0-15 min of reperfusion than at 60-75 min of coronary occlusion. The dialysis technique permits earlier detection of myoglobin release and separately monitors myoglobin release during ischemia and reperfusion [51].

Myocardial interstitial myoglobin levels can serve as an index of myocardial injury that is evoked by ischemia or reperfusion.

Lactate Dehydrogenase

Lactate dehydrogenase catalyses the conversion of pyruvate to lactate. Even a small increase in serum level of LDH is an indicator of cell damage. Because intracellular LDH levels are more than 500 fold from serum [52]. LDH has five isoenzymes (LDH1, LDH2, LDH3, LDH4 and LDH5). The cardiac muscles are rich in LDH1 and LDH2 (LDH1> LDH2). LDH1 isoenzyme is normally found in the heart muscle and LDH2 is found predominantly in blood serum. A LDH1 level higher than the LDH2 level suggests myocardial infarction. LDH1 is parallel to the total LDH activity and it begins to rise within 8-12 h after onset of the symptoms, and it reaches a peak value in 2-3 days and it remains elevated for 7-10 days before coming down to normal levels [53-55]. Until a near time, LDH was used as a myocardial injury marker. However, with the cause of low specificity, its use is discouraged. The low

specificity sources from its high level in progressive muscular dystrophy, myoglobinuria, leukemia, pernicious anemia, megaloblastic and hemolytic anemia and renal disease [56].

Ji et al. used adult male rats in their study. The experimental protocol was that: They made a slip knot around the left anterior descending coronary artery about 2-3 mm from its origin. After 30 min of ischemia, the slipknot was released, and the myocardium was reperfused for 3h. Blood samples were taken at the end of 3h of reperfusion and they measured the LDH levels. LDH levels were increased to 3,924+_437 UI/I in MI/R rats [57].

In licka et al.'s study, their I/R group (coronary recanalisation was provided by intravenous thrombolysis and percutaneous transluminal coronary angioplasty, or by both procedures) was including 23 patients. LDH activities were determined at 25 degree. And they accepted the upper limit of normal LDH, 220 IU/I at this warmth. They found mean LDH (max) level in this 23 patients 635,1 (IU/I) [41].

Thirty six healthy male rabbits were used in Wu et al.'s study. The major marginal branch of the left circumflex coronary artery was ligated. After 45 min, the ligature was released and the myocardium was reperfused for 180 min. They demonstrated that, the level of serum LDH slightly increased during ischemia and increased dramatically after reperfusion [58].

Karaca et al. studied in 80 male patients with good ventricular function undergoing elective first time coronary artery by-pass grafting (CABG) surgery. They measured the LDH levels before (LDH0), immediately after (LDH1) surgery and at post operative first day (LDH2) of surgery. LDH0: 211,22+_18,95, LDH1: 235,12+_26,84, LDH2: 313,80+_36,99 were found in the measurements [59].

We can clearly see the different levels of enzymes between before reperfusion and after reperfusion. Consequently, LDH can be used as an I/R marker.

Aspartate Aminotransferase

Aspartate aminotransferase was defined as a biochemical marker for the diagnosis of AMI in 1954 [60]. AST is a member of the transaminases. It catalyses the transfer of amino and keto groups between alpha-amino acids and alpha-keto acids thereby acquiring the term transferase. AST is found in the liver, heart, skeletal muscle, and some other organs. Most of AST is in the liver and then in the heart [61]. So after damage of these organs, its serum level increases. The amount of AST in the blood is directly related to the extent of the tissue damage. It is not cardiac specific. AST has two isoenzymes. One of them is cytosolic isoenzyme (cAST), derives mainly from red blood cells and heart, and the other one is mitochondrial isoenzyme (mAST), is presented mostly in the liver. 8-12 h after the onset of the myocardial ischemia, AST begins to rise and peaks within 1-2 days. It returns to normal limits within 3-6 days [53].

Panteghini et al. examined the AST isoenzymes' activities in serum of 28 patients with myocardial infarction who were to receive intracoronary urokinase (reperfusion group) and conventional therapy (non reperfusion group-to control). Peripheral venous blood was sampled for determination of AST isoenzymes in the serum of both groups. cAST activity increased immediately after recanalisation, reaching a maximum 12 h after the onset of infarction. In the conventional therapy received group, this peak was reached 28 h after the onset. Peak cAST activity was similar in both groups. Peak time and peak activity for mAST were the same for the two groups of patients. There may be some advantages to measuring mAST, which is briefly influenced by reperfusion, instead of the usual cytosolic enzymes for assessment of myocardial damage in patients with myocardial infarction treated with thrombolytic therapy [62].

In the "Investigation of myocardial tissue injury and oxidant stress during by-pass" named study of Taskiran et al., they measured the AST activity. 22 patients with elective coronary by-pass grafting were included to study. After cardiac arrest, a part of operation procedure, was provided, all distal anastomosis are made under cross clamp and proximal anastomosis was made under a clamp on the aorta. For the biochemical analyses before operation from radial artery (T0) and during coronary by-pass at five different times (T1: The sample received from coronary sinus before surgery (coronary basal condition) , T2: Before clamp on aorta was lifted? (End of ischemia), T3: 5 min after clamp on aorta was lifted (early reperfusion), T4: 5 min after lateral clamp was lifted (absolute-exact? reperfusion), T5: 15 min after lateral clamp was lifted (late reperfusion)) from coronary sinus, blood was received. They analyzed and determined, serum AST levels are significantly increased after ischemia, and it remains elevated in all reperfusion periods. These symptoms, in their study, indicate us, during coronary by-pass, myocardial damage occurs, and this also indicates us damage begins in the ischemia period [63].

The Combined Studies

Enzymes used in the diagnosis of MI/R injury have different characteristics. According to the our aim we can use them. Our aim can include high specificity, early elevation or remaining elevated for a long time. To see the differences between these enzymes, investigators have done and are doing some combined studies. We wrote some of these studies in this section.

Zabel et al. done serial measurements of creatine kinase (CK), its isoenzyme CK-MB, Mb, and troponin T in 63 consecutive patients undergoing thrombolysis, to determine their value for the noninvasive prediction of

coronary artery patency. Blood samples were drawn every 15 minutes during the first 90 minutes, every 30 minutes during the first 4 hours, every 4 hours during the first 24 hours, and every 8 hours during the first 72 hours. The perfusion status of the infarct-related artery was assessed angiographically 90 minutes after initiation of thrombolysis. For each marker, time to its peak concentration and its early initial slope were determined. When myoglobin slope was assessed together with other clinical reperfusion markers (resolution of chest pain or ST segment elevation, occurrence of reperfusion arrhythmias) by logistic regression analysis, only the myoglobin slope was an independent predictor of coronary artery patency. In conclusion, with regard to noninvasive prediction of coronary artery patency after thrombolytic therapy, measurement of the early initial slopes of the serum markers within only 90 minutes after the initiation of therapy is as accurate as the determination of the time to their peak concentration. Compared with the other markers examined, myoglobin appears to have advantages because of its earlier rise [64].

The early peaking of enzymes in reperfused patients can be used as a marker for thrombolysis. Kwong et al. measured activities of some enzymes in serum after therapy with intracoronary streptokinase in acute myocardial infarction. They followed the enzymes in 14 patients. In the 10 patients, thrombolysis was successful and in the other 4 not. Serum CK activities of patients in the reperfused group were highest 12.8+_5.3 h after the onset of symptoms, 9 h earlier than the 21.6+_3.9 h for those patients who did not reperfuse. The mean maximum rate of increase of CK in the reperfused group was more than threefold that in the non-reperfused group. The other enzymes followed the same trend as CK. However, LDH peaked significantly later than CK [20].

According to the study used I/R procedures, enzyme wash out appears to be a general phenomenon for cardiac enzymes. The release of liver AST, the result of poor hepatic perfusion after myocardial infarction, makes it a less specific marker. LDH is similarly nonspecific. Moreover, the later peaking of LDH (25 h) is also a disadvantage [21].

Conclusions

Myocardial ischemia is an absolute or relative decrease in the blood supply, a shortage of oxygen, glucose and other nutrients. Ultimately, this can cause severe damage because of the potential for an accumulation of metabolic wastes. The restoration of blood is called reperfusion. The reperfusion is important to maintain the liveliness of ischemic tissue. However, the reperfusion can lead to an increase in enzyme washout. To evaluate the effectiveness of PTCA or thrombolysis, these enzymes can be measured [7].

Use of various biochemical markers, including CK, troponins, Mb, LDH and AST has been investigated for noninvasive assessment of reperfusion.

Total CK, LDH and AST have low specificity. There are more specific alternative biomarkers. Because of its high sensitivity and superior tissue specificity compared with the other available biomarkers of necrosis, cardiac troponin is the preferred biomarker for the detection of myocardial injury. The advantage of cardiac troponin over other biomarkers of necrosis has been firmly established in clinical studies. Cardiac troponin provides a superior discrimination of myocardial injury when the concentration of CK-MB is normal or minimally increased. If cardiac troponin is not available, the second best alternative is CK-MB. Although total CK is a sensitive marker of myocardial damage, it has poor specificity due to its high concentration in skeletal muscle. Mb has some limitations due to the its high concentration in skeletal muscle. However, on account of its small molecular size and consequent rapid rise, it can be used a very early marker of MI. Clinical studies have shown that the combined use of myoglobin and a more specific marker of myocardial necrosis (cardiac troponin or CK-MB) may be useful for the early detection of MI [65].

Danase and Montagnana are claiming that after more than 60 years of research we have now come to a point when hs-cTN immunoassays should be considered as “the best there is”. However, with ongoing technological advances and increasing knowledge of the pathophysiology of myocardial ischemia, it seems premature to conclude that hs-cTn will also be “the best there will ever be” [32]. Assessment of biochemical markers will continue to have an important role in diagnosis of MI/R injury.

Conflict of Interest Statements

All authors declare that they have no conflicts of interest.

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