Advances in the study of heart attack markers

Yankun Xu [1], Mingxun Zang [2+], Zhenyu Song [2+], Lingyuan Kong [2+], Weiping Zhang [2], Tianyuan Fei [2,*]

[1] College of Pharmacy, Shandong University of Traditional Chinese Medicine, Jinan, Shandong Province 250355, China.
[2] College of Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan, Shandong Province 250355, China.

+There authors have contributed equally to this work and share first authorship

Abstract: Heart attacks are a highly prevalent and often life-threatening disease in modern society. Numerous studies have now shown that many biomarkers in blood have been identified as markers for the detection of heart attack and some are widely used in clinical practice, including protein-based and nucleic acid-based markers. With further research into the pathogenesis of heart attacks, new, simpler and earlier biomarkers have been identified. In this paper, we present a comprehensive review of the role of protein, nucleic acid and cytokine markers in the diagnosis of heart attack based on the pathogenesis of heart attack. It is expected that the discovery of markers based on heart attack will help in the clinical diagnosis of acute heart attack and provide some data to support the early detection and treatment of patients with sudden acute heart attack, thus improving the quality of life and long-term outcome of patients.

Keywords: Heart attack; biomarkers; clinical diagnosis; proteins; enzymes.

1. Heart attack and clinical diagnosis

Heart attack (generally referred to as acute myocardial infarction) is an acute condition in which myocardial necrosis is caused by acute,persistent ischaemia and hypoxia in the coronary arteries,resulting in impaired cardiac function. It is characterised by severe and persistent retrosternal pain,fever,increased leucocytosis, increased erythrocyte sedimentation rate, increased serum myocardial enzyme activity and progressive electrocardiographic changes,and can be complicated by arrhythmias,shock or heart failure,which can often be life-threatening. The pathophysiology of the infarcted myocardium is variable and,according to the pathological description,infarction is defined as the death of myocardial cells as a result of prolonged ischaemia. Early in the course of an acute infarction,the infarcted myocardium is thinned and dilated locally as a result of myocardial necrosis leading to an inward flow of inflammatory cells,including an influx of macrophages and other antigen-presenting cells leading to destruction of the collagen scaffold. These pathological changes that occur early in the development of an acute infarction,3-4 d,will have a significant impact on the evolution of the infarction into heart failure[1] . Heart attacks are a highly prevalent and often life-threatening condition in modern society. In recent years,the incidence of heart attack has been increasing year by year and the mortality rate is high,posing a serious threat to the life and health of the middle-aged and elderly,and posing a great risk to human life and health security.

The factors involved in the development of heart attacks are complex and varied. The following results were obtained through research and data analysis: (1) the incidence rate of men was significantly higher than that of women,and the age of onset was earlier than that of women; (2) the seasonal changes in autumn,winter and spring were the high incidence seasons for acute heart attacks; (3) the peak age group for acute heart attacks was 61-90 years old; (4) hypertension and diabetes were important risk factors for acute heart attacks; (5) there was a negative correlation between the level of education and the occurrence of acute heart attacks. negative correlation with the occurrence of acute heart attack. From the above results,we conclude that: (1) men are the priority group for heart attack prevention and treatment; (2) sudden temperature change is the critical period for heart attack prevention and treatment; (3) 60-90 years old is the critical age group for heart attack prevention,and there is a trend of forward movement; (4) prevention and treatment of diabetes is more important than prevention and treatment of hypertension for myocardial infarction; (5) humanistic care plays a very important role in the recovery of heart attack patients[2] .

The main clinical treatments for myocardial infarction are general pharmacological and nursing treatment, reperfusion myocardial intervention and coronary artery bypass graft treatment. There are various ways to treat myocardial infarction,but the general principle of treatment is to restore effective reperfusion to the myocardium as soon as possible,in order to save the dying myocardium,reduce the infarct size and improve cardiac

* Corresponding author: 1187608603@qq.com

function. Western medicine is more targeted and can restore effective reperfusion to the infarcted myocardium in a quicker time,which can significantly reduce the death rate of patients,but has more side effects and is more burdensome for patients; Chinese medicine has low side effects and can significantly improve the prognosis of heart attack patients,reduce their pain and improve their quality of life. At the same time,Chinese medicine can also play a preventive role in the occurrence of acute heart attack,which can reduce the incidence of heart attack. Therefore,it is important to continue to promote research on the treatment of heart attacks with Chinese and Western medicine in order to find a more economical,safe and efficient treatment method for heart attack patients. [3]

2. Overview of heart attack markers

A number of biomarkers in blood have been identified as markers for the detection of heart attacks and have been partially used in clinical practice,including proteins and nucleic acids. For example,myoglobin (MYO),creatine kinase (CK),creatine kinase isoenzyme (CK-MB),lactate dehydrogenase (LDH),aspartate aminotransferase (AST),alanine aminotransferase (ALT) aminotransferase (ALT),gamma glutamyl transferase (GGT),troponin T or I (CTnT/CTnI),lMiRNA,microRNA-1 (miR-1),alpha-hydroxybutyrate dehydrogenase (HBDH),lactate dehydrogenase (LDH),microRNA-874,matrix metalloproteinase-9,granzyme B level myoglobin (Myo),brain natriuretic peptide (BNP) and heart-type fatty acid binding protein (H-FABP). The correct use of heart attack markers has revolutionised the timely and accurate diagnosis of acute heart attacks and the monitoring of treatment outcomes. The combination of these infarction markers can compensate for the shortcomings of single tests and has a better clinical application. [4]

3. Protein

3.1 Glutamic oxalacetic transaminase

Glutathione transaminase (AST) is a protein-based marker that is high in the heart and is one of the cardiac enzymes that are frequently seen in patients with heart disease. The diagnostic sensitivity of AST markers generally tends to increase within 24 hours of the onset of chest pain in patients with AMI,and decreases after 48 hours. Abnormal blood biochemical markers of cardiac injury are an important diagnostic criterion for AMI and have received clinical attention for many years. Experts agree that factors that determine the characteristics of a biochemical marker associated with AMI include molecular size,intracellular distribution,release rate,half-life,and myocardial specificity. The traditional myocardial enzymes,AST,CK and LDH,are not specific to cardiomyocytes and are generally elevated in the blood only 6-8h after the onset of AMI and do not remain elevated in the blood for long,so their diagnostic sensitivity and specificity are not ideal[5] . The conclusion is that normal serum levels of glutathione are low. If the cells of the heart are damaged,this can cause the release of glutathione from the cell plasma into the blood,causing an increase in concentration. If glutathione is elevated,it can be used as an adjunctive test for myocardial infarction. However,glutathione is not found only in the heart muscle cells and therefore cannot be used as the sole indicator to detect the development of myocardial disease.

3.2 Lactate dehydrogenase

Lactate dehydrogenase (LDH) is a protein-based marker. LDH is found in small amounts in normal human plasma and is derived from tissue cells,but in some diseases the cells involved may release additional LDH into the blood or cerebrospinal fluid,so serum or cerebrospinal fluid LDH activity is commonly used to diagnose disease and administer medication. [6]LDH is one of the most important enzymes in the anaerobic enzymes of sugar and gluconeogenesis. It is widely found in the heart,liver,lung and other tissues of the body. H-subunit-containing LDH catalyzes HBDH,i.e. HBDH is the H-subtype of LDH,and this enzyme activity essentially represents the activity of LDl and LD2.[7] . Studies have shown that Heart Failure Combination (Astragalus membranaceus 30g,Scapularia scabra 15g,Morinda citrifolia 30g,Cinnamomum acuminata 15g,Poria 10g,Atractylodes macrocephala 10g,etc.) has a certain effect on apoptosis and lactate dehydrogenase release rate of hypertrophic cardiomyocytes,and Heart Failure Combination has the optimal dose[8] ,which is conducive to maintaining the normal life activity of cardiomyocytes. Lactate dehydrogenase starts to rise at 9-20h after myocardial infarction,reaches a peak at 36-60h and continues to return to normal for 6-10 days[9] ,so it can be used asAcute myocardial infarction Ancillary diagnostic indicators in the later stages.

3.3 Creatine kinase isoenzymes

Creatine kinase isoenzyme (CK-MB) is a protein-based marker. The isoenzymes of creatine kinase inClinical Diagnosis have great importance in various pathologies including Muscle atrophy and Myocardial infarction The level of creatine kinase in human serum increases rapidly when various lesions occur,and it is thought that measuring creatine kinase activity is more reliable than performing an ECG in the diagnosis of myocardial infarction. The traditional diagnosis of AMI relies on myocardial enzyme profiles,i.e. elevated creatine kinase (CK),glutamate aminotransferase (AST),and lactate dehydrogenase (LDH),with the earliest increase being in CK,which has four isoenzyme forms: muscle (MM),brain (BB),miscellaneous (MB) and mitochondrial (MiMi). In myocardial infarction,creatine kinase is elevated within 6 h of onset and peaks at 24 h. Because CK-MB is found mainly in cardiac myocytes,it has the highest diagnostic specificity. However,the presence of a small amount of CK-MB in skeletal muscle also reduces the high specificity of CK-MB for the myocardium,but even if CK-MB is not elevated it does not exclude a small degree of myocardial injury.[10] The protective effect of deer antler peptide (VAP) on myocardial ischemia-reperfusion

injury in rats and its effect on creatine kinase isoenzyme (CK-MB) levels were shown to be due to the protective effect of VAP pretreatment on myocardial ischemia-reperfusion injury. This effect may be related to the activation of Nrf2/antioxidant response element pathway by VAP. To study the role of troponin I (cTnI),creatine kinase isoenzyme (CK-MB) and myoglobin (Mb) concentration monitoring in the diagnosis of acute myocardial infarction (AMI),serum concentrations of cTnI,CK-MB and Mb were measured by electrochemiluminescence in 45 patients with acute myocardial infarction at five time points after the onset of chest pain,and 45 healthy subjects were used as controls. The data were statistically analyzed to study their diagnostic value. The study concluded that the simultaneous detection of cTnI and CK-MB serum markers is important for the early diagnosis of AMI and can help improve the prognosis of patients. The importance of creatine kinase isoenzymes for their physiological functions and clinical applications has attracted much attention and in-depth research.

3.4 Myoglobin

Myoglobin (MYO),a protein marker,is an oxygen-binding haemoglobin protein found mainly in cardiac and skeletal muscle tissue. Clinical studies have shown that MYO in the blood of patients with acute myocardial infarction begins to rise within one to two hours of the onset of chest pain,with the peak occurring approximately six to seven hours after the onset of chest pain,and then returns to normal after one day. However,myoglobin is less specific,and MYO may also increase in the presence of skeletal muscle disease and renal dysfunction. Therefore,as with myocardial enzyme profiles,there is some error in using MYO as an early diagnostic indicator of acute myocardial infarction. Elevated serum MYO levels result fromSkeletal muscle and/or Cardiac muscle cells release of injury (lysis/necrosis) into the circulation. Serum MYO is <70ng/ml and levels vary according to age,gender and ethnicity. Myocardial infarction MYO can be detected in the serum early afterwards,with a peak occurrence time (1-2 hours) that is longer than Creatine kinase (MYO has a small molecular weight and is easily excreted in the urine. Serum MYO levels increase rapidly after reperfusion therapy and have been used as a useful indicator to assess the success of reperfusion therapy or the size of myocardial infarction,but because of the short half-life of MYO (15 minutes),serum MYO levels that do not increase 6 to 12 hours after the onset of chest pain can help to exclude Acute myocardial infarction . Also,because MYO levels are elevated for a short period of time (<24 hours),MYO measurement can be useful in the course of an acute myocardial infarction to see if there is reinfarction or infarct extension. Frequent increases in MYO levels suggest that the original myocardial infarction is still ongoing. It should be noted that MYO is also a component of skeletal muscle and lacks specificity,so the clinical value of a series of MYO measurements after myocardial infarction is limited. In patients with chest discomfort with non-diagnostic ECG findings,the diagnosis of acute myocardial infarction cannot be made by Mb alone within the first 4-8 hours of onset,but needs to be supplemented by more specific tests such as CK-MB or Cardiac troponin . In summary,MYO can be used as an important clinical indicator for the diagnosis of myocardial infarction,but has certain drawbacks.

3.5 Gamma-glutamyltransferase

Gamma glutamyl transferase (GGT)[11] ,is a cell surface enzyme that cleaves extracellular glutathione (G-SH) or other γ-glutamyl compounds,whose main role is the availability of amino acids such as cysteine,the maintenance of G-SH homeostasis and the defence of the body against oxidative stress. Studies have confirmed[12-13] ,that serum GGT levels are strongly associated with cardiovascular diseases such as coronary heart disease,stroke and acute myocardial infarction,and that patients with high serum GGT levels have higher mortality rates. Inflammatory factors and oxidative stress can trigger an increase in GGT levels. GGT levels begin to rise 5-7 d after acute myocardial infarction (AMI) and reach a peak at 2-3 weeks. In myocardial potassium channel remodeling after myocardial infarction,GGT can regulate potassium channel function by mediating the deregulation of transient outward potassium current (Ito) channels by reduced glutathione (GSHo)[14] ,whose catalytic breakdown of GSHo reverses myocardial electrical remodeling. It is therefore hypothesized that the upregulation of GGT activity and elevated expression in myocardial infarction is a cellular compensatory mechanism to protect the protein from irreversible oxidative damage. irreversible oxidative damage.
Since the compensatory mechanism related to GGT is the result of compensatory proliferation during myocardial repair,GGT can be used as an infarction marker,and since AMI causes minimal changes in serum levels of GGT,GGT activity and its mRNA and protein expression can be measured to facilitate more effective clinical management of myocardial infarction.

3.6 Alanine aminotransferase

Alanine aminotransferase (ALT)[15] ,is a pyridoxal enzyme that catalyzes the reversible conversion of L-alanine and 2-oxoglutarate to pyruvate and L-glutamate. The human ALT isoenzyme is localized in the cytoplasmic lysosomes (c-ALT) and mitochondria (m-ALT) of tissues such as liver and heart muscle. ALT has been formally described since 1957 and was also an early serum marker thought to be associated with heart attacks,but since liver injury also leads to elevated serum levels of ALT,ALT is more commonly used as an indicator of liver damage. Jin Ming et al.[16] ,by measuring the levels of myocardial injury markers in the serum of AMI patients and normal subjects,found that the serum levels of ALT in AMI patients were about 1.7-8.0 times higher than those in normal subjects. The mechanism is that after the onset of AMI,patients suffer from myocardial necrosis and liver injury,which increases the permeability in cardiomyocytes and hepatocytes,and the intracellular plasma ALT is released and enters the bloodstream,resulting in increased serum levels of ALT in

patients The result is an increase in serum ALT levels. As liver injury such as cirrhosis and liver cancer can also lead to an increase in serum ALT levels[17] ,the diagnosis of whether a patient is suffering from myocardial infarction needs to be made with reference to ALT and other indicators.

3.7 Alpha-hydroxybutyrate dehydrogenase

Alpha-hydroxybutyrate dehydrogenase (HBDH)[18] ,mainly found in human heart muscle,liver,kidney and red blood cells,reflects the activity of LDH1 and LDH2,and because it is most abundant in the heart muscle,ischemia,hypoxia and necrosis of heart muscle cells can lead to the release of HBDH into the blood,and HBDH is present in the blood for a long time. The presence of HBDH in the blood for a long period of time makes it a marker of myocardial infarction,and it has been shown that HBDH can determine the size of the infarct in the early stages of myocardial infarction. Li Jing et al.[19] ,by measuring HBDH levels in acute ST-segment elevation myocardial infarction (STEMI),determined that HBDH was positively correlated with STEMI and that HBDH could effectively reflect the onset and progression of STEMI. Silvia Lee et al.[20] ,by investigating HBDH levels in stable patients undergoing subinguinal angioplasty and stenting,determined that HBDH was associated with postoperative atherosclerotic thrombosis. atherosclerotic thrombosis,i.e. HBDH is predictive of ischaemic outcome.

4. RNA class

In recent years,circulating miRNAs in blood have emerged as potential biomarkers for the diagnosis or prognosis of heart attack disease due to their stability and specificity in plasma. Numerous studies have confirmed the fact that miRNAs leak from the heart into the circulatory system after myocardial injury,during which miRNA expression is elevated and dynamic. Circulating miRNAs are stable and can be detected by real-time PCR. These miRNAs that are abundant in the heart,with four cardiac-enriched miRNAs (miRNA-208,miRNA-499,miRNA-1 and miRNA-133) are increasing in the plasma of patients[21] . In a study involving a total of 424 patients,miRNA-208b and miRNA-499 were expressed at higher levels in patients with myocardial infarction than in non-myocardial infarction patients and correlated well with cardiac troponin. The use of MiRNA as an infarct marker may improve the diagnostic accuracy and improve the use of serum troponin as a diagnostic indicator for AMI,whose delayed release time leads to lower sensitivity. Among these,MicroRNA-1 (miR-1) is expressed mainly in cardiac and skeletal muscle and is divided into two isoforms,miR1-1 and miR1-2,both of which share the same sequence but are encoded by two different genes on chromosomes 18 and 20,respectively. In rats,circulating miR-1 levels increased rapidly 1 hour after ligation of the coronary artery and peaked 6 hours after acute myocardial infarction,200-fold above baseline. miR-1 returned to basal levels 3 days after acute myocardial infarction and its expression was elevated earlier than traditional early AMI biomarkers (e.g. troponin)[22,23,24] . In a small clinical trial consisting of 31 AMI patients and healthy controls,serum miR-1 levels were elevated nearly 100-fold 6 hours after myocardial infarction. In a clinical trial consisting of 159 patients with AMI and healthy controls,serum miR-1 levels were significantly elevated in patients with AMI[25] . In a trial by Y. Cheng et al. applying an ischemic preconditioning model showed that ischemic preconditioning significantly reduced miR-1 and myocardial changes due to circulating ischemia-reperfusion injury,further demonstrating that miR-1 levels were significantly positively correlated with the area of myocardial infarction and significantly positively correlated with serum CK-MB. In conclusion,circulating miR-1 may be a new,non-invasive and sensitive biomarker for the diagnosis of acute myocardial infarction[26] .

5. Cytokine class

Because acute myocardial infarction is an injury caused by acute occlusion of coronary vessels following rupture of an atherosclerotic plaque,the superimposed thrombus at the lesion obstructs the blood supply to the myocardium,causing myocardial necrosis and ischemic inflammation. The immune response plays an important role in the inflammatory response and the immune system can be involved in myocardial apoptosis through the release of inflammatory cytokines such as tumour necrosis factor and Fas ligand and granzyme B (GZMB) when an infarction occurs. Therefore,the regulation of GZMB expression is expected to be one of the future targets for the treatment of acute myocardial infarction.

References

1. TANG Xuan,XI Yujie,GUO Feifei,YANG Hongjun. Overview of the disease evolution of "heart attack-heart failure" and progress in the study of the dynamic molecular network of the disease[J]. Chinese Journal of Experimental Formulation, 2022, 28(08):255-264. DOI: 10. 13422/ j.cnki. syfjx. 20211774.
2. Hu Donggen. A retrospective analysis of factors in the development of 532 patients with acute heart attack in a community[J]. Anhui Medical Medicine,2012,16(7):967-969.DOI:10.3969/j.issn.1009-6469.2012.07.037.
3. Tao QF,Xu JX. Research progress in the clinical treatment of acute myocardial infarction[J]. Popular Science and Technology,2022,24(07):80-83
4. Chen W B,Pan X L,Kang X X. Diagnostics [M]. 6th ed. Beijing: People's Health Publishing House, 2004:522-525.
5. Su HW,Li D,Li Y,Li NX. Comparison of acute myocardial infarction serum markers--creatine kinase and creatine kinase isoenzyme and glutamate transaminase for clinical applications[J]. Chinese Journal of Geriatric Cardiovascular and Cerebrovascular Diseases,2004(06):417.

6. HONG Qingtao,SONG Yue-tao,TANG Yipeng,LIU Chun-mei. Colorimetric determination of lactate dehydrogenase leakage rate from cell culture fluid and its application[J]. Journal of Cell Biology,2004(01):89-92.
7. WANG Lina,SONG Yanrong,SHI Jun. Differential diagnostic value of hydroxybutyrate dehydrogenase/lactate dehydrogenase in myocardial injury and liver injury[J]. China General Clinical,2006(02):128-129.
8. Tong T,Shang JJ,Xie XINR,Liu WEIH,Liu HX. Effect of heart failure combination on apoptosis and lactate dehydrogenase leakage rate in hypertrophic cardiomyocytes[J]. Chinese Journal of Traditional Chinese Medicine,2013,28(10):3086-3088.
9. Practical testing and clinical,Heilongjiang Science and Technology Press,2017.07,72
10. Liang ZH,Deng JD,Gu WX,Chen JJ. The role of troponin I (cTnI),creatine kinase isoenzyme (CK-MB),and myoglobin (Mb) concentration monitoring in the diagnosis of acute myocardial infarction (AMI)[J]. China Pharmaceutical Guide, 2013, 11(19):14-15.DOI:10.15912/j.cnki.gocm.2013.19.293.
11. Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci. 2001 Aug;38(4):263-355. doi: 10.1080/20014091084227. PMID: 11563810.
12. Mohapatra E,Priya R,Nanda R,Patel S. Serum GGT and serum ferritin as early markers for metabolic syndrome. J Family Med Prim Care. 2020 Jul 30;9(7): 3458-3463. doi: 10.4103/jfmpc.jfmpc_570_20. PMID: 33102313; PMCID: PMC7567201.
13. Ndrepepa G,Colleran R,Kastrati A. Gamma-glutamyl transferase and the risk of atherosclerosis and coronary heart disease. clin Chim Acta. 2018 Jan ;476:130-138. doi: 10.1016/j.cca.2017.11.026. epub 2017 Nov 23. pmid: 29175647.
14. Zheng MQ,Liu G,Guo JH.Role of γ-glutamyl transpeptidase in the mechanism of myocardial Ito channel remodeling in rats with myocardial infarction[J]. Journal of Clinical Cardiovascular Diseases,2013,29(03):179-183.DOI:10.13201/j.issn.1001-1439.2013.03.015.
15. Sakagishi Y. [Alanine aminotransferase (ALT)]. Nihon Rinsho. 1995 May;53(5):1146-50. japan. pmid: 7602770.
16. JIN Ming,CAI Zhenzhen,WANG Ningning,CAI Qibo,QIU Changchun. Diagnostic value analysis of myocardial injury markers in patients with acute heart attack[J]. Journal of Qiqihar Medical College,2021,42(12):1024-1027.
17. Wu CH,Liu A-Z,Qian Y,Chen Y. Clinical observation of ST-segment elevation myocardial infarction with acute liver damage [J]. Chinese Community Physician,2021,37(19):67-69.
18. Wang HJ,Cheng ZP. Changes and significance of blood α-hydroxybutyrate dehydrogenase in patients with AMI[J]. Zhong Yuan Medical Journal,1997(11):50.
19. Li J,Huang X,Jiang YZ,Luo FX,Mao ZW. Clinical significance of combined detection of RBP4,hs-CRP and α-HBDH in acute ST-segment elevation myocardial infarction[J]. Journal of Tropical Medicine,2021,21(02):238-242.
20. Lee S,Koppensteiner R,Kopp CW,Gremmel T. α-Hydroxybutyrate dehydrogenase is associated with atherothrombotic events following infrainguinal angioplasty and stenting. Sci Rep. 2019 Dec 3;9(1):18200. doi: 10.1038/s41598-019-54899-0. PMID: 31796860; PMCID: PMC6890648.
21. Song,T.; Liang,H.,Synchronized assembly of gold nanoparticles driven by a dynamic DNA-fueled molecular machine.JAm Chem Soc 2012,134(26),10803-6.
22. Jaffe AS,Ravkilde J,Roberts R,Naslund U,Apple FS, Galvani M,Katus H: It's time for a change to a troponin Standard. Circulation 2000,102:1216-1220.
23. Wang GK,Zhu JQ,Zhang JT,Li Q,Li Y,He J,et al. Circulating micro RNA: a novel potential biomarker for Early diagnosis of acute myocardial infarction in humans. Eur Heart J. 2010;31:659-66.
24. Cheng Y,Tan N,Yang J,Liu X,Cao X,He P,et al. A translational study of circulating cell-free micro RNA-1 inacute myocardial infarction. clin Sci (Lond). 2010; 119:87-95.
25. Y. Cheng,N. Tan,J. Yang et al. "A translational studyof circulating cell-free micro RNA-1 in acute myocardial infarction," Clinical Science,vol. 119,no. 2,pp. 87-95,2010.