Sri Lanka Journal of Medicine **SLJM**

Perspective

Citation: Ralapanawa U, 2021.Coronary Heart Disease: Historical Perspective. Sri Lanka Journal of Medicine, pp 22-29.
DOI: http://doi.org/10.4038/sljm.v30i2.320

Coronary Heart Disease: Historical Perspective

Ralapanawa U

Department of Medicine, University of Peradeniya, Sri Lanka

Correspondence: *Ralapanawa U*
Professor in Medicine, Senior Consultant Physician, Department of Medicine, University of Peradeniya, Sri Lanka
E-mail: udayapralapanawa@yahoo.com
: https://orcid.org/0000-000207416-7984

Abstract

Cardiovascular disease is the leading cause of mortality and morbidity worldwide. The 2011 annual report from the World Health Organization mentioned that, coronary heart disease and cerebro-vascular disease which were reported as the top two causes of mortality in 2004, are predicted to remain the major cause of death in the next 20 years. Coronary heart disease(CHD) and atherosclerosis were once thought to be a disease of modern humankind linked to modern lifestyle. However, researchers dispute this and has confirmed that atherosclerosis was common in preindustrial inhabitants too. Further, vascular system studies of mummies give substantial evidence of atherosclerosis as ancient human disease and clinical syndrome of angina pectoris existed in ancient Egypt. In 1768 the paper presented at the Royal College of Physicians in London on "Some account of a disorder of the breast" was an eye opener to medical professionals and later this excruciating "disorder of breast" was linked to the "hardening of the arteries''. In the past it was generally believed that MI virtually always resulted in death and identified in postmortem. In1878, the first case of coronary occlusion diagnosed during life was described. ECG was used to diagnose the condition in 1912 and the use of current 12-leads ECG became accepted practice since the 1950s. In addition to clinical evaluation and ECG, cardiac biomarkers play a pivotal role in diagnosis and management of acute coronary syndrome. Aspartate aminotransferase became the first biomarker used to diagnose and subsequently CK-MB isoenzyme, lactate dehydrogenase and myoglobin played very significant roles. Troponin is now considered the 'gold standard' biochemical test for the diagnosis. The definition, diagnosis, management and prognosis of coronary heart disease have changed over the decades with the development of medical science and knowledge. It is therefore interesting to appraise the historical aspect of evolution of CHD definitions and diagnosis. Moreover, clinicians should have updated knowledge on the evolution of definition, diagnosis, management and prognosis of this condition.

Keywords: *Coronary heart disease, Cardio vascular disease, Acute coronary syndrome, Historical, Bio markers*

INTRODUCTION

Cardiovascular disease (CVD) is the major cause of mortality and morbidity worldwide. The 2011 annual report from the World Health Organization (WHO) highlighted the mortality rate prediction of the population worldwide that, in 2030, CVD will become the major cause of deaths, and the mortality rate will be higher than infectious diseases such as human immunodeficiency virus

Received: 2021-11-11 **Accepted: 2021-11-25** **Published: 2022-01-25**

(HIV), tuberculosis, malaria[1]. Moreover, this report also mentioned that, among CVD, coronary heart disease (CHD) and cerebro-vascular disease (CeVD), which were reported as the top two causes of mortality in 2004, are expected to continue to be the major cause of death in the next 20 years[1]. Every year around 32 million people suffer from acute coronary and cerebral events and approximately 50% of these occur in people with established CHD and CeVD[2]. According to a WHO report on non-communicable diseases in 2018, 17.9 million people die from CVD annually[3]. As per WHO report, in 2016 total population in Sri Lanka was 20 798 000, while there were 143 000 deaths. About 34% of those deaths were due to CVD[3]. The definition of CHD, its diagnosis, management and prognosis changed over the decades with the development of science and medical knowledge. Hence it is interesting to evaluate the historical aspect of evolution of definitions and diagnosis of CHD. Moreover, clinicians should have updated knowledge on the definition of CHD, its diagnosis, management and prognosis

METHOD

During the literature search, a variety of search techniques were used to identify potentially relevant papers published from 1950 to 2021. The author conducted his searches manually and used a variety of sources, including high-impact journals, libraries (Elsevier ScienceDirect and Wiley) and internet databases (Medline, PubMed, ISI, IBSS, and Google Scholar). Additional articles were found in the reference lists of identified studies, review articles and meta-analyses. During the search, the following Medical Subject Headings (MeSH) and keywords were used alone or together: Ischaemic heart disease, Acute coronary syndrome, CHD, biomarkers, historical aspect of CHD. The author's first study selection was based on title and abstract screening followed by full-text screening of shortlisted articles. Letters, editorials, conference abstracts, and comments were all eliminated, as were publications in languages other than English. The articles were then re-evaluated for relevancy and duplicate content. After reading all of the pre-selected publications, the data abstraction was done. Abstracted details were noted down in details and it was decided then which pieces of data have values in writing this review. The information was organized into relevant categories and subcategories. Associations and relevance among data sets were identified and explored in detail and interpretations were made.

Historical background of Coronary Heart Disease

CHD is initially considered as a disease of modern human and aetiology was attributed to present-day lifestyle[4]. Also atherosclerosis is considered by many to be a modern disease related to modern lifestyle[5]. Study done by *Thompson et al* disputes this and confirms that atherosclerosis was common in four preindustrial inhabitants, including preagricultural hunter-gatherers[5]. Thompson and team studied 137 mummies from different geographic locations, with modern Computed Tomography (CT) Scanning to assess the degree of vascular calcification[5]. Calcium is considered as the universal component of a mature atherosclerotic plaque and is pathognomonic to atherosclerosis[6]. The population studied spanned > 4000 years from ancient Egypt, ancient Peru, the Roman Era, southwest America and Aleutian Island of modern-day Alaska[5]. Out of the 137 mummies, 47 (34%) revealed presence of atherosclerosis and authors concluded that that disease was common in premodern humans too[4,5].

In addition to radiological studies on mummies, several researchers have studied the vascular system of the mummies histologically[7]. These vascular system studies of mummies give ample evidence of atherosclerosis as ancient human disease[7]. Contributions done on this regards by Czermak (1852), Shattock (1909), Elliot Smith (1912), Ruffer (1921), Long (1931) and Shaw (1938) are important evidence of the disease[7]. In particular Long examined coronary arteries of a female Egyptian mummy of the 21th dynasty which showed calcification of one mitral cusp and thickening with calcification of coronary arteries[7]. The mummy of King Meneptah, a famous Pharaoh was unwrapped in 1907 by Elliot Smith. He described “the aorta of King Merneptah was affected with severe atheromatous disease with large calcified patches which was confirmed histologically by Shattock[7,8,9].

When there is obstruction to coronary blood flow patient develops chest pain called angina pectoris.

An ancient medical document known as the Ebers Papyrus has the following paragraph illustrating angina pectoris[4].

"Shouldst though examine a patient with stomach disease suffering from pain in the arms, the breast, and on the side of the stomach, say: 'Death threatens." And if though examinst a man for illness in his cardia, and he has pains in his arm, in his breast, and in side of his cardia, and it is said of him: It is due to something entering the mouth it is death that threatens him. Thou shalt prepare for him: Stimulating herbal remedies…" [4].

As such, clinical syndrome of angina pectoris existed in ancient Egypt. In the 7th century, the poem written by Qais accurately but incidentally describe angina pectoris as "My heart is firmly seized by a bird's claws; My heart is tightly squeezed, When Lila's name flows". An Arab cardiologist, Dr.H.A.Hajar Albinali claimed that this is the first clear and best description of angina in the history of Medicine[4,10]. In the 17th-19th century in Europe, it was customary to refer angina pectoris to William Heberden[4]. In 1768 the paper presented on "Some account of a disorder of the breast" at the Royal College of Physicians in London, was an eye opener to medical professionals[4].

In 18th century, John Hunter, Scottish surgeon and anatomist was the first in Europe who highlighted the effect of emotion in precipitating an angina. He died suddenly after a dispute with a colleague and the autopsy revealed marked atheroma in coronary[4]. However during this period, physicians showed pathological interest mainly and continued to illustrate coronary lesions on pathology specimen without correlating those to clinical features[4]. But Edward Jenner (1729-1823) and Celeb Parry (1755-1822) could link the excruciating "disorder of breast" to the "hardening of the arteries"[4]. Knowledge about atherosclerosis was growing by this time in Europe. In 1856, Rudolf Virchow, the "father of pathology", named the pathological elements in thrombus within the vascular system. Since this description, scientists began to study clinical implications of CHD more seriously[7,11,12,13] .The pathologist Ludvig Hektoen, in 1879 confirmed that MI is caused by coronary thrombosis secondary to sclerotic changes in the coronary arteries[4]. In 1910,two Russian clinicians described five patients with the clinical picture of acute MI which was confirmed at autopsy[4] .

In the past it was generally believed that MI virtually always leads to death. In1878, Hammer described a case of a patient in whom thrombotic occlusion of a coronary artery was suspected. This was the first case of coronary occlusion diagnosed during life[14,15]. Autopsy of this case revealed aortic valve endocarditis vegetation has blocked the orifice of the right coronary artery[14].In 1910, Obrastzow and Straschenko described several cases of MI whom the diagnosis was made during life. Though post mortem confirmation was not obtained, their clinical picture of "status anginosus" together with breathlessness was quite consistent[16]. In 1912, Herrick described 6 patients with myocardial infarction who died later and coronary thrombi were detected at autopsy in all of them[16,17].

In 1912, James Herrick stressed the need of bed rest and used ECG to diagnose the condition[4,18]. Another milestone of CHD is the invention of cardiac catheterization. In 1956, the Nobel prize in Physiology or Medicine was awarded jointly to three investigators namely, Werner Forssman, Andre Frederic Cournand and Dikinson Richards for their discoveries concerning cardiac catheterization and pathological changes in the circulatory system[4,18] . The introduction of coronary care unit (CCU) by Desmond Julian in 1961 in Great Britain improved the management of cardiac patients by reducing the mortality from 30% to 15% in the first hour of evaluation[4,19]. With great advancement of cardiovascular research and experiment a steady decline in CVD mortality over the late 20th and early 21st centuries was observed[18].

Evaluation of diagnosis of acute coronary syndrome

The term acute coronary syndrome (ACS) illustrates a range of conditions as a consequence of acute myocardial ischaemia. It comprises unstable angina (UA), non-STE-myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). ACS is often the first presentation of CHD and frequently presents first to primary health care physician[20].

In 1901, Einthoven introduced a "string galvanometer" by which the electrical activity of the heart could be recorded quantitatively. In 1902 Einthoven published the first electrocardiogram recorded by his string galvanometer. In 1924 for his invention Einthoven won the Nobel Prize[21,22].The use of current 12-leads ECG with 3 unipolar, 3 bipolar limb leads and 6 unipolar chest leads became accepted practice since the 1950s[21].The temporal changes in ST segment morphology during myocardial ischaemia and infarction were first described by Pardee in 1920[21]. At first, his findings did not gain complete acceptance. In 1928 the situation was clarified when Parkinson and Bedford described the serial ECG changes in acute and healing phase of MI[21].

The ECG is the most important tool in the initial evaluation and triage of patient in whom an ACS is suspected. Obtaining an ECG by emergency medical services personnel at the site of first medical contact with a patient will make a diagnosis in the majority of patients and allows early commencement of the management. ECG will guide the treating physicians regarding appropriate treatment of a suspected patient with ACS and its complications. ECG is incorporated into emergency department triage system in managing ACS patients[23]. Like most clinical tests the ECG gives both false-positive and false-negative results. A false positive result is exemplified by an apparently abnormal ECG in normal subjects. False negative results, on the other hand, occur when the ECG fails to show evidence of cardiac abnormality when it is really present. Current 12 leads ECG has limited sensitivity (30-70%) and specificity (70-100%) in detecting STEMI. The diagnostic value of ECG was not sufficient to detect small infarction and all reinfarctions[23]. Apart from clinical evaluation and ECG, cardiac biomarkers play a pivotal role in diagnosing and management of ACS.

Evolution of Biomarkers in acute coronary syndrome

Aspartate aminotransferase

Aspartate aminotransferase (AST) became the first biomarker used in the diagnosis of acute MI[24,25,26].In 1954,elevated activity of AST was reported in patients with MI[27,28].AST was extensively used in the 1960s and was incorporated into the WHO definition of acute MI[24,26].

Cytosolic (soluble) AST (s-AST or s-GOT) and mitochondrial AST (m-AST or m-GOT) respectively increased 6.0 hours and 9.0 hours after onset of chest pain[29,30]. Fleisher et al first reported detecting m-AST in the serum from 3 patients with acute MI. Boyde likewise found this isoenzyme increased after infarction, reaching peak 24-48 hours later[29]. In 1957, Fernando De Ritis showed the value of the transaminase ratio(AST/ALT) in diagnosis of AMI. Djakpo et al showed that AST/ALT ≥2 has a strong association with total coronary occlusion[31].

Creatine Kinase and CK-MB

Creatine kinase (CK) is an enzyme that consists of 2 subunits M and/or B. CK has 3 different isoenzymes; CK-BB,CK-MB and CK-MM[32].CK-BB is present in large quantities in the brain and many internal organs.CK-MB is the heart specific isoenzyme and is present in large quantities in heart muscles but not specific to myocardium as it is present in skeletal muscles and other tissues[33]. CK has 90% sensitivity to diagnose acute MI. It is released within 12 hours after the onset of symptoms, peaks in serum at 24-36 hours, and returns to normal in 48-72hours[33].

Elevated total CK activity in MI was detected in 1960[33].Six-years later it was demonstrated that CK-MB isoenzyme activity was found to be a more specific indicator of myocardial injury than total CK activity[33]. Progress of analytical methods led to development of immunoassays that measure enzyme concentration instead of activity. Determination of CK-MBm (CK-MB mass) was introduced in the early 1990s, and it has gradually replaced CK-MB activity in the diagnosis of MI. The recent guidelines for the redefinition of acute MI recommend the use of CK-MBm as opposed to CK-MB activity[33].

Lactate dehydrogenase and its isoenzymes

Elevated activity of serum lactate dehydrogenase (LDH) in MI was first detected in 1956[34]. In 1973, Cohen et al demonstrated that a rise in the LDH1:LDH2 above 1 was seen in all their patients with MI, but not in patients with angina pectoris who did not have evidence of MI[35]. According to Roe et al rise in the LDH1:2 more than 1 confirms

the diagnosis of MI[35]. Wagner et al demonstrated 90% sensitivity and 95% specificity when they used the LDH 1:2 in combination with CK isoenzymes[35].

Following MI. An increase in serum LDH activity can be observed within 6-12 hours and reaching maximum at about 48 hours and it remains elevated for 4-14 days before decreasing to normal levels. LDH assay played very significant role in the diagnosis of acute MI for two decades, and were included as one of the diagnostic criteria to rule out acute MI by the WHO in 1970[24,26].

Myoglobin

Myoglobin is a cytoplasmic haem-protein with molecular weight of 17,800D. It involves in O_2 binding, transport and storage of O_2 in red muscles (skeletal and cardiac). In 1956, it was demonstrated that myoglobin was released after an acute MI. Later with the introduction of automated myoglobin analyses, it became possible to use myoglobin as an early marker for the detection of an acute MI in daily practice[33]. Myoglobin appears in the blood earlier after myocardial injury than any other marker available so far[33,36]. In 1994 Bhayana showed myoglobin is superior to CK-MB mass and TnT for ruling out acute MI within 3-6 hours of symptom onset[33]. Within 6 hours after the symptoms onset, the overall diagnostic sensitivity and specificity ranged from 77-97% and 90-97.9% respectively[33].

Troponin

Troponin (Tn) is a highly sensitive biomarker of myocardial injury and has been used extensively in hospitals for the diagnosis of acute MI and risk stratification of patient with ACS[37,38,39]. Since the initial first generation assays, fifth generation high-sensitivity Tn (hsTn) assays have been developed and are widely used at present[24,26].The third universal definition of MI defines acute MI as evidence of myocardial necrosis in a patient with the clinical features of acute myocardial ischaemia, and defines the 99th percentile of cardiac Tns as the decision value for acute MI[24,26,40]. The cardiac Tns are now considered the 'gold standard' biochemical test for diagnosis of acute MI[41]. Clinical assessment,12-lead ECG and cardiac Tn I or T form the diagnostic cornerstones of patients with acute chest pain[24, 26].

In 1946 Bailey in a letter to *Nature* first described the Tn complex, but it was the work by Ebashi et al that showed the contraction of striated muscle and not smooth muscle was regulated by a special protein complex, now known as the Tn located on actin filaments[41]. The Tn complex consists of 3 subunits; TnC, TnI and TnT[32,42].

There are commercially developed antibody assays specific for cTnT and cTnI, but such assays have not been developed for cTnC due to lack of cardiac specificity[42]. It is important to note that there is misunderstanding that troponin elevation is secondary only to myocyte injury and necrosis But elevated cTn has been observed in many other clinical conditions[24,26,43, 44,45].

TnT assays

In 1989, Katus *et al* introduced a specific enzyme-linked immunosorbent assay (ELISA) method using 2 monoclonal antibodies for the detection of cTnT in serum[46]. In the 'first generation' TnT assay, only the capture antibody was completely cardiac specific. But, results showed only 78% of detected antibody was cardiac specific[47]. This assay had about 1-2% cross reactivity with skeletal muscle TnT[48]. So the 'first generation' test could give false-positive results in patient with severe skeletal muscle injury.

Later, a cardiac specific 'second generation' TnT assay using double monoclonal antibody technique was developed[49]. This assay was faster and the cross reactivity with human skeletal TnT was reduced to virtually zero.

Though bovine cardiac TnT was used as standard material in 'first' and 'second generation' TnT assays, in the 'third generation' TnT assay, standard material has been changed to a recombinant human cardiac TnT[50,51]. Cardiac TnT assays improved over the time, which have lowered their detection limits and functional sensitivities.

TnI assays

As cardiac troponin is expressed only in myocardium, theoretically it causes minimal problems in the detection of MI. In 1987, Cummins et al introduced a radioimmunoassay method to detect cTnI in serum[52]. Later, Bodor et al developed a double monoclonal enzyme

immunoassay[53]. At present, there are several monoclonal-antibody based assays for cTnI, unlike for cTnT.

High sensitive cardiac troponin

At present most hospitals have replaced conventional cTn tests with the new fifth generation high sensitive cardiac troponin (hs-cTnT and hs-cTnI) assays as those can detect Tn at concentrations 10- folds to 100-folds lower than conventional assays[24,54]. Essentially, hs-cTn assays detect troponin with higher sensitivity and precision at an earlier point of time, and allow detection and quantification in 50% to ideally 95% of healthy individuals[24 ,55,56,57].

CONCLUSION

CHD was initially considered to be a modern-day disease and aetiology was attributed to present-day lifestyle. However, studies have revealed that atherosclerosis and CHD were present in pre-modern humans as well. According to the literature, angina pectoris was described as early as the 7th century. Definition, diagnostic criteria and investigation of CHD are evolving in tandem with advances in science and medicine. Hence it is useful to know how and when these changes occur. ECG is the most important tool in the initial evaluation of CHD and in addition to clinical evaluation and ECG, cardiac biomarkers play a pivotal role in diagnosis and management of acute coronary syndrome. Though Aspartate aminotransferase became the first biomarker used to diagnose CHD, Troponin is now considered the 'gold standard' biochemical test for the diagnosis. Clinicians must be vigilant to keep up to date with current knowledge about CHD in order to provide the best possible care to patients with CHD.

REFERENCES

1. WHO | Global status report on noncommunicable diseases 2010. Accessed May 23, 2021. https://www.who.int/nmh/publications/ncd_report2010/en/
2. Mendis S, Abegunde D, Yusuf S, et al. WHO study on Prevention of REcurrences of Myocardial Infarction And StrokE (WHO-PREMISE). *Bull World Health Organ*. 2005;83(11):820-828. doi:/S0042-96862005001100011
3. WHO | Noncommunicable diseases country profiles 2018. Accessed May 23, 2021. https://www.who.int/nmh/publications/ncd-profiles-2018/en/
4. Hajar R. Coronary heart disease: From mummies to 21 st century . *Hear Views*. 2017;18(2):68. doi:10.4103/heartviews.heartviews_57_17
5. Thompson RC, Allam AH, Lombardi GP. Atherosclerosis Across 4000 Years of Human History: The Horus Study of Four Ancient Populations. *J Vasc Surg*. 2013;58(2):549. doi:10.1016/j.jvs.2013.06.006
6. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis: A report from the Committee on Vascular Lesions of the council on arteriosclerosis, American heart association. *Circulation*. 1995;92(5):1355-1374. doi:10.1161/01.CIR.92.5.1355
7. Sandison AT. *DEGENERATIVE VASCULAR DISEASE IN THE EGYPTIAN MUMMY*.
8. Zimmerman MR. *Historical Perspectives The Paleopathology of the Cardiovascular System*.
9. The History of Heart Disease: From Egyptian Mummies to the Present. Accessed May 23, 2021. https://www.healthline.com/health/heart-disease/history
10. Lila M, Ahmed H, Albinali H. Doha Quartets. *Glob Cardiol Sci Pract*. 2017;2012(2). doi:10.5339/gcsp.2012.16
11. Fishbein ∗ MC, Fishbein GA. Arteriosclerosis: facts and fancy. Published online 2015. doi:10.1016/j.carpath.2015.07.007
12. Hajar R. Evolution of myocardial infarction and its biomarkers: A historical perspective. *Hear Views*. 2016;17(4):167. doi:10.4103/1995-705x.201786
13. Minelli S, Minelli P, Montinari MR. Reflections on atherosclerosis: Lesson from the past and future research directions. *J Multidiscip Healthc*. 2020;13:621-633. doi:10.2147/JMDH.S254016
14. Lie JT. Centenary of the first correct antemortem diagnosis of coronary thrombosis by adam hammer (1818-1878): English translation of the original report. *Am J Cardiol*. 1978;42(5):849-852. doi:10.1016/0002-9149(78)90106-6
15. Gale AH. Adam Hammer, MD: The St. Louis Physician Who Made the First Ever Diagnosis of Coronary Thrombosis and Acute Myocardial Infarction in a Living Patient. *Mo Med*. 2017;114(2):80-81. Accessed May 27, 2021. http://www.ncbi.nlm.nih.gov/pubmed/30228542
16. Poole-Wilson PA, Jacques A, Lyon A. Treatment of angina: a commentary on new therapeutic approaches. doi:10.1093/eurheartj/sui093
17. Herrick JB. Clinical Features of Sudden Obstruction of the Coronary Arteries. *JAMA J Am Med Assoc*. 1983;250(13):1757-1762.

doi:10.1001/jama.1983.03340130075039
18. Nabel EG, Braunwald E. A Tale of Coronary Artery Disease and Myocardial Infarction. *n engl j med*. 2018;366:54-63. doi:10.1056/NEJMra1112570
19. Maris Gandour Rogério Sarmento-Leite SC, Maria Krepsky A, M Gottschall Porto Alegre CA, -Brazil R. *Sarmento-Leite et Al Acute Myocardial Infarction-History Arq Bras Cardiol 2001; 77: 602-10. Acute Myocardial Infarction. One Century of History Update*.
20. Fox KAA. Acute coronary syndromes: presentation-clinical spectrum and management. *Heart*. 2000;84:93-100. doi:10.1136/heart.84.1.93
21. Alghatrif M, Lindsay J. Journal of Community Hospital Internal Medicine Perspectives ISSN: (Print) 2000-9666 (Online) Journal homepage: https://www.tandfonline.com/loi/zjch20 A brief review: history to understand fundamentals of electrocardiography. *J Community Hosp Intern Med Perspect*. 1438;2(1). doi:10.3402/jchimp.v2i1.14383
22. Herring N, Paterson DJ. Review ECG diagnosis of acute ischaemia and infarction: past, present and future. doi:10.1093/qjmed/hcl025
23. Garvey JL, Zegre-Hemsey J, Gregg R, Studnek JR. Electrocardiographic diagnosis of ST segment elevation myocardial infarction: An evaluation of three automated interpretation algorithms HHS Public Access. *J Electrocardiol*. 2016;49(5):728-732. doi:10.1016/j.jelectrocard.2016.04.010
24. Garg P, Morris P, Fazlanie AL, et al. Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. *Intern Emerg Med*. 2017;12(2):147-155. doi:10.1007/s11739-017-1612-1
25. Ndrepepa G. Aspartate aminotransferase and cardiovascular disease—a narrative review. *J Lab Precis Med*. 2021;6(0):6-6. doi:10.21037/jlpm-20-93
26. Garg P, Morris P, Fazlanie AL, et al. Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. *Intern Emerg Med*. 2017;12(2):147-155. doi:10.1007/s11739-017-1612-1
27. KARMEN A, WROBLEWSKI F, LADUE JS. Transaminase activity in human blood. *J Clin Invest*. 1955;34(1):126-131. doi:10.1172/jci103055
28. LaDue JS, Wróblewski F, Karmen A. Serum glutamic oxaloacetic transaminase activity in human acute transmural myocardial infarction. *Science (80-)*. 1954;120(3117):497-499. doi:10.1126/science.120.3117.497
29. Inoue M, Hori M, Nishimoto Y, et al. Protected by copyright. *Br Heart J*. 1978;40:1251-1256. doi:10.1136/hrt.40.11.1251
30. Rabkin SW, Desjardins P. Mitochondrial and cytoplasmic isoenzymes of aspartate aminotransferase in sera of patients after myocardial infarction. *Clin Chim Acta*. 1984;138(3):245-257. doi:10.1016/0009-8981(84)90131-1
31. Djakpo DK, Wang ZQ, Shrestha M. The significance of transaminase ratio (AST/ALT) in acute myocardial infarction. *Arch Med Sci Atheroscler Dis*. 2020;5:e279-e283. doi:10.5114/amsad.2020.103028
32. Rashid S, Malik A, Khurshid R, Faryal U, Qazi S. The Diagnostic Value of Biochemical Cardiac Markers in Acute Myocardial Infarction. In: *Myocardial Infarction*. IntechOpen; 2019. doi:10.5772/intechopen.76150
33. Al-Hadi HA, Fox KA. Cardiac markers in the early diagnosis and management of patients with acute coronary syndrome. *Sultan Qaboos Univ Med J*. 2009;9(3):231-246. Accessed May 28, 2021. /pmc/articles/PMC3074795/
34. KARMEN A, WROBLEWSKI F, LADUE JS. Transaminase activity in human blood. *J Clin Invest*. 1955;34(1):126-131. doi:10.1172/jci103055
35. Vasudevan G, Mercer DW, Varat MA. *Lactic Dehydrogenase Isoenzyme Determination in the Diagnosis of Acute Myocardial Infarction*. Accessed June 14, 2021. http://ahajournals.org
36. Nigam PK. *BIOCHEMICAL MARKERS OF MYOCARDIAL INJURY CRITERIA FOR A TRUE BIOCHEMICAL MARKER OF MYOCARDIAL INJURY*. Vol 22.; 2007.
37. Bodor GS. *Biochemical Markers of Myocardial Damage*.
38. Rahman A, Broadley SA. Review article: Elevated troponin: Diagnostic gold or fool's gold? *EMA - Emerg Med Australas*. 2014;26(2):125-130. doi:10.1111/1742-6723.12203
39. Wilcox HM, Vickery AW, Emery JD. Cardiac troponin testing for diagnosis of acute coronary syndromes in primary care. *Med J Aust*. 2015;203(8):336.e1-336.e7. doi:10.5694/mja14.01154
40. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation*. 2012;126(16):2020-2035. doi:10.1161/CIR.0b013e31826e1058
41. Hasić S, Kiseljaković E, Jadrić R, Radovanović J, Winterhalter-Jadrić M. Cardiac troponin I: the gold standard in acute myocardial infarction diagnosis. *Bosn J Basic Med Sci*. 2003;3(3):41-44. doi:10.17305/bjbms.2003.3527
42. Cheng Y, Regnier M. Cardiac troponin structure-function and the influence of hypertrophic cardiomyopathy associated mutations on modulation of contractility. *Arch Biochem Biophys*. 2016;601:11-21. doi:10.1016/j.abb.2016.02.004
43. Aroney CN, Cullen L. Appropriate use of serum troponin testing in general practice: A narrative review. *Med J Aust*. 2016;205(2):91-94. doi:10.5694/mja16.00263
44. Okyay K, Sadıç BÖ, Şahinarslan A, et al. Turkish Society of Cardiology consensus report on the rational use of cardiac troponins in daily practice. *Anatol J Cardiol*. 2019;21(6):331-344. doi:10.14744/AnatolJCardiol.2019.42247
45. Skeik N, Patel DC. A review of troponins in ischemic heart disease and other conditions. *Int J Angiol*. 2007;16(2):53-58. doi:10.1055/s-0031-1278248
46. Katus HA, Remppis A, Looser S, Hallermeier K, Scheffold T, Kübler W. Enzyme linked immuno assay of cardiac troponin T for the detection of acute myocardial infarction in patients. *J Mol Cell Cardiol*. 1989;21(12):1349-1353. doi:10.1016/0022-2828(89)90680-9
47. Collinson PO, Boa FG, Gaze DC. Measurement of Cardiac Troponins. *Ann Clin Biochem Int J Lab Med*. 2001;38(5):423-449. doi:10.1177/000456320103800501
48. Katus HA. Diagnostic efficiency of troponin T measurements in acute myocardial infarction. *Circulation*. 1991;83(3):902-912. doi:10.1161/01.CIR.83.3.902

49. Improved troponin T ELISA specific for cardiac troponin T isoform: assay development and analytical and clinical validation - PubMed. Accessed May 29, 2021. https://pubmed.ncbi.nlm.nih.gov/9068589/
50. Goldmann BU, Christenson RH, Hamm CW, Meinertz T, Ohman EM. Implications of troponin testing in clinical medicine. *Curr Control Trials Cardiovasc Med*. 2001;2(2):75-84. doi:10.1186/CVM-2-2-075
51. Use of recombinant human cardiac Troponin T for standardization of third generation Troponin T methods - PubMed. Accessed May 29, 2021. https://pubmed.ncbi.nlm.nih.gov/10389211/
52. Cummins B, Auckland ML, Cummins P. Cardiac-specific troponin-l radioimmunoassay in the diagnosis of acute myocardial infarction. *Am Heart J*. 1987;113(6):1333-1344. doi:10.1016/0002-8703(87)90645-4
53. Development of monoclonal antibodies for an assay of cardiac troponin-I and preliminary results in suspected cases of myocardial infarction - PubMed. Accessed May 29, 2021. https://pubmed.ncbi.nlm.nih.gov/1424112/
54. A Brief Review of Troponin Testing for Clinicians - American College of Cardiology. Accessed May 29, 2021. https://www.acc.org/latest-in-cardiology/articles/2017/08/07/07/46/a-brief-review-of-troponin-testing-for-clinicians
55. Apple FS, Ler R, Murakami MAM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. *Clin Chem*. 2012;58(11):1574-1581. doi:10.1373/clinchem.2012.192716
56. Neumann JT, Sörensen NA, Ojeda F, et al. Early diagnosis of acute myocardial infarction using high-sensitivity troponin i. *PLoS One*. 2017;12(3). doi:10.1371/journal.pone.0174288
57. Kaura A, Panoulas V, Glampson B, et al. Association of troponin level and age with mortality in 250 000 patients: Cohort study across five UK acute care centres. *BMJ*. 2019;367. doi:10.1136/bmj.l6055