JMCRR

ISSN (Online): 2589-8655
(Print): 2589-8647

Journal of Medical Case Reports and Reviews

Volume 07
Year 2024

http://jmcrr.info/index.php/jmcrr

Journal Issue

Published by
Medical Editor & Educational Research Publisher
View Current Issue

Validity and reliability of visual analogue Scale (vas) for pain measurement

A case report Tongue injury after car accident in 1.5 years old boy :A case report

The Stigma of COVID-19 And Its Influence on The Management of COVID-19

COVID-19 Vaccine Acquired Haemophilia:A case study and literature review

Return to Article DetailsThe Contents of Calcium, Chlorine, Iodine, Potassium, Magnesium, Manganese, and Sodium in Thyroid Malignant Nodules and Thyroid Tissue Adjacent to Nodules

Keywords

Published Volumes

2018-2024

- 2024
- 2023
- 2022
- 2021
- 2020
- 2019
- 2018

EDITORIAL BOARD MEMBER

Submit Article
Subscribe

Meet Our Editorial Team

Dr. Andrii Puzyrenko
Editor-in-chief
Milwaukee, WI, USA
apuzyrenko@mcw.edu

Dr. Ozgur Karcioglu
Lead Editor
Fatih, Istanbul
Okarcioglu@gmail.com

Dr. Anna Pantouvaki
Senior Editor
Heraklion-Crete Greek
anna.pantouvaki@gmail.com

Dr. Xiangxia Liu
Associate Editor
Guangzhou, China
liuxsha@mail.sysu.edu.cn

Read More

Citation

Updated weekly Scholar

	All	Since 2019
Citations	5	5
h-index	1	1
i10-index	0	0

Language

English
Nederlands

Information

For Readers
For Authors
For Librarians

Journal of Medical Case Reports and Reviews
Open access, peer-reviewed Journal
ISSN:2589-8655 (Online) | 2589-8647 (Print)
editor@jmcrr.info

Journal Issue

Published by
Medical Editor & Educational Research Publisher
View Current Issue

Validity and reliability of visual analogue Scale (vas) for pain measurement

A case report Tongue injury after car accident in 1.5 years old boy :A case report

The Stigma of COVID-19 And Its Influence on The Management of COVID-19

COVID-19 Vaccine Acquired Haemophilia:A case study and literature review

Return to Article DetailsThe Contents of Calcium, Chlorine, Iodine, Potassium, Magnesium, Manganese, and Sodium in Thyroid Malignant Nodules and Thyroid Tissue Adjacent to Nodules

Keywords

Published Volumes

2018-2024

- 2024
- 2023
- 2022
- 2021
- 2020
- 2019
- 2018

Articles

Neuroendocrine Parotid Mass: Atypical Salivary Gland Case

Priscilla M. Dávila-Pérez , Jaime A. Aponte-Ortiz , Álvaro Gracia-Ramis

.

Citations ?

Online First: September 16, 2024 | DOI : 10.52845/JMCRR2024/7-9-2 | Google Scholar | Abstract : 12

Cite this: *Journal of Medical Case Reports and Reviews*, Vol. 7 No. 9 (2024), **September 16, 2024** , Page 1405-1409

Pdf

The Role of Troponin And Use of Troponin Assays

Nany Hairunisa , Yasmine Mashabi

.

Citations ?

Online First: September 16, 2024 | DOI : 10.52845/JMCRR2024/7-9-1 | Google Scholar | Abstract : 8

Cite this: *Journal of Medical Case Reports and Reviews*, Vol. 7 No. 9 (2024), **September 16, 2024** , Page 1392-1404

Pdf

Submit Article

Subscribe

Meet Our Editorial Team

Dr. Andrii Puzyrenko
Editor-in-chief
Milwaukee, WI, USA
apuzyrenko@mcw.edu

Dr. Ozgur Karcioglu
Lead Editor
Fatih, Istanbul
Okarcioglu@gmail.com

Dr. Anna Pantouvaki
Senior Editor
Heraklion-Crete Greek
anna.pantouvaki@gmail.com

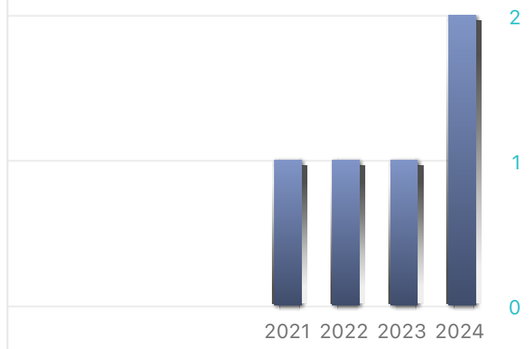
Dr. Xiangxia Liu
Associate Editor
Guangzhou, China
liuxsha@mail.sysu.edu.cn

Read More

Citation

Updated weekly Scholar

	All	Since 2019
Citations	5	5
h-index	1	1
i10-index	0	0



Language

English

Nederlands

Information

For Readers

For Authors

For Librarians

Journal of Medical Case Reports and Reviews

Received 25 Aug 2024 | Revised 30 Aug 2024 | Accepted 10 Sep 2024 | Published Online 16 Sep 2024

DOI:10.52845/JMCRR2024/7-9-1

JMCRR 07 (9), 1392-1404

ISSN (O) 2589-8655 | (P) 2589-8647 IF: 2.964

Original research Articles

The Role of Troponin And Use of Troponin Assays

Yasmine Mashabi[1*], Nany Hairunisa[2], Mario[1], Husnun Amalia[3], Ade DwiLestari[2], Emad Yousif[4]

1. Department of Clinical Pathology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

2. Department of Occupational Medicine, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

3. Department of Ophthalmology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia.

4. Department of Chemistry, Al-Nahrain University, Bagdad, Iraq

Abstract:- Troponin is a crucial protein present in various muscle types, including cardiac muscle (myocardium), and plays an essential role in muscle contraction, facilitating the heartbeat. Normally, only minimal levels of troponin are found in the blood. However, when myocardial injury occurs, cardiac troponin (cTn) is released into the bloodstream from the heart muscle. Monoclonal antibodies specific to cTn have enabled the development of assays for measuring cTn levels in the blood. The amount of troponin released is proportional to the severity of heart damage. During a heart attack, the heart muscle's lack of oxygen-rich blood causes damage and the subsequent release of troponin into the bloodstream.

There are three types of troponin: Troponin I (TnI), Troponin T (TnT), and Troponin C (TnC). Only TnI and TnT are used for diagnosing heart attacks because TnC cannot be identified as originating specifically from the heart muscle. Normal blood troponin levels are very low, typically between 0-0.04 nanograms per milliliter, which were difficult to measure accurately with initial tests. The advent of the high-sensitivity cardiac troponin test (hs-cTnT) now allows for detecting low levels of cardiac troponin, enabling earlier and more accurate diagnosis of heart attacks.

Troponin I can be analyzed using various methods such as Enzyme-Linked Immuno sorbent Assay (ELISA), Enzyme-Linked Fluorescent Assay (ELFA), Radioimmunoassay (RIA), Fluorescence Immunoassay, and Immuno chromatography (ICT). Plasma troponin T levels can be measured using ELISA based on the Biotin-Streptavidin principle and qualitative TnT examination by immunoassay (TnT-RA). High-sensitivity troponin T (hs-TnT) and high-sensitivity troponin I (hs-cTnI) are measured using the Electro chemiluminescence Immunoassay (ECLIA) method.

Keywords: Troponin, Cardiac Troponin, hs-cTnT, hs-cTn I, Fluorometry, Immuno chromatography, Immunoassay (ELISA), Electro chemiluminescence Immunoassay (ECLIA).

Supplementary information The online version of this article (https://doi.org/xx.xxx/xxx.xx) contains supplementary material, which is available to autho-rized users.

Corresponding Author: Yasmine Mashabi* Department of Clinical Pathology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

BACKGROUND :

The high prevalence of cardiovascular disease significantly impacts patients, doctors, and healthcare services. Chest pain, a potential sign of acute myocardial infarction (AMI), is one of the most common reasons for emergency department visits worldwide. Many clinical care advancements rely on cTn testing, with the most notable benefits observed in hospital settings. This cTn test detects myocardial injury, enabling the detection of low concentrations with high precision.[1-4] Cardiac troponin has been used clinically since 1995, following the approval of the first cardiac troponin T (cTnT) test.[5,6] Cardiac Troponin (cTn) is considered superior to creatinine kinase MB (CK-MB) for diagnostic and prognostic purposes.[4]

Troponin is a protein that regulates muscle tissue, specifically found in the heart muscle, known as cardiac troponin (cTn). During myocardial injury, cTn is released into the bloodstream from the myocardium. The development of cTn-specific tests using monoclonal antibodies has enabled the measurement of cTn concentrations in the blood. These assays have improved their analytical performance and are now the primary laboratory biomarker for diagnosing myocardial infarction (MI). The amount of troponin released correlates with the extent of myocardial damage, making quantitative cTn results valuable for prognosis.[4,7,8] Enhancements in cardiac specificity and sensitivity have significantly increased the frequency and accuracy of cardiovascular disorder diagnoses, particularly with high-sensitivity cardiac troponin tests.[9]

Troponin is a complex protein consisting of three subunits (T, I, and C) that play a role in muscle contraction regulation. Both cardiac and skeletal muscles contain troponin C, while troponin T and I are typically considered cardiac-specific. The three-unit troponin complex (troponin I, T, and C), along with tropomyosin, is situated on actin filaments and is crucial for the calcium-mediated regulation of muscle contractions. Tissue-specific isoforms of troponin I, T, and C exist, but since the cardiac isoform of troponin C is also present in slow-twitch skeletal muscle, it lacks cardiac specificity and is not used in diagnostic tests for cardiac injury.[10,11]

When cardiac injury occurs due to ischemia or other causes, cardiomyocytes release cardiac troponin into the bloodstream proportionally to the extent of the damage. Troponin levels rise within 3 to 4 hours after injury onset and remain elevated for 4 to 7 days for troponin I or 10 to 14 days for troponin T. Cardiac troponin T and I are integral components of the cardiomyocyte contractile apparatus and serve as biomarkers for necrosis. These troponins are the most commonly measured indicators in patients with acute coronary syndrome. Elevated cardiac troponin levels, even those below the detection limit for a positive test, may predict adverse cardiovascular events. Plasma cardiac troponin is a sensitive and specific biomarker commonly used for diagnosing myocardial infarction. The development of the highly sensitive troponin T (hs-cTnT) assay facilitates early detection of myocardial infarction and serves as a prognostic tool for stable coronary artery disease.[11] Cardiac troponin T (cTnT) and troponin I (cTnI) share similar amino acid sequences, differing from their skeletal muscle isoforms and being encoded by unique genes.[14] Human cTnI has 31 additional amino acid residues at the amino-terminal end compared to skeletal muscle TnI, conferring complete cardiac specificity.[15] cTnT is encoded by a gene distinct from that encoding the skeletal muscle isoform, with 11 additional amino acid residues at the amino-terminal end, providing unique cardiac specificity.[11]

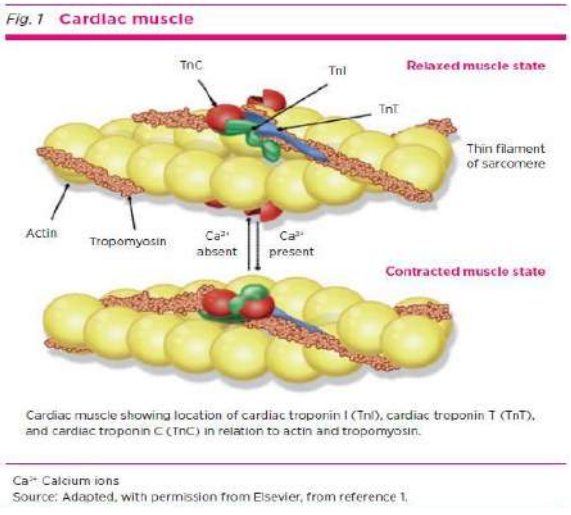


Figure1 Cardiac Muscle[10]

ETIOLOGY AND EPIDEMIOLOGY

Troponin exists in three different molecular forms according to specific isotypes. The molecular weights of cTnI and cTnT are 23,500 and 33,500 Daltons, respectively. Despite being smaller than CK-MB (86,000 Daltons), most troponin is released as a higher molecular weight complex.[16] The skeletal isotypes are similar in molecular size, about 20,000 Daltons, and show amino acid sequence heterogeneity of about 40%.[17,18] The cardiac isotype also shows approximately 40% sequence heterogeneity concerning the skeletal isotype and has 31 additional residues at the amino terminus. It is thus possible to differentiate cardiac troponin immunologically from bone troponin.[19] Before troponin, several cardiac biomarkers were used to identify myocardial injury.[20] In the 1960s and 1970s, biomarkers such as aspartate transaminase (AST), lactate dehydrogenase (LDH), and creatinine kinase (CK) were used. However, they were later replaced due to a lack of specificity for cardiac muscle.[17] The next generation of biomarkers was more specific for cardiac muscle, including CK-MB and LDH. However, these markers still had a very high false positive rate, necessitating the development of new, more specific biomarkers.[21] Troponin was first identified in 1965, but a reliable immunoassay to detect its levels in the blood was not developed until the late 1990s.[17] Troponin measurements were found to have nearly 100% sensitivity when examined 6 to 12 hours after the onset of chest pain and have significantly increased specificity for heart muscle damage compared with previous biomarkers.[21] Because of its clinical utility, serial troponin testing was added to the Fourth Universal Definition of Myocardial Infarction, the current definition used by the American College of Cardiology.[17]

PATHOPHYSIOLOGY

Myocardial infarction is not always caused by total occlusion of the coronary arteries. Subtotal obstruction accompanied by dynamic vasoconstriction can cause ischemia and necrosis of heart muscle tissue (myocardium).[22] During this process, cell membranes rupture, causing intracellular contents to spill into the extracellular space, which ultimately enters the bloodstream.[17,23] If the cellular contents, including troponin, are shed in large enough quantities, they can be detected in the blood circulation. Creatinine kinase-MB (CK-MB) or troponin I/T is a marker of cardiac myocyte necrosis and is a marker for the diagnosis of myocardial infarction. Troponin I/T as a marker of cardiac necrosis has higher sensitivity and specificity than CK-MB.[23]

An increase in cardiac markers only indicates myocyte necrosis, but cannot be used to determine the cause of myocyte necrosis (coronary/noncoronary causes). Troponin I/T can also increase due to non-coronary cardiac disorders such as tachyarrhythmias, cardiac trauma, heart failure, left ventricular hypertrophy, and myocarditis/pericarditis. Noncardiac conditions that can increase I/T troponin levels are sepsis, burns, respiratory failure, acute neurological disease, pulmonary embolism, pulmonary hypertension, chemotherapy, and renal insufficiency. Troponin T and troponin I provide balanced information on the occurrence of myocyte necrosis, except in cases of renal dysfunction. In this situation, troponin I has a higher specificity than troponin T.[22]

Troponin levels usually begin to increase in circulation within two to three hours after the onset of chest pain. The levels will continue to increase until they reach their peak, generally between 12 and 48 hours. Troponin levels will then fall to normal over the next four to ten days.[24,25] These expected troponin rises and falls can help differentiate myocardial infarction from other causes of troponin elevation.[25] The actual half-lives of cTnI and cTnT are short – about two hours in plasma. However, due to the continuous release of troponin from necrotic myocardium, its half-life is 24 hours, with cTnT being slightly longer.[26]

Cardiac marker examination should be carried out in a central laboratory. Examinations in the emergency room or cardiac intensive care unit (point of care testing) generally take the form of qualitative or semiquantitative tests, which are faster (15-20 minutes) but less sensitive. Point-of-care testing as a routine diagnostic tool is only recommended if the examination time at the central laboratory takes >1 hour. If cardiac markers using point-of-care testing show negative results, the examination must be repeated at a central laboratory.[22]

TROPONIN TEST GENERATION

Determination of troponin in the blood is carried out through different immunochemical methods (radioimmunoassay, enzyme immunoassay, immunofluorescence, and immune chemiluminescence). This process includes several successive stages of immunology, chemistry, and detection. There has been a long-standing need to create specific immunochemical tests to determine troponin I and troponin T to diagnose acute

myocardial infarction. In 1987, Cummins reported the first method (first-generation immunoassay) to determine troponin I.[27,28]

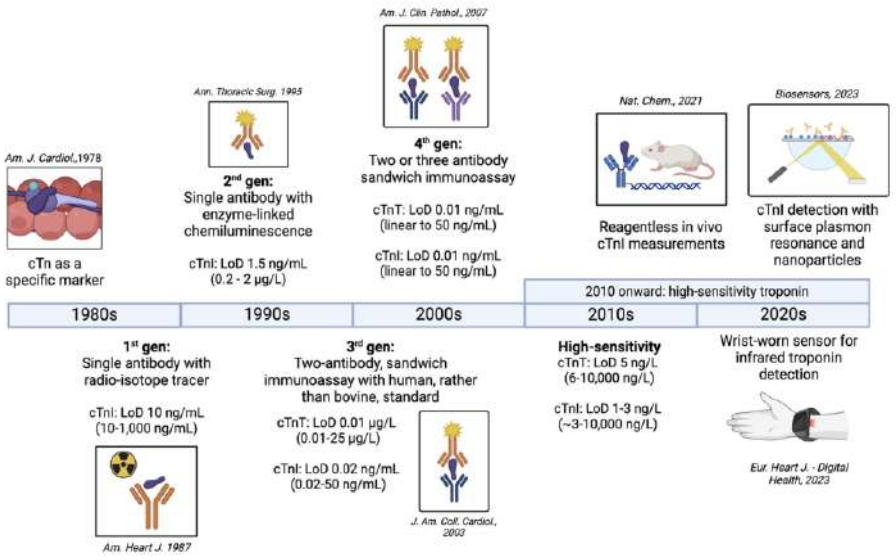


Figure 2 Evolution of troponin measurement assays from the 1980s to the 2020s, and the limits of detection (LoD) associated with each assay generation.[23]

Second Generation of Tn tests have better detection rates than first-generation tests (~1.5 ng/mL).[28] An important change was the introduction of direct enzyme-linked immunoassay (ELISA) technology as a replacement for radio-isotope reading. Measurement of TnI levels in serum is carried out using optical reading of visible light absorbance, which not only avoids exposure to radioactive labeling but also provides higher sensitivity because the enzyme is able to amplify the signal from minimal amounts of Tn antigen.[29] In addition, several second-generation tests began using two Tn-specific antibodies to increase specificity and sensitivity. A typical second-generation assay, using ELISA technology, has a range of 0.2–20 µg/L and a within-run coefficient of variation of 4.7%. In an important improvement over the first-generation test, the second-generation test can be performed within 30 minutes and shows no cross-reactivity with skeletal muscle. A limitation of most second-generation TnT assays is that calibration is performed with a TnT standard, which produces curves that are not always linear.[28,30] However, this limitation is addressed in third-generation Tn assays, described below.

Continued advancements in detection technology, such as the Roche Elecsys 2010 immunology analyzer, have significantly enhanced sensitivity compared to third-generation tests. Notably, this generation adopted human troponin standards for calibration, resolving non-linearity issues associated with bovine troponin standards. Due to the increased sensitivity, a study of 750 patients admitted to a coronary care unit revealed that an additional 35% of patients were diagnosed with acute myocardial infarction.[30] Additionally, because they are more sensitive, third-generation assays can identify a subgroup of patients with mild myocardial injury, who were found to have an increased risk of future cardiac events. The ability for mild Tn elevation to carry prognostic significance in subclinical disease will be a common feature for the next generation of Tn assays.[28]

The fourth-generation assay has further improved the sensitivity of troponin measurements compared to the third-generation. Many of these assays continue to employ the direct chemiluminescent technology introduced in the second-generation tests. Notably, fourth-generation tests use at least two unique antibodies, and some even utilize three. For instance, the ADVIA Centaur TnI-Ultra assay incorporates one monoclonal antibody and two polyclonal antibodies targeting the central region of TnI, enhancing binding efficiency. Combined with a proprietary blocking reagent that eliminates nonspecific binding, this technique achieves an assay range of 0.006-50 ng/mL, with a 99th percentile value of 0.04 ng/mL and a 10% coefficient of variation (CoV) of 0.02 ng/mL.[31] Another widely used fourth-generation assay, the Roche ElecsysTnT Stat, employs direct sandwich immunoassay technology, incorporating streptavidin-coated microparticles to enhance signal detection. This fourth-generation test offers an analytical sensitivity of 0.01 ng/mL, with a concentration of 0.03 ng/mL yielding a 10% coefficient of variation (CoV).[32]

TROPONIN T

Troponin T (TnT) is a component of the contractile apparatus of striated muscles. Although the function of TnT

is the same in all striated muscles, TnT originating exclusively from the myocardium (cardiac TnT, molecular weight 39.7 kDa) is clearly different from skeletal muscle TnT. As a result of its high tissue specificity, cardiac troponin T (cTnT) is a highly sensitive cardio-specific marker for myocardial damage.[33]cTnT increases approximately 3–4 hours after acute myocardial infarction (AMI) and can persist for up to 2 weeks afterward.[34-36] In contrast to ST-elevation myocardial infarction (STEMI), the diagnosis of non-ST-elevation myocardial infarction (NSTEMI) relies heavily on cardiac troponin results. Elevated cTnT levels correlate with the severity of coronary artery disease and poor outcomes regardless of natriuretic peptide (BNP or NT-proBNP) levels.[37-40] Myocardial cell injury, leading to increased blood cTnT concentrations, can also occur in various clinical conditions such as myocarditis, heart contusion, pulmonary embolism, and drug-induced cardiotoxicity. Elevated troponin levels in renal failure are linked to increased cardiovascular risk, with chronic cTnT elevations greater than 50 ng/L detected in over 50% of patients with severe renal failure.[41-46]

Troponin T is a cardiac protein found in striated muscle that functions as a specific regulator of muscle contraction in cardiac muscle. There are three ways to measure plasma troponin T levels, namely by ELISA (Biotin - Streptavidin principle), streptavidin-biotin technology has been effectively used to improve ELISA detection because of the strong affinity between biotin and streptavidin having a dissociation constant (Kd) in the femtomolar range.[47] Combined antibodies with biotin, followed by a streptavidin-conjugated enzyme step. Alternatively, it is possible to use an unlabeled primary antibody followed by an enzyme-coupled or biotinylated secondary antibody. If the secondary antibody is biotinylated, then a tertiary step is required for detection. In this case, treatment with a streptavidin enzyme conjugate is followed by a suitable substrate. Because biotin and streptavidin interact strongly, more analyte molecules can be captured on the ELISA plate.[47,48]

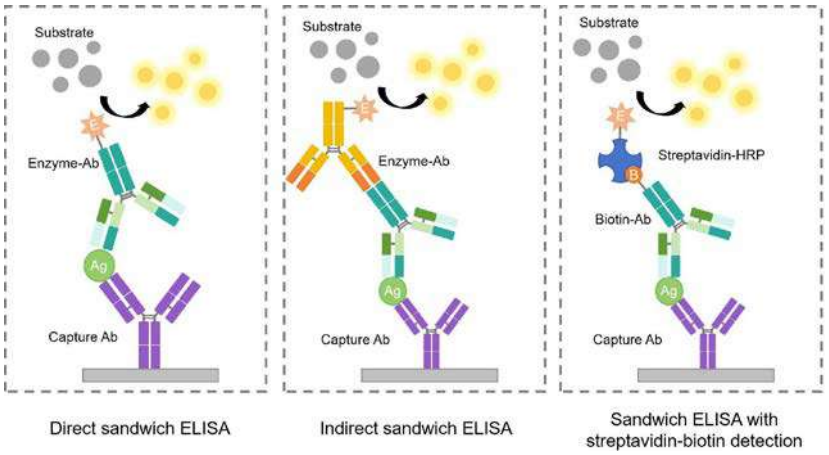


Figure 3 Normal mode and sandwich signal amplification mode of ELISA.[47]

The main advantage of sandwich ELISA is its high sensitivity. It is 2-5 times more sensitive than direct or indirect ELISA. Sandwich ELISA also provides high specificity because two antibodies are used to detect the antigen. This offers flexibility as both direct and indirect methods can be used. Sandwich ELISA also presents several disadvantages, namely that if a standard ELISA kit or the antibody pair being tested is not available, antibody optimization must be carried out as it is important to reduce cross-reactivity between the capture and detection antibody pairs. Sandwich ELISA is well suited for the analysis of complex samples, as antigens do not need to be purified before testing but still provide high sensitivity and specificity. The procedure for sandwich ELISA begins with coating the wells of the ELISA plate with capture antibodies. Next, the analyte or sample is added, followed by the detection antibody. Based on the detection principle and the use of enzyme-labeled capture antibodies, sandwich ELISA can be categorized into three forms: direct sandwich ELISA, indirect sandwich ELISA, and sandwich ELISA with streptavidin-biotin detection.[47]

The next method is qualitative TnT examination using the TnT – RA Immuno Assay. In September 1994, Boehringer Manheim released the troponin T Rapid Assay (TROPT®) test, which is a rapid immunological test based on two specific monoclonal antibodies with different labels, one of which is labeled gold and the other is labeled biotin.[49]TnT-RA was carried out using the Elisa dry chemistry method, based on the sandwich principle, and the results were expressed qualitatively. After adding 150 µL whole blood, the erythrocytes are absorbed by the glass fiber, while the plasma with antibody-troponin T-complex flows into the detection zone. In this zone, the troponin sandwich complex is concentrated on the streptavidin signal line by the affinity between streptavidin and biotin. The complex accumulation

on these lines can be detected visually by the purple color of the gold particles. Excess gold-labeled antibodies bound to the control line. This proves that the inspection went well. The results can be read 20 minutes after adding the blood sample. There is a minimum threshold value for the detection of TnT using TnT-RA with a serum TnT level of 0.3 ng/mL. In this way, the examination can be carried out immediately, even "bedside" (beside the bed).[49,50]

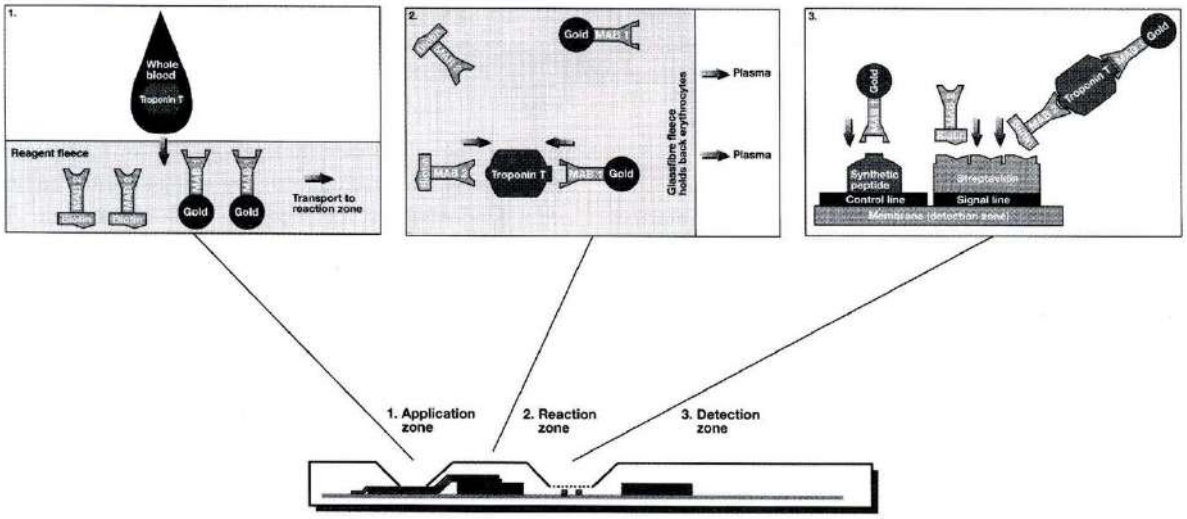


Figure 4 Test principle of TROPT® rapid test. MAB = monoclonal antibody[49]

Subsequently, Roche developed the troponin T point-of-care (POC) test based on the same principle as TROPT®. This test involves the instrument's optical system detecting two lines and measuring the intensity of the signal lines. The integrated software then converts the signal intensity into a quantitative result, displayed on the screen. The results are expressed quantitatively in units of ng/mL for troponin T levels. Normal troponin T levels are considered to be less than 50 ng/mL, values between 50-100 ng/mL are categorized as low, and values greater than 100 ng/mL indicate possible acute myocardial infarction (IMA). This quantitative immunological test is used to detect cardiac troponin T in heparinized venous blood, specifically designed for use with the Cobas H 232 instrument. It serves as an initial diagnostic aid for acute myocardial infarction and helps identify patients with a high risk of mortality.[51]

TROPONIN I

Troponin I is a component of cardiac and skeletal muscle proteins. It is part of the troponin protein complex, where it binds to actin in thin myofilaments to hold the actin-tropomyosin complex in place. Troponin I prevents myosin from binding to actin in relaxed muscles. After that, tropomyosin leaves the binding site for myosin on actin causing muscle contraction. It is a useful marker in the laboratory diagnosis of heart attack. It occurs in different plasma concentrations but the same circumstances as troponin T – both tests can be performed to confirm heart muscle damage and laboratories usually offer one test or the other.[52]

Troponin I is a more commonly used diagnostic marker for myocardial infarction because it is specific to myocardial tissue and has high sensitivity. In addition, it can detect the presence of small myocardial necrosis which is not detected on electrocardiogram examination or by CK MB. Troponin I is very specific to cardiac muscle tissue because it is not expressed by other tissues, is undetectable in healthy individuals, and shows an increase above normal limits in patients with myocardial infarction. Troponin I is the biological marker of choice according to the guidelines of The Third Global Myocardial Infarction Task Force World Health Organization (WHO).[53,54] Cardiac troponin I is expressed in cardiac muscle tissue by a single isoform with a molecular weight of 23,876 Da and consists of 209 amino acid residues. For more than 15 years, troponin I has been recognized in the literature as a reliable marker for cardiac muscle tissue injury and is considered more sensitive and significantly more specific in the diagnosis of myocardial infarction than CK MB.[55]

Troponin I is part of a three-subunit complex along with Troponin T and Troponin C. This complex, along with tropomyosin, regulates the activity of calcium-sensitive ATPase actomyosin in striated skeletal and cardiac muscle. Following a heart injury, Troponin I is released into the bloodstream within 4-6 hours after the onset of pain. Its pattern is similar to CK-MB, but while CK-MB levels normalize after 72 hours, Troponin I remains elevated for 6-10 days, providing a longer detection window for cardiac injury. The high specificity of cTnI measurements for identifying myocardial damage has been demonstrated in various conditions such as the perioperative period, post-marathon running,

and blunt chest trauma. cTnI release has also been observed in cardiac conditions other than acute myocardial infarction (AMI), such as unstable angina, congestive heart failure, and ischemic damage from coronary artery bypass surgery. Due to its high specificity and sensitivity for myocardial tissue, Troponin I has recently become the preferred biomarker for myocardial infarction.[56]

The cTnI One Step Troponin I (Whole Blood/Serum/Plasma) Test Kit is a simple test that uses a combination of anti-cTnI antibody-coated particles and capture reagents to selectively detect cTnI in whole blood, serum, or plasma. The minimum detection level is 1.0 ng/mL. Cardiac troponin I (cTnI) levels begin to increase three hours after injury, peak between 12-24 hours, and remain elevated for 5-7 days. cTnI levels in the bloodstream rise with the initial injury and decrease as the enzyme is cleared from circulation.[54,57] Troponin I can be examined using the Enzyme-Linked Immuno-absorbent Assay (ELISA), Enzyme-Linked Fluorescent Assay (ELFA), Radioimmunoassay (RIA), Fluorescence immunoassay and Immunochromatography (ICT). The samples used also vary, you can use serum samples, heparin plasma, and Ethylene Diamine Tetra-Acetic (EDTA) or whole blood.[58]

The One Step Troponin I (Whole Blood/Serum/Plasma) cTnI Test Device is a qualitative membrane-based immunoassay for detecting cTnI in whole blood, serum, or plasma. The membrane is coated with a capture reagent on the test line area of the test. During testing, whole blood, serum or plasma specimens react with particles coated with anti-cTnI antibodies. The mixture migrates up the membrane chromatographically by capillary action to react by capturing reagents on the membrane and producing colored lines. The appearance of this colored line in the test line area indicates a positive result, whereas if it does not appear it indicates a negative result. To serve a procedural control, a colored line will always appear in the control line region indicating that the correct specimen volume has been added and membrane wicking has occurred.[56]

In Indonesia, many qualitative cTnI kits are circulating, but they cannot be used to follow the course of the disease and stratify the risk of mortality. Recently introduced a quantitative cTnI rapid test kit with serum material and a small device. The fluorometric method for cTnI is quite fast but requires a fluorometer, while quantitative cTnI measurements using the enzyme immunoassay method require a long time. Due to variations in the sensitivity and specificity of the cTnI test, a separate study is needed.[59]

EXAMINATION OF THE HIGH-SENSITIVE CARDIAC TROPONIN (HS CTN) TEST

The role of cardiac troponin as a diagnostic biomarker of myocardial injury in the context of Acute Coronary Syndrome (ACS) is well established. Since the first generation test, the development of the 5th generation high sensitivity cardiac troponin (hs-cTn) test has marked significant progress and is now widely used.[60] This change has increased the sensitivity of the analysis, which is almost one-third of the previous value, from 0.010 µg/L (= 10 ng/L) to 0.003µg/L (=3 ng/L). For the hs-cTnT test, the 99th percentile value, obtained from a multicenter reference population, yields a cut-off value of 14 pg/mL (=14 ng/L).[61,62] Use of the hs-cTn test is found at low levels even in plasma-healthy subjects. The hs-cTn test can be found in 95% of the reference population. The ability to find cTn in healthy people requires determining the clinical limit value for cTn levels, namely a "positive" cTn result.[63]

In some tests, cTn is not found in 50% of individuals who do not appear sick, while in the hs-cTn test it can be found in up to 90%. The joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation (ESC/ACCF/AHA/WHF) seeks to clarify the universal boundaries of myocardial infarction. The hs-cTn test detects early cTn release from the previous cTn test, which increases the initial sensitivity for diagnosing AMI. Because the frequency of detection is high and slightly higher than the hs-cTn value in the community, especially in patients with cardiovascular comorbidities, it is important to know that an increase in hs-cTn levels alone is not enough to diagnose AMI.[53]

According to current guidelines, the analytical coefficient of variation (CV) of a cardiac troponin test should be <10% at the 99th percentile upper reference limit (URL) of a normal reference population.[64,65] Additionally, the same guidelines claim that a cardiac troponin test should measure analyte concentration above the limit of detection (LOD) in ≥50% of the normal reference population. If cardiac troponin tests can meet these two requirements, they are called high-sensitivity cardiac troponin T (hs-cTnT) and high-sensitivity cardiac troponin I (hs-cTnI) tests.[64,66] For the diagnosis of AMI, the clinician must consider the patient's clinical presentation, studies electrocardiogram, and imaging, as well as cardiac troponin plasma concentrations. Especially in the emergency department (ED), physicians try to exclude AMI quickly, and compared with using the older cardiac troponin test, using the hs-cTnT and hs-cTnI tests reduces the time to rule out AMI.[64]

Comparing high sensitivity cardiac troponin I (hs-cTnI) and high sensitivity cardiac troponin T (hs-cTnT) assays can be challenging due to different reference ranges for the general population and varying assay-specific pre-analytic and analytical variables. False positives and false negatives may arise from non-reproducible "flyers" or interference with assay-specific native antibodies. Currently, the patented hs-cTnT test is only available from Roche Diagnostics. In contrast, six hs-cTnI assays (from Abbott, Beckman Coulter, BioMerieux, Pathfast, Siemens, and Singulex) are commercially available. Of these, the Roche hs-cTnT assay (Elecsys platform) and the Abbott hs-cTnI assay (Architect platform) have been extensively investigated in large diagnostic studies, including the successful derivation and validation of the 0/1 hour and 0/2 hour algorithms.[67]

A recent study by Boeddinghaus et al. validating the Siemens hs-cTnI assay for early diagnosis of AMI and comparing its performance with the Roche and Abbott assays is an important step forward to increase our knowledge of commercially available hs-cTnI assays. Boeddinghaus et al. concluded, that the diagnostic accuracy and clinical utility of the Siemens hs-cTnI assay were adequate and comparable to those of the Roche hs-cTnT and Abbott hs-cTnI assays.[64,67] The hs-cTnI assay (CLIA) is a high-sensitivity troponin I method with high precision, sensitivity, and high specificity. The clinical diagnostic performance of hs-cTnI (CLIA) is comparable to the established ARCHITECT hs-cTnI assay. The Mindray hs-cTnI (CLIA) assay is an attractive alternative for the diagnosis of myocardial infarction with high levels of accuracy and safety.[68]

The Roche ElecsyscTnT-hs test (high sensitive troponin T assay) and the Roche ElecsyscTnT-hs STAT test (Roche Diagnostics GmbH, Mannheim, Germany) can be used on the Roche Elecsys 2010 analyzer and the Cobas Modular Analytics e series immunoassay analyzer, e411 platforms. This assay is a quantitative, sandwich electro chemiluminescence immunoassay (ECLIA) for serum and plasma samples. Results are available within 18 minutes with the standard test and within 9 minutes if the STAT test is used. Both assay versions were able to detect cTnT in 61% of the reference population and had a recommended 99th percentile cutoff of 14 ng/l, with a CV < 10%. Both versions of the test are CE-marked and available for the NHS.[69,70]

The Abbott ARCHITECT hs-cTnI STAT assay (Abbott Laboratories, Chicago, IL, USA) can be used using the Abbott ARCHITECT i2000SR and i1000SR. The assay is a quantitative chemiluminescent micro particle immunoassay (CMIA) for serum or plasma samples. Results are available within 16 minutes. The STAT ARCHITECT hs-cTnI assay can detect cTnI in 96% of the reference population, and has a recommended 99th percentile cutoff of 26.2 ng/l, with a CV of 4%. The test is CE-marked and available on the NHS.[70]

The AccuTnI + 3 hs-cTnI assay is approved for use with the Beckman Coulter Access 2 and DxI devices. This assay uses a quantitative two-site paramagnetic particle chemiluminescent sandwich immunoassay method for serum or plasma samples. The AccuTnI+ 3 assay has a recommended 99th percentile limit of 40 ng/l, with a CV < 10%. Recently a study reported data showing that the assay could detect cTnI in 88% of the reference population when used on the Access II analyzer and in 58% of the reference population when used on the DxI analyzer. The same study reported differences in the 99th percentile upper reference limits between the two analyzers (41 ng/l for Access II and 34 ng/l for DxI).[70]

The hs-cTn I assay was performed using the ELFA measurement procedure on a Vidas 3 analyzer. Vidas troponin I is a quantitative test using a one-step immunoenzymatic sandwich method. Serum samples were transferred to wells containing anti-hs-cTn I antibody (conjugate) labeled with alkaline phosphatase. This allows the formation of a sandwich structure with troponin I, immunoglobulin, and conjugate bound to the inner wall of the solid phase. In the final stage, the substrate is hydrolyzed by the conjugate enzyme to become a fluorescent product (4-methyl-umbelliferone). The fluorescence intensity is proportional to the antigen concentration. The volume of serum required for analysis is 150 µl. Analysis time under 17 minutes.[71]

The PATHFAST POC hs-cTnI method uses a benchtop immunometric analyzer called PATHFAST™ (PHC Europe B.V., Nijverheidsweg, Netherlands; distributed in Italy by GEPA, Bollate, Milano), which incorporates chemiluminescence (CLEIA) technology for signal detection (alkaline phosphatase enzyme bound to anticTnI monoclonal antibodies) and magnetic migration (called Magtration®) for separation of bound phases, using antibodies tagged by magnetic particles. This instrument requires a volume of 100 mL of whole blood, plasma, or serum; Up to 6 samples can be analyzed simultaneously. PATHFAST TM provides high accuracy and precision of test results similar to central laboratory analyzers, combined with the flexibility of a POCT test in 17 minutes.[72]

The Mindray High Sensitivity cTnI (CLIA) is an immunoenzymatic assay designed to determine the concentration of cardiac troponin I (cTnI) in samples. This assay was specifically developed to assess the analytical

performance of Mindray's new high-sensitivity cardiac chemiluminescent troponin I (hs-cTnI) immunoassay on the Mindray CL-1200i chemiluminescence analyzer. The evaluation of this hs-cTnI immunoassay includes calculations of the limit of blank (LOB), limit of detection (LOD), functional sensitivity, imprecision, linearity, and the 99th percentile upper reference limit (URL), as well as a method comparison with Beckman. Our assessment of the new Mindray hs-cTnI immunoassay on the CL-1200i indicates that its overall analytical performance is comparable to other commercially available cTnI methods, making it a viable alternative to other methods.[73]

The Siemens Healthineers ADVIA Centaur TNIH test is a 3-site sandwich immunoassay using direct chemiluminometric technology. The solid phase reagent is a magnetic latex particle conjugated to streptavidin with two bound biotinylated capture monoclonal antibodies that each recognize a unique cTnI epitope. siemens-healthineers.com/TNIH Lite reagent consists of a conjugate whose architecture consists of a proprietary acridinium ester and a recombinant sheep cTnI antihuman Fab covalently attached to bovine serum albumin (BSA) for chemiluminescent detection. The accumulated light signal is directly related to the cTnI concentration of the sample.[74]

The Siemens Healthineers ADVIA Centaur TNIH assay uses a recombinant ahu cTnI antibody fragment attached to a BSA carrier with multiple TSPAE (trisulfopropyl AE), to achieve low assay interference and signal amplification (signal/binding event), respectively. The new TNIH assay provides an approximately 10-fold increase in low-end precision and sensitivity in part due to the Acridinium Ester architecture and this new high-efficiency conjugate. The ADVIA Centaur® High-Sensitivity Troponin I (TNIH) test is for in vitro diagnostic use in the quantitative measurement of cardiac troponin I in human serum or plasma using the ADVIA Centaur® XP and ADVIA Centaur® XPT systems. This test can be used to help diagnose acute myocardial infarction (AMI).[74]

CONCLUSION

The high incidence of cardiovascular disease in society highlights the need for biomarkers with excellent specificity. Previous markers such as AST, LDH, and CK-MB had very high false positive rates, necessitating the development of new, more specific biomarkers. Continuous advancements in cardiac biomarkers have led to the development of high-sensitivity tests for cardiac troponin I and T, which offer both high sensitivity and specificity. The use of these new generation high-sensitivity cardiac troponin (hs-cTn) tests is now recommended by international guidelines as a primary tool for diagnosing myocardial infarction.

Despite their high cardiac specificity, these biomarkers are not exclusively specific to Acute Coronary Syndrome (ACS), as many cardiac and even non-cardiac conditions can cause elevated hs-cTn levels. Nevertheless, the use of hs-cTn for the rapid rule-out of ACS is considered safe and efficient. The point-of-care testing (POCT) method for hs-cTn measurements should be considered in various clinical settings. However, it remains necessary to confirm the results obtained with the hs-cTn POCT method using automated platforms in clinical laboratories.

Implementing the hs-cTnI POCT method requires not only thorough education of the personnel responsible for biomarker measurements but also a careful evaluation of clinical issues that may arise during routine use. Special attention must be given to pre-analytical and analytical phases due to the possibility of analytical interference and clinical difficulties in interpreting results. Additionally, validated systems must be in place to ensure proper information systems integration (e.g., connection with Laboratory Information Systems, LIS), quality control of procedures, and accurate reporting of results.

REFERENCE

1. Cullen L, Collinson PO, Giannitsis E. Point-of-care testing with high-sensitivity cardiac troponin assays: the challenges and opportunities. *Emergency Medicine Journal.* 2022;**39:**861-6

2. Greenslade JH, Parsonage W, Foran L, et al. Widespread introduction of a high- sensitivity troponin assay: assessing the impact on patients and health services. J Clin Med. 2020;9:1883.

3. Collet JP, Thiele H, Barbato E. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST- segment elevation. Eur Heart J. 2020;2021:1289–367.

4. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Circulation. 2018; 138:618-51

5. Stark M, Kerndt CC, Sharma S. Troponin. [Updated 2023 Apr 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507805/

6. Xu RY, Zhu XF, Yang Y, Ye P. High-sensitive cardiac troponin T. J GeriatrCardiol. 2013 Mar;10(1):102-9. [PMC free article] [PubMed]

7. Januzzi JL, Mahler SA, Christenson RH, et al. Recommendations for institutions transitioning to high-sensitivity troponin testing - JACC scientific expert panel. JACC. 2019; 73:1059–77

8. deFilippi CR, Herzog CA. Interpreting Cardiac Biomarkers in the Setting of Chronic Kidney Disease. Clin Chem. 2017; 63:59-65

9. Potocki M, Reichlin T, Thalmann S, Zellweger C, Twerenbold R, Reiter M, et al. Diagnostic and prognostic impact of copeptin and high-sensitivity cardiac troponin T in patients with pre-existing coronary artery disease and suspected acute myocardial infarction. Heart. 2012 Apr;98(7):558-65. [PubMed]

10. Potter JM, Hickman PE, Cullen L. Troponins in myocardial infarction and injury. Aust Prescr. 2022 Apr;45(2):53-7. doi: 10.18773/austprescr.2022.006.

11. Michos ED, Berger Z, Yeh HC, et al. Cardiac Troponins Used as Diagnostic and Prognostic Tests in Patients With Kidney Disease [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Aug. (Comparative Effectiveness Review, No. 135.) Executive Summary. Available from: https://www.ncbi.nlm.nih.gov/books/NBK241518/

12. White HD. Pathobiology of troponin elevations do elevations occur with myocardial ischemia as well as necrosis? J Am Coll Cardiol. 2011;57:2406–8.

13. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med. 2009;361: 2538–47.

14. Kontos MC, Diercks DB. High Sensitivity Troponins and Ischemia Testing: Are We Doing Too Much? Am Heart J. 2021 Jun;236:97-9. [PubMed]

15. Geyer M, Wild J, Münzel T, Gori T, Wenzel P. State of the Art-High-Sensitivity Troponins in Acute Coronary Syndromes. Cardiol Clin. 2020 Nov;38(4):471-9. [PubMed]

16. Babuin L, Jaffe AS. Troponin: biomarker pilihanuntukmendeteksicederajantung. CMAJ. 2005 November 8; 173(10):1191-202. DOI: 10.1503/CMAJ/051291.

17. Chapman AR, Adamson PD, Shah ASV, Anand A, Strachan FE, Ferry AV, et al. High-Sensitivity Cardiac Troponin and the Universal Definition of Myocardial Infarction. Circulation. 2020;141(3):161-71

18. Brotto MA, Biesiadecki BJ, Brotto LS, Nosek TM, Jin JP. Coupled expression of troponin T and troponin I isoforms in single skeletal muscle fibers correlates with contractility. Am J Physiol Cell Physiol. 2006 Feb;290(2):C567-76.

19. Wei B, Jin JP. TNNT1, TNNT2, and TNNT3: Isoform genes, regulation, and structure-function relationships. Gene. 2016 May 10;582(1):1-13.

20. Jacob R, Khan M. Cardiac Biomarkers: What Is and What Can Be. Indian J Cardiovasc Dis Women WINCARS. 2018 Dec;3(4):240-244

21. Garg P, Morris P, Fazlanie AL, Vijayan S, Dancso B, Dastidar AG, Plein S, Mueller C, Haaf P. Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. Internal and emergency medicine. 2017 Mar:12(2):147-155. doi: 10.1007/s11739-017-1612-1. Epub 2017 Feb 11

22. PerhimpunanDokterSpesialisKardiovaskular Indonesia, PedomanTatalaksanaSindromKoronerAkut, 2015 ed 3 http: //jki.or.id

23. Zeymer U. [Diagnosis and initial management of acute myocardial infarction]. MMW Fortschritte der Medizin. 2019 Mar:161(4):34-36. doi: 10.1007/s15006-019-0223-3. Epub

24. Kontos MC, Turlington JS. High-Sensitivity Troponins in Cardiovascular Disease. Current cardiology reports. 2020 Mar 30:22(5):30. doi: 10.1007/s11886-020-01279-0. Epub 2020 Mar 30 [PubMed PMID: 32232671]

25. Clerico A, Zaninotto M, Passino C, Padoan A, Migliardi M, Plebani M. High-sensitivity methods for cardiac troponins: The mission is not over yet. Advances in clinical chemistry. 2021:103():215-252. doi: 10.1016/bs.acc.2020.08.009. Epub 2020 Oct 9

26. Holzmann MJ. Clinical implications of high-sensitivity cardiac troponins. Journal of internal medicine. 2018 Jul:284(1):50-60. doi: 10.1111/joim.12779. Epub 2018 Jun 14

27. Chaulin AM. Cardiac troponins: current information on the main analytical characteristics of determination methods and new diagnostic possibilities. Medwave 2021;21(11):002132

28. Gokhan, I.; Dong, W.; Grubman, D.; Mezue, K.; Yang, D.; Wang, Y.; Gandhi, P.U.; Kwan, J.M.; Hu, J.-R. Clinical Biochemistry of Serum Troponin. Diagnostics 2024, 14, 378. https://doi.org/10.3390/ diagnostics14040378

29. Du,X.; Su, X.; Zhang, W.; Yi, S.; Zhang, G.; Jiang, S.; Li, H.; Li, S.; Xia, F. Progress, Opportunities, and Challenges of Troponin Analysis in the Early Diagnosis of Cardiovascular Diseases. Anal. Chem. 2022, 94, 442–463.

30. Jernberg, T.; Venge, P.; Lindahl, B. Comparison between Second and Third Generation Troponin T Assay in Patients with Symptoms Suggestive of an Acute Coronary Syndrome but without ST Segment Elevation. Cardiology 2003, 100, 29–35

31. Melanson, S.E.F.; Morrow, D.A.; Jarolim, P. Earlier Detection of Myocardial Injury in a Preliminary Evaluation Using a New Troponin I Assay with Improved Sensitivity. Am. J. Clin. Pathol. 2007, 128, 282–286.

32. Ambrose, T. 510(k) Approval Letter for Elecsys Troponin T Stat Assay (K051752). U.S. Food and Drug Administration, Office of In Vitro Diagnostic Device Evaluation and Safety. 2005. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf5/K0 51752.pdf. (Accesed on 23 Juni 2024)

33. European patent 394819 and US patent 6376206 by Roche Diagnostics GmbH. Specific antibodies to Troponin T, their production and use in a reagent for the determination of myocardial necrosis.

34. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndrome in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2016 Jan 14;37(3):267-315. PubMed 26320110

35. Katus HA, Remppis A, Looser S, Hallermeier K, Scheffold T, Klüber W. Enzyme linked immunoassay of cardiac troponin T for the detection of acute myocardial infarction in patients. *J Mol Cell Cardiol.* 1989 Dec;21(12):1349-1353. PubMed 2632816

36. Katus HA, Scheffold T, Remppis A, Zehlein J. Proteins of the troponin complex. *Laboratory Medicine.* 1992 May 1;23(5):311-317. Available at https://doi.org/10.1093/labmed/23.5.311. Accessed January 2021.

37. Latini R, Masson S, Anand IS, et al. Prognostic Value of Very Low Plasma Concentrations of Troponin T in Patients with Stable Chronic Heart Failure. Circulation 2007;116:1242-1249.

38. Omland T, De Lemos JA, Christophi C, et al. Distribution and determinants of very low levels of cardiac troponin T in patients with stable coronary artery disease: The PEACE trial. Eur Heart J 2008;9(202):1342.

39. European patent 1890154 Cardiac Troponin as an indicator of advanced coronary artery disease.

40. European patent 1837659 Means and methods for the differentiation of acute and chronic myocardial necrosis in symptomatic patients.

41. Lauer B, Niederau C, Kühl U, et al. Cardiac troponin T in patients with clinically suspected myocarditis. JACC 1997;30:1354-1359.

42. Swaanenburg JC, Klaase JM, DeJongste MJ, et al. Troponin I, troponin T, CK-MB-activity and CK-MB mass as markers for the detection of myocardial contusion in patients who experienced blunt trauma. Clin Chim Acta 1998;272:171-181.

43. Giannitsis E, Müller-Bardorff M, Kurowski V, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. Circulation 2000;102:211-217.

44. Herman EH, Lipshultz SE, Rifai N, et al. Use of cardiac troponin T levels as an indicator of doxorubicin-induced cardiotoxicity. Cancer Res 1998;58:195-197.

45. Sharma R, Gaze DC, Pellerin D, et al. Cardiac structural and functional abnormalities in end stage renal disease patients with elevated cardiac troponin T. Heart. 2006 Jun;92(6):804-9. Epub 2005 Oct 10.

46. Deegan PB, Lafferty ME, Blumsohn A, et al. Prognostic value of troponin T in hemodialysis patients is independent of comorbidity. Kidney Int. 2001 Dec;60(6):2399-405.

47. Creative Biolabs. Protocol of Sandwich ELISA with Streptavidin-biotin Detection. Manual user

48. BIO-RAD. Protocol: Sandwich ELISA with streptavidin-biotin detection. Manual user

49. Collinson PO, Gerhardt W, Katus HA, Müller-Bardorff M, Braun S, Schricke U, Vogt W, Nagel D, Zander M, Leinberger R, Mangold D, Zerback R. Multicentre evaluation of an immunological rapid test for the detection of troponin T in whole blood samples. Eur J Clin Chem Clin Biochem. 1996 Jul;34(7):591-8. PMID: 8864412.

50. Widhongyudana L, Rita S. Mulyawan S. Gideon S. Uji Diagnostik Troponin T-RA Pada PenderitaMiokarditisAkut. JKM. Vol. 1, No. 1, 2001, 54 – 64

51. Roche. CARDIAC POC Troponin T tes by cobas h232 manual user

52. Takeda, Soichi; Yamashita, Atsuko; Maeda, Kayo; Maéda, Yuichiro (July 2003). "Structure of the core domain of human cardiac troponin in the Ca2+ saturated form". *Nature*. **424** (6944): 35–41.

53. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR and White HD. Third Universal Definition of Myocardial Infarction. Circulation. 2012; 126: 2020–35.

54. Jarolim P. High Sensitivity Cardiac Troponin Assays in the Clinical Laboratories. Clin Chem Lab Med. 2015; 53(5): 635-52.

55. EUROlyser. Troponin I test. Manual user

56. Atlas Medical. CTnI One Step Troponin I Test Device (Whole Blood / Serum / Plasma) A rapid, one step test for the qualitative detection of cardiac Troponin I in whole blood, serum or plasma. Manual User

57. Samsu N, Sargowo D. Sensitivitas dan Spesifitas Troponin T dan I pada Diagnosis InfarkMiokardAkut. MajalahKedokteran Indonesia. 2007; 57: 363–72.

58. Sheila Febriana, AsvinNurulita, UlengBahrun. Penilaian Uji Troponin I Dengan Point of Care Testing (Evaluation of Troponin I Assay with Point of Care Testing). Indonesian Journal of Clinical Pathology and Medical Laboratory, Vol. 22, No. 2 Maret 2016: 114–118.

59. Siti Fatonah, AnikWidijanti, Tinny EndangHernowati. Nilai Diagnostik Uji Troponin I KuantitatifMetodeImmunokromatografi. Indonesian Journal of Clinical Pathology and Medical Laboratory, Vol. 14, No. 1, November 2007: 20-23

60. Garg, P., Morris, P., Fazlanie, A.L., Vijayan, S., Dancso, B., Dastidar, A.G., Plein, S., Mueller, C., Haaf, P. Cardiac Biomarkers of Acute Coronary Syndrome: from History to High-Sensitivity Cardiac Troponin. Intern Emerg Med. 2017; 12:147–155.

61. Giannitsis E, Katus HA. Myocardial Infarction.Current Recommendations for Interpretation of the Highly Sensitive Troponin T Assay for Diagnostic, Therapeutic and Prognostic Purposes in Patients with a Non-ST-segment-elevation Acute Coronary Syndrome. (touch briefings). Gemany. Med. Departement III. Heidelberg Univ. Hosp. 2010: 44–47.

62. Xu, R.Y., Zhu, X.F., Yang, Y., Ye, P., High-Sensitive Cardiac Troponin T. Journal of Geriatric Cardiology. 2013; 10: 102−109

63. Mahajan VS, Jarolim P. How to Interpret Elevated Cardiac Troponin Levels. Circulation J. 2011; 124: 2350–54.

64. Giuliani S, Dieplinger B, Mueller T.Head-to-head comparison of three different high-sensitivitycardiac troponin assays for early rule-in and rule-out of acutemyocardial infarction. J Lab Precis Med 2019;4:4

65. Wu AHB, Christenson RH, Greene DN, et al. Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem 2018;64:645-55

66. Andruchow JE, Kavsak PA, McRae AD. Contemporary Emergency Department Management of Patients withChest Pain: A Concise Review and Guide for the High-Sensitivity Troponin Era. Can J Cardiol 2018;34:98-108

67. Boeddinghaus J, Twerenbold R, Nestelberger T, et al. Clinical Validation of a Novel High-Sensitivity Cardiac Troponin I Assay for Early Diagnosis of Acute Myocardial Infarction. Clin Chem 2018;64:1347-60.

68. Li L, Shu X, Zhang L, Xu A, Yang J, Jing Y, Wang H, Zhang Z. Evaluation of the analytical and clinical performance of a new high-sensitivity cardiac troponin I assay: hs-cTnI (CLIA) assay. Clin Chem Lab Med. 2023 Sep 26;62(2):353-360. doi: 10.1515/cclm-2023-0529. PMID: 3774685

69. Roche. Elecsys Troponin T hs by Cobas e 402. Manual User

70. Westwood M, van Asselt T, Ramaekers B, *et al*. High-sensitivity troponin assays for the early rule-out or diagnosis of acute myocardial infarction in people with acute chest pain: a systematic review and cost-effectiveness analysis. Southampton (UK): NIHR Journals Library; 2015

71. Nergiz Zorbozan, Gokce Filiz Atikeler. Evaluation of high-sensitivity cardiac troponin measurement procedure performance in serum: the vidas 3 high sensitivity cardiac troponin I. Int J Med Biochem . 2020; 3(3): 161-165

72. Aldo Clerico, Martina Zaninotto, Alberto Aimo, *et.al.* High-sensitivity Point of Care Testing (POCT) methods for Cardiac Troponins: analytical features and clinical relevance. A consensus document by the Study Group on Cardiac Biomarkers from the Italian Society of Biochemical Chemistry (SIBioC) and the European Ligand Assay Society (ELAS). Biochimica Clinica, 2023

73. Giuseppe Lippi, Laura Pighi, Elisa Paviati, *et al*. Analytical evaluation of the novel Mindray high sensitivity cardiac troponin I immunoassay on CL-1200i. Clin Chem Lab Med 2024; Jan 8. DOI: 10.1515/cclm-2023-144

74. Siemens Healthcare Diagnostics Inc. ADVIA Centaur High-Sensitivity Troponin I Assay. Manual Users

Turn it in The Role of Troponin And Use of Troponin Assays

by yasmine mashabi

Submission date: 18-Sep-2024 07:01AM (UTC+0700)
Submission ID: 2456639095
File name: Yasmine.pdf (678.08K)
Word count: 8093
Character count: 45605

Journal of Medical Case Reports and Reviews

Received 25 Aug 2024 | Revised 30 Aug 2024 | Accepted 10 Sep 2024 | Published Online 16 Sep 2024

DOI:10.52845/JMCRR2024/7-9-1

JMCRR 07 (9), 1392-1404

ISSN (O) 2589-8655 | (P) 2589-8647 IF: 2.964

Original research Articles

The Role of Troponin And Use of Troponin Assays

Yasmine Mashabi[1*], Nany Hairunisa[2], Mario[1], Husnun Amalia[3], Ade DwiLestari[2], Emad Yousif[4]

1. Department of Clinical Pathology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

2. Department of Occupational Medicine, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

3. Department of Ophthalmology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia.

4. Department of Chemistry, Al-Nahrain University, Bagdad, Iraq

Abstract:- Troponin is a crucial protein present in various muscle types, including cardiac muscle (myocardium), and plays an essential role in muscle contraction, facilitating the heartbeat. Normally, only minimal levels of troponin are found in the blood. However, when myocardial injury occurs, cardiac troponin (cTn) is released into the bloodstream from the heart muscle. Monoclonal antibodies specific to cTn have enabled the development of assays for measuring cTn levels in the blood. The amount of troponin released is proportional to the severity of heart damage. During a heart attack, the heart muscle's lack of oxygen-rich blood causes damage and the subsequent release of troponin into the bloodstream.

There are three types of troponin: Troponin I (TnI), Troponin T (TnT), and Troponin C (TnC). Only TnI and TnT are used for diagnosing heart attacks because TnC cannot be identified as originating specifically from the heart muscle. Normal blood troponin levels are very low, typically between 0-0.04 nanograms per milliliter, which were difficult to measure accurately with initial tests. The advent of the high-sensitivity cardiac troponin test (hs-cTnT) now allows for detecting low levels of cardiac troponin, enabling earlier and more accurate diagnosis of heart attacks.

Troponin I can be analyzed using various methods such as Enzyme-Linked Immuno sorbent Assay (ELISA), Enzyme-Linked Fluorescent Assay (ELFA), Radioimmunoassay (RIA), Fluorescence Immunoassay, and Immuno chromatography (ICT). Plasma troponin T levels can be measured using ELISA based on the Biotin-Streptavidin principle and qualitative TnT examination by immunoassay (TnT-RA). High-sensitivity troponin T (hs-TnT) and high-sensitivity troponin I (hs-cTnI) are measured using the Electro chemiluminescence Immunoassay (ECLIA) method.

Keywords: Troponin, Cardiac Troponin, hs-cTnT, hs-cTn I, Fluorometry, Immuno chromatography, Immunoassay (ELISA), Electro chemiluminescence Immunoassay (ECLIA).

Supplementary information The online version of this article (https://doi.org/xx.xxx/xxx.xx) contains supplementary material, which is available to autho-rized users.

Corresponding Author: Yasmine Mashabi* Department of Clinical Pathology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia

BACKGROUND :

The high prevalence of cardiovascular disease significantly impacts patients, doctors, and healthcare services. Chest pain, a potential sign of acute myocardial infarction (AMI), is one of the most common reasons for emergency department visits worldwide. Many clinical care advancements rely on cTn testing, with the most notable benefits observed in hospital settings. This cTn test detects myocardial injury, enabling the detection of low concentrations with high precision.[1-4] Cardiac troponin has been used clinically since 1995, following the approval of the first cardiac troponin T (cTnT) test.[5,6] Cardiac Troponin (cTn) is considered superior to creatinine kinase MB (CK-MB) for diagnostic and prognostic purposes.[4]

Troponin is a protein that regulates muscle tissue, specifically found in the heart muscle, known as cardiac troponin (cTn). During myocardial injury, cTn is released into the bloodstream from the myocardium. The development of cTn-specific tests using monoclonal antibodies has enabled the measurement of cTn concentrations in the blood. These assays have improved their analytical performance and are now the primary laboratory biomarker for diagnosing myocardial infarction (MI). The amount of troponin released correlates with the extent of myocardial damage, making quantitative cTn results valuable for prognosis.[4,7,8] Enhancements in cardiac specificity and sensitivity have significantly increased the frequency and accuracy of cardiovascular disorder diagnoses, particularly with high-sensitivity cardiac troponin tests.[9]

Troponin is a complex protein consisting of three subunits (T, I, and C) that play a role in muscle contraction regulation. Both cardiac and skeletal muscles contain troponin C, while troponin T and I are typically considered cardiac-specific. The three-unit troponin complex (troponin I, T, and C), along with tropomyosin, is situated on actin filaments and is crucial for the calcium-mediated regulation of muscle contractions. Tissue-specific isoforms of troponin I, T, and C exist, but since the cardiac isoform of troponin C is also present in slow-twitch skeletal muscle, it lacks cardiac specificity and is not used in diagnostic tests for cardiac injury.[10,11]

When cardiac injury occurs due to ischemia or other causes, cardiomyocytes release cardiac troponin into the bloodstream proportionally to the extent of the damage. Troponin levels rise within 3 to 4 hours after injury onset and remain elevated for 4 to 7 days for troponin I or 10 to 14 days for troponin T. Cardiac troponin T and I are integral components of the cardiomyocyte contractile apparatus and serve as biomarkers for necrosis. These troponins are the most commonly measured indicators in patients with acute coronary syndrome. Elevated cardiac troponin levels, even those below the detection limit for a positive test, may predict adverse cardiovascular events. Plasma cardiac troponin is a sensitive and specific biomarker commonly used for diagnosing myocardial infarction. The development of the highly sensitive troponin T (hs-cTnT) assay facilitates early detection of myocardial infarction and serves as a prognostic tool for stable coronary artery disease.[11] Cardiac troponin T (cTnT) and troponin I (cTnI) share similar amino acid sequences, differing from their skeletal muscle isoforms and being encoded by unique genes.[14] Human cTnI has 31 additional amino acid residues at the amino-terminal end compared to skeletal muscle TnI, conferring complete cardiac specificity.[15] cTnT is encoded by a gene distinct from that encoding the skeletal muscle isoform, with 11 additional amino acid residues at the amino-terminal end, providing unique cardiac specificity.[11]

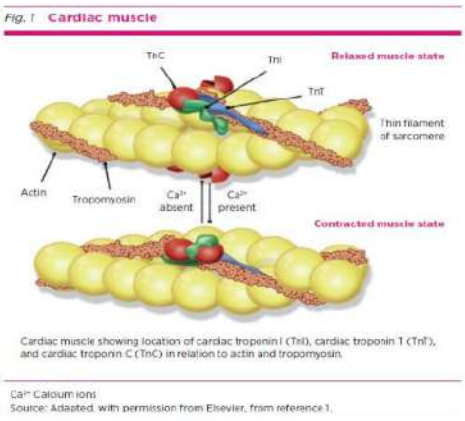


Figure1 Cardiac Muscle[10]

ETIOLOGY AND EPIDEMIOLOGY

Troponin exists in three different molecular forms according to specific isotypes. The molecular weights of cTnI and cTnT are 23,500 and 33,500 Daltons, respectively. Despite being smaller than CK-MB (86,000 Daltons), most troponin is released as a higher molecular weight complex.[16] The skeletal isotypes are similar in molecular size, about 20,000 Daltons, and show amino acid sequence heterogeneity of about 40%.[17,18] The cardiac isotype also shows approximately 40% sequence heterogeneity concerning the skeletal isotype and has 31 additional residues at the amino terminus. It is thus possible to differentiate cardiac troponin immunologically from bone troponin.[19] Before troponin, several cardiac biomarkers were used to identify myocardial injury.[20] In the 1960s and 1970s, biomarkers such as aspartate transaminase (AST), lactate dehydrogenase (LDH), and creatinine kinase (CK) were used. However, they were later replaced due to a lack of specificity for cardiac muscle.[17] The next generation of biomarkers was more specific for cardiac muscle, including CK-MB and LDH. However, these markers still had a very high false positive rate, necessitating the development of new, more specific biomarkers.[21] Troponin was first identified in 1965, but a reliable immunoassay to detect its levels in the blood was not developed until the late 1990s.[17] Troponin measurements were found to have nearly 100% sensitivity when examined 6 to 12 hours after the onset of chest pain and have significantly increased specificity for heart muscle damage compared with previous biomarkers.[21] Because of its clinical utility, serial troponin testing was added to the Fourth Universal Definition of Myocardial Infarction, the current definition used by the American College of Cardiology.[17]

PATHOPHYSIOLOGY

Myocardial infarction is not always caused by total occlusion of the coronary arteries. Subtotal obstruction accompanied by dynamic vasoconstriction can cause ischemia and necrosis of heart muscle tissue (myocardium).[22] During this process, cell membranes rupture, causing intracellular contents to spill into the extracellular space, which ultimately enters the bloodstream.[17,23] If the cellular contents, including troponin, are shed in large enough quantities, they can be detected in the blood circulation. Creatinine kinase-MB (CK-MB) or troponin I/T is a marker of cardiac myocyte necrosis and is a marker for the diagnosis of myocardial infarction. Troponin I/T as a marker of cardiac necrosis has higher sensitivity and specificity than CK-MB.[23]

An increase in cardiac markers only indicates myocyte necrosis, but cannot be used to determine the cause of myocyte necrosis (coronary/noncoronary causes). Troponin I/T can also increase due to non-coronary cardiac disorders such as tachyarrhythmias, cardiac trauma, heart failure, left ventricular hypertrophy, and myocarditis/pericarditis. Noncardiac conditions that can increase I/T troponin levels are sepsis, burns, respiratory failure, acute neurological disease, pulmonary embolism, pulmonary hypertension, chemotherapy, and renal insufficiency. Troponin T and troponin I provide balanced information on the occurrence of myocyte necrosis, except in cases of renal dysfunction. In this situation, troponin I has a higher specificity than troponin T.[22]

Troponin levels usually begin to increase in circulation within two to three hours after the onset of chest pain. The levels will continue to increase until they reach their peak, generally between 12 and 48 hours. Troponin levels will then fall to normal over the next four to ten days.[24,25] These expected troponin rises and falls can help differentiate myocardial infarction from other causes of troponin elevation.[25] The actual half-lives of cTnI and cTnT are short – about two hours in plasma. However, due to the continuous release of troponin from necrotic myocardium, its half-life is 24 hours, with cTnT being slightly longer.[26]

Cardiac marker examination should be carried out in a central laboratory. Examinations in the emergency room or cardiac intensive care unit (point of care testing) generally take the form of qualitative or semiquantitative tests, which are faster (15-20 minutes) but less sensitive. Point-of-care testing as a routine diagnostic tool is only recommended if the examination time at the central laboratory takes >1 hour. If cardiac markers using point-of-care testing show negative results, the examination must be repeated at a central laboratory.[22]

TROPONIN TEST GENERATION

Determination of troponin in the blood is carried out through different immunochemical methods (radioimmunoassay, enzyme immunoassay, immunofluorescence, and immune chemiluminescence). This process includes several successive stages of immunology, chemistry, and detection. There has been a long-standing need to create specific immunochemical tests to determine troponin I and troponin T to diagnose acute

myocardial infarction. In 1987, Cummins reported the first method (first-generation immunoassay) to determine troponin I.[27,28]

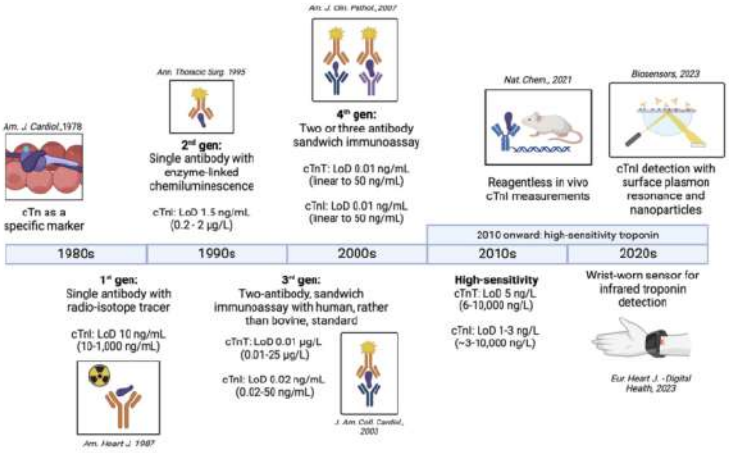


Figure 2 Evolution of troponin measurement assays from the 1980s to the 2020s, and the limits of detection (LoD) associated with each assay generation.[23]

Second Generation of Tn tests have better detection rates than first-generation tests (~1.5 ng/mL).[28] An important change was the introduction of direct enzyme-linked immunoassay (ELISA) technology as a replacement for radio-isotope reading. Measurement of TnI levels in serum is carried out using optical reading of visible light absorbance, which not only avoids exposure to radioactive labeling but also provides higher sensitivity because the enzyme is able to amplify the signal from minimal amounts of Tn antigen.[29] In addition, several second-generation tests began using two Tn-specific antibodies to increase specificity and sensitivity. A typical second-generation assay, using ELISA technology, has a range of 0.2–20 µg/L and a within-run coefficient of variation of 4.7%. In an important improvement over the first-generation test, the second-generation test can be performed within 30 minutes and shows no cross-reactivity with skeletal muscle. A limitation of most second-generation TnT assays is that calibration is performed with a TnT standard, which produces curves that are not always linear.[28,30] However, this limitation is addressed in third-generation Tn assays, described below.

Continued advancements in detection technology, such as the Roche Elecsys 2010 immunology analyzer, have significantly enhanced sensitivity compared to third-generation tests. Notably, this generation adopted human troponin standards for calibration, resolving non-linearity issues associated with bovine troponin standards. Due to the increased sensitivity, a study of 750 patients admitted to a coronary care unit revealed that an additional 35% of patients were diagnosed with acute myocardial infarction.[30] Additionally, because they are more sensitive, third-generation assays can identify a subgroup of patients with mild myocardial injury, who were found to have an increased risk of future cardiac events. The ability for mild Tn elevation to carry prognostic significance in subclinical disease will be a common feature for the next generation of Tn assays.[28]

The fourth-generation assay has further improved the sensitivity of troponin measurements compared to the third-generation. Many of these assays continue to employ the direct chemiluminescent technology introduced in the second-generation tests. Notably, fourth-generation tests use at least two unique antibodies, and some even utilize three. For instance, the ADVIA Centaur TnI-Ultra assay incorporates one monoclonal antibody and two polyclonal antibodies targeting the central region of TnI, enhancing binding efficiency. Combined with a proprietary blocking reagent that eliminates nonspecific binding, this technique achieves an assay range of 0.006-50 ng/mL, with a 99th percentile value of 0.04 ng/mL and a 10% coefficient of variation (CoV) of 0.02 ng/mL.[31] Another widely used fourth-generation assay, the Roche ElecsysTnT Stat, employs direct sandwich immunoassay technology, incorporating streptavidin-coated microparticles to enhance signal detection. This fourth-generation test offers an analytical sensitivity of 0.01 ng/mL, with a concentration of 0.03 ng/mL yielding a 10% coefficient of variation (CoV).[32]

TROPONIN T

Troponin T (TnT) is a component of the contractile apparatus of striated muscles. Although the function of TnT

is the same in all striated muscles, TnT originating exclusively from the myocardium (cardiac TnT, molecular weight 39.7 kDa) is clearly different from skeletal muscle TnT. As a result of its high tissue specificity, cardiac troponin T (cTnT) is a highly sensitive cardio-specific marker for myocardial damage.[33]cTnT increases approximately 3–4 hours after acute myocardial infarction (AMI) and can persist for up to 2 weeks afterward.[34-36] In contrast to ST-elevation myocardial infarction (STEMI), the diagnosis of non-ST-elevation myocardial infarction (NSTEMI) relies heavily on cardiac troponin results. Elevated cTnT levels correlate with the severity of coronary artery disease and poor outcomes regardless of natriuretic peptide (BNP or NT-proBNP) levels.[37-40] Myocardial cell injury, leading to increased blood cTnT concentrations, can also occur in various clinical conditions such as myocarditis, heart contusion, pulmonary embolism, and drug-induced cardiotoxicity. Elevated troponin levels in renal failure are linked to increased cardiovascular risk, with chronic cTnT elevations greater than 50 ng/L detected in over 50% of patients with severe renal failure.[41-46]

Troponin T is a cardiac protein found in striated muscle that functions as a specific regulator of muscle contraction in cardiac muscle. There are three ways to measure plasma troponin T levels, namely by ELISA (Biotin - Streptavidin principle), streptavidin-biotin technology has been effectively used to improve ELISA detection because of the strong affinity between biotin and streptavidin having a dissociation constant (Kd) in the femtomolar range.[47] Combined antibodies with biotin, followed by a streptavidin-conjugated enzyme step. Alternatively, it is possible to use an unlabeled primary antibody followed by an enzyme-coupled or biotinylated secondary antibody. If the secondary antibody is biotinylated, then a tertiary step is required for detection. In this case, treatment with a streptavidin enzyme conjugate is followed by a suitable substrate. Because biotin and streptavidin interact strongly, more analyte molecules can be captured on the ELISA plate.[47,48]

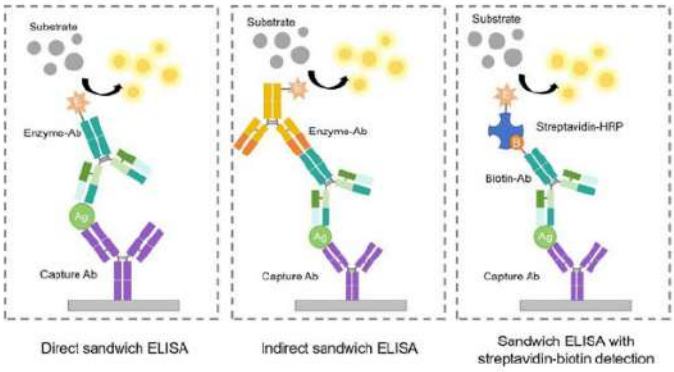


Figure 3 Normal mode and sandwich signal amplification mode of ELISA.[47]

The main advantage of sandwich ELISA is its high sensitivity. It is 2-5 times more sensitive than direct or indirect ELISA. Sandwich ELISA also provides high specificity because two antibodies are used to detect the antigen. This offers flexibility as both direct and indirect methods can be used. Sandwich ELISA also presents several disadvantages, namely that if a standard ELISA kit or the antibody pair being tested is not available, antibody optimization must be carried out as it is important to reduce cross-reactivity between the capture and detection antibody pairs. Sandwich ELISA is well suited for the analysis of complex samples, as antigens do not need to be purified before testing but still provide high sensitivity and specificity. The procedure for sandwich ELISA begins with coating the wells of the ELISA plate with capture antibodies. Next, the analyte or sample is added, followed by the detection antibody. Based on the detection principle and the use of enzyme-labeled capture antibodies, sandwich ELISA can be categorized into three forms: direct sandwich ELISA, indirect sandwich ELISA, and sandwich ELISA with streptavidin-biotin detection.[47]

The next method is qualitative TnT examination using the TnT – RA Immuno Assay. In September 1994, Boehringer Manheim released the troponin T Rapid Assay (TROPT®) test, which is a rapid immunological test based on two specific monoclonal antibodies with different labels, one of which is labeled gold and the other is labeled biotin.[49]TnT-RA was carried out using the Elisa dry chemistry method, based on the sandwich principle, and the results were expressed qualitatively. After adding 150 µL whole blood, the erythrocytes are absorbed by the glass fiber, while the plasma with antibody-troponin T-complex flows into the detection zone. In this zone, the troponin sandwich complex is concentrated on the streptavidin signal line by the affinity between streptavidin and biotin. The complex accumulation

on these lines can be detected visually by the purple color of the gold particles. Excess gold-labeled antibodies bound to the control line. This proves that the inspection went well. The results can be read 20 minutes after adding the blood sample. There is a minimum threshold value for the detection of TnT using TnT-RA with a serum TnT level of 0.3 ng/mL. In this way, the examination can be carried out immediately, even "bedside" (beside the bed).[49,50]

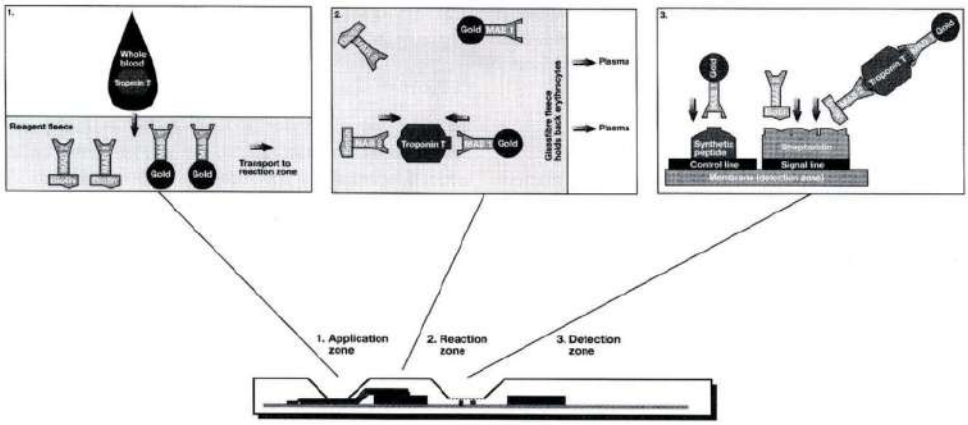


Figure 4 Test principle of TROPT® rapid test. MAB = monoclonal antibody[49]

Subsequently, Roche developed the troponin T point-of-care (POC) test based on the same principle as TROPT®. This test involves the instrument's optical system detecting two lines and measuring the intensity of the signal lines. The integrated software then converts the signal intensity into a quantitative result, displayed on the screen. The results are expressed quantitatively in units of ng/mL for troponin T levels. Normal troponin T levels are considered to be less than 50 ng/mL, values between 50-100 ng/mL are categorized as low, and values greater than 100 ng/mL indicate possible acute myocardial infarction (IMA). This quantitative immunological test is used to detect cardiac troponin T in heparinized venous blood, specifically designed for use with the Cobas H 232 instrument. It serves as an initial diagnostic aid for acute myocardial infarction and helps identify patients with a high risk of mortality.[51]

TROPONIN I

Troponin I is a component of cardiac and skeletal muscle proteins. It is part of the troponin protein complex, where it binds to actin in thin myofilaments to hold the actin-tropomyosin complex in place. Troponin I prevents myosin from binding to actin in relaxed muscles. After that, tropomyosin leaves the binding site for myosin on actin causing muscle contraction. It is a useful marker in the laboratory diagnosis of heart attack. It occurs in different plasma concentrations but the same circumstances as troponin T – both tests can be performed to confirm heart muscle damage and laboratories usually offer one test or the other.[52]

Troponin I is a more commonly used diagnostic marker for myocardial infarction because it is specific to myocardial tissue and has high sensitivity. In addition, it can detect the presence of small myocardial necrosis which is not detected on electrocardiogram examination or by CK MB. Troponin I is very specific to cardiac muscle tissue because it is not expressed by other tissues, is undetectable in healthy individuals, and shows an increase above normal limits in patients with myocardial infarction. Troponin I is the biological marker of choice according to the guidelines of The Third Global Myocardial Infarction Task Force World Health Organization (WHO).[53,54] Cardiac troponin I is expressed in cardiac muscle tissue by a single isoform with a molecular weight of 23,876 Da and consists of 209 amino acid residues. For more than 15 years, troponin I has been recognized in the literature as a reliable marker for cardiac muscle tissue injury and is considered more sensitive and significantly more specific in the diagnosis of myocardial infarction than CK MB.[55]

Troponin I is part of a three-subunit complex along with Troponin T and Troponin C. This complex, along with tropomyosin, regulates the activity of calcium-sensitive ATPase actomyosin in striated skeletal and cardiac muscle. Following a heart injury, Troponin I is released into the bloodstream within 4-6 hours after the onset of pain. Its pattern is similar to CK-MB, but while CK-MB levels normalize after 72 hours, Troponin I remains elevated for 6-10 days, providing a longer detection window for cardiac injury. The high specificity of cTnI measurements for identifying myocardial damage has been demonstrated in various conditions such as the perioperative period, post-marathon running,

and blunt chest trauma. cTnI release has also been observed in cardiac conditions other than acute myocardial infarction (AMI), such as unstable angina, congestive heart failure, and ischemic damage from coronary artery bypass surgery. Due to its high specificity and sensitivity for myocardial tissue, Troponin I has recently become the preferred biomarker for myocardial infarction.[56]

The cTnI One Step Troponin I (Whole Blood/Serum/Plasma) Test Kit is a simple test that uses a combination of anti-cTnI antibody-coated particles and capture reagents to selectively detect cTnI in whole blood, serum, or plasma. The minimum detection level is 1.0 ng/mL. Cardiac troponin I (cTnI) levels begin to increase three hours after injury, peak between 12-24 hours, and remain elevated for 5-7 days. cTnI levels in the bloodstream rise with the initial injury and decrease as the enzyme is cleared from circulation.[54,57] Troponin I can be examined using the Enzyme-Linked Immunoabsorbent Assay (ELISA), Enzyme-Linked Fluorescent Assay (ELFA), Radioimmunoassay (RIA), Fluorescence immunoassay and Immunochromatography (ICT). The samples used also vary, you can use serum samples, heparin plasma, and Ethylene Diamine Tetra-Acetic (EDTA) or whole blood.[58]

The One Step Troponin I (Whole Blood/Serum/Plasma) cTnI Test Device is a qualitative membrane-based immunoassay for detecting cTnI in whole blood, serum, or plasma. The membrane is coated with a capture reagent on the test line area of the test. During testing, whole blood, serum or plasma specimens react with particles coated with anti-cTnI antibodies. The mixture migrates up the membrane chromatographically by capillary action to react by capturing reagents on the membrane and producing colored lines. The appearance of this colored line in the test line area indicates a positive result, whereas if it does not appear it indicates a negative result. To serve a procedural control, a colored line will always appear in the control line region indicating that the correct specimen volume has been added and membrane wicking has occurred.[56]

In Indonesia, many qualitative cTnI kits are circulating, but they cannot be used to follow the course of the disease and stratify the risk of mortality. Recently introduced a quantitative cTnI rapid test kit with serum material and a small device. The fluorometric method for cTnI is quite fast but requires a fluorometer, while quantitative cTnI measurements using the enzyme immunoassay method require a long time. Due to variations in the sensitivity and specificity of the cTnI test, a separate study is needed.[59]

EXAMINATION OF THE HIGH-SENSITIVE CARDIAC TROPONIN (HS CTN) TEST

The role of cardiac troponin as a diagnostic biomarker of myocardial injury in the context of Acute Coronary Syndrome (ACS) is well established. Since the first generation test, the development of the 5th generation high sensitivity cardiac troponin (hs-cTn) test has marked significant progress and is now widely used.[60] This change has increased the sensitivity of the analysis, which is almost one-third of the previous value, from 0.010 µg/L (= 10 ng/L) to 0.003µg/L (=3 ng/L). For the hs-cTnT test, the 99th percentile value, obtained from a multicenter reference population, yields a cut-off value of 14 pg/mL (=14 ng/L).[61,62] Use of the hs-cTn test is found at low levels even in plasma-healthy subjects. The hs-cTn test can be found in 95% of the reference population. The ability to find cTn in healthy people requires determining the clinical limit value for cTn levels, namely a "positive" cTn result.[63]

In some tests, cTn is not found in 50% of individuals who do not appear sick, while in the hs-cTn test it can be found in up to 90%. The joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation (ESC/ACCF/AHA/WHF) seeks to clarify the universal boundaries of myocardial infarction. The hs-cTn test detects early cTn release from the previous cTn test, which increases the initial sensitivity for diagnosing AMI. Because the frequency of detection is high and slightly higher than the hs-cTn value in the community, especially in patients with cardiovascular comorbidities, it is important to know that an increase in hs-cTn levels alone is not enough to diagnose AMI.[53]

According to current guidelines, the analytical coefficient of variation (CV) of a cardiac troponin test should be <10% at the 99th percentile upper reference limit (URL) of a normal reference population.[64,65] Additionally, the same guidelines claim that a cardiac troponin test should measure analyte concentration above the limit of detection (LOD) in ≥50% of the normal reference population. If cardiac troponin tests can meet these two requirements, they are called high-sensitivity cardiac troponin T (hs-cTnT) and high-sensitivity cardiac troponin I (hs-cTnI) tests.[64,66] For the diagnosis of AMI, the clinician must consider the patient's clinical presentation, studies electrocardiogram, and imaging, as well as cardiac troponin plasma concentrations. Especially in the emergency department (ED), physicians try to exclude AMI quickly, and compared with using the older cardiac troponin test, using the hs-cTnT and hs-cTnI tests reduces the time to rule out AMI.[64]

Comparing high sensitivity cardiac troponin I (hs-cTnI) and high sensitivity cardiac troponin T (hs-cTnT) assays can be challenging due to different reference ranges for the general population and varying assay-specific pre-analytic and analytical variables. False positives and false negatives may arise from non-reproducible "flyers" or interference with assay-specific native antibodies. Currently, the patented hs-cTnT test is only available from Roche Diagnostics. In contrast, six hs-cTnI assays (from Abbott, Beckman Coulter, BioMerieux, Pathfast, Siemens, and Singulex) are commercially available. Of these, the Roche hs-cTnT assay (Elecsys platform) and the Abbott hs-cTnI assay (Architect platform) have been extensively investigated in large diagnostic studies, including the successful derivation and validation of the 0/1 hour and 0/2 hour algorithms.[67]

A recent study by Boeddinghaus et al. validating the Siemens hs-cTnI assay for early diagnosis of AMI and comparing its performance with the Roche and Abbott assays is an important step forward to increase our knowledge of commercially available hs-cTnI assays. Boeddinghaus et al. concluded, that the diagnostic accuracy and clinical utility of the Siemens hs-cTnI assay were adequate and comparable to those of the Roche hs-cTnT and Abbott hs-cTnI assays.[64,67] The hs-cTnI assay (CLIA) is a high-sensitivity troponin I method with high precision, sensitivity, and high specificity. The clinical diagnostic performance of hs-cTnI (CLIA) is comparable to the established ARCHITECT hs-cTnI assay. The Mindray hs-cTnI (CLIA) assay is an attractive alternative for the diagnosis of myocardial infarction with high levels of accuracy and safety.[68]

The Roche ElecsyscTnT-hs test (high sensitive troponin T assay) and the Roche ElecsyscTnT-hs STAT test (Roche Diagnostics GmbH, Mannheim, Germany) can be used on the Roche Elecsys 2010 analyzer and the Cobas Modular Analytics e series immunoassay analyzer, e411 platforms. This assay is a quantitative, sandwich electro chemiluminescence immunoassay (ECLIA) for serum and plasma samples. Results are available within 18 minutes with the standard test and within 9 minutes if the STAT test is used. Both assay versions were able to detect cTnT in 61% of the reference population and had a recommended 99th percentile cutoff of 14 ng/l, with a CV < 10%. Both versions of the test are CE-marked and available for the NHS.[69,70]

The Abbott ARCHITECT hs-cTnI STAT assay (Abbott Laboratories, Chicago, IL, USA) can be used using the Abbott ARCHITECT i2000SR and i1000SR. The assay is a quantitative chemiluminescent micro particle immunoassay (CMIA) for serum or plasma samples. Results are available within 16 minutes. The STAT ARCHITECT hs-cTnI assay can detect cTnI in 96% of the reference population, and has a recommended 99th percentile cutoff of 26.2 ng/l, with a CV of 4%. The test is CE-marked and available on the NHS.[70]

The AccuTnI + 3 hs-cTnI assay is approved for use with the Beckman Coulter Access 2 and DxI devices. This assay uses a quantitative two-site paramagnetic particle chemiluminescent sandwich immunoassay method for serum or plasma samples. The AccuTnI+ 3 assay has a recommended 99th percentile limit of 40 ng/l, with a CV < 10%. Recently a study reported data showing that the assay could detect cTnI in 88% of the reference population when used on the Access II analyzer and in 58% of the reference population when used on the DxI analyzer. The same study reported differences in the 99th percentile upper reference limits between the two analyzers (41 ng/l for Access II and 34 ng/l for DxI).[70]

The hs-cTn I assay was performed using the ELFA measurement procedure on a Vidas 3 analyzer. Vidas troponin I is a quantitative test using a one-step immunoenzymatic sandwich method. Serum samples were transferred to wells containing anti-hs-cTn I antibody (conjugate) labeled with alkaline phosphatase. This allows the formation of a sandwich structure with troponin I, immunoglobulin, and conjugate bound to the inner wall of the solid phase. In the final stage, the substrate is hydrolyzed by the conjugate enzyme to become a fluorescent product (4-methyl-umbelliferone). The fluorescence intensity is proportional to the antigen concentration. The volume of serum required for analysis is 150 µl. Analysis time under 17 minutes.[71]

The PATHFAST POC hs-cTnI method uses a benchtop immunometric analyzer called PATHFAST™ (PHC Europe B.V., Nijverheidsweg, Netherlands; distributed in Italy by GEPA, Bollate, Milano), which incorporates chemiluminescence (CLEIA) technology for signal detection (alkaline phosphatase enzyme bound to anticTnI monoclonal antibodies) and magnetic migration (called Magtration®) for separation of bound phases, using antibodies tagged by magnetic particles. This instrument requires a volume of 100 mL of whole blood, plasma, or serum; Up to 6 samples can be analyzed simultaneously. PATHFAST TM provides high accuracy and precision of test results similar to central laboratory analyzers, combined with the flexibility of a POCT test in 17 minutes.[72]

The Mindray High Sensitivity cTnI (CLIA) is an immunoenzymatic assay designed to determine the concentration of cardiac troponin I (cTnI) in samples. This assay was specifically developed to assess the analytical

performance of Mindray's new high-sensitivity cardiac chemiluminescent troponin I (hs-cTnI) immunoassay on the Mindray CL-1200i chemiluminescence analyzer. The evaluation of this hs-cTnI immunoassay includes calculations of the limit of blank (LOB), limit of detection (LOD), functional sensitivity, imprecision, linearity, and the 99th percentile upper reference limit (URL), as well as a method comparison with Beckman. Our assessment of the new Mindray hs-cTnI immunoassay on the CL-1200i indicates that its overall analytical performance is comparable to other commercially available cTnI methods, making it a viable alternative to other methods.[73]

The Siemens Healthineers ADVIA Centaur TNIH test is a 3-site sandwich immunoassay using direct chemiluminometric technology. The solid phase reagent is a magnetic latex particle conjugated to streptavidin with two bound biotinylated capture monoclonal antibodies that each recognize a unique cTnI epitope. siemens-healthineers.com/TNIH Lite reagent consists of a conjugate whose architecture consists of a proprietary acridinium ester and a recombinant sheep cTnI antihuman Fab covalently attached to bovine serum albumin (BSA) for chemiluminescent detection. The accumulated light signal is directly related to the cTnI concentration of the sample.[74]

The Siemens Healthineers ADVIA Centaur TNIH assay uses a recombinant ahu cTnI antibody fragment attached to a BSA carrier with multiple TSPAE (trisulfopropyl AE), to achieve low assay interference and signal amplification (signal/binding event), respectively. The new TNIH assay provides an approximately 10-fold increase in low-end precision and sensitivity in part due to the Acridinium Ester architecture and this new high-efficiency conjugate. The ADVIA Centaur® High-Sensitivity Troponin I (TNIH) test is for in vitro diagnostic use in the quantitative measurement of cardiac troponin I in human serum or plasma using the ADVIA Centaur® XP and ADVIA Centaur® XPT systems. This test can be used to help diagnose acute myocardial infarction (AMI).[74]

CONCLUSION

The high incidence of cardiovascular disease in society highlights the need for biomarkers with excellent specificity. Previous markers such as AST, LDH, and CK-MB had very high false positive rates, necessitating the development of new, more specific biomarkers. Continuous advancements in cardiac biomarkers have led to the development of high-sensitivity tests for cardiac troponin I and T, which offer both high sensitivity and specificity. The use of these new generation high-sensitivity cardiac troponin (hs-cTn) tests is now recommended by international guidelines as a primary tool for diagnosing myocardial infarction.

Despite their high cardiac specificity, these biomarkers are not exclusively specific to Acute Coronary Syndrome (ACS), as many cardiac and even non-cardiac conditions can cause elevated hs-cTn levels. Nevertheless, the use of hs-cTn for the rapid rule-out of ACS is considered safe and efficient. The point-of-care testing (POCT) method for hs-cTn measurements should be considered in various clinical settings. However, it remains necessary to confirm the results obtained with the hs-cTn POCT method using automated platforms in clinical laboratories.

Implementing the hs-cTnI POCT method requires not only thorough education of the personnel responsible for biomarker measurements but also a careful evaluation of clinical issues that may arise during routine use. Special attention must be given to pre-analytical and analytical phases due to the possibility of analytical interference and clinical difficulties in interpreting results. Additionally, validated systems must be in place to ensure proper information systems integration (e.g., connection with Laboratory Information Systems, LIS), quality control of procedures, and accurate reporting of results.

REFERENCE

1. Cullen L, Collinson PO, Giannitsis E. Point-of-care testing with high-sensitivity cardiac troponin assays: the challenges and opportunities. *Emergency Medicine Journal.* 2022;**39:**861-6

2. Greenslade JH, Parsonage W, Foran L, et al. Widespread introduction of a high- sensitivity troponin assay: assessing the impact on patients and health services. J Clin Med. 2020;9:1883.

3. Collet JP, Thiele H, Barbato E. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST- segment elevation. Eur Heart J. 2020;2021:1289–367.

4. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Circulation. 2018; 138:618-51

5. Stark M, Kerndt CC, Sharma S. Troponin. [Updated 2023 Apr 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507805/

6. Xu RY, Zhu XF, Yang Y, Ye P. High-sensitive cardiac troponin T. J GeriatrCardiol. 2013 Mar;10(1):102-9. [PMC free article] [PubMed]

7. Januzzi JL, Mahler SA, Christenson RH, et al. Recommendations for institutions transitioning to high-sensitivity troponin testing - JACC scientific expert panel. JACC. 2019; 73:1059–77

8. deFilippi CR, Herzog CA. Interpreting Cardiac Biomarkers in the Setting of Chronic Kidney Disease. Clin Chem. 2017; 63:59-65

9. Potocki M, Reichlin T, Thalmann S, Zellweger C, Twerenbold R, Reiter M, et al. Diagnostic and prognostic impact of copeptin and high-sensitivity cardiac troponin T in patients with pre-existing coronary artery disease and suspected acute myocardial infarction. Heart. 2012 Apr;98(7):558-65. [PubMed]

10. Potter JM, Hickman PE, Cullen L. Troponins in myocardial infarction and injury. Aust Prescr. 2022 Apr;45(2):53-7. doi: 10.18773/austprescr.2022.006.

11. Michos ED, Berger Z, Yeh HC, et al. Cardiac Troponins Used as Diagnostic and Prognostic Tests in Patients With Kidney Disease [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Aug. (Comparative Effectiveness Review, No. 135.) Executive Summary. Available from: https://www.ncbi.nlm.nih.gov/books/NBK241518/

12. White HD. Pathobiology of troponin elevations do elevations occur with myocardial ischemia as well as necrosis? J Am Coll Cardiol. 2011;57:2406–8.

13. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med. 2009;361: 2538–47.

14. Kontos MC, Diercks DB. High Sensitivity Troponins and Ischemia Testing: Are We Doing Too Much? Am Heart J. 2021 Jun;236:97-9. [PubMed]

15. Geyer M, Wild J, Münzel T, Gori T, Wenzel P. State of the Art-High-Sensitivity Troponins in Acute Coronary Syndromes. Cardiol Clin. 2020 Nov;38(4):471-9. [PubMed]

16. Babuin L, Jaffe AS. Troponin: biomarker pilihanuntukmendeteksicederajantung. CMAJ. 2005 November 8; 173(10):1191-202. DOI: 10.1503/CMAJ/051291.

17. Chapman AR, Adamson PD, Shah ASV, Anand A, Strachan FE, Ferry AV, et al. High-Sensitivity Cardiac Troponin and the Universal Definition of Myocardial Infarction. Circulation. 2020;141(3):161-71

18. Brotto MA, Biesiadecki BJ, Brotto LS, Nosek TM, Jin JP. Coupled expression of troponin T and troponin I isoforms in single skeletal muscle fibers correlates with contractility. Am J Physiol Cell Physiol. 2006 Feb;290(2):C567-76.

19. Wei B, Jin JP. TNNT1, TNNT2, and TNNT3: Isoform genes, regulation, and structure-function relationships. Gene. 2016 May 10;582(1):1-13.

20. Jacob R, Khan M. Cardiac Biomarkers: What Is and What Can Be. Indian J Cardiovasc Dis Women WINCARS. 2018 Dec;3(4):240-244

21. Garg P, Morris P, Fazlanie AL, Vijayan S, Dancso B, Dastidar AG, Plein S, Mueller C, Haaf P. Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. Internal and emergency medicine. 2017 Mar:12(2):147-155. doi: 10.1007/s11739-017-1612-1. Epub 2017 Feb 11

22. PerhimpunanDokterSpesialisKardiovaskular Indonesia, PedomanTatalaksanaSindromKoronerAkut, 2015 ed 3 http: //jki.or.id

23. Zeymer U. [Diagnosis and initial management of acute myocardial infarction]. MMW Fortschritte der Medizin. 2019 Mar:161(4):34-36. doi: 10.1007/s15006-019-0223-3. Epub

24. Kontos MC, Turlington JS. High-Sensitivity Troponins in Cardiovascular Disease. Current cardiology reports. 2020 Mar 30:22(5):30. doi: 10.1007/s11886-020-01279-0. Epub 2020 Mar 30 [PubMed PMID: 32232671]

25. Clerico A, Zaninotto M, Passino C, Padoan A, Migliardi M, Plebani M. High-sensitivity methods for cardiac troponins: The mission is not over yet. Advances in clinical chemistry. 2021:103():215-252. doi: 10.1016/bs.acc.2020.08.009. Epub 2020 Oct 9

26. Holzmann MJ. Clinical implications of high-sensitivity cardiac troponins. Journal of internal medicine. 2018 Jul:284(1):50-60. doi: 10.1111/joim.12779. Epub 2018 Jun 14

27. Chaulin AM. Cardiac troponins: current information on the main analytical characteristics of determination methods and new diagnostic possibilities. Medwave 2021;21(11):002132

28. Gokhan, I.; Dong, W.; Grubman, D.; Mezue, K.; Yang, D.; Wang, Y.; Gandhi, P.U.; Kwan, J.M.; Hu, J.-R. Clinical Biochemistry of Serum Troponin. Diagnostics 2024, 14, 378. https://doi.org/10.3390/ diagnostics14040378

29. Du,X.; Su, X.; Zhang, W.; Yi, S.; Zhang, G.; Jiang, S.; Li, H.; Li, S.; Xia, F. Progress, Opportunities, and Challenges of Troponin Analysis in the Early Diagnosis of Cardiovascular Diseases. Anal. Chem. 2022, 94, 442–463.

30. Jernberg, T.; Venge, P.; Lindahl, B. Comparison between Second and Third Generation Troponin T Assay in Patients with Symptoms Suggestive of an Acute Coronary Syndrome but without ST Segment Elevation. Cardiology 2003, 100, 29–35

31. Melanson, S.E.F.; Morrow, D.A.; Jarolim, P. Earlier Detection of Myocardial Injury in a Preliminary Evaluation Using a New Troponin I Assay with Improved Sensitivity. Am. J. Clin. Pathol. 2007, 128, 282–286.

32. Ambrose, T. 510(k) Approval Letter for Elecsys Troponin T Stat Assay (K051752). U.S. Food and Drug Administration, Office of In Vitro Diagnostic Device Evaluation and Safety. 2005. Available online: https://www.accessdata.fda.gov/cdrh_docs/pdf5/K0 51752.pdf. (Accesed on 23 Juni 2024)

33. European patent 394819 and US patent 6376206 by Roche Diagnostics GmbH. Specific antibodies to Troponin T, their production and use in a reagent for the determination of myocardial necrosis.

34. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndrome in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2016 Jan 14;37(3):267-315. PubMed 26320110

35. Katus HA, Remppis A, Looser S, Hallermeier K, Scheffold T, Klüber W. Enzyme linked immunoassay of cardiac troponin T for the detection of acute myocardial infarction in patients. *J Mol Cell Cardiol.* 1989 Dec;21(12):1349-1353. PubMed 2632816

36. Katus HA, Scheffold T, Remppis A, Zehlein J. Proteins of the troponin complex. *Laboratory Medicine.* 1992 May 1;23(5):311-317. Available at https://doi.org/10.1093/labmed/23.5.311. Accessed January 2021.

37. Latini R, Masson S, Anand IS, et al. Prognostic Value of Very Low Plasma Concentrations of Troponin T in Patients with Stable Chronic Heart Failure. Circulation 2007;116:1242-1249.

38. Omland T, De Lemos JA, Christophi C, et al. Distribution and determinants of very low levels of cardiac troponin T in patients with stable coronary artery disease: The PEACE trial. Eur Heart J 2008;9(202):1342.

39. European patent 1890154 Cardiac Troponin as an indicator of advanced coronary artery disease.

40. European patent 1837659 Means and methods for the differentiation of acute and chronic myocardial necrosis in symptomatic patients.

41. Lauer B, Niederau C, Kühl U, et al. Cardiac troponin T in patients with clinically suspected myocarditis. JACC 1997;30:1354-1359.

42. Swaanenburg JC, Klaase JM, DeJongste MJ, et al. Troponin I, troponin T, CK-MB-activity and CK-MB mass as markers for the detection of myocardial contusion in patients who experienced blunt trauma. Clin Chim Acta 1998;272:171-181.

43. Giannitsis E, Müller-Bardorff M, Kurowski V, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. Circulation 2000;102:211-217.

44. Herman EH, Lipshultz SE, Rifai N, et al. Use of cardiac troponin T levels as an indicator of doxorubicin-induced cardiotoxicity. Cancer Res 1998;58:195-197.

45. Sharma R, Gaze DC, Pellerin D, et al. Cardiac structural and functional abnormalities in end stage renal disease patients with elevated cardiac troponin T. Heart. 2006 Jun;92(6):804-9. Epub 2005 Oct 10.

46. Deegan PB, Lafferty ME, Blumsohn A, et al. Prognostic value of troponin T in hemodialysis patients is independent of comorbidity. Kidney Int. 2001 Dec;60(6):2399-405.

47. Creative Biolabs. Protocol of Sandwich ELISA with Streptavidin-biotin Detection. Manual user

48. BIO-RAD. Protocol: Sandwich ELISA with streptavidin-biotin detection. Manual user

49. Collinson PO, Gerhardt W, Katus HA, Müller-Bardorff M, Braun S, Schricke U, Vogt W, Nagel D, Zander M, Leinberger R, Mangold D, Zerback R. Multicentre evaluation of an immunological rapid test for the detection of troponin T in whole blood samples. Eur J Clin Chem Clin Biochem. 1996 Jul;34(7):591-8. PMID: 8864412.

50. Widhongyudana L, Rita S. Mulyawan S. Gideon S. Uji Diagnostik Troponin T-RA Pada PenderitaMiokarditisAkut. JKM. Vol. 1, No. 1, 2001, 54 – 64

51. Roche. CARDIAC POC Troponin T tes by cobas h232 manual user

52. Takeda, Soichi; Yamashita, Atsuko; Maeda, Kayo; Maéda, Yuichiro (July 2003). "Structure of the core domain of human cardiac troponin in the Ca2+ saturated form". *Nature*. **424** (6944): 35–41.

53. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR and White HD. Third Universal Definition of Myocardial Infarction. Circulation. 2012; 126: 2020–35.

54. Jarolim P. High Sensitivity Cardiac Troponin Assays in the Clinical Laboratories. Clin Chem Lab Med. 2015; 53(5): 635-52.

55. EUROlyser. Troponin I test. Manual user

56. Atlas Medical. CTnI One Step Troponin I Test Device (Whole Blood / Serum / Plasma) A rapid, one step test for the qualitative detection of cardiac Troponin I in whole blood, serum or plasma. Manual User

57. Samsu N, Sargowo D. Sensitivitas dan Spesifitas Troponin T dan I pada Diagnosis InfarkMiokardAkut. MajalahKedokteran Indonesia. 2007; 57: 363–72.

58. Sheila Febriana, AsvinNurulita, UlengBahrun. Penilaian Uji Troponin I Dengan Point of Care Testing (Evaluation of Troponin I Assay with Point of Care Testing). Indonesian Journal of Clinical Pathology and Medical Laboratory, Vol. 22, No. 2 Maret 2016: 114–118.

59. Siti Fatonah, AnikWidijanti, Tinny EndangHernowati. Nilai Diagnostik Uji Troponin I KuantitatifMetodeImmunokromatografi. Indonesian Journal of Clinical Pathology and Medical Laboratory, Vol. 14, No. 1, November 2007: 20-23

60. Garg, P., Morris, P., Fazlanie, A.L., Vijayan, S., Dancso, B., Dastidar, A.G., Plein, S., Mueller, C., Haaf, P. Cardiac Biomarkers of Acute Coronary Syndrome: from History to High-Sensitivity Cardiac Troponin. Intern Emerg Med. 2017; 12:147–155.

61. Giannitsis E, Katus HA. Myocardial Infarction.Current Recommendations for Interpretation of the Highly Sensitive Troponin T Assay for Diagnostic, Therapeutic and Prognostic Purposes in Patients with a Non-ST-segment-elevation Acute Coronary Syndrome. (touch briefings). Gemany. Med. Departement III. Heidelberg Univ. Hosp. 2010: 44–47.

62. Xu, R.Y., Zhu, X.F., Yang, Y., Ye, P., High-Sensitive Cardiac Troponin T. Journal of Geriatric Cardiology. 2013; 10: 102−109

63. Mahajan VS, Jarolim P. How to Interpret Elevated Cardiac Troponin Levels. Circulation J. 2011; 124: 2350–54.

64. Giuliani S, Dieplinger B, Mueller T.Head-to-head comparison of three different high-sensitivitycardiac troponin assays for early rule-in and rule-out of acutemyocardial infarction. J Lab Precis Med 2019;4:4

65. Wu AHB, Christenson RH, Greene DN, et al. Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. Clin Chem 2018;64:645-55

66. Andruchow JE, Kavsak PA, McRae AD. Contemporary Emergency Department Management of Patients withChest Pain: A Concise Review and Guide for the High-Sensitivity Troponin Era. Can J Cardiol 2018;34:98-108

67. Boeddinghaus J, Twerenbold R, Nestelberger T, et al. Clinical Validation of a Novel High-Sensitivity Cardiac Troponin I Assay for Early Diagnosis of Acute Myocardial Infarction. Clin Chem 2018;64:1347-60.

68. Li L, Shu X, Zhang L, Xu A, Yang J, Jing Y, Wang H, Zhang Z. Evaluation of the analytical and clinical performance of a new high-sensitivity cardiac troponin I assay: hs-cTnI (CLIA) assay. Clin Chem Lab Med. 2023 Sep 26;62(2):353-360. doi: 10.1515/cclm-2023-0529. PMID: 3774685

69. Roche. Elecsys Troponin T hs by Cobas e 402. Manual User

70. Westwood M, van Asselt T, Ramaekers B, *et al.* High-sensitivity troponin assays for the early rule-out or diagnosis of acute myocardial infarction in people with acute chest pain: a systematic review and cost-effectiveness analysis. Southampton (UK): NIHR Journals Library; 2015

71. Nergiz Zorbozan, Gokce Filiz Atikeler. Evaluation of high-sensitivity cardiac troponin measurement procedure performance in serum: the vidas 3 high sensitivity cardiac troponin I. Int J Med Biochem . 2020; 3(3): 161-165

72. Aldo Clerico, Martina Zaninotto, Alberto Aimo, *et.al.* High-sensitivity Point of Care Testing (POCT) methods for Cardiac Troponins: analytical features and clinical relevance. A consensus document by the Study Group on Cardiac Biomarkers from the Italian Society of Biochemical Chemistry (SIBioC) and the European Ligand Assay Society (ELAS). Biochimica Clinica, 2023

73. Giuseppe Lippi, Laura Pighi, Elisa Paviati, *et al.* Analytical evaluation of the novel Mindray high sensitivity cardiac troponin I immunoassay on CL-1200i. Clin Chem Lab Med 2024; Jan 8. DOI: 10.1515/cclm-2023-144

74. Siemens Healthcare Diagnostics Inc. ADVIA Centaur High-Sensitivity Troponin I Assay. Manual Users

Turn it in The Role of Troponin And Use of Troponin Assays

ORIGINALITY REPORT

17%	10%	11%	7%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

MATCH ALL SOURCES (ONLY SELECTED SOURCE PRINTED)

1%

★ Edy Parwanto, David Tjahyadi, Sisca Sisca, Husnun Amalia et al. "Low Doses of Kretek Cigarette Smoke Altered Rat Lung Histometric, and Overexpression of the p53 Gene", The Open Respiratory Medicine Journal, 2024

Publication

Exclude quotes	On	Exclude matches	< 10 words
Exclude bibliography	On		

Turn it in The Role of Troponin And Use of Troponin Assays

GRADEMARK REPORT

FINAL GRADE

/0

GENERAL COMMENTS

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11

PAGE 12

PAGE 13