JOURNAL OF INTERNATIONAL CRISIS AND RISK COMMUNICATION RESEARCH
ISSN: 2576-0017
2024, VOL 7, NO S8

The Role of Troponins in the Laboratory Diagnosis of Heart Failure

Hana Mohammed Abduallah Alneami[1], Yahya Abdu Ali Hazmi[2], Hussien Ali Majrashi[3], Khalil Mohd Ibrahim Hawi[4], Mohammed Ali Shami Abutawail[5], Hessah Turki Alqahtani[6], Abdullah Abdulaziz Aljabr[7], Faris Khaled Alharbi[8], Megrenfaisal Almotiri[9], Bandr Sheried Almotiri[10], Abdulmajeed Salman MatroukAlenazi[11], Abdullah Ali Salih Alwagesi[12], Hassan Ahmed Yahya Asiri[13], Yazeed Abdulaziz Alhumaidan[14], Yasmin Abdullah H Alnezyan[15].

1. Specialist-Laboratory, Jazan Regional Laboratory and Blood Bank, Ministry of Health, Kingdom of Saudi Arabia. Hamalneami@moh.gov.sa
2. Technican-Laboratory, Hussaini PHC, Ministry of Health, Kingdom of Saudi Arabia.yahazmi@moh.gov.sa
3. Senior immunologist, Jazan Regional laboratory, Jizan Health Cluster, kSA, Ministry of Health, Kingdom of Saudi Arabia. ham-1@hotmail.com
4. Technician-Laboratory, alhussini primary health care, Ministry of Health, Kingdom of Saudi Arabia. khawi@moh.gov.sa
5. Technician-Laboratory, Jazan Regional Laboratory and Blood Bank,Ministry of Health, Kingdom of Saudi Arabia. mabutawail@moh.gov.sa
6. Laboratory, Almuzahmiah General Hospital, Ministry of Health, Kingdom of Saudi Arabia. alh93535@gmail.com
7. Lab specialist, King saud hospital Unayzah, Ministry of health, Kingdom of Saudi Arabia, a.aljabr5353@gmail.com
8. Lab specialist, Primary health care center in Dhibiyah , Ministry of health, Kingdom of Saudi Arabia, Fareska@moh.gov.sa
9. Lab specialist, King saud hospital Unayzah, Ministry of health, Kingdom of Saudi Arabia, m.34m@outlooksa
10. Lab technician, Al Badaya General Hospital, Ministry of health, Kingdom of Saudi Arabia, balmutry@moh.gov.sa
11. Laboratory Specialist, Maternity And Children Hospital In Buraydah, Ministry of health, Kingdom of Saudi Arabia. abalenazi@moh.gov.sa
12. Laboratory Specialist, Maternity And Children Hospital In Buraydah, Ministry of health, Kingdom of Saudi Arabia. Aalwagesi@moh.gov.sa
13. Medical Laboratory Sciences,Prince Mohammed bin Abdulaziz Hospital in Riyadh , Ministry of health, Kingdom of Saudi Arabia. asirih@pmah.med.sa
14. Medical Laboratory SciencesPrince Mohammed bin Abdulaziz Hospital in Riyadh, Ministry of health, Kingdom of Saudi Arabia. YAZEED.6100@gmail.com
15. laboratory technician, Branch of the Ministry of Health in Riyadh, Ministry of Health, Kingdom of Saudi Arabia. Yasmin.o9@hotmail.com

Abstract

Cardiac troponins, particularly troponin I and troponin T, have emerged as valuable biomarkers for diagnosing and prognosticating ventricular dysfunction and heart failure. The introduction of high-sensitivity assays has revealed that cardiac troponins are frequently detectable in various acute and chronic conditions, including cardiac and non-cardiac diseases. Troponin elevation occurs regardless of ischemic or non-ischemic etiology, indicating that elevated levels are not exclusively specific to ischemic injury. In acute heart failure, troponin elevation is hypothesized to signify cardiomyocyte injury and cell death, with proposed mechanisms including neurohormonal activation, inflammatory cytokines, increased wall stress, ischemia, and oxidative stress. Elevated troponin levels in acute heart failure provide incremental prognostic information beyond established risk factors and are associated with poorer outcomes. In chronic heart failure, high-sensitivity assays have dramatically increased the proportion of patients with detectable troponin levels, and elevated levels predict adverse outcomes. High-sensitivity troponin assays also offer significant prognostic value for assessing the likelihood of future heart failure in patients with stable coronary artery disease and aortic stenosis. While troponin measurement aids prognostication, specific interventions targeting elevated levels in heart failure remain unsupported by current data. Further research is needed to elucidate the mechanisms of troponin release and develop targeted therapeutic strategies.

Keywords: Troponins, HF, heart failure, Laboratory Diagnosis

Introduction

Over the past four decades, while there has been a decline in both the incidence and mortality rates associated with acute myocardial infarction, the incidence of heart failure has only recently begun to plateau. Despite advancements in pharmacologic and non-pharmacologic treatment options, hospitalization and mortality rates associated with severe heart failure remain elevated(Braunwald, 2013). For instance, in the United States, the prevalence of heart failure is estimated to exceed 5 million cases. Annually, over 1 million hospital discharges are reported with heart failure as the primary diagnosis (Roger et al., 2012), and it is estimated that heart failure accounts for more than 3 million physician visits each year. Consequently, heart failure, particularly among older populations, represents a significant strain on healthcare systems in Western countries.

The clinical signs and symptoms of heart failure are often nonspecific and show poor correlation with objective indices of cardiac function. As a result, diagnosing heart failure based solely on medical history and physical examination findings can pose challenges for clinicians. While findings from electrocardiograms and chest radiographs may provide useful insights in certain cases, the diagnostic accuracy of these tools alone is relatively limited. Objective evaluations of cardiac function using echocardiography or other imaging techniques can support the diagnostic and prognostic assessment of heart failure, but these modalities are expensive and show limited correlation with symptomatic and functional status. Furthermore, cardiac imaging often fails to distinguish between acute and chronic ventricular dysfunction. The limitations of clinical evaluations and imaging in diagnosing and prognosing ventricular dysfunction and heart failure have driven efforts to identify circulating biomarkers that provide incremental value. Among these, biomarkers of myocardial injury, particularly the myofibrillar proteins troponin I and troponin T, have emerged as promising tools.

The introduction of more sensitive assays in clinical practice has improved diagnostic accuracy for acute coronary syndromes. Additionally, these high-sensitivity assays have revealed that cardiac troponins are frequently detectable in a range of acute and chronic conditions, including both cardiac and non-cardiac diseases such as acute heart failure and chronic left ventricular dysfunction, whether symptomatic or asymptomatic (Omland, 2010). Troponin elevation occurs regardless of ischemic or non-ischemic etiology, indicating that elevated cardiac troponin levels are not exclusively specific to ischemic injury. Moreover, epidemiological studies have demonstrated detectable levels of circulating cardiac troponins in a substantial proportion of ostensibly healthy individuals. These findings suggest that chronic, low-grade cardiac troponin release may result from mechanisms other than ischemic injury, such as chronic low-grade myocardial ischemia, necrosis, apoptosis, and autophagy.

This review provides a summary of current literature on the clinical performance and utility of cardiac troponin measurements as diagnostic and prognostic tools. It focuses on their application in patients with symptomatic heart failure (Stage C heart failure) and those with asymptomatic left ventricular dysfunction, as well as clinical phenotypes at high risk for developing heart failure, including stable coronary artery disease, left ventricular hypertrophy, and aortic stenosis.

Troponin Molecule/Biology of Troponin

The troponin complex is composed of three distinct polypeptides: troponin C, troponin T, and troponin I. These subunits are found in both striated skeletal and cardiac muscle tissues. Troponin C functions as the calcium-binding subunit, troponin T as the tropomyosin-binding subunit, and troponin I modulates actin-myosin interactions by inhibiting actomyosin ATPase activity. Collectively, the troponin complex regulates contraction by interacting with sarcomere thin filaments.

There are several isoforms of troponin T and I, which are differentially expressed in fetal and adult cardiomyocytes and skeletal muscle cells. In adult cardiomyocytes, only one isoform is typically expressed, while this isoform is downregulated in adult skeletal muscle cells with concurrent upregulation of skeletal muscle-specific isoforms. As a result, troponin T and I in adult cardiac and skeletal muscle tissues are genetically and antigenically distinct. However, troponin C is identical in both cardiac and skeletal muscle cells. The isoforms of troponin I and T found in adult cardiac tissue are referred to as cardiac troponin I and cardiac troponin T.

The molecular weights of cardiac troponin I and T are distinct, with cardiac troponin T weighing approximately 38 kDa and cardiac troponin I weighing about 24 kDa. Within cardiomyocytes, cardiac troponins I and T exist in two pools. Over 90% are bound to the myofibrillar apparatus, while a smaller proportion remains unbound in the cytosol. The unbound pool of cardiac troponins is released relatively quickly, within one to two hours following myocardial injury, resulting in a transient increase in circulating levels. For instance, transient elevations in troponin levels can occur following paroxysmal supraventricular tachycardia. In contrast, troponins bound to the myofibrillar apparatus are released gradually after cell necrosis, and their presence in the bloodstream can be detected for several days following acute injury.

Although the clearance mechanisms of cardiac troponins are not fully understood, their circulating half-life is estimated to be approximately two hours. Various biochemical processes, including proteolysis, phosphorylation, and oxidation, may modify the structure of circulating troponins. Renal failure has been associated with elevated circulating cardiac troponin levels, often attributed to decreased renal elimination.

However, evidence suggests that increased release of troponins may also play a significant role. For example, in patients with end-stage renal disease, renal transplantation does not significantly reduce circulating cardiac troponin concentrations.

In addition to renal failure, studies in various populations indicate that multiple factors, such as gender, age, and comorbidities (e.g., diabetes mellitus, hypertension, and atherosclerotic disease), can influence circulating troponin levels. These factors are critical for interpreting troponin results in patients suspected of having acute heart failure or acute coronary syndromes (Omland, 2010).

3. Pathophysiology of Myocardial Ischemia

The prevailing theory for the pathogenesis of acute coronary syndrome (ACS) suggests that inflammation triggers plaque rupture or erosion, leading to the formation of local occlusive or non-occlusive thrombi (Hamm et al., 2012). The clinical presentation of ACS spans a spectrum, from unstable angina (UA) to non-ST-elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI), depending on the degree of arterial obstruction. A key distinction between NSTEMI and unstable angina is the detection of elevated cardiac troponin levels.

4. Definition of Myocardial Infarction

Acute myocardial infarction (AMI) is defined as myocardial necrosis due to ischemia, characterized by a detectable rise and subsequent fall in circulating troponin levels. The enhanced precision of high-sensitivity cardiac troponin T (hs-cTnT) assays in the low analytical range has improved the timeliness of clinical decisions. According to the universal definition, myocardial infarction is diagnosed in patients presenting with cardiac ischemia symptoms, electrocardiographic changes, imaging evidence of new myocardial loss or regional wall motion abnormalities, or identification of an intracoronary thrombus via angiography or autopsy (Thygesen et al., 2012). This definition requires a troponin rise and fall with at least one measurement exceeding the 99th percentile upper reference limit. However, there is no universal agreement on the magnitude of change necessary to qualify as significant, as both biological and analytical variability must be considered.

The classification of myocardial infarction includes five clinical types. Type 1 refers to spontaneous myocardial infarction caused by atherosclerotic plaque disruption leading to thrombosis, which reduces myocardial blood flow and causes myocyte necrosis. Type 2 results from ischemic imbalance. Type 3 is assigned to fatal myocardial infarction cases where biomarker data are unavailable. Type 4a pertains to myocardial infarction associated with percutaneous coronary intervention (PCI), characterized by a cTn elevation exceeding five times the 99th percentile in patients with normal baseline values, alongside additional evidence such as ischemic symptoms or imaging findings. Type 4b involves myocardial infarction due to stent thrombosis, identified by coronary angiography or autopsy, coupled with a rise or fall in cardiac biomarkers exceeding the 99th percentile. Type 5 is associated with coronary artery bypass grafting (CABG), defined by a tenfold elevation in cTn above the 99th percentile, with supplementary findings like pathological Q waves, imaging evidence, or angiographic documentation.

5. High-Sensitivity (hs) cTn Assays

In recent years, manufacturers have developed novel high-sensitivity cardiac troponin (hs-cTn) assays to meet the European Society of Cardiology (ESC) and American College of Cardiology (ACC) precision criteria. Enhancements in sensitivity and precision have involved refining existing assays or creating new formats. For example, the fourth-generation cTnT assay was optimized by increasing sample volume, enhancing detection antibody ruthenium concentrations, and reducing background signals through buffer improvements. Additionally, interferences from heterophilic anti-mouse antibodies (HAMA) or autoimmune antibodies were minimized by replacing the constant C1 region of the FAB with a human IgG-C1 region, resulting in a mouse-human chimeric detection antibody (Giannitsis et al., 2010). Alternative approaches by other manufacturers included adding secondary detection or capture antibodies to achieve higher analytical sensitivity (Panteghini, 2009).

Despite these advancements, cTnI assays lack standardization, with substantial differences across manufacturers in antibody configurations and epitope locations. Furthermore, cTnI exhibits multiple isoforms and is susceptible to degradation, oxidation, and phosphorylation, affecting recovery rates and release kinetics following myocardial injury. Consequently, the analytical characteristics of each cTnI assay, such as the 99th percentile, limit of detection (LoD), and limit of quantitation (LoQ), must be individually validated in clinical trials. Comparative studies of 19 cTn assays revealed significant heterogeneity in analytical sensitivity, underscoring the variability in detecting cTn concentrations in healthy populations (Apple et al., 2012).

The definition of high sensitivity remains a topic of debate. A "scorecard" concept was introduced to systematically classify assays. To qualify as high sensitivity, an assay must meet two criteria: total imprecision at the 99th percentile should be $\leq$10%, and measurable concentrations below the 99th percentile must be achievable in $\geq$50% of healthy individuals (ideally >95%). Many assays marketed as high sensitivity fail to meet these criteria, with some achieving measurable concentrations in only 25% of cases. High-sensitivity assays measure cTn in nanograms per liter, offering enhanced analytical sensitivity compared to conventional assays. Early studies demonstrated that hs-cTnT and several contemporary cTnI assays outperformed the conventional

fourth-generation cTnT assay in diagnostic performance for ACS. Some studies have also shown superior long-term outcome prediction with hs-cTnT compared to hs-cTnI. However, few studies have directly compared the clinical performance of hs-cTn assays for detecting reversible ischemia or prognosticating outcomes (Mueller et al., 2012; Omland et al., 2013).

6. Timing and Measurement of hs-cTn in ACS

To comply with European guidelines and the universal definition of myocardial infarction [9], at least two hs-cTn measurements are required to distinguish between acute and stable cTn elevations. Several conditions besides acute myocardial infarction can cause elevated troponin levels. It is important to note that troponin elevation is not synonymous with coronary plaque rupture. Transient troponin rises have been observed in various contexts, such as marathon runners and healthy individuals following exercise tests (Tjora et al., 2011), challenging the notion that troponin release solely signifies irreversible myocardial damage.

7. Acute Heart Failure/AMI Type I/II

Cardiac troponins are considered indispensable for diagnosing acute myocardial infarction (AMI). However, troponin release is observed in clinical settings beyond the classical acute coronary syndrome (ACS) scenario, such as in patients presenting with dyspnea and acute heart failure. These patients frequently exhibit troponin levels above the detection threshold of both contemporary sensitive and high-sensitivity assays, even in studies explicitly excluding individuals with chest pain or other ACS indicators. For example, a subgroup analysis of the PRIDE study, which excluded suspected ACS cases, revealed that 96 of 209 patients (46%) with acute heart failure had cardiac troponin T levels above the detection limit (≥ 0.01 μg/L). Similarly, data from the ADHERE Registry reported that 4,240 of 67,924 admissions (6.2%) for acute heart failure had detectable troponin levels using earlier-generation assays. The adoption of high-sensitivity troponin (hs-cTn) assays has significantly increased the rates of detectable troponin. Pascual-Figal et al. found that 98% of patients with acutely destabilized heart failure had detectable hs-cTnT levels (≥ LoB, 3 ng/L), with a median concentration of 32 ng/L (IQR 16–57 ng/L).

Although studies show variability in detectable troponin levels, likely due to differences in assay sensitivity, all consistently demonstrate poorer outcomes in acute heart failure patients with elevated troponin compared to those with normal levels. Mortality rates progressively increase with rising hs-cTnT concentrations(Pascual-Figal et al., 2012). The strong prognostic significance of troponin elevation in acute heart failure has been further validated by the EFFECT study. Elevated troponin in acute heart failure provides incremental prognostic information beyond established risk factors, including B-type natriuretic peptide levels, suggesting troponins reflect additional pathological processes in these patients.

Troponin elevation in acute heart failure is hypothesized to signify cardiomyocyte injury and cell death, supported by evidence of dynamic troponin increases during acute episodes. Proposed mechanisms for troponin release include neurohormonal activation, inflammatory cytokines, increased wall stress, ischemia, and oxidative stress. Notably, findings from the ADHERE Registry indicate troponin levels in acute heart failure do not reliably differentiate between ischemic and non-ischemic etiologies. Various factors, including arrhythmias, infection, or ACS, contribute to acute heart failure exacerbation (Hamm et al., 2012). Mechanisms of troponin release include myocardial protein turnover, neurohormonal toxicity, inflammation, infiltrative processes, myocardial apoptosis or autophagy, ischemia due to supply-demand mismatch, and epicardial coronary artery disease or endothelial dysfunction. Multimarker strategies, combining troponins with other biomarkers like natriuretic peptides or interleukin receptor family member ST2, provide enhanced risk stratification for acutely decompensated heart failure (Januzzi et al., 2012; Pascual-Figal et al., 2011).

Serial hs-cTn measurements often reveal dynamic changes reflecting hemodynamic and systemic effects. These changes, like natriuretic peptides, can indicate the response to therapeutic interventions. Patients whose troponin levels do not decrease after acute heart failure episodes have worse outcomes than those who exhibit reductions during follow-up. Measuring troponin on admission and during follow-up is recommended for consistent prognostic insights. The Universal MI Global Task Force Heart Failure section advises prompt cTn measurement to rule out type I MI as a precipitant of acute heart failure. Elevated troponin levels, particularly when showing significant rise and/or fall, should raise suspicion of type I MI. However, troponin patterns cannot conclusively differentiate coronary from non-coronary mechanisms or exclude ACS. Independent of MI, elevated troponin is linked to adverse outcomes, but specific therapeutic interventions targeting elevated troponin in acute heart failure remain undefined.

Discriminating between type I and type II MI in acute heart failure is challenging, as subendocardial ischemia caused by oxygen supply-demand mismatch contributes to troponin release. Higher troponin levels may suggest type I MI with larger focal necrosis, but exceptions exist, such as severe hypoxemia causing diffuse myocardial necrosis (Mather et al., 2013). Elevated troponin is not confined to heart failure with reduced ejection fraction; it is also seen in preserved ejection fraction cases, likely related to left ventricular mass and relaxation abnormalities.

8. Chronic Heart Failure/Prognostic Value in CHF

Initially identified as markers of acute ischemic injury, circulating cardiac troponins were first reported in 1997 in patients with severe non-ischemic injury. Subsequent studies using conventional troponin assays confirmed that detectable troponin levels were associated with more severe ventricular dysfunction and higher mortality risk. For instance, in a cohort of 238 patients with severe non-ischemic chronic heart failure, approximately 50% had detectable troponin I levels, a finding replicated in another cohort. In both studies, detectable troponins predicted worse outcomes.

The advent of high-sensitivity cardiac troponin assays has dramatically increased the proportion of chronic heart failure patients with detectable troponin levels. In a pivotal 2007 study involving over 4,000 patients with systolic dysfunction from the Val-HeFT trial, more than 90% had detectable levels using high-sensitivity cardiac troponin T assays compared to only 10% with conventional assays. High-sensitivity assays provided superior prognostic information, even after adjusting for other risk markers, including natriuretic peptide levels. Serial hs-cTn measurements add prognostic value beyond baseline measurements, as shown in pooled analyses of the Val-HeFT and GISSI-HF trials. A meta-analysis confirmed that elevated cTn in chronic heart failure was associated with a 2.85-fold increased risk of death, regardless of assay sensitivity. Recent studies also validate the prognostic strength of hs-cTn assays in elderly patients with ischemic chronic systolic heart failure (Gravning et al., 2014).

The Universal MI Global Task Force Heart Failure section recommends cTn measurement in chronic heart failure patients due to the strong association of elevated cTn levels with adverse outcomes. While troponin measurement aids prognostication, specific interventions targeting elevated cTn levels in chronic heart failure remain unsupported by current data.

Cardiac troponins are also elevated in heart failure with preserved ejection fraction, albeit at lower levels than in reduced ejection fraction cases. Echocardiographic studies suggest that left ventricular mass and relaxation abnormalities significantly influence circulating troponin levels in these patients. Elevated troponin levels predict adverse outcomes in heart failure with preserved ejection fraction (Perna et al., 2012). However, troponins are more indicative of risk than imaging indices of heart failure. They complement echocardiography or cardiac magnetic resonance imaging rather than acting as surrogate markers for left ventricular function or hypertrophy (Neeland et al., 2013).

The advent of high-sensitivity cardiac troponin assays has enabled precise detection of circulating cardiac troponins not only in patients with established stage C heart failure but also in individuals at elevated risk of developing heart failure. Patients with coronary artery disease are particularly predisposed to systolic heart failure, while those with chronic pressure overload conditions such as arterial hypertension or aortic stenosis are more likely to develop left ventricular hypertrophy—a phenotype often considered a precursor to heart failure with preserved ejection fraction. Recent evidence indicates that high-sensitivity troponin assays offer significant prognostic value for assessing the likelihood of future heart failure in patients with stable coronary artery disease who do not yet exhibit heart failure or reduced systolic function. For instance, in a large-scale study involving over 3,700 patients, detectable levels of high-sensitivity troponin T (hs-TnT) and high-sensitivity troponin I (hs-TnI) were observed in over 90% of participants. Both biomarkers were strongly associated with the risk of fatal and nonfatal heart failure events, independent of traditional risk markers and other cardiovascular biomarkers such as high-sensitivity C-reactive protein and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Notably, adding hs-TnT and hs-TnI to conventional risk models provided a modest but significant improvement in the models' predictive accuracy, as reflected by an increment in the C-statistic. Interestingly, hs-TnT and hs-TnI exhibited only moderate correlation and provided independent prognostic information.

The relationship between high-sensitivity cardiac troponins and heart failure risk has also been established through several large-scale epidemiological studies, including the Dallas Heart Study, the Atherosclerosis Risk in Communities (ARIC) Study, the Cardiovascular Health Study, the Framingham Heart Study, and the MORGAM Study. The Dallas Heart Study, which incorporated advanced phenotypic characterizations using cardiac magnetic resonance imaging and electron beam computed tomography, offered critical insights into the pathophysiological correlates of circulating troponin levels. The study revealed that left ventricular mass and function were more closely associated with troponin concentrations than the severity of coronary artery disease. Furthermore, the combination of increased left ventricular mass and elevated troponin T levels identified a high-risk phenotype with a heightened likelihood of heart failure development.

Another population at elevated risk for heart failure where cardiac troponin measurement has shown promise includes patients with aortic stenosis. Current guidelines recommend surgical intervention for symptomatic patients (exhibiting dyspnea, chest pain, or syncope) or those with clinical signs of myocardial remodeling or failure, such as arrhythmias or congestion. However, many patients—particularly older individuals with sedentary lifestyles—may experience irreversible myocardial remodeling before manifesting symptoms or clinical indicators of heart failure. Thus, an early biomarker capable of identifying patients with aortic stenosis at risk of irreversible myocardial remodeling could hold substantial clinical importance. In a

pioneering study, it was demonstrated that patients with moderate to severe aortic stenosis frequently exhibited detectable troponin levels using high-sensitivity assays, with left ventricular mass emerging as a key determinant of circulating troponin levels. Interestingly, epicardial coronary artery disease did not appear to influence hs-TnT concentrations in these patients. Additionally, patients with high hs-TnT levels had a worse prognosis compared to those with low levels, even after accounting for comorbidities, echocardiographic indices, and NT-proBNP levels. These findings were corroborated by Chin et al. in two independent cohorts of patients with aortic stenosis [60]. Similarly, hs-TnI levels were influenced by left ventricular mass and myocardial fibrosis, as assessed by cardiac magnetic resonance imaging, but not by coronary artery disease. Furthermore, hs-TnI levels provided stronger prognostic value than NT-proBNP for predicting the combined endpoint of aortic valve replacement or cardiovascular death.

Although myocardial ischemia due to a supply-demand mismatch may contribute to troponin release in patients with aortic stenosis, existing literature does not support undetected coronary artery disease as a significant factor underlying the strong prognostic value of troponin levels in this population. This conclusion aligns with findings from studies showing no specific increase in high-sensitivity troponin levels in individuals with reversible myocardial ischemia, as assessed through myocardial perfusion imaging or atrial pacing. Instead, high-sensitivity troponins likely reflect myocardial remodeling and fibrosis in aortic stenosis patients (Chin et al., 2014). These results are consistent with data from the Dallas Heart Study, which support the role of hs-TnT as a biomarker for identifying high-risk myocardial remodeling phenotypes in the general population.

Conclusion

In conclusion, the role of troponins in the laboratory diagnosis of heart failure has evolved significantly, particularly with the advent of high-sensitivity assays that enhance diagnostic accuracy and prognostic capabilities. Troponins, specifically cardiac troponin I and T, serve as critical biomarkers not only for acute myocardial infarction but also for various forms of heart failure, including both symptomatic and asymptomatic left ventricular dysfunction. The ability to detect elevated troponin levels in patients with acute heart failure underscores their importance in clinical practice, providing valuable insights into myocardial injury and potential outcomes.

The findings presented in this review highlight that elevated troponin levels are indicative of underlying pathophysiological processes beyond ischemic injury, reflecting a spectrum of cardiac stress and damage. This broadens the understanding of heart failure diagnostics and emphasizes the need for clinicians to consider troponin measurements alongside traditional diagnostic methods. As the prevalence of heart failure continues to rise, integrating troponin testing into routine clinical assessments will be essential for improving patient management and outcomes.

Future research should focus on standardizing troponin assays and further elucidating the mechanisms behind troponin release in various cardiac conditions. This will enhance the reliability of troponin as a diagnostic tool and refine its role in risk stratification for patients at risk of developing heart failure. Ultimately, a comprehensive approach that combines clinical evaluation with biomarker analysis will lead to better-informed therapeutic strategies and improved care for patients with heart failure.

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