Troponin in Heart Failure

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KEYWORDS

• Troponin • Heart failure • Prognosis • Biomarker • Mortality

KEY POINTS

- Troponin is often elevated in patients with chronic and acute heart failure, with and without coexisting coronary artery disease.
- As high sensitive assays become more common in clinical practice, more patients with heart failure will have detectable troponin.
- Measuring high sensitive troponin in patients at risk for heart disease does provide additional predictive ability regarding incident heart failure.
- Troponin elevation in acute, chronic heart failure with reduced and preserved ejection fraction has prognostic value for future poor outcomes.

INTRODUCTION

Measurement and interpretation of cardiac troponin (cTn) is an integral part of the management of patients with acute coronary syndrome (ACS).[1] A rise-and-fall pattern of cTn is a part of the diagnostic criteria for acute myocardial infarction (AMI), and elevated cTn provides prognostic value in multiple noncardiac conditions.[2] Heart failure (HF) is a chronic, progressive condition that affects an estimated 5.7 million Americans.[3] It is a rising global epidemic with greater than 37.7 million affected worldwide.[4,5] Older individuals are particularly affected, with over half of patients hospitalized greater than 75 years of age.[6] Biomarkers play an critical role in the management of patients with or at risk for HF.[7] The American Heart Association (AHA) recently published a scientific statement regarding the role of biomarkers in the management of HF.[7] The role of troponin in the management of patients with HF is evolving with a growing body of evidence for its potential. In this review, the authors discuss the role of troponin in prediction, management, and prognostication of patients with HF. Specifically, the authors detail the unique role in acute and chronic HF, as well differences in reduced ejection fraction versus preserved ejection fraction HF. Finally, the authors discuss novel data using high sensitive troponin assays and potential strategies in the future to improve the use of troponin in caring for patients with HF.

HEART FAILURE

HF is defined by the American College of Cardiology and the AHA as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.[8] The result is a constellation of signs and symptoms related to either congestion or low cardiac output. HF is most often subtyped in to 2 categories: reduced or preserved ejection fraction (HFrEF or HFpEF, respectively).

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The cause of HF can vary, with higher income regions frequently affected by ischemic heart disease and low-income regions by hypertensive, rheumatic and myocarditis.[5] An analysis of 24 large HF trials demonstrated coronary artery disease (CAD) was the underlying cause in nearly 65% of patients.[9] The importance and relevance of cTn in HF not only lies in those with ischemic HF but also non-ischemic HF. The burden of HF is large, with the direct costs and prevalence of HF estimated to increase by 200% and 25%, respectively, over the next 20 years.[10,11] Thus, there exists a need for additional tools to help improve care for this costly and high-risk population.

TROPONIN

Troponin proteins are involved in the regulation of cardiac muscle contraction. Troponin I (inhibitory), troponin C (calcium binding) and troponin T (tropomyosin binding) proteins form the troponin complex.[12] There are variable isoforms of each subtype of troponin found within cardiac and skeletal muscle. Although most cTn is part of the contractile apparatus, some troponin I (cTnI) and troponin T (cTnT) is found free in the cytosol.[13] Detectable levels of cTnI and cTnT in the serum are always found in patients with myocardial infarction with a typical rise-and-fall pattern. This elevation in cTn is part of the diagnostic criteria for acute myocardial infarction.[14] Clinical assays exist for the detection of cTnT and cTnI with varying degrees of sensitivity and limits of detection. More recently, high sensitive assays have been developed and routinely used in clinical practice; these detect cTn levels to nanogram and picogram levels. To be considered a high sensitive assay, detectable cTn should be found in greater than 50% of healthy subjects.[2,15] A high sensitive troponin assay (Roche) was recently approved by the Food and Drug Administration for use in the United States. Most studies of the utility of cTn in HF were performed with contemporary sensitive assays, although the volume of data regarding high sensitive cTn (hs-cTn) is growing.

MECHANISMS OF CARDIAC TROPONIN ELEVATION IN HEART FAILURE

There are multiple theories as to why patients with HF have detectable cTn. The most prevailing theory is related to persistent subendocardial ischemia, which may or may not be related to epicardial obstructive CAD.[16] In acute decompensated HF, reduced cardiac output and increased ventricular filling pressures can worsen the coronary perfusion gradient. These mechanisms lead to cardiac ischemia and release of cTn. In chronic HF, continuous upregulation of the renin-angiotensin aldosterone system may lead to persistent cell injury and death. Detectable cTn has been consistently found in patients with ischemic and nonischemic HF.[17] In patients with nonischemic HF, there is an association with cTn and a restrictive mitral Doppler pattern as well as left ventricular (LV) concentric remodeling.[16] When cTn is elevated in a new case of acute HF (AHF), it is often questioned as to whether ischemia was the trigger for the episode itself or if cTn release is sequelae from the decompensated state. Serial measurements and clinical history are imperative in distinguishing between these two hypotheses. Other theories as to the mechanism behind cTn release in HF include myocyte damage from inflammatory cytokines or oxidative stress,[18] apoptosis of hibernating myocardium,[19] or injured myocardium and permeable membranes with leakage.[20] As the sensitivity for cTn assays have improved, many acute conditions, including sepsis, arrhythmia, hypertension, cardiotoxicity from chemotherapy, and renal failure, have associated elevated cTn.[21]

TROPONIN TO PREDICT INCIDENT HEART FAILURE

In patients without a diagnosis of HF, multiple biomarkers have shown an association with the development of future HF. Biomarkers, such as soluble ST-2, growth differentiation factor 15, and natriuretic peptides, have shown modest predictive ability in the Framingham Heart Study to predict incident HF.[22–24] Troponin as a marker of underlying myocyte dysfunction may also have potential as a predictor of new HF. Chronic and low-level myocyte injury may be ongoing in individuals, which can precede the development of clinical HF. DeFilippi and colleagues[25] studied the role of hs-cTnT in 4221 subjects older than 65 years from the Cardiovascular Heart Study cohort. From the cohort, 66.2% of subjects had baseline detectable cTnT. The baseline and an increase from the baseline to 2 years' follow-up both were associated with the development of HF. When added to a prediction model (including demographics, clinical risk factors, medications, and biomarkers N-terminal pro b-type natriuretic peptide and C-reactive protein), hs-cTnT provided a modest addition to a risk prediction for future HF. A similar analysis by Saunders and colleagues[26] studying the Atherosclerosis Risk in Community (ARIC) cohort demonstrated measurable cTnT in