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An Overview on Troponin I in Myocardial Injury

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Abstract:

In the last several decades serum levels of cardiac enzymes and isoenzymes have become the final arbiters by which myocardial damage is diagnosed or excluded. Because conventionally used enzymes are neither perfectly sensitive nor specific, there is need for a new sensitive and cardiospecific marker of myocardial damage. Cardiac troponin T (TnT) is a contractile protein unique to cardiac muscle and can be differentiated by immunologic methods from its skeletalmuscle isoform. An enzyme immunoassay specific for cardiac TnT is now available in a commercial kit for routine use. The biggest advantage of this assay is its cardiospecificity. TnT measurements, however, are also highly sensitive in diagnosis of myocardial injury and accurately discern even small amounts of myocardial necrosis. TnT measurements are, therefore, particularly useful in patients with borderline CK-MB and in clinical settings in which traditional enzymes fail to diagnose myocardial damage efficiently because of lack of specificity-for example, perioperative myocardial infarction or blunt heart trauma. TnT release kinetics reveal characteristics of both soluble, cytoplasmic, and structurally bound molecules. It starts to increase a few hours after the onset of myocardial damage and remains increased for several days. TnT allows late diagnosis of myocardial infarction. The diagnostic efficiency remains at 98% until 6 d after the onset of infarct-related symptoms. TnT is also useful in monitoring the effectiveness of thrombolytic therapy in myocardial infarction patients. The ratio of peak TnT concentration on day 1 to TnT concentration at day 4 discriminates between patients with successful (>1) and failed (≤1) reperfusion. TnT measurements are very sensitive and specific for the early and late diagnosis of myocardial damage and could, therefore, provide a new criterion in laboratory diagnosis of the occurrence of myocardial damage.

Keywords: Troponin I, Pediatric, Myocardial Injury.

Introduction:

Myocardial injury is defined as any cTn concentration above the 99 percentile URL. Myocardial injury is considered *acute* if there is a rise and/or fall of cTn concentrations exceeding biological and/or analytical variation. No standard exists for how much rise and/or fall of hs-cTn identifies acute injury; typically an increase in the cTn concentration greater than the reference change value **(biological variation of an assay)** is considered acute for both cTnT and cTnI assays if the initial cTn value is < 99 percentile. If the first cTn level is > 99 percentile then an increase of at least 50% of the 99 percentile or a change > 20% may be considered acute.

While small changes in cTn concentration have poor specificity, a large rise and/or fall is much more specific for acute myocardial injury with the largest increases typically occurring in acute MI ; the larger the rise and/or fall of cTn, the higher the positive predictive value for MI **(1)**.

To diagnose any of the five types of MI , in addition to acute myocardial injury, there must be clinical evidence of acute myocardial ischemia. The diagnosis of myocardial ischemia requires at least one of the following: 1) symptoms of myocardial ischemia, 2) new ischemic electrocardiographic changes, 3) new ischemic regional wall motion abnormalities on cardiac imaging, or 4) acute coronary thrombus on coronary angiography. In the absence of these pre-requisites, MI cannot be diagnosed. Differentiating type 2 MI from myocardial injury can be particularly challenging. Both entities can have overlapping precipitants but they are differentiated by the presence of ischemia which is needed to diagnose type 2 MI. However, evaluating for the presence of ischemia can be challenging in certain situations such as the intubated patient or when atypical symptoms exist **(2)**.

At lower cTn concentrations, which are the most often frequently encountered in clinical practice; besides ischemic mechanisms leading to acute MI, several other mechanisms of acute myocardial injury have been described, including those that cause increase cTn release such as myocardial strain, inflammation, apoptosis, and cell injury, or those that decrease cTn clearance such as acute or chronic kidney injury ; all must be considered in the differential diagnosis if the presentation is ambiguous **(3)**.

A cTn result above the 99 percentile URL without a rise and/or fall over a period of serial measurements **(e.g. over 8 hours)** is characteristic of *chronic* myocardial injury in the appropriate clinical setting **(4)**.

Epidemiology

The reported incidence of myocardial injury has varied according to the setting in which the cTn was measured . In a cohort of 918 consecutive patients presenting to the emergency department **(ED)** *without* symptoms of MI, the incidence of myocardial injury was 12% **(of which 4% of patients were had MI)**. Predictably, among patients presenting to the ED with suspicion of MI the incidence of myocardial injury is higher. In the Use of TROPonin In Acute coronary syndrome **(UTROPIA)** study, a prospective observational study of 1,640 ED patients undergoing serial hs-cTnI **(Abbott)** measurements on clinical indication, Sandoval and colleagues found that 26% of patients had at least one cTnI >99 percentile, of which 58% were determined to be myocardial injury. The investigators found that the most frequent etiologies of myocardial injury were renal failure, HF, and neurological conditions. The High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome **(HighSTEACS)** trial was a stepped-wedge, cluster-randomized controlled trial that prospectively evaluated the implementation of a hs-cTnI assay among 48,282 consecutive patients presenting with suspected MI to ten hospitals in Scotland. The investigators found the incidence of myocardial injury to be 21%, of which 69% were diagnosed with MI. Notably, few epidemiological studies to date have differentiated acute from chronic myocardial injury. Examining 39,558 patients presenting to the ED with chest pain, Kadesjo and colleagues found that 3,855 patients had a hs-cTn concentration greater than the 99 percentile. Of these, 29% had type 1 MI, 6.5% had type 2 MI, 29.5% had acute myocardial injury, and the majority **(35%)** had chronic myocardial injury **(5)**.

In the current era of hs-assays, myocardial injury may now be the most common cause of increased cTn when examined in hospitalized patients. Using the Veterans Affairs centralized databases, McFalls *et al.* identified patients hospitalized with increased cTn concentrations in 2006. Among 100, 433 patients who had a troponin **(cTnT or cTnI)** measured during their index admission, 24% were diagnosed with myocardial injury; the majority **(57%)** were not found to have MI. Of the patients with non-infarction cTn increases, more than 40% carried a primary diagnosis of cardiac origin, such as HF and chronic coronary artery disease **(CAD)**, while others were diagnosed with infections or diseases related to the renal, gastrointestinal, and neurologic systems. Similarly, examining 3,762 patients with hs-cTnI measured during index hospitalization, Sarkisian *et al.* found the incidence of myocardial injury to be 42% and only 31% of these patients were diagnosed with MI. Dolci *et al.* found the incidence of ischemic and non-ischemic myocardial injury among hospitalized patients to be slightly higher at 59% **(6)**.

Differential Diagnosis

The differential diagnosis for myocardial injury is broad and can be divided into acute or chronic causes **(7).**

Acute Myocardial Injury

When a rise and/or fall of cTn with at least one concentration >99 percentile URL is encountered, acute MI is a primary consideration; the larger the magnitude of the cTn increase, the more likely acute MI is the cause. That said, even when faced with moderate degrees of injury, a broad range of precipitants of myocardial injury should be considered. *Cardiovascular* causes of acute myocardial injury include MI, pulmonary embolism **(PE)**, myocarditis, and/or myopericarditis, aortic dissection, cardiac surgery, or procedures **(e.g. cardioversion or ablation)**, hypertension, arrhythmias, acute HF, acute valvular heart disease **(e.g.: aortic regurgitation or mitral regurgitation)**, Takotsubo cardiomyopathy, and cardiac contusions **(including chest compressions)**. If accompanying clinical evidence of acute myocardial ischemia is identified, then acute MI should be diagnosed. For example, in the absence of overt myocardial ischemia, most patients with acute HF should be categorized as having myocardial injury; however, acute HF can occur due to myocardial ischemia, and when these patients are identified to have clinical evidence of myocardial ischemia, then acute MI is diagnosed. *Non-cardiovascular* causes and/or triggers of myocardial injury include acute renal failure, sepsis, anemia, hypotension, hypoxia, non-cardiac surgery, critical illness, rhabdomyolysis, drug induced **(e.g. chemotherapy)**, stroke, and extreme exertion. A common vexing issue is the effect of renal dysfunction on cTn concentrations. One prevalent hypothesis is that myocardial injury in patients with advanced kidney disease is a consequence of decreased clearance of cardiac troponin. However, its presence is likely multifactorial and also influenced by other factors such as underlying CAD, and left ventricular mass **(8)**.

Chronic Myocardial Injury

Cardiovascular causes of chronic myocardial injury include chronic HF, infiltrative cardiomyopathies **(amyloidosis, hemochromatosis, and sarcoidosis)**, hypertrophic cardiomyopathy, stable CAD, hypertension, valvular heart disease, and persistent arrhythmias **(e.g. atrial fibrillation)**. *Non-cardiovascular* causes include chronic renal disease, pulmonary hypertension, toxins, and diabetes mellitus **(9)**.

Prognosis

Emerging evidence from several observational studies indicates that myocardial injury pertains a concerning prognosis . Most studies have not delineated acute versus chronic myocardial injury without infarction, and there remains limited data on differences in outcomes between these two entities **(10)**.

One small retrospective study showed that patients with non-cardiac precipitating factors for their increased cTnI at presentation have higher in-hospital mortality **(26.7% vs. 13.4%, p=0.002)** compared to cardiac-related precipitants. Beyond the initial hospitalization, myocardial injury has high short term mortality; 11% at 6 months and 26% at 2-years. Age, maximum cTnI concentration, and a history of HF were predictive of 2-year mortality. Longer term outcomes were examined by Chapman and colleagues, who found that 5-year mortality was as high as 72%. The long-term mortality from myocardial injury was mostly driven from noncardiovascular causes **(62%)**. Accordingly, some of this mortality risk may not be modifiable. Cardiovascular event rates, however, are also high among this population. The 5-year MACE rates were 31% with 28% of patients experiencing a cardiovascular death. Over 5-years, 4.8% of patients with myocardial injury experience a non-fatal MI, 5.6% a HF hospitalization, and 3.9% a stroke. Patients with myocardial injury in the absence of MI, had a higher risk of allcause mortality compared to type 1 MI but a lower risk of MACE . A large retrospective analysis of 9,800 patients with myocardial injury without MI, diagnosed by either conventional or hs-cTn, included in the SWEDEHEART registry found similarly morbid long term outcomes; with 15.4% of patients having MACE **(composite of all-cause mortality, MI, readmission for HF, or stroke at a median follow-up 4.9 years)**. Furthermore, they reported that the magnitude of myocardial injury was an important predictor of mortality, with successive increases in hazard ratios across troponin tertiles, even when adjusting for presence of cardiovascular disease or prevalent comorbidities. Examining outcomes among patients with myocardial injury diagnosed in the ED, Kadesjo *et al.* found that patients with acute myocardial injury had a 21% higher risk of all-cause mortality

and a 30% higher risk of HF compared to patients with chronic myocardial injury over a median follow-up of 3.9 years **(11)**.

Myocardial injury occurs in a heterogeneous group of patients; consisting of both cardiac and non-cardiac types of insult; which likely confer different prognostic implications. A prospective study on patients with myocardial injury categorized patients based on etiology: ischemic, non-ischemic cardiac **(e.g. major cardiac surgery)**, noncardiac **(e.g. infection)** or multifactorial **(at least 2 cardiac or non-cardiac conditions)** conditions. Researchers found that after adjusting for covariates, cardiac ischemic and non-ischemic patients had similar mortality rates. However, diagnoses of noncardiac and multifactorial causes of myocardial injury carried higher mortality compared to cardiac ischemic types of injury . Patients with chronic HF often have evidence of myocardial injury and a meta-analysis of 9,289 patients found that cTn increases predicted allcause mortality **(hazard ratio (HR)** 1.48, p<0.001), cardiovascular death **(HR 1.40, p<0.001)**, and cardiovascular hospitalization **(HR 1.42, p<0.001) (12)**.

Troponin levels may correlate with clinical prognosis in some cases. Increases in cTnI concentrations in patients undergoing high dose chemotherapy for aggressive malignancies have been correlated with future reductions in left ventricular ejection fraction. In patients with chronic kidney disease and end-stage renal disease, increased cTn concentrations are associated with higher rates of all-cause mortality. In patients with amyloidosis or pulmonary embolism, detection of cTn were found to be strong predictors of all-cause mortality. Troponin detection can also be induced by exercise, though the clinical implication of the cTn elevation not well understood. Prognostication using cTn certainly does not apply for all causes of myocardial injury nor would peak cTn level necessarily enable prognostication across various causes of myocardial injury, which can cause vastly different levels of cTn elevation **(13)**.

Risk stratification for patients with myocardial injury and identification of patients would benefit from close monitoring and further testing is an area of ongoing investigation, especially given the evidence that increased cTn concentrations carry prognostic significance. Risk stratification may guide frequency of follow-up visits post-discharge facilitating surveillance for symptoms of ischemia, HF, and optimization of preventative therapies. The TARRACO **(Troponin Assessment for Risk stRatification of patients without Acute COronary atherothrombosis)** risk score was recently developed to risk stratify patients with type 2 MI or myocardial injury and externally validated in a cohort of 401 patients. The score combines incorporates cTn concentrations and predictors of adverse cardiovascular events in this population, including age, hypertension, absence of chest pain, dyspnea, and anemia. MACE events were five times higher in the high-risk patients compared to the lowest risk patients based on this score. The utility of this score to alter the prognosis of patients **(by guiding further investigation or therapeutic intervention)** will however need evaluation in a clinical trial **(14)**.

Taken together, these trends in morbidity and mortality underscore the reality that myocardial injury with ‘negative’ ischemic work-up does not offer reassurance; rather, a careful evaluation for alternate etiologies should be considered. Furthermore, trivializing such circumstances as a "troponin leak" or "troponinemia" is strongly discouraged. Although prospective studies are needed to demonstrate that outcomes for patients with myocardial injury are indeed modifiable, the consistency of the evidence that myocardial injury is associated with very poor outcomes across a broad range of healthcare settings requires clinicians to take elevated troponin seriously **(15)**.

Evaluating Myocardial Injury

The initial assessment of myocardial injury focuses on the 1) assessment of ischemic symptoms, 2) review of the patients past medical history and cardiovascular risk factors, 3) serial 12-lead electrocardiograms, 4) serial cTn measurements assessed over 3-12 hour periods depending on sensitivity of the assay, 5) imaging: an echocardiogram to assess for regional wall motion abnormalities and exclude the presence of cardiomyopathy and/or structural heart disease, and/or 6) coronary angiography **(computerized tomography or invasive)**.

If the patient reports symptoms of angina—even atypical—they nominally meet the Universal Definition for acute MI, and an ischemic evaluation should be undertaken, if not previously performed. If myocardial

infarction is excluded the subsequent assessment includes a comprehensive history and physical examination, laboratory testing, and where appropriate, cardiac imaging **(16)**.

History and Physical Examination

Inquiring about the presence and nature of chest discomfort is important. Pleuritic discomfort may suggest PE, pneumonia, or myocarditis. Discomfort radiating to the back may suggest aortic dissection. Symptoms suggestive of HF **(dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema)**, valvular heart disease **(syncope, angina, and dyspnea)**, cardiac arrhythmias **(palpitations)**, and infections **(fevers, chills)** should be explored. Recent procedures **(cardiac and non-cardiac)**, use of cardiotoxic medications **(in particular chemotherapy and substance abuse)**, activity **(intense exercise regimens)**, life stressors **(Takotsubo cardiomyopathy)**, recent travel, and past medical history **(specifically cardiovascular, pulmonary, and renal comorbidities)** should be reviewed **(17)**.

The physical examination must include an appraisal of the patients' vital signs, cardiovascular system **(heart rate and rhythm, murmurs, presence of congestion)**, pulmonary system **(wheezing, rhonchi, and crackles)**, and potential sources of infection **(13)**.

Laboratory Data and Imaging

Serial cTn measurements are informative to differentiate acute from chronic myocardial injury; when using hs-cTn assays. In early and late presenters or in those in whom symptom onset is uncertain and distinguishing acute vs. chronic injury from infarction remains uncertain, a 3 sample can be helpful as up to 26% of patients with acute MI may not demonstrate a significant rise and/or fall. A 12-lead electrocardiogram should be obtained at presentation and reviewed for signs of ischemia/infarction, arrhythmias, acute right ventricular strain, and signs of conduction or structural disease **(e.g. left ventricular hypertrophy)**. We recommend assessment of renal function and measurement of a natriuretic peptide to provide complementary information regarding common causes of non-MI related injury, such as chronic kidney disease or HF, respectively). A complete blood count **(anemia or infection)** should be attained. Additional laboratory testing such as d-dimer **(considering PE and aortic dissection)**, and infectious/inflammatory markers **(e.g. c-reactive protein)** can be guided by clinical assessment. An echocardiogram should be obtained to assess for systolic or diastolic dysfunction, left ventricular hypertrophy, wall motion abnormalities, or valvular abnormalities. Further imaging such as cardiac magnetic resonance imaging may be obtained depending on the clinical scenario **(e.g. suspected myocarditis or infiltrative cardiomyopathy) (4)**.

Treatment

For type 1 MI, an evidence-based treatment is well established. For type 2 MI, present recommendations are to individualize care and correct the supply/demand alteration **(e.g.: anemia, tachycardia, hypotension, etc.)** leading to myocardial ischemia. The DEtermining the Mechanism of myocardial injury AND role of coronary disease in type 2 Myocardial Infarction trial is attempting to improve our understanding of the mechanisms of ischemic myocardial injury by engaging computed tomography coronary angiography, invasive coronary angiography, and cardiac magnetic resonance imaging. The Appropriateness of Coronary investigation in myocardial injury and Type 2 myocardial infarction **(ACT-2)** trial is randomizing 300 patients with myocardial injury to invasive angiography **(or computed tomography angiography)** within 5 days of randomization versus conservative management **(with or without functional testing at clinician discretion)** with a primary endpoint of all-cause mortality at 2 years. Cost-effectiveness will be determined based on clinical events, quality of life, and resource utilization over 24 months **(18)**.

Beyond those patients with ischemic myocardial injury, unfortunately, no consensus exists regarding routine management of patients with myocardial injury. The management of myocardial injury may thus focus on the identification and treatment of the underlying precipitant **(e.g. HF) (15)**.

Whether therapies to attenuate injury itself are of benefit remains unclear and data are largely retrospective and/or inconclusive. The WOSCOPS **(West of Scotland Coronary Prevention Study)**

investigators found pravastatin reduced hs-cTnI concentrations in an ambulatory population free of prior MI by an average of 13%, and change in troponin at 1year was associated with future MI risk reduction independent of cholesterol lowering **(9)**.

However, this was a primary prevention study, and the applicability of these findings to patients with acute non-ischemic myocardial injury is uncertain. The MANAGE **(Management of Myocardial Injury After Noncardiac Surgery)** trial found that dabigatran lowered major vascular event rates when compared with placebo **(11% versus 15%, p=0.02)** among patients with myocardial injury after noncardiac surgery. Nonetheless, the results of this trial should be interpreted cautiously as the trial was terminated early and medication discontinuation rates were high. Further, given the heterogeneity in etiologies, it is difficult to conceive that one-single approach can be used for all patients and the primary composite endpoint was broad **(vascular mortality, non-fatal MI, non-hemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism)**. Lastly, sodium-glucose cotransporter 2 inhibitors **(SGLT2i)** have been shown to enhance diuresis, reduce blood pressure, and improve left ventricular remodeling. In patients with diabetes mellitus, canagliflozin delayed a rise in troponin over 2-years when compared to placebo. Thus, these agents, along with others with alter hemodynamic stress, warrant investigation among patients with myocardial injury **(19)**.

Troponin I in Pediatrics

The 2018 Expert Opinion from the AACC and IFCC recommends that hs-cTn methods meet two fundamental criteria. First, these laboratory tests should measure the 99th percentile URL with an imprecision **(expressed as coefficient of variation)** ≤10%. Second, these assays should be able to detect the biomarker concentration at or above the limit of detection **(Ufongene et al.)** in 50% of healthy individuals. The estimation of the 99th percentile URL strongly depends not only on demographic and physiological variables of the reference population but also on the analytical performance of laboratory methods and the mathematical algorithm used to calculate the 99th percentile value . Identifying the URL is a very challenging task, typically undertaken in the context of multicenter studies **(7)**.

Only the most recent hs-cTnI and hs-cTnT methods fully satisfy these analytical specifications . Their analytical sensitivity ranges from 1 to 3 ng/L, allowing for the measurement of the URL with a mean imprecision of about 5% **(i.e., half of the level required by guidelines)** . The few studies using hs-cTnI and hs-cTnT methods in apparently healthy infants and children have shown that biomarker values are generally higher compared to those observed in apparently healthy individuals aged >18 years . Specifically, hs-cTnI and hs-cTnT are higher in healthy neonates and infants compared to children and adolescents, while boys generally have higher values than girls . Therefore, the sensitivity of commercially available hs-cTnI and hs-cTnT methods appears more than adequate to accurately measure circulating levels of biomarkers in the pediatric population. This is crucial because it is unclear whether some of the cTnI methods , cited in a 2016 systematic review , actually meet the quality specifications for hs-cTn assays . For this reason, only the circulating levels of biomarkers measured with hs-cTnI and hs-cTnT methods in healthy neonates, children, and adolescents. **(9)**

The two most important limitations of studies on reference intervals for hs-cTnI and hs-cTnT, particularly in neonates, infants, and children, are the volume of blood typically collected **(about 0.5–1.0 mL)** and the number of subjects needed to accurately measure the distribution values of biomarkers. Indeed, nearly 300 apparently healthy individuals are needed for each age group **(i.e., neonates, infants, or children)** and sex group **(boys or girls)** to calculate the URL with a 99% confidence interval . Unfortunately, even larger studies do not meet the criteria of at least 300 cases for different age and sex groups **(11)**.

Studies in adult subjects have reported large systematic differences in hs-cTnI values measured through different methods, including URL and reference values . There are concerns about the ability to reliably harmonize results across hs-cTnI methods. At present, data are available for only one hs-cTnI method in the pediatric population , but these systematic differences should be considered in future studies **(12)**.

hs-cTn levels during the pediatric age

Studies on hs-cTnI and hs-cTnT levels across the pediatric age confirm the trends previously reported

with less sensitive methods . In particular, hs-cTnI and hs-cTnT show a similar trend, with the highest values occurring in the first month of life, followed by a rapid decline during the first six months, and then a slower decrease during childhood, ultimately reaching a plateau during adolescence . Minor sex-specific differences have been observed in healthy adolescents, with higher concentrations in boys , consistent with results from adult cohorts including healthy individuals aged >18 years . These observations underscore the importance of interpreting hs-cTnI and hs-cTnT concentrations according to age and sex . Differences between the clinical utility of hs-cTnI and hs-cTnT are not well understood, especially in the pediatric population, and there is a lack of harmonization in hs-cTnI methods. This presents clinical challenges and complicates the comparison and interpretation of study findings, particularly in pediatrics, where the literature is more limited **(14)**.

Differences between the clinical utility of hs-cTnI and hs-cTnT are not well understood, especially in the pediatric age group. Furthermore, there is a lack of harmonization in hs-cTnI methods, which presents clinical challenges and complicates the comparison and interpretation of study findings, particularly in pediatrics, where the literature is more limited . Circulating hs-cTn in healthy adult subjects may be considered a reliable index of cardiomyocyte renewal **(16)**.

The mean imprecision profile **(expressed as CV%)** among three hs-cTnI methods **(i.e., Architect, Access, and ADVIA Centaur XPT)** and the ECLIA hs-cTnT method was estimated using a standardized protocol, as previously reported in detail . Specifically, for the calculation of the mean imprecision profile, 11 plasma pools collected from healthy normal subjects and patients with cardiac disease were repeatedly measured **(more than 30 times on different working days using at least two lots of reagents and standards)** with the hs-cTnI and hs-cTnT methods. These plasma pools cover the biomarker concentration range from the LoD **(about 1–3 ng/L)** to the 99th percentile URL values **(from 13 to 50 ng/L)** for the hs-cTn methods . Four different graphical symbols were used to represent the mean biomarker values measured with the four hs-cTn methods. A curvilinear relationship was then calculated between the CV values **(Y axis)** and the respective hs-cTn concentrations using the mean values obtained from the plasma pools measured with the four hs-cTn methods . Finally, the best fitting **(reciprocal equation)** among the 44 mean values of the 11 plasma samples measured with the four hs-cTn methods was calculated using the JMP 15.2.1 statistical program **(SAS Institute Inc.)**, also including the correlation coefficient R **(1)**.

The varying rates of cardiomyocyte renewal during pediatric development may account for different hs-cTn levels in neonates, infants, and children . Other possible reasons for this heterogeneity include the expression of fetal cardiac troponin in skeletal muscle, transient hypoxia at birth, and/or cardiac leakage . Sex-specific differences in healthy adolescents are commonly explained by the greater cardiac mass in males **(2)**.

hs-cTn Increase After Physical Exercise

Increased hs-cTnI and hs-cTnT levels have been observed in preadolescent and adolescent healthy athletes after intense physical exercise . In particular, hs-cTn levels usually increase during prolonged exercise or within a few hours after exercise ends, resolving within 24–48 hours **(20)**.

Nie et al. examined the effect of two 45-minute constant-load treadmill runs separated by 255 minutes of recovery in 12 trained adolescent runners **(aged 14.5 ± 1.5 years)**. cTnT was undetectable before exercise but was elevated post-exercise in 67% of runners, and then progressively decreased thereafter . Peretti et al. evaluated hs-cTnT and natriuretic peptides in 21 healthy male athletes **(aged 9.2 ± 1.7 years)** after intensive cycling training until muscular exhaustion **(mean duration 16 minutes) (21)**.

The majority of preadolescent athletes **(62%)** had an elevation of cardiac biomarkers: specifically, six children had increased hs-cTnT, and three had an elevation of NT-proBNP as well . hs-cTnT elevation had no relationship with heart rate, age, or exercise duration . The release of hs-cTn might be related to a temporary mismatch between oxygen delivery and consumption, and the degree of training may influence the hs-cTn increase **(4)**.

The transient elevation of hs-cTn usually represents a physiological phenomenon but can unmask a subclinical cardiac disease . The influence of different confounders **(age, sex, sport type/intensity/duration, and**

training level) should be better clarified to establish individualized normal ranges for post-exercise hs-cTnI and hs-cTnT elevation **(3)**.

Both in well-trained athletes and in healthy subjects free of cardiovascular disease, hs-cTnI and hs-cTnT levels show only a moderate increase after endurance exercise and usually return to pre-exercise values within 24–48 hours . In contrast, the kinetic curve of cTn concentrations in patients with myocardial infarction **(22)** is much longer **(from 4 to 10 days)** and may cover several orders of magnitude **(from 100 to 100,000 ng/L)** . Furthermore, the circulating forms of cTnI and cTnT measured after intense exercise could differ from those found in patients with cardiac or renal disorders **(18)**.

Specifically, degraded fragments **(molecular weight, MW, of 14–18 kDa)** are the main circulating forms after strenuous exercise . These lower molecular forms of cTnT seem more similar to those observed in patients with end-stage renal disease **(ESRD)** . Conversely, intact cTnT **(MW about 40 kDa)** is measured during the first hours of an MI, while in the following days, some degraded forms with lower MW **(14–20 kDa)** are predominantly detected . Therefore, hs-cTnI and hs-cTnT elevation due to physical exercise can be easily distinguished due to their shorter kinetics and lower MW isoforms of the biomarker **(19)**.

Comparison of Troponin I with Other Biomarkers (e.g., CK-MB, BNP)

The comparison of Troponin I **(TnI)** with other biomarkers, such as Creatine Kinase-MB **(CK-MB)** and B-type Natriuretic Peptide **(BNP)**, plays a critical role in diagnosing myocardial injury and assessing cardiac conditions, especially in the context of acute myocardial infarction **(23)** and heart failure. **(17)**

Troponin I is considered the gold standard biomarker for diagnosing myocardial injury due to its high specificity and sensitivity for cardiac muscle damage. It is released into the bloodstream when the heart muscle is injured, making it a reliable marker for detecting both minor and major myocardial damage. However, its role is often complemented by other biomarkers, such as CK-MB and BNP, which provide additional diagnostic insights, particularly in distinguishing between different forms of cardiac dysfunction. **(15)**

CK-MB has historically been a popular marker for myocardial injury, especially in cases of acute myocardial infarction. While CK-MB is specific to myocardial tissue, it can also be elevated in conditions involving other muscle tissues, limiting its specificity compared to troponin I. Studies have shown that CK-MB, when used in combination with TnI, enhances diagnostic accuracy, especially in detecting acute myocardial infarction and other cardiovascular events . However, it is not as sensitive as TnI, particularly for minor cardiac injury or in patients with chronic conditions .**(13)**

BNP, on the other hand, is primarily used in the diagnosis and management of heart failure. It is a hormone released from the ventricles of the heart in response to increased wall stress. BNP levels are significantly elevated in patients with heart failure and other conditions that cause cardiac dilation and strain. It provides valuable information in the context of acute decompensated heart failure, where elevated BNP levels help to distinguish between heart failure and other potential causes of symptoms such as shortness of breath . Unlike troponin, which is specific to myocardial injury, BNP is more useful in the broader context of heart failure and fluid overload. Studies have indicated that combining BNP with other biomarkers like CK-MB and troponin I increases the overall sensitivity and negative predictive value, allowing for better diagnostic differentiation between heart failure and acute myocardial injury **(24)**.

While each of these biomarkers—Troponin I, CK-MB, and BNP—has distinct roles, their combined use provides a comprehensive diagnostic approach, especially in complex clinical scenarios. Troponin I remains the most specific marker for myocardial injury, particularly in acute settings, while CK-MB offers complementary diagnostic benefits, especially in the detection of more acute forms of injury. BNP is invaluable for heart failure management, serving as an adjunct to the traditional biomarkers of myocardial injury . Combining these markers enhances diagnostic precision and clinical decision-making, allowing for better management of patients with cardiovascular disease. **(10)**

For example, in patients undergoing percutaneous coronary intervention **(PCI)**, the combination of TnI and BNP has been shown to improve diagnostic accuracy and prognostic outcomes . Furthermore, the ongoing evolution of biomarker panels that incorporate TnI, BNP, and CK-MB promises to refine the diagnostic processes for both myocardial injury and heart failure, improving patient outcomes through early and accurate detection **(8)**.

References:

1. SHAH, A. S., SANDOVAL, Y., NOAMAN, A., SEXTER, A., VASWANI, A., SMITH, S. W., GIBBINS, M., GRIFFITHS, M., CHAPMAN, A. R. & STRACHAN, F. E. 2017. Patient selection for high sensitivity cardiac troponin testing and diagnosis of myocardial infarction: prospective cohort study. Bmj, 359.
2. AYDIN, S., UGUR, K., AYDIN, S., SAHIN, İ. & YARDIM, M. 2019. Biomarkers in acute myocardial infarction: current perspectives. *Vascular health and risk management***,** 1-10.
3. CHAULIN, A., KARSLYAN, L., BAZYUK, E., NURBALTAEVA, D. & DUPLYAKOV, D. 2019. Clinical and diagnostic value of cardiac markers in human biological fluids. *Kardiologiia,* 59**,** 66-75.
4. BODOR, G. S. 2016. Biochemical markers of myocardial damage. *Ejifcc,* 27**,** 95.
5. SÖRENSEN, N. A., NEUMANN, J. T., OJEDA, F., GIANNITSIS, E., SPANUTH, E., BLANKENBERG, S., WESTERMANN, D. & ZELLER, T. 2019. Diagnostic evaluation of a high-sensitivity troponin I point-of-care assay. *Clinical Chemistry,* 65**,** 1592-1601.
6. DU, X., SU, X., ZHANG, W., YI, S., ZHANG, G., JIANG, S., LI, H., LI, S. & XIA, F. 2021. Progress, opportunities, and challenges of troponin analysis in the early diagnosis of cardiovascular diseases. *Analytical Chemistry,* 94**,** 442-463.
7. BARBERI, C. & VAN DEN HONDEL, K. E. 2018. The use of cardiac troponin T **(cTnT)** in the postmortem diagnosis of acute myocardial infarction and sudden cardiac death: A systematic review. *Forensic science international,* 292**,** 27-38.
8. NEUMANN, J. T., SÖRENSEN, N. A., SCHWEMER, T., OJEDA, F., BOURRY, R., SCIACCA, V., SCHAEFER, S., WALDEYER, C., SINNING, C. & RENNÉ, T. 2016. Diagnosis of myocardial infarction using a high-sensitivity troponin I 1-hour algorithm. *JAMA cardiology,* 1**,** 397-404.
9. RASMUSSEN, M. & JIN, J.-P. 2021. Troponin variants as markers of skeletal muscle health and diseases. *Frontiers in physiology,* 12**,** 747214.
10. APPLE, F. S., SANDOVAL, Y., JAFFE, A. S. & ORDONEZ-LLANOS, J. 2017. Cardiac troponin assays: guide to understanding analytical characteristics and their impact on clinical care. *Clinical chemistry,* 63**,** 73-81.
11. KIMENAI, D. M., JANSSEN, E. B., EGGERS, K. M., LINDAHL, B., DEN RUIJTER, H. M., BEKERS, O., APPELMAN, Y. & MEEX, S. J. 2018. Sex-specific versus overall clinical decision limits for cardiac troponin I and T for the diagnosis of acute myocardial infarction: a systematic review. *Clinical chemistry,* 64**,** 1034-1043.
12. CHEN, Y., TAO, Y., ZHANG, L., XU, W. & ZHOU, X. 2019. Diagnostic and prognostic value of biomarkers in acute myocardial infarction. *Postgraduate medical journal,* 95**,** 210-216.
13. JACOB, R. & KHAN, M. 2018. Cardiac biomarkers: what is and what can be. *Indian journal of cardiovascular disease in women WINCARS,* 3**,** 240.
14. MUELLER-HENNESSEN, M., LINDAHL, B., GIANNITSIS, E., BIENER, M., VAFAIE, M., DEFILIPPI, C. R., CHRIST, M., SANTALO-BEL, M., PANTEGHINI, M. & PLEBANI, M. 2016. Diagnostic and prognostic implications using age-and gender-specific cut-offs for high-sensitivity cardiac troponin T—sub-analysis from the TRAPID-AMI study. *International journal of cardiology,* 209**,** 26-33.

15. BOSELLO, S., DE LUCA, G., BERARDI, G., CANESTRARI, G., DE WAURE, C., GABRIELLI, F. A., DI MARIO, C., FORNI, F., GREMESE, E. & FERRACCIOLI, G. 2019. Cardiac troponin T and NT-proBNP as diagnostic and prognostic biomarkers of primary cardiac involvement and disease severity in systemic sclerosis: A prospective study. *European Journal of Internal Medicine,* 60**,** 46-53.

16. MAIR, J., LINDAHL, B., MÜLLER, C., GIANNITSIS, E., HUBER, K., MÖCKEL, M., PLEBANI, M., THYGESEN, K. & JAFFE, A. S. 2018. What to do when you question cardiac troponin values. *European heart journal: acute cardiovascular care,* 7**,** 577-586.

17. WESTERMANN, D., NEUMANN, J. T., SÖRENSEN, N. A. & BLANKENBERG, S. 2017. High-sensitivity assays for troponin in patients with cardiac disease. *Nature Reviews Cardiology,* 14**,** 472-483.

18. WU, Y., PAN, N., AN, Y., XU, M., TAN, L. & ZHANG, L. 2021. Diagnostic and prognostic biomarkers for myocardial infarction. *Frontiers in cardiovascular medicine,* 7**,** 617277.

19. BOEDDINGHAUS, J., TWERENBOLD, R., NESTELBERGER, T., BADERTSCHER, P., WILDI, K., PUELACHER, C., DU FAY DE LAVALLAZ, J., KESER, E., RUBINI GIMÉNEZ, M. & WUSSLER, D. 2018. Clinical validation of a novel high-sensitivity cardiac troponin I assay for early diagnosis of acute myocardial infarction. *Clinical chemistry,* 64**,** 1347-1360.

20. BLANKENBERG, S., SALOMAA, V., MAKAROVA, N., OJEDA, F., WILD, P., LACKNER, K. J., JØRGENSEN, T., THORAND, B., PETERS, A. & NAUCK, M. 2016. Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium. *European heart journal,* 37**,** 2428-2437.

21. LAZAR, D. R., LAZAR, F.-L., HOMORODEAN, C., CAINAP, C., FOCSAN, M., CAINAP, S. & OLINIC, D. M. 2022. High-Sensitivity Troponin: A Review on Characteristics, Assessment, and Clinical Implications. *Disease Markers,* 2022**,** 9713326.

22. FELTES, T. F., BACHA, E., BEEKMAN III, R. H., CHEATHAM, J. P., FEINSTEIN, J. A., GOMES, A. S., HIJAZI, Z. M., ING, F. F., DE MOOR, M. & MORROW, W. R. 2011. Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. *Circulation,* 123**,** 2607-2652.

23. DEUTSCH, N., SWINK, J., MATISOFF, A. J., OLIVIERI, L. J., CROSS, R. R., WABERSKI, A. T., UNEGBU, C., CRONIN, I. F., KANTER, J. P. & SCHWARTZ, J. M. 2019. Anesthetic considerations for magnetic resonance imaging-guided right-heart catheterization in pediatric patients: A single institution experience. *Pediatric Anesthesia,* 29**,** 8-15.

24. WELSH, P., PREISS, D., HAYWARD, C., SHAH, A. S., MCALLISTER, D., BRIGGS, A., BOACHIE, C., MCCONNACHIE, A., PADMANABHAN, S. & WELSH, C. 2019. Cardiac troponin T and troponin I in the general population: comparing and contrasting their genetic determinants and associations with outcomes. *Circulation,* 139**,** 2754-2764.