

Elevated serum cardiac troponin concentration in the absence of an acute coronary syndrome

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INTRODUCTION — The diagnosis of an acute myocardial infarction (MI) has traditionally relied upon the combination of chest pain, electrocardiographic (ECG) abnormalities, and elevations in serum biomarkers of cardiac injury (also called cardiac enzymes). Symptoms and ECG abnormalities, however, may be absent or nonspecific. Thus, the diagnosis of an acute MI has increasingly depended upon evaluation of cardiac enzymes, particularly cardiac troponins.

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The 2007 Joint European Society of Cardiology/American College of Cardiology/American Heart Association/World Health Federation (ESC/ACC/AHA/WHF) Task Force for the definition of myocardial infarction **emphasized the importance of both elevated cardiac biomarkers and clinical evidence for myocardial ischemia** [1]. This expert consensus document suggests that the term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. In this setting, detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit is one of the criteria to diagnose myocardial infarction together with symptomatic, electrocardiographic or echocardiographic evidence of myocardial ischemia [1]. (See "Diagnosis of an acute myocardial infarction", section on Definitions). 這個大型的共識會議認為臨床表現與心肌酵素要一起考慮，上升的troponin合併有心肌缺血的證據才能說是AMI
Clinical evidence of myocardial ischemia is necessary because serum troponin elevations are not necessarily due to an acute coronary syndrome (ACS). They can also be seen in a variety of other diseases, such as **sepsis, hypovolemia, atrial fibrillation, heart failure, pulmonary embolism, myocarditis, myocardial contusion, and renal failure**.

Among patients with a high pretest probability of thrombotic coronary heart disease (CHD), the diagnostic and prognostic value of troponin is clear. However, in patients with a low pretest probability of CHD, troponin elevations are nonspecific and may divert attention from the true underlying clinical problem. This can lead to unnecessary cardiac evaluation, including invasive testing.

Potential causes of troponin elevation unrelated to coronary thrombosis, and the evaluation and management of patients with these conditions will be reviewed here. The biochemical characteristics of troponins and the utility of troponins for the diagnosis of acute MI are discussed in detail separately. (See "Troponins; creatine kinase; and CK isoforms as biomarkers of cardiac injury", section on Troponins, and see "Excitation-contraction coupling in myocardium" and see "Diagnosis of an acute myocardial infarction", section on Cardiac enzymes, and see "Management of suspected acute coronary syndrome in the emergency department", section on Cardiac biomarkers (enzymes)).

CARDIAC TROPONINS — Cardiac troponins are regulatory proteins that control the calcium-mediated interaction of actin and myosin. The troponin complex consists of 3 subunits, troponin T (cTnT), troponin I (cTnI), and troponin C. (See "Excitation-contraction coupling in myocardium", section on Role of Troponin and troponins).

Troponin assays — The skeletal and cardiac isoforms of troponin T and troponin I are distinct, and skeletal isoforms are not detected by the monoclonal antibody-based assays currently in use [2]. This specificity for cardiac isoforms is the basis for the clinical utility of cTnT and cTnI assays.

Contemporary troponin assays are quite sensitive and can detect very small amounts of myocardial necrosis (<1 g). Troponin C is not used clinically because both cardiac and smooth muscle share troponin C isoforms.

The ESC/ACC recommended that the diagnosis of MI be based on troponin levels in excess of the 99th percentile of a reference control group. As cTnT and cTnI levels are undetectable in most normal subjects, the 99th percentile is very low (eg, 0.04 to 0.5 micrograms/L). However, most assays are imprecise at this low level, and so it has been recommended that the definition of MI be raised to that value at which a specific assay has a coefficient of variation of 10 percent or less [3]. New guidelines embrace 99th percentile for two reasons. This level is also low (0.1 to 1.2 micrograms/L), but higher than the 99th percentile standard. Due to variations in assay precision and individual laboratory policies, the upper limit of normal varies between laboratories, but in all cases is above the 99th percentile. (See "Troponins; creatine kinase; and CK isoforms as biomarkers of cardiac injury", section on Variations in assays).

Troponin release without necrosis — In prolonged ischemia, myocytes are irreversibly damaged. The cell membrane degrades, followed by the gradual release of myofibril-bound cytosolic complexes [4]. However, **it is possible that cardiac troponins can also be released into the circulation without myocyte necrosis**.

Troponin release in the absence of necrosis may occur in conditions that produce increased myocyte membrane permeability. As an example, it may be that **myocardial infarction factors** (released in the setting of sepsis and other inflammatory states) cause degradation of free troponin to lower-molecular-weight fragments [5]. With increased membrane permeability, those smaller troponin fragments could be released into the systemic circulation. In this setting, troponin may be elevated although myocyte necrosis may not have occurred. This hypothesis is also supported by the clinical observation that **myocardial depression during sepsis is a fully reversible process in most surviving patients** [6]. However, direct proof of this phenomenon is lacking and it is highly controversial.

CAUSES — Troponin elevations have been reported in a variety of clinical scenarios other than acute coronary syndromes. The following is a list of some of the causes for the elevation of troponin in the absence of a thrombotic occlusion of the coronary artery [1]:

- Tachy- or bradyarrhythmias, or heart block
- Critically ill patients, especially with diabetes, respiratory failure or sepsis
- Hypertrophic cardiomyopathy
- Coronary vasospasm
- Acute neurological disease, including stroke or subarachnoid hemorrhage
- Cardiac contusion or other trauma including surgery, ablation, pacing, implantable cardioverter defibrillator shocks, cardioversion, endomyocardial biopsy, cardiac surgery, following interventional closure of atrial septal defects
- Rhabdomyolysis with cardiac injury
- Congestive heart failure-acute and chronic
- Pulmonary embolism, severe pulmonary hypertension
- Renal failure
- Aortic dissection
- Aortic valve disease
- Apical ballooning syndrome - Takotsubo Cardiomyopathy
- Inflammatory diseases (ie, amyloidosis, hemochromatosis, sarcoidosis, and scleroderma)
- Infectious diseases (ie, myocarditis or myocardial extension of endo-/pericarditis, Kawasaki disease)
- Drug toxicity or toxins (ie, adriamycin, 5-fluorouracil, surfeitin, snake venom)
- Burns, especially if affecting >25 percent of body surface area
- Extreme exertion
- Transplant vasculopathy

The 2007 joint ESC/ACC/AHA/WHF task force recommends that an elevated value of cardiac troponin, in the absence of clinical evidence of ischemia, should prompt a search for other causes of myocardial necrosis as listed above [1].

In one series of 21 patients with elevated troponin levels and a normal coronary angiogram, the following etiologies for troponin elevations were suggested [7]:

- Tachycardia - 28 percent
- Pericarditis - 10 percent
- Heart failure - 5 percent
- Strenuous exercise - 10 percent
- No clear precipitating event - 47 percent

Elevation in the general population — A review of stored plasma samples from 3557 participants in the population-based Dallas Heart Study evaluated the prevalence of cTnT elevations in the general population [8]. The data strongly support the concept that normal individuals have very low (in this study undetectable) levels of troponin. Values ≥0.01 microg/L, which is the 99th percentile of the reference range, were seen in 0.7 percent, which is lower than one would expect from a general population as opposed to a presumably normal population.

Troponin T elevations primarily occurred in individuals with heart failure, left ventricular hypertrophy, chronic kidney disease, or diabetes, each of which was independently associated with a cTnT elevation. These associations were seen even with minimal elevations in cTnT (0.01 to 0.029 microg/L). Elevations in cTnT were rare in individuals without these underlying disorders, who were more similar to a normal population.

In summary, these observations demonstrate that a small number of troponin elevations can be due to structural heart disease in the absence of any acute process. The cTnT elevations seen in patients with renal failure may also be due to structural abnormalities and are invariably associated with pathological evidence of myocardial injury. Although some may prefer cTnI to diagnose ACS in these patients, cTnT can be used equally well by simply observing rising values [9]. If cardiac troponin is being used for prognostic purposes in renal failure patients, cTnT is preferred. (See "Serum cardiac enzymes in patients with renal failure").

Demand ischemia — The concept of **"demand ischemia"** refers to a mismatch between myocardial oxygen demand and supply. The term was originally applied to patients with evidence of ischemia, but no CHD. Although the same pathophysiologic principle may be valid in patients with CHD, it is often more difficult to identify the predominant mechanism of ischemia in such patients. The 2007 Joint European Society of Cardiology/American College of Cardiology/American Heart Association/World Health Federation (ESC/ACC/AHA/WHF) Task Force for the definition of myocardial infarction refers to a Type 2 myocardial infarction when the event is secondary to ischemia due to either an increased oxygen demand or a decreased supply in the absence of a primary coronary event [1]. Examples include coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension.

Myocardial oxygen demand and serum troponins are increased in a number of clinical settings: sepsis, septic shock, and the systemic inflammatory response syndrome (SIRS) [10,11]; hypotension or hypovolemia [12]; noncardiac critically ill patients presented to the Emergency Department [13]; and atrial fibrillation or other tachyarrhythmias [7,14]. In these settings, increased myocardial oxygen demand can be due to:

- Tachycardia
- Changes in cardiac loading conditions
- Increases in cardiac output to accommodate increased systemic oxygen consumption
- Myocardial depression

Simultaneously, myocardial oxygen delivery may be reduced due to the following:

- Reduced coronary perfusion, due to both tachycardia, which reduces diastolic time, during which coronary flow occurs, and reduced perfusion pressure in the setting of hypotension and increased cardiac filling pressures.
- Decreased oxygen delivery to the heart.

Ultimately, these forces combine to create mismatch in myocardial oxygen supply and demand, resulting in ischemia and the release of troponin into the systemic circulation.

Critical illness — Troponin elevations in patients with critical illness are associated with a worse prognosis [10-13,15].

The incidence and significance of demand ischemia in sepsis and SIRS were illustrated in a report of 20 patients treated in a medical intensive care unit (ICU) [10]:

- 17 patients (85 percent) had elevated cTnI levels.
- 10 of these 17 patients had no evidence of significant CHD.
- Five patients with an elevated cTnI died, all of whom had autopsies, and the coronary arteries were normal in four of these cases.

The potential causes and prognostic implications of demand ischemia were further described in a report of 58 patients, the majority of whom were admitted to an ICU for sepsis, septic shock, or SIRS [11]:

- 32 patients (55 percent) had elevated troponin levels.
- Mortality was significantly higher in patients with troponin elevations (22 versus 5 percent).
- Tumor necrosis factor-α, interleukin-6, and C-reactive protein levels were significantly higher in patients with elevated troponin levels.
- Significant coronary artery disease was excluded in 72 percent of troponin-positive patients.

Thus, **troponin elevation among patients with sepsis and SIRS is common**. Affected patients often have no evidence of significant CHD. In this setting, **troponin elevation is associated with a worse prognosis, but it is unclear whether any cardiovascular intervention could improve outcomes**. Although a causal relationship has yet to be established, inflammatory mediators in conjunction with a myocardial oxygen demand-supply mismatch are potential explanations for this phenomenon.

Troponin elevations suggestive of demand ischemia have also been described in a broader range of critically ill patients. A 2006 review evaluated 20 observational studies involving 3278 critically ill patients in which cardiac troponin concentrations were reported [15]. The following findings were noted:

- The frequency of elevated cardiac troponin was 12 to 85 percent, with a median of 43 percent.
- In six studies in which adjusted analyses were performed, elevated cardiac troponin was associated with a significantly increased risk of death (OR, 2.5; 95 percent CI, 1.9 to 3.4).

Tachycardia — Tachycardia alone has been implicated as a cause of troponin elevations in small case series. In one series of 21 patients with elevated cTnI levels and normal coronary angiograms, tachycardia was determined to be the explanation of the troponin elevation in six patients [7]. A second series described four patients with troponin elevations after episodes of supraventricular tachycardia (SVT), who had no evidence of CHD. These reports illustrate that myocardial troponin can be released as a consequence of tachycardia alone in the absence of myodepressive factors, inflammatory mediators, and CHD.

Left ventricular hypertrophy — Cardiac troponin elevation also has been described in the context of left ventricular hypertrophy (LVH). In a series of 74 consecutive patients without clinical evidence of active myocardial ischemia (referred to in routine echocardiography, seven of 25 patients in the tertile with the greatest LV mass had an elevated cTnI. In contrast, one patient in the intermediate range, and none of patients in the lowest tertile had an elevated troponin level [16].

It is well recognized that LVH can lead to occult subendocardial ischemia via increased oxygen demand from increased muscle mass, coupled with decreased flow reserve due to remodeled coronary microcirculation. Similar observations have been made in the setting of aortic valve disease, in which elevated troponin level was associated with greater left ventricular wall thickness and higher pulmonary artery systolic pressures [17].

Coronary vasospasm — Myocardial ischemia caused by coronary vasospasm (Prinzmetal angina) can lead to troponin elevations. This was illustrated in a series of 93 patients with suspected myocardial ischemia in whom coronary angiography revealed no hemodynamically significant lesions [18]. Twenty-three (25 percent) had elevated levels of cTnI. **Ergonovine provocation testing showed evidence of coronary vasospasm** in 41 patients, and in 17 of the 23 patients with cTnI elevations. (See "Variant angina").

Acute stroke — Both elevated cardiac troponin levels and ischemic ECG changes have been described in the setting of acute stroke or intracranial hemorrhage. In one series of 149 patients with symptoms of acute stroke, 27 percent were found to have elevated serum cTnI [19]. (See "Cardiac complications of stroke").

Elevations in cTnI have also been noted in two case series of patients with subarachnoid hemorrhage (SAH) [20,21]. **In these reports, cTnI elevations correlated with both the severity of neurologic injury and cardiovascular abnormalities including left ventricular dysfunction, pulmonary edema, and hypotension requiring pressors**. In one of the studies, elevations in cTnI also predicted a higher likelihood of in-hospital death or severe disability at discharge, although this relationship was no longer significant at three months [21]. (See "Etiology, clinical manifestations, and diagnosis of aneurysmal subarachnoid hemorrhage", section on Cardiac abnormalities).

The most likely explanation of troponin elevation and myocardial damage in this setting is an imbalance of the autonomic nervous system, with resulting excess of sympathetic activity and increased catecholamine effect on the myocardial cells [20,22].

The magnitude of troponin elevation in these reports is less than that seen with the acute myocardial infarction due to coronary artery occlusion. Thus, it is not clear to what extent the LV dysfunction and hemodynamic compromise reported in these case series were due to acute myocardial injury in the setting of the stroke, or reflect new myocardial and hemodynamic stress in patients with underlying cardiovascular disease.

In addition, since follow-up echocardiograms were not routinely obtained, it is not known how many of these patients may have had improvement in left ventricular function after recovering from the acute stroke. **Reversible LV dysfunction in the setting of acute noncardiac illness is an increasingly reported phenomenon**, and autonomic imbalance with **catecholamine excess is proposed to play a role in both stroke-related myocardial injury and stress-induced cardiomyopathy**. (See "Stress-induced (takotsubo) cardiomyopathy").

Direct myocardial damage — Troponin elevation can occur in the setting of myocardial injury by traumatic or inflammatory processes.

Trauma — The incidence and significance of cTnI elevations following blunt thoracic trauma were illustrated in a report of 333 patients, in whom serial ECGs and cTnI values were followed over eight hours [23]. Elevation in cTnI occurred in 145 patients (44 percent); 44 patients (13 percent) had evidence of clinically significant blunt cardiac injury, defined by hypotension, arrhythmias, anatomic abnormalities, or depressed cardiac index, 32 of whom had cTnI elevations. Thus, a degree of direct cardiac injury, as evidenced by cTnI elevations, is common after blunt chest trauma, although **only a minority of patients with troponin elevations in this setting develop significant clinical complications attributable to cardiac injury**.

Additional causes — Several other clinical conditions in which direct myocardial injury may occur have been associated with elevated troponin levels. These include:

- Implantable cardioverter defibrillator shocks [24].
- Inflammatory disorders such as amyloidosis; it has been postulated that extracellular amyloid deposition may lead to myocyte compression injury, leading to myocardial damage and troponin release [25].
- High-dose chemotherapy; troponin levels have been suggested as a method for detecting cardiotoxicity and predicting the development of future left ventricular dysfunction in this population [26].
- Inflammatory disorders including acute pericarditis [27] and myocarditis [28]. (See "Clinical manifestations and diagnosis of myocarditis in adults", section on Cardiac enzymes).
- Immune response after heart transplantation. Chronically elevated troponin levels after cardiac transplantation may be associated with a poorer prognosis. In a prospective cohort study of 110 consecutive patients after cardiac transplantation, troponin levels remained persistently elevated in 51 percent of patients and were associated with more fibrous deposition in the microvasculature and among myocytes, as well as a significant increase in the risk for coronary artery disease and graft failure [29].

Heart failure — Heart failure can lead to the release of cardiac troponin via two related mechanisms, myocardial strain and myocyte death.

Myocardial strain — Volume and pressure overload of both the right and left ventricle can produce excessive wall tension or "myocardial strain," with resulting myofibrillar damage [17]. Support for a connection between myocardial strain and elevated troponin levels comes from several lines of evidence:

- There is a close correlation between troponin levels and B-type natriuretic peptide (BNP), and BNP is itself a marker of right and left ventricular wall strain [30].
- Troponin degradation has been demonstrated with increased preload, independent of myocardial ischemia, in isolated rat hearts [31].
- Increased myocardial wall stress may lead to decreased subendocardial perfusion, with resulting troponin elevation and decline in left ventricular systolic function [32].
- Troponin elevation in normal persons after ultra-endurance exercise have been described [33,34]. This may be related to an increase in myocardial strain during exercise, although catecholamine-induced vasospasm has also been invoked as an explanation [4].

Myocyte death — In addition, in vitro experiments with myocytes established a link between myocardial wall stretch and programmed cell death, which may also contribute to troponin elevations in this setting [35]. Progressive myocyte loss is now thought to play a prominent role in the progression of cardiac dysfunction and may explain the ominous prognosis of patients with heart failure and elevated troponin levels. Several factors may contribute to myocyte death, including:

- Activation of the renin-angiotensin system
- Sympathetic stimulation
- Inflammatory mediators
- Integrin stimulation

Clinical significance — Troponin elevations tend to be associated with advanced heart failure and an adverse prognosis [32]. The clinical evidence supporting this association is presented separately. (See "Predictors of survival in heart failure due to systolic dysfunction", section on Serum troponins).

Pulmonary diseases — Troponin elevations are also described in a variety of pulmonary diseases, usually associated with significant right heart strain.

Pulmonary embolism — Serum troponins are elevated in 30 to 50 percent of patients with moderate to severe pulmonary embolism. The presumed mechanism is acute right heart overload and elevated levels are associated with a significant increase in mortality. **The troponin elevations usually resolve within 40 hours** with pulmonary embolism in contrast to the more prolonged elevation with acute myocardial injury. (See "Diagnosis of acute pulmonary embolism", section on Serum troponins).

Pulmonary hypertension — Levels of cTnT were elevated in 8 of 56 patients (14 percent) with chronic pulmonary hypertension in one series [36]. cTnT elevations were associated with the following:

- Higher heart rates
- Lower mixed venous oxygen saturation
- Higher levels of B-type natriuretic peptide
- Significantly lower two year survival (29 versus 81 percent with normal cTnI levels)

Exacerbation of **chronic obstructive pulmonary disease** can also increase troponin levels and has been identified as **an independent predictor of in-hospital mortality** [37].

Chronic kidney disease — Persistent elevation of cardiac troponin is frequently observed in patients with end-stage renal disease; cTnI is the preferred test in this setting. This issue is discussed in detail separately. (See "Serum cardiac enzymes in patients with renal failure", section on Troponins).

Burns — Severe thermal injury is associated with cardiac contractile dysfunction and elevated cardiac troponin. Elevation of cardiac troponin is demonstrated among patients who have **sustained >25 percent (total body surface area) of thermal injury**. The rise in cardiac troponin appears to be related to the extent of burns rather than patient's age, pre-existing medical conditions or the administration of resuscitation fluid [38].

Kawasaki disease — The association of elevated cardiac troponin and myocarditis among patients with Kawasaki disease (KD) is not clear. One group suggested that among children with Kawasaki disease there is a significant increase in the cardiac troponin, which would indicate acute myocarditis and myocardial cell injury in the early stages of the disease [39]. On the contrary, another study did not demonstrate significant elevation in cardiac troponin among KD patients [40].

Cardioversion — Cardioversion can lead to mild but significant rise in cardiac troponin levels. This rise is more pronounced among patients with relatively large left ventricular end diastolic dimensions [41].

SUMMARY AND RECOMMENDATIONS

- Troponin is a highly sensitive biomarker that aids in the detection of myocardial cell damage, which is often, but not always, due to thrombotic obstruction of a coronary artery. Thus, while troponin may be useful to **"rule out" a non-ST-segment elevation MI (NSTEMI), it is less useful to "rule in" this event because it is not specific for an acute coronary syndrome (ACS)**. As a result, if troponin testing is applied indiscriminately in broad populations with a low pretest probability of thrombotic disease, the positive predictive value for NSTEMI is greatly diminished.
- Troponin elevation in the absence of an ACS still retains significant prognostic value, and screening may be justified on this basis. Troponin elevations in a variety of settings predict worse short- and long-term survival. The reasons for this increase in mortality are currently poorly understood, but may be related to several factors, including myocardial necrosis with myocyte loss, or underlying quiescent coronary artery disease. Alternatively, increased troponin levels may reflect a more fulminant disease process. Regardless of the reason for poorer prognosis, patients with troponin elevation require appropriate diagnostic evaluation and therapy aimed at the underlying disorder.
- Determining whether a troponin elevation is due to an ACS can be difficult. Factors that suggest CHD and an ACS include ischemic ECG changes, chest pain, wall-motion abnormalities on echocardiography, and the presence of atherosclerotic risk factors. If present, these should guide the use of further cardiovascular evaluation, including early risk stratification [2].
- Patients with a low pretest probability of CHD are unlikely to derive benefit from a treatment strategy aimed at coronary thrombosis (eg, aggressive antiplatelet therapy, coronary angiography, and revascularization). In such patients, the main goal is to identify the underlying cause of the troponin elevation. This frequently becomes evident after a thorough history and physical examination, which can identify conditions such as myocarditis, pericarditis, cardiac contusion, sepsis, pulmonary embolism, and heart failure. Therapy in these circumstances should target the underlying cause.

- ★ There are currently no data from randomized, controlled trials evaluating the efficacy of therapies aimed at reducing risk in patients with troponin elevations in the absence of an ACS. **As a result, we do not generally treat patients with nonthrombotic troponin elevation with aggressive antithrombotic and antiplatelet agents.**
- ★ No current data support an early invasive mechanical revascularization strategy in patients in whom the suspicion of thrombotic CHD is low. **We do recommend aspirin, unless it is contraindicated, as it appears to be relatively safe in most clinical circumstances.**

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