

Narrative Review: Alternative Causes for Elevated Cardiac Troponin Levels when Acute Coronary Syndromes Are Excluded

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Current guidelines for the diagnosis of non-ST-segment elevation myocardial infarction are largely based on an elevated troponin level. While this rapid and sensitive blood test is certainly valuable in the appropriate setting, its widespread use in a variety of clinical scenarios may lead to the detection of troponin elevation in the absence of thrombotic acute coronary syndromes. Many diseases, such as sepsis, hypovolemia, atrial fibrillation, congestive heart failure, pulmonary embolism, myocarditis, myocardial contusion, and renal failure, can be associated with an increase in troponin level. These elevations may arise from various causes other than thrombotic coronary artery occlusion. Given the lack of any supportive data at present, patients with nonthrombotic tro-

ponin elevation should not be treated with antithrombotic and antiplatelet agents. Rather, the underlying cause of the troponin elevation should be targeted. However, troponin elevation in the absence of thrombotic acute coronary syndromes still retains prognostic value. Thus, cardiac troponin elevations are common in numerous disease states and do not necessarily indicate the presence of a thrombotic acute coronary syndrome. While troponin is a sensitive biomarker to “rule out” non-ST-segment elevation myocardial infarction, it is less useful to “rule in” this event because it may lack specificity for acute coronary syndromes.

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In September 2000, the Joint European Society of Cardiology/American College of Cardiology (ESC/ACC) Committee proposed a new definition of myocardial infarction based predominantly on the detection of the cardiac-specific biomarkers troponin T and troponin I in the appropriate clinical setting (1). The rationale of including troponin assays in the diagnostic pathway was based on the assumption that myocardial necrosis, regardless of its magnitude, should be characterized as a myocardial infarction. Contemporary troponin assays are quite sensitive and can detect even very small episodes of myocardial necrosis (<1 g). The Committee's recommendation for the diagnosis of myocardial infarction based on troponin elevation categorizes a cohort of patients whose values exceed the 99th percentile of a reference control group with an acceptable imprecision (coefficient of variation) of 10% or less. Unfortunately, few assays in current clinical use meet this standard. It has therefore been proposed that an increase in cardiac troponin levels above the 10% coefficient of variation be considered indicative of myocardial injury (2). Given that numerous troponin assays are commercially available and in clinical use, each individual laboratory should confirm the range of reference values in their specific setting and define the value that is considered a “significant” troponin elevation.

The ESC/ACC Committee consensus document states that “any amount of myocardial damage . . . implies an impaired clinical outcome for the patient” and there is “no discernible threshold below which an elevated value of cardiac troponin would be deemed harmless” (1). This view is also reflected in the updated 2002 ACC/American Heart Association (AHA) practice guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction (3). However, the ACC/AHA guidelines do indicate that the myocardial necrosis signified by troponin elevation may not necessarily be due to atherosclerotic coronary artery disease and that myocar-

dial infarction should therefore be diagnosed in conjunction with other supportive evidence.

The implementation of these new guidelines in clinical practice has led to a substantial increase in the frequency of myocardial infarction diagnosis. For example, among 2181 patients presenting with chest pain to an inner-city tertiary care center, diagnoses of myocardial infarction based on cardiac troponin level increased up to 195% as compared with diagnoses made according to creatine kinase-MB criteria (4). Mortality at 30 days was significantly higher among patients with elevated troponin levels at presentation than among patients with no biomarkers detected, but it was not as high as among patients with elevated creatine kinase-MB levels. In several studies of acute coronary syndromes, troponin elevation has likewise been associated with a worse prognosis (5). Furthermore, the risk for subsequent death appears to be related to the degree of troponin elevation: There is a statistically significant increase in mortality with increasing levels of troponin, and the relative risk for death is 7.8 in the group with the highest troponin levels (6). While the presence of thrombus and impaired epicardial blood flow are both associated with troponin elevation (7, 8), impaired myocardial perfusion is a more robust and independent predictor of troponin elevation among patients with acute coronary syndromes (9).

Among patients with a high pretest probability or clinical suspicion of thrombotic coronary artery disease, the diagnostic and prognostic value of troponin is clear. However, troponin testing is now also being used as a screening tool among patients with a low pretest probability of

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thrombotic coronary artery disease. Given the high sensitivity of cardiac troponin for detecting even minimal myocardial-cell necrosis, these markers may become “positive” even in the absence of thrombotic acute coronary syndromes. This may occasionally be related to a spurious troponin elevation (usually easily detectable by obtaining a second sample) but may also be due to several nonthrombotic cardiac and systemic diseases. In many instances, these troponin elevations may arise from demand ischemia, with or even without significant coronary artery disease or microcirculatory dysfunction, rather than “supply-side” thrombotic ischemia. For example, among 1000 consecutive patients presenting to the emergency department of a large urban hospital, troponin I level was elevated on admission in 112 patients, and 45% of these patients had a final diagnosis other than acute coronary syndrome (10). Given the high sensitivity but low specificity among these patients with a low pretest probability of disease, the detection of even minimal troponin elevation may divert attention from the true underlying clinical problem and may lead to unnecessary cardiac evaluation, including invasive testing. The goal of this article is to review potential causes of troponin elevation that are unrelated to coronary thrombosis (Table) and to provide guidance on the evaluation and management of patients with nonthrombotic troponin elevation.

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, which binds to tropomyosin and facilitates contraction; troponin I, which binds to actin and inhibits actin–myosin interactions; and troponin C, which binds to calcium ions (11). The amino acid sequences of the skeletal and cardiac isoforms of cardiac troponin T and troponin I are sufficiently dissimilar and therefore detectable by monoclonal antibody–based assays (3). Troponin C is not used clinically because both cardiac and smooth muscle share troponin C isoforms. The release of cardiac troponin from the myocyte to the blood can be due to reversible or irreversible cell damage. In prolonged ischemia, cells are irreversibly damaged as the cell membrane degrades, followed by the gradual release of myofibril-bound cytosolic complexes (11). However, the notion that troponin is increased only after irreversible myocardial necrosis has recently been challenged by the observation that some patients with unstable angina have only transient troponin elevations, with values returning to baseline within a few hours (12). This pattern of troponin increase may not be consistent with permanent myocardial damage. It is, therefore, conceivable that myocardial troponin can also be released in the setting of increased membrane permeability. For example, it is thought that myocardial depressive factors (released in the setting of sepsis and other inflammatory states) cause deg-

Table. Nonthrombotic Causes and Presumed Mechanism for Elevated Cardiac Troponin Level

Diagnosis	Mechanism
Demand ischemia	
Sepsis/systemic inflammatory response syndrome	Myocardial depression/supply–demand mismatch
Hypotension	Decreased perfusion pressure
Hypovolemia	Decreased filling pressure/output
Supraventricular tachycardia/atrial fibrillation	Supply–demand mismatch
Left ventricular hypertrophy	Subendocardial ischemia
Myocardial ischemia	
Coronary vasospasm	Prolonged ischemia with myonecrosis
Intracranial hemorrhage or stroke	Imbalance of autonomic nervous system
Ingestion of sympathomimetic agents	Direct adrenergic effects
Direct myocardial damage	
Cardiac contusion	Traumatic
Direct current cardioversion	Traumatic
Cardiac infiltrative disorders	Myocyte compression
Chemotherapy	Cardiac toxicity
Myocarditis	Inflammatory
Pericarditis	Inflammatory
Cardiac transplantation	Inflammatory/immune-mediated
Myocardial strain	
Congestive heart failure	Myocardial wall stretch
Pulmonary embolism	Right ventricular stretch
Pulmonary hypertension or emphysema	Right ventricular stretch
Strenuous exercise	Ventricular stretch
Chronic renal insufficiency	Unknown

radation of free troponin in situ to lower-molecular-weight fragments (13). With increased membrane permeability, those smaller troponin fragments could be released into the systemic circulation. In this setting, myocyte damage may not be permanent, and thus cell necrosis does not occur. This notion is also supported by the clinical observation that myocardial depression during sepsis is a fully reversible process in most surviving patients (14).

NONTHROMBOTIC MECHANISMS OF TROPONIN ELEVATION

Demand Ischemia

The concept of “demand ischemia” without significant coronary artery disease refers to a mismatch between myocardial oxygen demand and supply in the absence of flow-limiting epicardial stenosis. Although theoretically the same pathophysiologic principle may be valid in the presence of coronary artery disease, it may be more difficult to identify the predominant mechanism that accounts for myocardial ischemia in that clinical scenario. Myocardial oxygen demand frequently increases in the setting of sepsis or septic shock and the systemic inflammatory response syndrome (15–17), hypotension or hypovolemia (18), and

atrial fibrillation or other tachyarrhythmias (19, 20). All of these clinical scenarios are either due to or can lead to tachycardia with various loading conditions on the heart. This increases myocardial oxygen demand while decreasing myocardial oxygen supply by shortening diastolic time, a period during which the majority of the myocardial perfusion occurs. In addition, sepsis and other systemic inflammatory processes may lead to myocardial depression, greatly increased oxygen consumption, reduced perfusion pressure, and decreased oxygen delivery to the heart, ultimately resulting in the release of troponin into the systemic circulation (16). Among 20 septic patients treated in an intensive care unit, 85% were noted to have elevated troponin levels (16). The majority (59%) had no evidence of significant coronary artery disease. Similarly, Guest and colleagues found that elevated cardiac troponin level is a common finding among critically ill patients and is associated with a significant increase in mortality (15). In a more recent study, Ammann and colleagues evaluated 58 patients who were admitted to the intensive care unit for diagnoses other than acute coronary syndromes (17). Among the 55% of patients with elevated troponin levels, tumor necrosis factor- α , interleukin-6, and C-reactive protein levels were significantly higher than among patients with undetectable troponin, and mortality was fourfold higher in the troponin-positive group. Of note, significant coronary artery disease was excluded in 72% of troponin-positive patients. Thus, troponin elevation among patients with sepsis and the systemic inflammatory response syndrome with or without shock in the intensive care unit setting is common and largely affects patients without significant coronary artery disease. Troponin elevation is associated with a worse prognosis, but whether any cardiovascular intervention could improve outcomes among these patients is unclear. Although a causal relationship has yet to be established, inflammatory mediators in conjunction with a myocardial oxygen demand–supply mismatch may be likely explanations for this phenomenon.

Other potential causes of “demand ischemia” in the absence of obstructive coronary artery disease include tachycardia and several tachyarrhythmias. In reviewing the causes of elevated troponin levels in 21 patients with a normal coronary angiogram, Bakshi and colleagues found that tachycardia was the culprit in 28%, pericarditis in 10%, congestive heart failure in 5%, and strenuous exercise in 10%; no precipitating event was identified for 47% of patients (19). Likewise, Zellweger and associates reported on 4 patients with supraventricular tachycardia who were found to have elevated troponin levels without evidence of epicardial coronary stenoses (20). These reports illustrate that myocardial troponin can be released as a consequence of tachycardia alone in the absence of myodepressive factors, inflammatory mediators, and coronary artery disease.

Cardiac troponin elevation also has been described in the context of left ventricular hypertrophy. Among 74 patients without clinical evidence of active myocardial isch-

emia, almost one third in the tertile with the greatest left ventricular mass had elevated troponin levels, as opposed to no patients in the lowest tertile of left ventricular mass (21). It is well recognized that left ventricular hypertrophy 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 (22).

Myocardial Ischemia in the Absence of Fixed Obstructive Coronary Artery Disease

In the absence of acute coronary syndromes with thrombus formation and total vessel occlusion or distal embolization, myocardial ischemia can be caused by vasospasm (Prinzmetal angina). Among 93 patients with suspected myocardial ischemia and a subsequent diagnosis of insignificant coronary artery disease, 25% had elevated troponin levels (23). Subsequent ergonovine provocation testing explained 74% of elevated troponin levels in these patients, suggesting that vasospasm may lead to prolonged ischemia and myonecrosis.

Elevated cardiac troponin levels along with ischemic changes on the electrocardiogram are frequently observed in the setting of acute stroke or intracranial hemorrhage. Up to 27% of patients with acute stroke symptoms (24) and 20% of patients with a diagnosis of subarachnoid hemorrhage (25) were found to have increased troponin levels. 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, rather than preexisting coronary artery disease (26). Similar effects can be observed after the ingestion of sympathomimetics, not infrequently leading to myocardial damage and troponin elevation.

Direct Myocardial Damage

Troponin elevation can occur in the presence of structural heart disease. The mechanisms of troponin release in these circumstances include cell injury by traumatic or inflammatory processes. Velmahos and colleagues’ recent study of 333 consecutive patients with significant blunt thoracic trauma showed the value of troponin testing in the detection of cardiac contusion (27). The positive and negative predictive values of an elevated troponin level were 21% and 94%, making troponin testing a valuable tool in excluding significant myocardial injury after trauma. Other reasons for traumatic troponin elevation include implantable cardioverter defibrillator shocks (28) and infiltrative disorders such as amyloidosis (29). It has been postulated that extracellular amyloid deposition may lead to myocyte compression injury, leading to myocardial damage and troponin release. Troponin measurements may also aid in the assessment of the cardiotoxic effects of

high-dose chemotherapy and predict the development of future left ventricular dysfunction in this population (30).

Inflammatory disorders leading to troponin elevation include acute pericarditis (31), myocarditis (32), and an immune response after heart transplantation. In fact, 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% of patients and were associated with more fibrin deposition in the microvasculature and among myocytes, as well as a significant increase in the risk for coronary artery disease and graft failure (33).

Myocardial Strain

Volume and pressure overload of both the right and left ventricle, as in congestive heart failure, can lead to the release of cardiac troponin in the absence of myocardial ischemia. This may be due to excessive wall tension or “myocardial strain,” with resulting myofibrillary damage. Myocardial strain may be defined as the percentage change of a structure from its initial length with the application of stress (22). Support for the “strain” theory comes from multiple studies that demonstrate a close correlation between troponin and B-type natriuretic peptide (34), a marker of right and left ventricular wall strain. Furthermore, *in vitro* experiments with myocytes established a link between myocardial wall stretch and programmed cell death (35), and troponin degradation has been demonstrated as a result of increased preload independently from myocardial ischemia in isolated rat hearts (36). It has also been hypothesized that increased myocardial wall stress may lead to decreased subendocardial perfusion, with resulting troponin elevation and decline in left ventricular systolic function (37). In the setting of acute or chronic congestive heart failure, additional factors, including the activation of the renin–angiotensin system, sympathetic stimulation, and inflammatory mediators, may be partially responsible for myocyte injury and cell death. Progressive myocyte loss is now thought to play a prominent role in the progression of cardiac dysfunction; it may explain the ominous prognosis of patients with congestive heart failure and elevated troponin levels. In fact, several small studies documented troponin elevation in the presence of congestive heart failure without evidence of an acute coronary syndrome. They have also established a relationship between troponin elevation and increased mortality during follow-up. Of 238 patients with advanced heart failure who were referred for cardiac transplantation evaluation, 49% were found to have elevated cardiac troponin levels (37). Patients with detectable troponin had significantly higher B-type natriuretic peptide levels, higher pulmonary wedge pressures, lower cardiac indices, and a twofold increase in mortality.

Many reports have described troponin elevation in normal persons after ultraendurance exercise (38, 39). This

may be related to an increase in myocardial strain during exercise, although catecholamine-induced vasospasm has also been invoked as an explanation (11).

Cardiopulmonary Disease and Right-Heart Strain

Similarly, patients with right-heart strain are frequently found to have elevated troponin levels. The reported incidence of troponin elevation among patients with acute pulmonary embolism varies from 16% to 50%, and elevated levels are associated with a significant increase in mortality (40). Among patients with chronic pulmonary hypertension, troponin was detectable in 14% of cases and was associated with higher heart rates, lower mixed venous oxygen saturation, and higher levels of B-type natriuretic peptide, as well as significantly worse cumulative survival at 2 years (81% vs. 29%) (41). Exacerbation of chronic obstructive pulmonary disease can also increase troponin levels and has been identified as an independent predictor of in-hospital mortality (42).

Cardiac Troponin in Chronic Renal Insufficiency

Persistently elevated cardiac troponin is frequently observed among patients with end-stage renal disease (43–45). Therefore, a higher troponin threshold was proposed for the diagnosis of myocardial ischemia in patients with chronic renal insufficiency (46). Despite these permanent elevations, troponin was found to be an independent predictor of death or myocardial infarction across the entire spectrum of renal function in a recent analysis of 7033 patients with acute coronary syndrome in the GUSTO IV (Global Use of Strategies to Open Occluded Coronary Arteries IV) trial (47).

The prevalence of increased troponin values among patients with chronic renal failure in the absence of clinically suspected ischemia may be as high as 53% (45). This may be the result of small areas of clinically silent myocardial necrosis, but other causes, such as increased left ventricular mass and impaired renal troponin excretion, have also been proposed. Although the exact mechanism of troponin elimination is unknown, it is believed to be cleared by the reticuloendothelial system given the relatively large molecular size of troponin (45). However, recent evidence demonstrates that troponin T is fragmented into molecules small enough to be renally excreted; this may explain the high prevalence of troponin elevation in patients with severe renal failure (48). Irrespective of the cause, detectable troponin among stable patients with end-stage renal disease appears to be a powerful predictor of increased intermediate-term mortality (44) and may be an even stronger risk factor in conjunction with elevated C-reactive protein levels (43). Of note, multivessel coronary artery disease was more prevalent across progressively higher quartiles of troponin T, suggesting an ischemic mechanism for the troponin increase in this patient population (43).

SIGNIFICANCE OF TROPONIN ELEVATION IN THE ABSENCE OF ACUTE CORONARY SYNDROMES AND POTENTIAL TREATMENT STRATEGIES

Both short- and long-term survival are impaired among patients with troponin elevation in many different clinical settings, including congestive heart failure, sepsis, pulmonary disease, acute pulmonary embolism, and renal insufficiency. The reasons for this increase in mortality are currently poorly understood but may be related to myocardial necrosis with myocyte loss or underlying quiescent coronary artery disease. However, another possibility is that increased troponin merely reflects a more fulminant disease process. Given this substantially increased risk for adverse outcomes, patients with troponin elevation in general require appropriate diagnostic evaluation and therapy aimed at the underlying disorder.

The assessment of whether a troponin elevation is thrombotic or nonthrombotic in origin can be challenging. Ischemic electrocardiogram changes, chest pain, wall-motion abnormalities on echocardiography, and the presence of atherosclerotic risk factors may be associated with a thrombotic origin of the troponin elevation and should guide the use of further cardiovascular evaluation, including early risk stratification (3). On the other hand, patients with a low pretest probability of coronary artery disease will most likely not derive any benefit from a treatment strategy aimed at coronary thrombosis. In this population, the main goal is to identify the underlying cause of the troponin elevation, which frequently becomes evident after a thorough history and physical examination (in conditions such as myocarditis, pericarditis, cardiac contusion, sepsis, pulmonary embolism, and congestive heart failure). Therapy in these circumstances should target the underlying cause rather than the “troponin leak” itself.

No data from randomized, controlled trials are available to assess the efficacy of therapies aimed at reducing the risk for adverse events among patients with troponin elevations in the absence of an acute coronary syndrome. As outlined in this review, cardiac troponin elevations are common in numerous disease states and do not necessarily indicate the presence of a thrombotic acute coronary syndrome. Therefore, in the absence of any supportive data at present, in our practice, patients with nonthrombotic troponin elevation are generally not treated with antithrombotic and antiplatelet agents. Likewise, no current data support an early invasive mechanical revascularization strategy among these patients, in whom the suspicion of thrombotic coronary artery disease is low. Unless aspirin is contraindicated, we frequently recommend the use of this drug, which appears to be relatively safe in most clinical circumstances.

CONCLUSIONS

Troponin is a highly sensitive biomarker that aids in the detection of myocardial cell damage. It is often, but by

no means always, caused by thrombotic obstruction and impaired myocardial perfusion in the context of an acute coronary syndrome. This marker is frequently “positive” in other disease states in the absence of thrombotic acute coronary syndromes. Therefore, while troponin is a sensitive biomarker to “rule out” non-ST-segment elevation myocardial infarction, it is less useful to “rule in” this event because it is not specific for acute coronary syndromes. As a result, if troponin testing is applied indiscriminately in broad populations that have a low pretest probability of thrombotic disease, the positive predictive value of the marker is greatly diminished. While troponin elevation in a patient with suspected acute coronary syndrome may guide management decisions, such as the need for antithrombotic, antiplatelet, and interventional therapies, no data support the role of these therapies in the management of patients with a nonthrombotic syndrome. Treatment should be aimed at the underlying disorder. However, troponin elevation in the absence of thrombotic acute coronary syndromes still retains prognostic value, and screening may be justified on this basis.

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References

1. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000;36:959-69. [PMID: 10987628]
2. Apple FS, Wu AH, Jaffe AS. European Society of Cardiology and American College of Cardiology guidelines for redefinition of myocardial infarction: how to use existing assays clinically and for clinical trials. *Am Heart J*. 2002;144:981-6. [PMID: 12486421]
3. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction—summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol*. 2002;40:1366-74. [PMID: 12383588]
4. Kontos MC, Fritz LM, Anderson FP, Tatum JL, Ornato JP, Jesse RL. Impact of the troponin standard on the prevalence of acute myocardial infarction. *Am Heart J*. 2003;146:446-52. [PMID: 12947361]
5. Heidenreich PA, Alloggiamento T, Melsop K, McDonald KM, Go AS, Hlatky MA. The prognostic value of troponin in patients with non-ST elevation acute coronary syndromes: a meta-analysis. *J Am Coll Cardiol*. 2001;38:478-85. [PMID: 11499741]
6. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med*. 1996;335:1342-9. [PMID: 8857017]

7. Benamer H, Steg PG, Benessiano J, Vicaut E, Gaultier CJ, Aubry P, et al. Elevated cardiac troponin I predicts a high-risk angiographic anatomy of the culprit lesion in unstable angina. *Am Heart J*. 1999;137:815-20. [PMID: 10220629]
8. Heesch C, van Den Brand MJ, Hamm CW, Simoons ML. Angiographic findings in patients with refractory unstable angina according to troponin T status. *Circulation*. 1999;100:1509-14. [PMID: 10510053]
9. Wong GC, Morrow DA, Murphy S, Kraimer N, Pai R, James D, et al. Elevations in troponin T and I are associated with abnormal tissue level perfusion: a TACTICS-TIMI 18 substudy. *Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction*. *Circulation*. 2002;106:202-7. [PMID: 12105159]
10. Ng SM, Krishnaswamy P, Morrissey R, Clopton P, Fitzgerald R, Maisel AS. Mitigation of the clinical significance of spurious elevations of cardiac troponin I in settings of coronary ischemia using serial testing of multiple cardiac markers. *Am J Cardiol*. 2001;87:994-9; A4. [PMID: 11305993]
11. Higgins JP, Higgins JA. Elevation of cardiac troponin I indicates more than myocardial ischemia. *Clin Invest Med*. 2003;26:133-47. [PMID: 12858947]
12. Hamm CW, Ravkilde J, Gerhardt W, Jorgensen P, Peheim E, Ljungdahl L, et al. The prognostic value of serum troponin T in unstable angina. *N Engl J Med*. 1992;327:146-50. [PMID: 1290492]
13. Wu AH. Increased troponin in patients with sepsis and septic shock: myocardial necrosis or reversible myocardial depression? [Editorial] *Intensive Care Med*. 2001;27:959-61. [PMID: 11497152]
14. Parrillo JE. Pathogenetic mechanisms of septic shock. *N Engl J Med*. 1993;328:1471-7. [PMID: 8479467]
15. Guest TM, Ramanathan AV, Tuteur PG, Schechtman KB, Ladenson JH, Jaffe AS. Myocardial injury in critically ill patients. A frequently unrecognized complication. *JAMA*. 1995;273:1945-9. [PMID: 7783306]
16. Ammann P, Fehr T, Minder EI, Gunter C, Bertel O. Elevation of troponin I in sepsis and septic shock. *Intensive Care Med*. 2001;27:965-9. [PMID: 11497154]
17. Ammann P, Maggiorini M, Bertel O, Haenseler E, Joller-Jemelka HI, Oechslin E, et al. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. *J Am Coll Cardiol*. 2003;41:2004-9. [PMID: 12798573]
18. Arlati S, Brenna S, Prencipe L, Marocchi A, Casella GP, Lanzani M, et al. Myocardial necrosis in ICU patients with acute non-cardiac disease: a prospective study. *Intensive Care Med*. 2000;26:31-7. [PMID: 10663277]
19. Bakshi TK, Choo MK, Edwards CC, Scott AG, Hart HH, Armstrong GP. Causes of elevated troponin I with a normal coronary angiogram. *Intern Med J*. 2002;32:520-5. [PMID: 12412934]
20. Zellweger MJ, Schaer BA, Cron TA, Pfisterer ME, Osswald S. Elevated troponin levels in absence of coronary artery disease after supraventricular tachycardia. *Swiss Med Wkly*. 2003;133:439-41. [PMID: 14562187]
21. Hamwi SM, Sharma AK, Weissman NJ, Goldstein SA, Apple S, Canos DA, et al. Troponin-I elevation in patients with increased left ventricular mass. *Am J Cardiol*. 2003;92:88-90. [PMID: 12842258]
22. Nunes JP, Mota Garcia JM, Farinha RM, Carlos Silva J, Magalhaes D, Vidal Pinheiro L, et al. Cardiac troponin I in aortic valve disease. *Int J Cardiol*. 2003;89:281-5. [PMID: 12767553]
23. Wang CH, Kuo LT, Hung MJ, Cherng WJ. Coronary vasospasm as a possible cause of elevated cardiac troponin I in patients with acute coronary syndrome and insignificant coronary artery disease. *Am Heart J*. 2002;144:275-81. [PMID: 12177645]
24. Trooyen M, Indredavik B, Rossvoll O, Slordahl SA. [Myocardial injury in acute stroke assessed by troponin I]. *Tidsskr Nor Lægeforen*. 2001;121:421-5. [PMID: 11255854]
25. Tung P, Kopelnik A, Banki N, Ong K, Ko N, Lawton MT, et al. Predictors of neurocardiogenic injury after subarachnoid hemorrhage. *Stroke*. 2004;35:548-51. [PMID: 14739408]
26. Homma S, Grahame-Clarke C. Editorial comment—myocardial damage in patients with subarachnoid hemorrhage [Editorial]. *Stroke*. 2004;35:552-3. [PMID: 14757896]
27. Velmahos GC, Karaskakis M, Salim A, Toutouzias KG, Murray J, Asensio J, et al. Normal electrocardiography and serum troponin I levels preclude the presence of clinically significant blunt cardiac injury. *J Trauma*. 2003;54:45-50; discussion 50-1. [PMID: 12544898]
28. Hasdemir C, Shah N, Rao AP, Acosta H, Matsudaira K, Neas BR, et al. Analysis of troponin I levels after spontaneous implantable cardioverter defibrillator shocks. *J Cardiovasc Electrophysiol*. 2002;13:144-50. [PMID: 11900289]
29. Cantwell RV, Aviles RJ, Bjornsson J, Wright RS, Freeman WK, Oh JK, et al. Cardiac amyloidosis presenting with elevations of cardiac troponin I and angina pectoris. *Clin Cardiol*. 2002;25:33-7. [PMID: 11808838]
30. Cardinale D, Sandri MT, Martinoni A, Tricca A, Civelli M, Lamantia G, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol*. 2000;36:517-22. [PMID: 10933366]
31. Brandt RR, Filzmaier K, Hanrath P. Circulating cardiac troponin I in acute pericarditis. *Am J Cardiol*. 2001;87:1326-8. [PMID: 11377371]
32. Smith SC, Ladenson JH, Mason JW, Jaffe AS. Elevations of cardiac troponin I associated with myocarditis. Experimental and clinical correlates. *Circulation*. 1997;95:163-8. [PMID: 8994432]
33. Labarrere CA, Nelson DR, Cox CJ, Pitts D, Kirlin P, Halbrook H. Cardiac-specific troponin I levels and risk of coronary artery disease and graft failure following heart transplantation. *JAMA*. 2000;284:457-64. [PMID: 10904509]
34. Logeart D, Beyne P, Cusson C, Tokmakova M, Leban M, Guiti C, et al. Evidence of cardiac myolysis in severe nonischemic heart failure and the potential role of increased wall strain. *Am Heart J*. 2001;141:247-53. [PMID: 11174339]
35. Cheng W, Li B, Kajstura J, Li P, Wolin MS, Sonnenblick EH, et al. Stretch-induced programmed myocyte cell death. *J Clin Invest*. 1995;96:2247-59. [PMID: 7593611]
36. Feng J, Schaus BJ, Fallavollita JA, Lee TC, Canty JM Jr. Preload induces troponin I degradation independently of myocardial ischemia. *Circulation*. 2001;103:2035-7. [PMID: 11319190]
37. Horwich TB, Patel J, MacLellan WR, Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. *Circulation*. 2003;108:833-8. [PMID: 12912820]
38. Rifai N, Douglas PS, O'Toole M, Rimm E, Ginsburg GS. Cardiac troponin T and I, echocardiographic [correction of electrocardiographic] wall motion analyses, and ejection fractions in athletes participating in the Hawaii Ironman Triathlon. *Am J Cardiol*. 1999;83:1085-9. [PMID: 10190525]
39. Neumayr G, Gaenzler H, Pfister R, Sturm W, Schwarzscher SP, Eibl G, et al. Plasma levels of cardiac troponin I after prolonged strenuous endurance exercise. *Am J Cardiol*. 2001;87:369-71, A10. [PMID: 11165984]
40. Yalamanchili K, Sukhija R, Aronow WS, Sinha N, Fleisher AG, Lehrman SG. Prevalence of increased cardiac troponin I levels in patients with and without acute pulmonary embolism and relation of increased cardiac troponin I levels with in-hospital mortality in patients with acute pulmonary embolism. *Am J Cardiol*. 2004;93:263-4. [PMID: 14715366]
41. Torbicki A, Kurzyna M, Kuca P, Fijalkowska A, Sikora J, Florczyk M, et al. Detectable serum cardiac troponin T as a marker of poor prognosis among patients with chronic precapillary pulmonary hypertension. *Circulation*. 2003;108:844-8. [PMID: 12900346]
42. Baillard C, Boussarsar M, Fosse JP, Girou E, Le Toumelin P, Cracco C, et al. Cardiac troponin I in patients with severe exacerbation of chronic obstructive pulmonary disease. *Intensive Care Med*. 2003;29:584-9. [PMID: 12589528]
43. deFilippi C, Wasserman S, Rosanio S, Tibbler E, Sperger H, Tocchi M, et al. Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. *JAMA*. 2003;290:353-9. [PMID: 12865376]
44. Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. *Circulation*. 2002;106:2941-5. [PMID: 12460876]
45. Freda BJ, Tang WH, Van Lente F, Peacock WF, Francis GS. Cardiac troponins in renal insufficiency: review and clinical implications. *J Am Coll Cardiol*. 2002;40:2065-71. [PMID: 12505215]
46. Van Lente F, McElean ES, DeLuca SA, Peacock WF, Rao JS, Nissen SE. Ability of troponins to predict adverse outcomes in patients with renal insufficiency and suspected acute coronary syndromes: a case-matched study. *J Am Coll Cardiol*. 1999;33:471-8. [PMID: 9973028]
47. Aviles RJ, Askari AT, Lindahl B, Wallentin L, Jia G, Ohman EM, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med*. 2002;346:2047-52. [PMID: 12087140]
48. Diris JH, Hackeng CM, Kooman JP, Pinto YM, Hermens WT, van Dieijen-Visser MP. Impaired renal clearance explains elevated troponin T fragments in hemodialysis patients. *Circulation*. 2004;109:23-5. [PMID: 14691043]

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