

# Common Causes of Troponin Elevations in the Absence of Acute Myocardial Infarction\*

## Incidence and Clinical Significance

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**Cardiac troponin is a preferred biomarker of acute myocardial infarction (MI). Unfortunately, elevation of troponin can be detected in a variety of conditions other than acute MI. This review focuses on the incidence and clinical significance of increased troponin in conditions commonly associated with troponin elevations, particularly in those that may resemble acute MI.**

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**Key words:** false-positive; heart failure; pericarditis; pulmonary embolism; sepsis; troponin

**Abbreviations:** CAD = coronary artery disease; CK = creatinine kinase; HF = heart failure; MI = myocardial infarction; PE = pulmonary embolism; TnI = troponin I; TnT = troponin T

Cardiac troponins are the most sensitive and specific biochemical markers of myocardial damage.<sup>1</sup> In patients with clear-cut unstable angina, cardiac troponin measurements provide superior prognostic information over creatinine kinase (CK).<sup>2</sup> The current guidelines<sup>3</sup> from the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction (MI) state that cardiac troponins are the preferred markers for detecting myocardial cell injury. Therefore, one of the cardiac troponins is routinely measured in patients presenting with acute chest pain syndrome, acute dyspnea, or other complaints in which acute MI is one of the differential diagnoses. However, troponin elevations indicate the presence but not the mechanism of myocardial injury, and myocardial damage can occur from a variety of mechanisms other than acute ischemia. Although a thorough clinical evaluation and the time course of troponin elevation will often help discriminate acute MI from other causes, knowledge about the potential elevations of troponin in these condi-

tions may minimize unnecessary discomfort and cost associated with cardiac testing to exclude coronary artery disease (CAD).

Furthermore, all of the currently available troponin measurements utilize two-site immunoassays. Similar to other immunoassays, spurious elevations of cardiac troponin from interference in the absence of MI, known as false-positive troponin, have been reported.<sup>4-5</sup> This review will focus on the incidence, magnitude, and clinical significance of troponin elevations in conditions other than acute MI, particularly in those conditions that may resemble acute coronary syndrome (Table 1), and the common causes of false-positive troponin.

### ACUTE PERICARDITIS

Patients with acute pericarditis usually present with chest pain and ST-segment changes on ECG. Modest elevation of the MB fraction of CK (CK-MB) has been found in patients with acute pericarditis.<sup>6</sup> Troponin elevation has also been reported in patients with acute pericarditis.<sup>7-8</sup> However, the available data on the prevalence and extent of troponin elevation in this condition are limited.

Bonnefoy et al<sup>8</sup> reported that approximately one half of their 69 consecutive patients (49%) with acute idiopathic pericarditis had troponin I (TnI) levels > 0.5 ng/mL. Twenty-two percent had TnI levels > 1.5 ng/mL, their cut-off level for acute MI. The average TnI level was 8 ± 12 ng/mL (range, 0 to 48 ng/mL). The median level was, however, only 1

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**Table 1—Conditions Commonly Associated With Cardiac Troponin Elevations in the Absence of Acute MI**

Acute PE
Acute pericarditis
Acute or severe HF
Myocarditis
Sepsis and/or shock
Renal failure
False-positive troponin

ng/mL. ST-segment elevation was found in almost every patient (93%) with TnI levels > 1.5 ng/mL, compared to 65% in the entire group. A troponin level above the cut-off for acute MI was more common in younger patients (37 years vs 52 years,  $p = 0.002$ ) and in those with a history of recent infection (66% vs 31%,  $p = 0.01$ ). Elevation of troponin in acute pericarditis is believed to represent injury of the epicardial layer of myocardium adjacent to visceral pericardium where the active inflammation occurs.

#### ACUTE PULMONARY EMBOLISM

Patients with acute pulmonary embolism (PE) often present with acute dyspnea and/or chest pain. Echocardiographic evidence of right ventricular dysfunction was reported in 40 to 55% of patients with acute PE.<sup>9–10</sup> Right ventricular dysfunction in acute PE has been associated with increased mortality.<sup>9–10</sup> Elevation of CK-MB has been reported in acute massive PE.<sup>11–12</sup> Since cardiac troponins are more sensitive than CK-MB in detecting myocardial injury, measurement of cardiac troponin may provide superior information for the management of patients with PE.

Giannitis et al<sup>13</sup> reported the incidence and prognostic significance of troponin T (TnT) elevation in patients with confirmed acute PE. Of the 56 patients, 32% had elevated TnT levels ( $\geq 0.1$  ng/mL). In contrast, only 7% had CK levels above twice the upper limit of normal. Using a clinical grading system adapted from Goldhaber,<sup>14</sup> 23%, 46%, and 30% of the patients were classified as having small PE, moderate-to-large PE, and massive PE, respectively. Elevated TnT was only observed in patients with either moderate-to-large PE or massive PE. None of those with small PE had increased TnT.

TnT-positive patients were more likely to have right ventricular dysfunction, severe hypoxemia, prolonged hypotension, or cardiogenic shock. They also more often required inotropic therapy or mechanical ventilation than those with negative TnT. Complete

or incomplete right bundle-branch block or ST-T changes on ECG were also more prevalent in TnT-positive subgroup. More importantly, TnT positivity was associated with approximately 30-fold increased risk of in-hospital mortality. In addition, TnT level was found to be an independent predictor of the 30-day outcome. Survival rates at 30 days were 60% and 95%, respectively, for those with and without TnT elevation (Table 2).

Right ventricular dilation and strain from sudden increase in pulmonary arterial resistance is believed to be the cause of troponin release in acute PE.<sup>15</sup> Unfortunately, coexisting CAD is not uncommon in patients with acute PE. In the study by Giannitis et al,<sup>13</sup> a 20% incidence of previous MI was reported. Twelve percent of their patients had previous coronary revascularization. Significant CAD, defined as a  $\geq 50\%$  luminal diameter stenosis, was also more common in TnT-positive than TnT-negative patients (40% vs 27%, respectively). Although left ventricular infarction may not be completely excluded in patients with concomitant CAD, troponin elevations were observed even in those without CAD. Moreover, a recent study<sup>15</sup> in patients with submassive PE, defined as all confirmed PE except massive PE associated with hypotension, cardiogenic shock, or respiratory failure, has strongly suggested that myocardial ischemia from CAD is not the major cause of troponin elevation in acute PE. In this study by Douketis et al,<sup>15</sup> patients with a history of confirmed CAD, congestive heart failure, or cardiomyopathy were excluded. Of 24 patients, 21% had TnI levels  $\geq 0.4$  ng/mL. TnI levels above the cut-off for acute MI in their laboratory (2.3 ng/mL) were detected in 4% of the patients. The lower incidence of troponin elevation in the latter study is likely due to the exclusion of patients with massive PE.

#### ACUTE OR SEVERE HEART FAILURE

Acute coronary syndrome occasionally presents with a sudden increase of dyspnea without typical angina. In elderly, dyspnea is a major complaint in a large number of patients with acute MI.<sup>16</sup> In patients with severe but stable heart failure (HF), a modest increase of cardiac troponin has been reported.<sup>17</sup> Using a highly sensitive TnI assay with a lower detection limit at 3 pg/mL, Missov et al<sup>17</sup> found a significantly higher level of TnI in patients with stable HF than in control subjects (72 pg/mL vs 25 pg/mL,  $p < 0.01$ ). However, a TnI level > 0.1 ng/mL, a normal detectable level on standard assay, was found in only 1 of their 35 patients (0.206 ng/mL). A much higher incidence of detectable TnI has been reported in a combined population of hospitalized

**Table 2—Incidence and Clinical Significance of Troponin Elevations in Various Conditions\***

Conditions	Troponin Subunit	Cut-offs, ng/mL	Incidence, %	Clinical Significance of Troponin Elevation
Acute pericarditis	TnI	0.5	49	Correlates with recent infection
		1.5	22	
Acute PE Overall	TnT	0.1	32	Increased risk of in-hospital mortality, poor 30-d outcome, right ventricular dysfunction, shock/hypotension, and need for mechanical ventilation
			53	
			0	
			21	
Massive	TnI	0.4	21	
		2.3	4	
Small	TnI	0.1	3	Independent predictor of long-term survival or readmission for HF; correlates with worse functional class, and lower ejection fraction
			15	
Submassive	TnT	0.1	3	
			7	
HF	TnT	0.1	7	
			2	
Severe but stable	TnI	0.3	23	
			0	
Hospitalized HF	TnI	1.0	20	
			55	
Stable or unstable	TnT	1.0	7	
			7	
Acute left HF	TnI	1.0	0	
			34	
Cor pulmonale	TnI	1.0	0	Correlates with recent onset of HF and more diffuse myocarditis
			34	
Myocarditis	TnI	3.1	34	Correlates with APACHE II score and degree of hypotension; increased in-hospital mortality; independent predictor of left ventricular dysfunction
			58–85	
Severe sepsis/shock	TnI	0.1	58–85	
			50	
Renal failure	TnT	0.4	36–69	Independent predictor of poor long-term outcome
			6	
	TnI	0.1	6	
			1	
	TnT	0.4	53	
			20	

\*APACHE = acute physiology and chronic health evaluation.

HF and stable HF patients seen in the outpatient clinic.<sup>18</sup> Using Stratus II (Dade International; Deerfield, IL) TnI assays, La Vecchia et al<sup>18</sup> found TnI levels above the detection limit (0.3 ng/mL) in 23% of their 26 patients. Unfortunately, the proportions of patients with stable and unstable HF were not reported. Nevertheless, the degree of TnI elevation was similarly modest, with the highest level of only 0.8 ng/mL.

The incidence of elevated TnT in chronic HF has also been reported.<sup>19–20</sup> In 33 patients with stable HF, Missov and Mair<sup>19</sup> found that 15% had detectable TnT (> 0.1 ng/mL). However, only 9% and 3% of their patients had TnT levels > 0.5 ng/mL and > 1.0 ng/mL, respectively.

Setsuda et al<sup>20</sup> reported TnT levels of at least 0.02

ng/mL in 52% of their 58 patients hospitalized for HF. Of all patients with detectable TnT in the latter study, 87% had TnT levels between 0.02 ng/mL and 0.1 ng/mL, 10% had TnT levels between 0.1 ng/mL and 1.0 ng/mL, and only 3% had TnT levels > 1 ng/mL.

Published data on troponin elevations in patients with acute HF, particularly right HF from cor pulmonale, are limited. Perna et al<sup>21</sup> recently reported a 55% incidence of TnT of  $\geq$  0.1 ng/mL in patients with acute cardiogenic pulmonary edema. The highest level of TnT in these patients was 2.6 ng/mL, and 7% of the patients had TnT levels > 1 ng/mL. Guler et al<sup>22</sup> studied 41 patients with acute left heart failure and 17 patients with worsening of right HF. In 23 of 41 patients with left HF, CAD was

the responsible cause. A TnI level  $> 1$  ng/mL was found in 20% of the patients with left HF but in none of those with cor pulmonale. None of the patients had TnI levels  $> 2$  ng/mL.

Although most of the troponin elevations in HF are only modest, troponin positivity was found to correlate with a worse clinical and functional status. In a study by La Vecchia et al,<sup>18</sup> left ventricular ejection fraction was  $17 \pm 2\%$  vs  $27 \pm 3\%$  ( $p < 0.0001$ ) and New York Heart Association functional class was  $3.7 \pm 0.5$  vs  $2.5 \pm 0.8$  ( $p = 0.003$ ), respectively, for troponin-positive vs troponin-negative groups. In hospitalized patients with HF, Setsuda et al<sup>20</sup> found detectable TnT in 92%, 68%, and 18% of patients with New York Heart Association classes IV, III, and II, respectively. In acute HF, patients with elevated TnT levels, as a group, were older and had a higher prevalence of CAD.<sup>21</sup> However, the elevations of troponin in HF have been found in both ischemic and nonischemic cardiomyopathy.<sup>17-20</sup> None of the TnI-positive patients in the study by La Vecchia et al<sup>18</sup> had CAD, whereas 24% of patients with detectable TnT in the report by Setsuda et al<sup>20</sup> had previous MI. In patients with stable HF, troponin levels were not significantly different between the ischemic and nonischemic groups.<sup>17,19</sup>

The presence of detectable cardiac troponin in HF appears to predict a poorer long-term outcome. In the study by Setsuda et al,<sup>20</sup> in which hospitalized HF patients were followed up for at least 12 months, the 1-year risk of death or rehospitalization due to worsening HF was 66% for patients with hospital admission TnT levels  $\geq 0.05$  ng/mL and 15% for those with hospital admission TnT levels  $< 0.5$  ng/mL ( $p = 0.004$ ).<sup>20</sup> TnT levels were at least 0.5 ng/mL in 86% of the patients who died during follow-up. Similarly, in patients with acute left HF, the 3-year survival for patients with TnT  $< 0.1$  ng/mL was 76%, compared to 29% in those with TnT levels  $\geq 0.1$  ng/mL ( $p = 0.04$ ).<sup>21</sup> More importantly, TnT levels were found to be a strong independent predictor of long-term mortality in patients with HF.<sup>20-21</sup>

Additionally, serial measurements of troponin after treatment may provide prognostic information. La Vecchia et al<sup>18</sup> found that troponin levels became undetectable in patients whose HF improved after the treatment but remained elevated in those who eventually died from intractable HF. Setsuda et al<sup>20</sup> found that TnT levels decreased significantly after treatment of HF in 75% of their 12 patients whose serial measurements of TnT were available. In one third of this group, TnT levels dropped below detectable limit after treatment. Unfortunately, the value of the pattern of TnT response to medical therapy in predicting the long-term outcome was not reported. These data, however, suggest that serial measurements of troponin may provide important

information in the management of patients with HF, and further confirmation in larger studies are warranted.

The mechanism of troponin release in heart failure remains unclear. In these studies, patients with acute coronary syndrome were excluded. Acute myocarditis was also excluded in some but not all of these patients. Release of TnI from cytosolic pool as a result of myocardial cell membrane injury without damage of structurally bound TnI has been reported.<sup>23</sup> However, cytosolic TnI has been estimated to account for  $< 2\%$  of total intracellular TnI.<sup>17</sup> It is perhaps more likely that detectable troponin in HF reflects ongoing degradation of contractile protein and cellular injury. An increased level of neurohormonal factors, oxidative stress, and a number of cytokines are universal in HF. Each of these factors is known to promote cardiac cell death; therefore, they may be responsible for the elevation of troponin in HF.<sup>17</sup>

## MYOCARDITIS

Inflammation can lead to myocardial necrosis in patients with myocarditis. Smith et al<sup>24</sup> detected elevation of TnI in 24 of 26 mice with autoimmune myocarditis. The same article<sup>24</sup> also reported the prevalence and clinical correlates of TnI in 88 patients with  $< 2$  years of unexplained HF referred to the Myocarditis Treatment Trial. All patients underwent endomyocardial biopsy as a part of the trial. Histologic evidences of myocarditis were present in 53 patients (60%). The Stratus analyzer (Dade International) was used for TnI assay. The upper limit of the reference range was 3.1 ng/mL.

TnI elevation was found in 34% and 11% of patients with and without evidence of myocarditis, respectively ( $p = 0.01$ ). CK-MB was elevated in only 6% of patients with biopsy-proven myocarditis ( $p = 0.001$ , compared to TnI elevation). Elevations of TnI in myocarditis were significantly correlated with recent ( $\leq 1$  month) onset of HF symptoms. TnI levels  $\geq 3.1$  ng/mL were present in 55% of patients with  $< 1$  month of HF symptoms, but were observed in  $< 10\%$  of those with longer duration of symptoms. The degree of TnI elevations was higher in patients with diffuse myocarditis (25.5 ng/mL) compared to those with focal (8.9 ng/mL) or borderline myocarditis (5.1 ng/mL). The difference, however, did not reach statistical significance, probably in part due to a relatively small sample size.

## SEPSIS/CRITICALLY ILL PATIENTS

Numerous reports on cardiac troponin elevation in various groups of critically ill patients have been

published.<sup>25–28</sup> Ammann et al<sup>25</sup> evaluated patients with sepsis, 40% of whom were in shock. Seventeen of their 20 patients (85%) had TnI elevation. TnI levels ranged from 0.17 to 15.4 ng/mL, with a median value of 0.57 ng/mL. ver Elst et al<sup>26</sup> found TnI levels of at least 0.4 ng/mL in 50% of their 46 patients with early septic shock. Similarly, a relatively low median level (1.4 ng/mL) of the peak concentrations of TnI was observed in this study. In patients with severe sepsis, septic shock, or hypovolemic shock, Arlati et al<sup>27</sup> found elevated TnI elevation in 74% of the cases. All of their 12 patients with hypovolemic shock and 58% of those with severe sepsis or septic shock had elevated TnI.

Elevation of TnT in sepsis has also been reported.<sup>26,28</sup> ver Elst et al<sup>26</sup> found cardiac TnT elevations ( $\geq 0.1$  ng/mL) in 36% of their cases. A much higher incidence of TnT elevation was reported by Spies et al<sup>28</sup>; in their 26 patients with sepsis, 69% had TnT levels  $\geq 0.2$  ng/mL.

Furthermore, elevations of troponin in these patients appear to correlate with severity of the disease process. TnI levels were found to correlate with the degree of hypotension<sup>27</sup> and APACHE (acute physiology and chronic health evaluation) II score.<sup>26</sup>

The causes of troponin elevations in these critically ill patients are not well understood. These reports, in general, had a relatively small sample size and included a heterogeneous group of patients. Some of these patients had CAD, and stress-induced MI may have been responsible for troponin release in this particular subgroup of patients. Acute coronary events have, however, been excluded in some of these patients. For example, Ammann et al<sup>25</sup> were able to exclude CAD in 10 of 17 TnI-positive patients. These findings indicated that other mechanisms are also involved.

In one study,<sup>26</sup> patients with elevated troponin levels are older and more likely to have hypertension or previous history of MI, suggesting that their underlying cardiovascular disease may, to some degree, contribute to troponin elevation. However, these findings were not observed in another study.<sup>28</sup> It also remains unclear whether infection with any specific pathogens is more likely to result in troponin elevations. *Streptococcal pneumoniae* infection was the cause of sepsis in 41% of TnI-positive patients in one study,<sup>25</sup> whereas Gram-negative bacteria were the offending pathogens in 63% of cases in another study.<sup>26</sup> Spies et al<sup>28</sup> found no difference in terms of the causes of sepsis between patients with or without troponin elevation.

Nevertheless, there are several potential mechanisms, other than acute MI, for troponin release in septic patients. First, it is well known that a number of local and circulating mediators (*eg*, cytokines or

reactive oxygen species) possess direct cardiac myocytotoxic properties.<sup>26</sup> Secondly, myocardial injury from the effect of bacterial endotoxins has been demonstrated. Finally, dysfunction of the microcirculation has been described in sepsis.<sup>29</sup> This microvascular dysfunction can lead to ischemia and reperfusion injury of the myocardial cell.

More importantly, troponin measurements in these patients appear to provide valuable prognostic information. ver Elst et al<sup>26</sup> reported that both TnI and TnT were independent markers of left ventricular dysfunction in patients with sepsis. They detected left ventricular dysfunction by transesophageal echocardiography in 78% and 9% of patients with and without TnI elevation, respectively ( $p < 0.001$ ). Several studies<sup>26,28,30</sup> also found a weak correlation between elevated cardiac troponin and hospital mortality.

## RENAL FAILURE

The prevalence and clinical significance of elevated troponins in patients with renal failure have been recently reviewed elsewhere.<sup>31</sup> In brief, TnT is more commonly elevated in patients with renal failure than TnI. Although the exact causes of troponin elevation in renal failure remain debatable, patients with elevated troponin generally have worse clinical outcome than those without it.

## FALSE-POSITIVE TROPONIN

Troponin complex is located on the thin filament of skeletal and myocardial muscle. An important feature of troponin complex is that its I and T subunits are sufficiently unique so that specific antisera can differentiate these two tissue forms. The high sensitivity and specificity of cardiac troponin for detecting myocardial injury is well documented.<sup>32–33</sup> However, various factors can interfere with the TnI assay, leading to falsely elevated levels (Table 3). These include heterophilic antibodies,<sup>34</sup> rheumatoid factor,<sup>35</sup> fibrin clots,<sup>36</sup> microparticles,<sup>36</sup> and malfunction of the analyzer itself.<sup>37</sup>

The role of heterophilic antibodies in causing interference in immunoassays has been reported in a

**Table 3—Common Causes of False-Positive Troponin**

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Heterophilic antibodies
Rheumatoid factor
Fibrin clots
Microparticles
Analyzer malfunction

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number of studies.<sup>34,38-41</sup> The incidence of this interference varies considerably in the literature,<sup>40-43</sup> ranging from 0.17 to 40%. Various sources have been proposed to give rise to heterophilic antibodies, and these include the use of mouse monoclonal antibodies in diagnostic imaging and cancer therapy,<sup>44</sup> exposure to microbial antigens,<sup>39,45</sup> exposure to foreign animal proteins,<sup>41</sup> and autoimmune diseases such as rheumatoid arthritis.<sup>38,40</sup>

Recognizing the significance of this interference by heterophilic antibodies, the manufacturers recommend using the antibody blocking agents along with their cardiac troponin immunoassays whenever this interference is suspected.<sup>46-47</sup> However, the results of these blocking agents are not very convincing.<sup>34,37,48-53</sup> Therefore, it is important that the manufacturers continue to improve their assays. In this regard, Kim et al<sup>43</sup> evaluated the performance of the revised Dimension cardiac TnI assay (Dade Behring; Deerfield, IL). They found that the revised Dimension cardiac TnI assay removed the interference in most of the samples with which the original Dimension cardiac TnI assay had given falsely elevated levels, and greatly decreased the interference in the remaining samples.

Rheumatoid factor is another cause of interference in the immunoassays. It has been reported that 5% of healthy patients might have circulating rheumatoid factor, and approximately 1% of patients with elevated cardiac TnI levels may have this elevation solely because of the rheumatoid factor.<sup>54</sup> When this scenario is suspected, a rheumatoid factor-blocking agent can be used.<sup>38</sup>

Excess fibrin is another well-reported source of falsely elevated cardiac TnI levels.<sup>36</sup> Roberts et al<sup>55</sup> observed that incompletely clotted specimen contributed to the false elevations in cardiac TnI levels with the Stratus II batch analyzer (Dade International). The manufacturers mention this possibility in the package insert and advise care with the specimens from patients receiving anticoagulant therapy. The investigators found three approaches to be useful to correct this interference: (1) heparinizing the tubes before analysis, (2) removing excess fibrin by repeating the centrifugation, and (3) adding SuperSerum (TTC; Edison, NJ), which contains protamine sulfate, thrombin, and snake venom to enhance coagulation.

In addition, Roberts et al<sup>55</sup> found that some of the interference due to free fibrin and microparticles can be avoided with repeat centrifugation of the sample and/or the use of a clot activator. However, Beyne et al,<sup>56</sup> in an open comparative study, found that a single centrifugation of collection tubes containing thrombin as a clot activator is not enough to avoid

false-positive cardiac TnI results on the ACCESS analyzer (Beckman Coulter; Fullerton, CA).

Finally, malfunction of the analyzer itself is another reported cause of false elevations in cardiac TnI results. Galambos et al<sup>37</sup> reported several cases of falsely elevated plasma cardiac TnI levels due to a temporary malfunction of the AxSYM analyzer (Abbott Laboratories; Abbott Park, IL). The operation manual provided by the manufacturer mentions the possibility of a solution dispenser misalignment if the dispensers are repositioned incorrectly during the weekly maintenance.<sup>57</sup> The authors recommend running quality-control samples after each maintenance of the analyzer.

## CONCLUSIONS

Cardiac troponin can be elevated in a variety of conditions other than acute MI. Therefore, an accurate diagnosis in a patient with elevated troponin relies heavily on the clinical information in that particular case. Increased levels of troponin in these conditions generally provide significant prognostic information. Knowledge about the incidence, clinical correlation, and clinical significance of increased troponin in these conditions are important in the current era of widespread and indiscriminate testing of troponin in clinical practice.

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