

## Troponin: the biomarker of choice for the detection of cardiac injury

Luciano Babuin, Allan S. Jaffe

### ABSTRACT

It has been known for 50 years that transaminase activity increases in patients with acute myocardial infarction. With the development of creatine kinase (CK), biomarkers of cardiac injury began to take a major role in the diagnosis and management of patients with acute cardiovascular disease. In 2000 the European Society of Cardiology and the American College of Cardiology recognized the pivotal role of biomarkers and made elevations in their levels the “cornerstone” of diagnosis of acute myocardial infarction. At that time, they also acknowledged that cardiac troponin I and T had supplanted CK-MB as the analytes of choice for diagnosis. In this review, we discuss the science underlying the use of troponin biomarkers, how to interpret troponin values properly and how to apply these measurements to patients who present with possible cardiovascular disease.

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**T**roponin is the biomarker of choice for the detection of cardiac injury. To use it properly, one must understand how sensitive the specific assay being used is for detecting cardiac injury, the fact that elevated troponin levels are highly specific for cardiac injury and some critical issues related to the basic science of the protein and its measurement. In this article, we review the biology of troponin, characteristics of assays that measure serum troponin levels and how to apply these measurements to patients who present with possible cardiovascular disease. We also discuss other clinical situations in which troponin levels may be elevated.

### The biology of troponin

The 3-unit troponin complex (troponin I, T and C) along with tropomyosin is located on the actin filament and is essential for the calcium-mediated regulation of skeletal and cardiac muscle contraction.<sup>1</sup> There are tissue-specific isoforms of troponin I, T and C.<sup>2,3</sup> Because the cardiac isoform of troponin C is shared by slow-twitch skeletal muscles, troponin C does not have cardiac specificity and thus is not used in assays for the diagnosis of cardiac injury.<sup>4</sup>

There is one cardiac troponin I (cTnI) isoform in myocardial tissue.<sup>5</sup> This isoform has a post-translational tail of 32

amino acids on the N-terminus.<sup>6,7</sup> This sequence and the 42% and 45% dissimilarity with sequences of the other isoforms<sup>8</sup> have made possible the generation of highly specific monoclonal antibodies without cross-reactivity with other noncardiac forms.<sup>9</sup>

Three genes control cardiac troponin T (cTnT).<sup>10</sup> These genes and alternative mRNA splicing produce a series of isoforms<sup>10,11</sup> with variable sequences close to the regions of the N-terminus and C-terminus.<sup>10,12</sup> Human cardiac muscle contains 4 troponin T isoforms, but only one is characteristic of the normal adult heart.<sup>13,14</sup> Highly specific antibodies have been made to the N-terminus-specific sequence of this cTnT isoform.<sup>15</sup>

The skeletal isoforms present in the fetal heart are replaced by cTnI and cTnT late during fetal development.<sup>16,17</sup> cTnI is not expressed in skeletal muscle or other tissues during development<sup>17</sup> or in response to degenerative or regenerative muscle disease processes.<sup>18</sup> Thus, it is unlikely to be re-expressed in damaged tissues. The situation is more complex for cTnT. Re-expression of fetal forms occurs in cardiac tissue<sup>12</sup> and in diseased skeletal muscle.<sup>19</sup> With the first-generation cTnT assay, this problem was compounded by a nonspecific tag antibody that cross-reacted with troponin T in skeletal muscle.<sup>20</sup> Once this antibody was replaced by one with high specificity, false-positive elevations from skeletal muscle were eliminated.<sup>15</sup> Studies using immunohistochemistry and polymerase chain reaction have confirmed that these fetal isoforms are not detected by the assay used today.<sup>21,22</sup> Thus, the assay used to measure cTnT levels has cardiac specificity equivalent to that of assays for cTnI.

### Characteristics of troponin assays

Most troponin is found in the 3-unit complex (troponin I, T and C) of the contractile apparatus in myofibrils. There is also what has been termed a “cytosolic pool” of unbound troponin that is released acutely,<sup>23,24</sup> mimicking the appearance kinetics of other cytosolic proteins such as creatine kinase (CK). This pool represents about 6% of cTnT<sup>23</sup> and 3% of cTnI,<sup>24</sup> which is similar to the concentration of the CK-MB isoenzyme.<sup>24</sup> The 13–15-fold increased amount of troponin per gram of myocardium is mostly complexed,<sup>23,24</sup> which explains the late but not early release of troponin. Thus, the increased overall amount of troponin in the heart is not why troponin is more sensitive than CK-MB.<sup>25,26</sup> The increased early sensitivity likely reflects the fact that the percentage of

**Box 1: Critical values to know about troponin assays**

- *Lower limit of detection:* The lowest level detectable that differs from zero. Assays with a lower limit of detection are more sensitive.
- *Upper limit of normal:* Usually defined as the 95th percentile (mean  $\pm$  2 standard deviations) in a presumably normal “reference” population. For troponin, the European Society of Cardiology / American College of Cardiology task force recommended that the 99th percentile (mean  $\pm$  approximately 3 standard deviations) be used as the cut-off point, above which any value should be considered abnormal.
- *Coefficient of variation (CV):* A measure of how consistently an assay is able to produce the same result on the same sample. A CV of 10% is the level of precision suggested for troponin assays.
- *Receiver operating characteristic (ROC) curve:* The value at which the sensitivity of the troponin level is equivalent to that of the CK-MB level.

Note: CK-MB = creatine kinase MB isoenzyme.

troponin released that reaches the blood after cardiac injury is greater for troponin than for CK-MB.<sup>27,28</sup> Elevated troponin levels then persist in the blood owing to the slow release and degradation of the structural pool,<sup>23,29</sup> since the half-life of troponin and its complex is about 2 hours.<sup>30</sup> The prolonged window during which troponin levels are elevated allows for increased clinical detection of cardiac events and thus, functionally, greater clinical sensitivity.

With the first-generation troponin assays, about 33% of patients presenting with symptoms of acute coronary syndromes were found to have elevated troponin levels in the absence of elevated CK-MB levels.<sup>31</sup> As assays have become more sensitive, an even greater number of patients have been identified with elevated troponin levels. Although the degree of improvement depends on the troponin assay used, the cut-off values adopted and the assay’s sensitivity for CK-MB, the use of troponin rather than CK-MB has clearly increased the ability to detect myocardial damage secondary to ischemia perhaps as much as 130%.<sup>32</sup> However, there is huge variability in the sensitivity of assays, which is in no way reflected in the values reported for the various assays. The appropriate cut-off value for each assay is unique and cannot be compared with any other.<sup>33,34</sup> These differences are due in part to the heterogeneity of the antibodies and matrix components of the assays.<sup>9,35</sup> They are also due to the fact that there are various fragments of troponin that circulate, and the antibodies used in the various assays detect these fragments differently.<sup>36</sup>

Troponin assays are not only more sensitive but are also more specific than CK-MB assays. Expression of CK-MB is not unique to the heart.<sup>37</sup> CK-MB is found in skeletal muscle and the gastrointestinal tract as well as in the uterus of pregnant women.<sup>38</sup> Moreover, in patients with myopathies, the CK-MB content of skeletal muscle can increase markedly to up to 50% of the total amount per gram of tissue.<sup>39</sup> In addition,

CK-MB complexes with immunoglobulins can form.<sup>40,41</sup> Thus, elevated CK-MB levels can occur because of analytical problems, macrocomplexes, trauma, rhabdomyolysis, myopathies or renal failure (owing to a myopathy), or during the peripartum period.<sup>42,43</sup> The specificity of CK-MB can be enhanced by the calculation of the CK-MB/CK ratio. However, the use of this ratio markedly reduces sensitivity in patients with concurrent cardiac and skeletal muscle injury.<sup>44,45</sup>

For all intents and purposes, cTnI and cTnT provide comparable information, except in patients with renal failure (see “Troponin and renal failure”).

The International Federation of Clinical Chemistry and Laboratory Medicine published quality specifications for cardiac troponin assays.<sup>36</sup> The values that are used to characterize a troponin assay are presented in Box 1.<sup>46</sup> The wide range in the ability of various assays to detect low levels of troponin is highlighted by the range in the different cut-off values (the lower limit of detection, the 99th percentile, the 10% coefficient of variation and the receiver operating characteristic [ROC] curve) (Table 1). This table may be used by clinicians to correlate troponin values obtained at hospitals using different assays from their own. The sensitivity of the different cut-off values in detecting acute myocardial infarction is illustrated in Fig. 1.

## Role of troponin in acute myocardial infarction

In 2000 a joint committee of the European Society of Cardiology and the American College of Cardiology (ESC/ACC) issued new criteria that acknowledged that elevations in biomarkers were fundamental to the diagnosis of acute myocardial infarction,<sup>47,48</sup> because symptoms may be atypical or nonexistent and electrocardiogram changes may be absent or nonspecific.<sup>49</sup> By this time, cardiac troponin had supplanted MB-CK as the biomarker of choice for the detection of cardiac injury.<sup>50</sup> The ESC/ACC criteria are included in Box 2.

To avoid false-positive results, the 99th percentile should be used as the cut-off value for diagnosing acute myocardial infarction. The use of 2 cut-off values<sup>51,52</sup> — one to define infarction and a second designation for unstable angina with some degree of myocardial necrosis — has been suggested.<sup>51,52</sup> The ESC/ACC joint committee felt that this approach lacked a scientific basis.<sup>50</sup> Given the multiplicity of assays and the fact that different assays and laboratories advocate different cut-off values, the use of 2 cut-off values would have markedly increased the heterogeneity of diagnoses. In addition, with assays becoming more sensitive, the category of patients with unstable angina and myocardial necrosis would have increased in number. In addition, patients with elevated troponin levels have short- and long-term risk profiles, anatomy and pathophysiology similar to those of patients with conventionally diagnosed non-Q-wave myocardial infarction; therefore, singling this group out arbitrarily made little sense to the committee.<sup>50</sup>

The 99th percentile as a cut-off value can be applied con-

sistently across assays even if the assays change. For some assays, but not others, there may be a need to alter the 99th percentile based on the patient's age, sex or race.<sup>53-55</sup>

The 99th percentile should be measurable with an imprecision (coefficient of variation) of 10% or less. In July 2004 the first assay met these criteria.<sup>56</sup> We and others have advocated using the value at which there is 10% coefficient of variation, to avoid analytical false-positive results.<sup>57</sup>

Like CK-MB, cardiac troponin concentrations begin to rise 4-6 hours after the onset of symptoms. Thus, a blood sample should be obtained on admission and again 6-9 hours later. Peak values occur at 18-24 hours after symptom onset. If it is difficult to ascertain the onset of symptoms, sampling should be based on the time of presentation. Values should be available within 60 minutes.<sup>47,48</sup> Troponin elevations reflect myocardial damage but do not indicate its mechanism. In the absence of clinical evidence that the injury is due to coronary ischemia, other causes for cardiac damage should be sought.

If cardiac troponin assays are not available, the best alternative is CK-MB measurement (preferably CK-MB mass). As with the troponin assays, the 99th percentile should also be used as the cut-off value. Measurement of analytes such as myoglobin and CK isoforms was suggested only if the test results would result in a change in therapy. With the improvement of troponin assays, it has become less clear that these analytes play any role<sup>58</sup> (Fig. 1). Previous studies that suggested they were of benefit were often based on high assay cut-off values or insensitive assays.<sup>59,60</sup>

## Prognostic value of troponin in acute coronary syndromes

Prognosis and diagnosis are different, and thus troponin elevations may in some situations help to make a diagnosis but may not be prognostic. The reason for this may be that inadequate studies have been done or that the effect is too small to detect, if it exists at all. Nonetheless, in almost all series, even minor elevations in troponin levels presage short- and long-term events.<sup>50</sup> However, for patients with acute coronary syndromes and, increasingly, other entities such as heart failure and pulmonary embolism, diagnostic elevations of troponin invariably have prognostic and therapeutic significance. In patients with acute coronary syndromes, elevated levels of cTnI or cTnT are an adverse prognostic indicator (Fig. 2), even after adjustment for clinical predictors and electrocardiogram findings.<sup>61,62</sup> These effects are short and long term.<sup>31,63</sup>

In patients with non-ST-segment elevation myocardial infarction (non-STEMI), angiographic data suggest that there are more acute and more complex plaques, more extensive disease, more thrombi and reduced Thrombolysis in Myocardial Infarction (TIMI) flow grades when troponin levels are elevated.<sup>64,65</sup> The increased coagulation observed probably represents more severe disease rather than any other association. Since more severe disease may benefit from newer and more aggressive interventions, troponin elevations identify a group of patients who will benefit from therapy with delteparin and enoxaparin, studies of which showed a reduction in both mortality and recurrent

**Table 1:** Cut-off values of cardiac troponin assays

Assay	LLD	99th percentile	10% CV*	ROC curve
ARCH STAT Troponin-I, Abbott Diagnostics	0.009	0.012	0.032	0.3
AxSYM Troponin-I ADV, Abbott Diagnostics	0.02	0.04	0.16	0.4
i-STAT,† Abbott Laboratories	0.02	0.08 (WB)	0.1	ND
Centaur, Bayer Diagnostics	0.02	0.1	0.35	1.0
Access AccuTnI Troponin I, Beckman Coulter	0.01	0.04	0.06	0.5
Triage Cardiac Panel,† Biosite	0.19	< 0.19	0.5	0.4
Dimension RxL, Dade Behring	0.04	0.07	0.14	0.6-1.5
Stratus CS,† Dade Behring	0.03	0.07	0.06	0.6-1.5
Immulate, Diagnostic Products Corporation	0.1	0.2	0.6	1.0
Vitros, Ortho-Clinical Diagnostics	0.02	0.08	0.12	0.4
Response,† Ortho-Clinical Diagnostics	0.03	< 0.03 (WB)	0.21	ND
Elecsys, Roche Diagnostics	0.01	< 0.01	0.03	0.1
Reader,† Roche Diagnostics	0.05	< 0.05 (WB)	ND	0.1
Tosoh AIA, Global Medical Instrumentation Inc.	0.06	< 0.06	0.06	0.31-0.64

Note: LLD = lower limit of detection, CV = coefficient of variation, ROC = receiver operating characteristic, ND = not determined, WB = whole blood.

\*Per manufacturer.

†Point-of-care assay FDA-cleared as high-sensitivity assay 2004 (CS).

Source: Apple et al.<sup>57</sup>

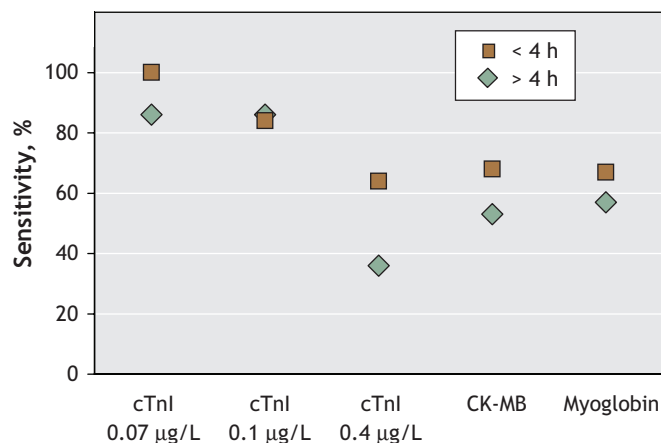
myocardial infarction;<sup>66,67</sup> no benefit was observed among patients without elevated troponin levels. A large number of trials, including at least 3 randomized trials,<sup>68–70</sup> have investigated the use of glycoprotein IIb/IIIa platelet inhibitors and have shown that troponin elevations identify a group in which a more aggressive antiplatelet aggregation therapy is useful. Subsequent nonrandomized<sup>71</sup> and randomized studies<sup>72,73</sup> have confirmed that early coronary intervention also attenuates the adverse prognostic impact of troponin elevations.<sup>74,75</sup> Of the agents used to treat acute coronary syndromes, only clopidogrel seems to benefit patients with and without troponin elevations.<sup>76</sup> Although there are no direct data, this is likely also true for ASA.

Elevated troponin levels on admission are also of value for patients with ST-segment elevation myocardial infarction (STEMI). Regardless of therapy, an elevated troponin level is an independent predictor of death at 30 days and during long-term follow-up.<sup>77,78</sup> This is because elevations predict incomplete epicardial and more severely impaired myocardial perfusion despite normal epicardial flow.<sup>79</sup> Some of this effect may be attenuated by stenting.

With both STEMI and non-STEMI, there is relation between the extent of the increase in troponin levels and adverse events.<sup>61,77</sup> The prognostic value of cTnT and of cTnI appear equivalent.<sup>80,81</sup>

## Can troponin detect reversible cardiac injury?

The question of whether biomarkers in general, or troponin in particular, are released after reversible or irreversible injury has been debated for years.<sup>82</sup> In animal experiments, increased CK activity in blood has been associated with evi-



**Fig. 1:** Sensitivity of different cut-off values of cardiac troponin I (cTnI) over time; 0.07 mg/L = 99th percentile, 0.1 mg/L = 10% coefficient of variation, 0.4 mg/L = receiver operating characteristic (ROC) curve. Reprinted, with permission, from Eggers KM, Oldgren J, Nordenskjold A, et al. Diagnostic value of serial measurement of cardiac markers in patients with chest pain: limited value of adding myoglobin to troponin I for exclusion of myocardial infarction. *Am Heart J* 2004;148:574-81.

### Box 2: 1999 ESC/ACC criteria for the diagnosis of acute, evolving or recent myocardial infarction (MI)

Either one of the following criteria satisfies the diagnosis of acute, evolving or recent MI:

- Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
  - Ischemic symptoms
  - Development of pathological Q waves on ECG
  - ECG changes indicative of ischemia (ST-segment elevation or depression)
  - Coronary artery intervention (e.g., coronary angioplasty)
- Pathological findings of acute MI

Note: ESC/ACC = European Society of Cardiology / American College of Cardiology, CK-MB = creatine kinase MB isoenzyme, ECG = electrocardiogram. Source: *Eur Heart J* 2000;21:1502-13,<sup>47</sup> and *J Am Coll Cardiol* 2000;36:959-69.<sup>48</sup>

dence of irreversible cardiac injury (cell disruption).<sup>83</sup> Troponin elevations have not been detected in humans who experienced reversible ischemia after exercise stress testing.<sup>84</sup>

The molecular weights of cTnI and cTnT are 23 500 and 33 500 Daltons respectively. However, even if free troponin chains are smaller than CK-MB (86 000 Daltons), much of the troponin is released as a complex with a higher molecular weight.<sup>85,86</sup> Some have argued that the transient troponin release in experimental models of vital exhaustion,<sup>87</sup> experimental studies with longer ischemia times<sup>88</sup> and in some exercise studies<sup>89,90</sup> may be due to the release of troponin from the “cytosolic pool” only. This also has been observed in patients with pulmonary embolism<sup>91,92</sup> and sepsis.<sup>93</sup> The failure of continuing release has been attributed to the lack of release of structurally bound troponin and thus “reversible injury.”<sup>91,92</sup> Such speculation fits with the known difficulty of causing right ventricular infarction<sup>94</sup> and with the recovery of left ventricular function in patients with septic shock.<sup>95,96</sup>

Since one cannot distinguish one type of release from the other, and given that the situation for troponin is likely the same for all biomarkers, it is unclear how important this issue is clinically.<sup>50</sup>

## Chest pain in the emergency department

Patients who present with chest pain, in whom unstable coronary disease is possible but not overt, are at higher risk of cardiac events if troponin is elevated. In a landmark study, Hamm and colleagues<sup>97</sup> evaluated the effectiveness of rapid triage using bedside tests to detect cTnI and cTnT in 733 patients with acute chest pain in an emergency department as long as one sample was obtained at least 6 hours after the onset of symptoms. Patients with normal troponin values had a negligible incidence of events over a 30-day follow-up.<sup>97</sup> The assays used in that study were less sensitive than contemporary assays. In another study involving patients who presented with chest

pain but who had normal ECGs, coronary artery disease was found in 90% of those with an elevated troponin level and in 23% of those with a normal troponin level ( $p < 0.001$ ).<sup>98</sup> Had the 99th percentile been used instead of the much higher ROC cut-off value for the troponin levels, even more patients with coronary artery disease would likely have been identified.

When using low cut-off values for patients with a low pretest probability of disease, it is important to understand that analytical false-positive results may occur owing to imprecision of the assays at low levels.<sup>46</sup>

## Troponin and the detection of myocardial reinfarction

Reinfarction is difficult to detect with any biomarker while values are rising or falling. Troponin is no different. However, a recent study<sup>99</sup> compared the patterns of increases in cTnI and CK-MB levels in 3 patients with acute myocardial infarction who had a reinfarction in hospital. In each case, substantial re-elevations in cTnI levels occurred (Fig. 3). These findings are similar to previous data,<sup>100,101</sup> which suggests that changes in troponin levels are adequate to diagnose reinfarction and that CK-MB measurement is not needed in this situation.

## Troponin and infarct size

Infarct size can be estimated from the troponin value measured at 72 hours. The data are stronger for this approach with cTnT than with cTnI,<sup>102,103</sup> which suggest that the cTnT level measured at 72 hours is a good estimate of scintigraphic infarct size whether patients were reperfused or not.<sup>103</sup> For cTnI, peak levels work better,<sup>28,104</sup> but the data vary depending on whether or not there has been acute reperfusion.<sup>104</sup> The estimates of infarct size are superior to those provided by CK or CK-MB.

## Troponin after percutaneous coronary interventions

After percutaneous coronary interventions (PCIs), increases in troponin levels above the 99th percentile are indicative of cardiac cell injury and thus fulfill the definition of acute myocardial infarction.<sup>47,48</sup> This may be a situation in which diagnosis and prognosis are different. Thus, the ESC/ACC group recommended that these cases of acute myocardial infarction be considered separately from spontaneous infarctions, that they be reported separately in clinical trials and that they have different reimbursement codes.<sup>47,48</sup>

The mechanisms by which PCIs cause cardiac damage are poorly defined despite the adverse consequences.<sup>105,106</sup> Thus, whether minor troponin elevations have similar prognostic influence is unclear. It may depend on the cause of the elevation. Some degree of cardiac injury may be necessary to accomplish an adequate procedure, and in that situation a minor amount of cardiac injury may not be adverse.<sup>107,108</sup> In other cases, elevated troponin levels may reflect more severe or diffuse disease.

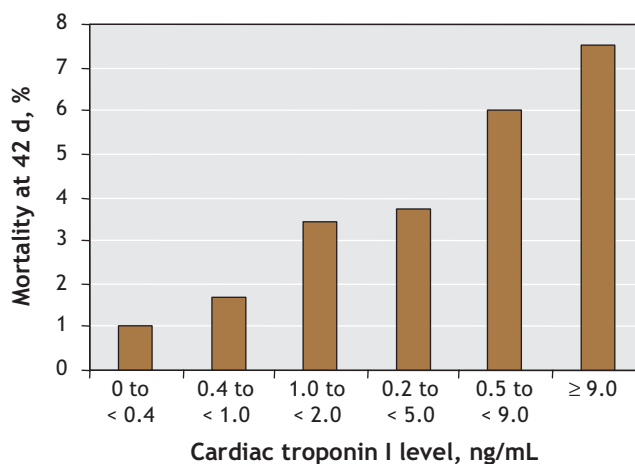
Several considerations are important in regard to elevated troponin levels after PCI.

- Patients with acute coronary syndromes may have elevated troponin levels at baseline that increase owing to the continuing release of troponin rather than the release after PCI-related cardiac injury. It is known that elevated levels at baseline have prognostic importance.<sup>77,79</sup> Some have suggested that increases of more than 25% should be considered due to the procedure,<sup>58</sup> but such increases could still be part of the initial insult with rising troponin values. This may be a group of patients in which post-PCI infarction cannot be diagnosed in the absence of clear-cut complications. A baseline troponin level is essential for the proper interpretation of post-PCI elevations.<sup>109,110</sup>
- Troponin measurement every 6–8 hours for 24 hours is ideal.<sup>111</sup>
- Only one troponin assay should be used given the heterogeneity of assays. This is particularly important for multi-centre trials.
- Values above the 99th percentile should be used to define elevations.
- Long-term follow-up (2–3 years) may well be helpful to define the prognostic effects of elevations.<sup>112</sup>

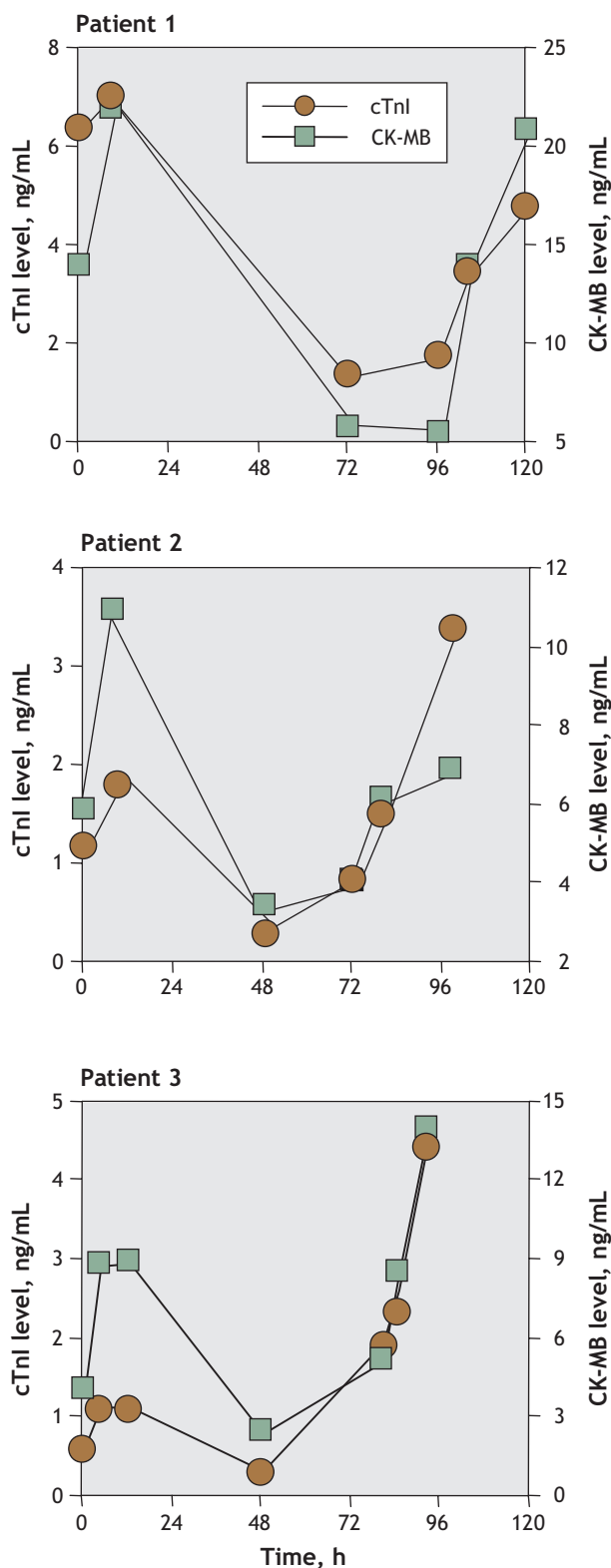
None of the studies present in the literature has dealt with all of these issues. The same criteria should be used to investigate the relation between specific therapies (e.g., statins<sup>113</sup>) and the prevention of myocardial damage after PCI.

## Troponin after cardiac surgery

Factors related to cardiac surgery that contribute to myocardial damage include the duration of cross clamping and cardiopulmonary bypass; potential occlusion of a graft; the nature, temperature and adequacy of the cardioplegia; the use of cardiopulmonary bypass itself (owing to activation of



**Fig. 2:** Mortality rates according to level of cardiac troponin I at baseline. Reprinted, with permission, from Antman EM, Tanasijevic MJ, Thompson B, 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. Copyright © 1996 Massachusetts Medical Society. All rights reserved.



**Fig. 3:** Cardiac troponin I and CK-MB levels in patients with acute myocardial infarction who experienced a reinfarction in hospital. Reprinted, with permission, from Apple FS, Murakami MM. Cardiac troponin and creatine kinase MB monitoring during in-hospital myocardial reinfarction. *Clin Chem* 2005;51(2):460-3.

platelets, complement and cytokines); direct trauma to the heart; coronary artery or venous graft embolism; and other complications of the procedure.<sup>114</sup>

Some damage is unavoidable. The relevant clinical issue is to define whether the degree of myocardial damage is “clinically significant.”<sup>114</sup> Biomarkers cannot determine the mechanism of injury.<sup>57</sup> However, irrespective of the mechanism, the higher the value after surgery, the greater the damage<sup>115,116</sup> and the worse the prognosis.<sup>117,118</sup> Some have suggested that late-peaking elevations are indicative of graft occlusion,<sup>119</sup> but proof of this concept is unavailable. Eventually, the ability to monitor cardiac biomarkers should be a useful way to improve strategies for myocardial protection<sup>120,121</sup> and surgical approaches.<sup>122,123</sup>

### Troponin and renal failure

Troponin is the biomarker of choice for detecting cardiac injury in patients with renal failure, including those with end-stage renal disease (ESRD) receiving long-term dialysis.<sup>124,125</sup> Among 7033 patients with suspected coronary syndromes enrolled in the Global Use of Strategies to Open Occluded Coronary Arteries IV (GUSTO-IV) trial for whom complete baseline data on cTnT levels and creatinine clearance rates were available, elevated TnT levels were found to predict short-term prognosis regardless of creatinine clearance.<sup>126</sup> This correlation is probably also true for cTnI.

However, the concept that increases could be “artificial”<sup>109,110</sup> remains, because asymptomatic ESRD patients are more apt to have elevated levels of cTnT than of cTnI despite the fact that the newer cTnT assays do not detect cross-reacting isoforms from skeletal muscle.<sup>15,21</sup> Numerous studies have confirmed the importance of cardiovascular diseases in ESRD patients.<sup>127,128</sup> Atherosclerotic risk factors such as diabetes,<sup>129,130</sup> hypercholesterolemia,<sup>131,132</sup> left ventricular hypertrophy<sup>133,134</sup> and severe coronary artery calcification<sup>135</sup> are associated with increases in cTnT levels in hemodialysis patients, which supports the concept that elevations are secondary to myocardial injury.<sup>136,137</sup> In a study by Ooi and colleagues,<sup>138</sup> minor elevations in troponin levels were invariably associated with pathological evidence of myocardial damage in patients with and without renal failure. Furthermore, prognostic studies have confirmed that such elevations are indicators of future cardiac events. Apple and colleagues<sup>139</sup> evaluated survival among 773 ESRD patients. Those with elevated cTnT levels (defined by the 99th percentile cut-off value) had an increased risk of death after 1, 2 and 3 years of follow-up. Increases in cTnT and cTnI levels in ESRD patients showed a 2- to 5-fold increase in mortality, with greater numbers of patients having an increased cTnT. These data have been confirmed in subsequent studies. Some have suggested that C-reactive protein elevations augment the prognostic significance of troponin elevations in this setting.<sup>140,141</sup>

Most studies have shown that only minor changes in troponin levels occur with dialysis. There are differences between cTnI and cTnI concentrations before and after dialysis: cTnI decreases or does not change, whereas cTnT concentrations increase after dialysis, albeit minimally. CK-MB can also

be elevated in these patients in the absence of cardiac disease and its measurement is not helpful in these patients.<sup>109</sup>

The critical clinical question is how to distinguish between troponin elevations that are due to acute coronary syndromes and those that are due to more chronic conditions. One way is to obtain a baseline value for comparison. The FDA has approved cTnT measurement for risk stratification and for this purpose. One can also use changing values to define acute episodes. If there are dynamic changes, acute disease is likely present. In the absence of a changing pattern, one may need to address the more chronic problem rather than treat emergently.

There is no definitive information about the diagnostic etiologies or the therapeutic and preventive strategies appropriate for dialysis patients with elevated troponin levels.<sup>142</sup> These elevations could reflect silent myocardial necrosis,<sup>127</sup> especially in patients with a history of ischemic heart disease;<sup>132,136</sup> left ventricular hypertrophy associated with perfusion defects or abnormal coronary vasomotion;<sup>136,143</sup> left ventricular systolic dysfunction;<sup>134</sup> increased cardiac preload with myocardial stretch;<sup>129,144</sup> microvascular disease, especially in diabetic patients;<sup>127,129</sup> endothelial dysfunction secondary to oxidative stress and inflammation;<sup>145,146</sup> episodes of hypotension during dialysis;<sup>147</sup> or cardiac injury secondary to calcium and oxalate deposition.<sup>148</sup> Troponin elevations are unlikely owing to delayed clearance of troponin despite recent claims.<sup>149</sup>

## Other clinical situations in which troponin levels may be elevated

The increased sensitivity and specificity of troponin assays now make it clear how often some degree of cardiac damage occurs. In critically ill patients, such elevations have profound prognostic importance.<sup>150,151</sup> Elevations can be due to occult coronary artery or toxic substances such as tumour necrosis factor and heat-shock protein, as occurs in sepsis.<sup>93</sup> Elevations can also be due to either acute or more chronic processes (Box 3).

Direct damage could be secondary to physical energy of different types: mechanical (i.e., contusion, as in cardiac trauma or cardiac surgery) or electrical (e.g., cardioversion, ablation or implantable cardioverter defibrillator [ICD] firings).

- **Cardiac trauma:** Blunt cardiac trauma ("cardiac contusion") includes a broad spectrum of nonpenetrating trauma to the chest. CK-MB elevations are common and can come from injury to skeletal muscle. Troponin elevations are highly specific and usually indicate cardiac trauma.<sup>45,152</sup> Elevations are usually modest; more extreme elevations may be due to concomitant coronary artery disease or coronary trauma. It is unclear whether troponin elevations can be used to predict complications or guide therapy.<sup>153,154</sup>
- **Cardioversion, ablation and cardiac arrest:** Elective electrical cardioversion in most patients does not result in troponin elevations.<sup>155,156</sup> When present, elevations are mild.<sup>157,158</sup> Elevations are more common in patients with cardiac arrest who have undergone direct-current shock (often multiple) or prolonged resuscitation, or both.<sup>159,160</sup>

### Box 3: Conditions in which troponin levels may be elevated without overt ischemic heart disease

- Trauma (e.g., contusion, ablation, pacing, ICD firings, cardioversion, endomyocardial biopsy, cardiac surgery)
- Congestive heart failure, acute and chronic
- Aortic valve disease and hypertrophic obstructive cardiomyopathy with significant left ventricular hypertrophy
- Hypertension
- Hypotension, often with arrhythmias
- Noncardiac surgery without complications
- Renal failure
- Severe asthma
- Critical illness, especially diabetes, respiratory failure, hemolytic uremic syndrome
- Drug toxicity (e.g., adriamycin, 5-fluorouracil, herceptin, snake venoms)
- Hypothyroidism
- Coronary vasospasm, including apical ballooning syndrome
- Inflammatory disease (e.g., myocarditis, parvovirus B19 infection, Kawasaki disease, myocardial extension of bacterial endocarditis)
- Percutaneous coronary intervention without complications
- Pulmonary embolism, severe pulmonary hypertension
- Sepsis
- Burns, especially if total body surface area affected is > 30%
- Infiltrative diseases, including amyloidosis, hemochromatosis, sarcoidosis and scleroderma
- Acute neurologic diseases, including cerebrovascular accident and subarachnoid bleed
- Rhabdomyolysis with cardiac injury
- Transplant-related vasculopathy
- Vital exhaustion

Note: ICD = implantable cardioverter defibrillator.

Substantial elevations should suggest the presence of myocardial injury from causes (ischemic or not ischemic) unrelated to resuscitation.<sup>157</sup> Elevations after ablations are related to the amount of energy used but are usually modest.<sup>161,162</sup> This is also the case for ICD firings and endomyocardial biopsies.

There also could be a variety of toxic insults that may exacerbate underlying ischemic heart disease or could function to damage the heart directly.

- **Sepsis:** Troponin elevations in patients with sepsis are common.<sup>163,164</sup> The mechanism in any given patient is unclear. Elevations could be due to underlying coronary artery disease, hypotension, septic microemboli, high doses of vasoactive drugs, or the effects of cytokines such as heat-shock protein and tumour necrosis factor- $\alpha$ .<sup>165</sup> Clinically, elevations occur more frequently in patients with more severe left ventricular systolic dysfunction<sup>163,164</sup> and higher

critical illness scores.<sup>164,166</sup> Most studies found a relation between increased troponin levels and mortality.<sup>167,168</sup>

- **Chemotherapy:** Cardiotoxicity is a common complication of high-dose chemotherapy. Troponin elevations, soon after chemotherapy and in the short-term follow-up period, are associated with left ventricular dysfunction and cardiac events.<sup>169</sup>
- **Other toxins:** Snake venom and other agents (e.g., catecholamines) either ingested, infused or released systemically can cause troponin elevations.
- **Cardiac rhabdomyolysis:** Increases in troponin levels can identify cardiac involvement with rhabdomyolysis.<sup>170</sup> Such elevations are associated with an adverse prognosis.<sup>171</sup> Damage could be secondary to inflammation (i.e., myocarditis or acute rejection) or an infiltrative process that involves the myocardium (i.e., pericarditis).
- **Myocarditis:** Lymphocytic infiltration of the heart, be it focal or diffuse, can easily explain troponin elevations.<sup>172</sup> Acutely, myocarditis can mimic acute myocardial infarction. Chronically, elevations are time-dependent<sup>173,174</sup> and generally occur early after the onset of symptoms. Myocarditis might also be the reason for troponin elevations after vaccination in some patients, and after systemic inflammatory illnesses such as Kawasaki disease.
- **Pericarditis:** In acute pericarditis, troponin elevations are common, especially when ST-segment elevation is present.<sup>175,176</sup> Troponin release probably represents inflammatory involvement of the epicardium.<sup>176</sup>
- **Amyloidosis:** Troponin elevations occur often in patients with amyloid infiltration of the myocardium<sup>177</sup> and likely in patients with other infiltrative myopathies as well. The extent of cardiac involvement in patients with primary systemic amyloidosis is the most important predictor of clinical outcome.<sup>178</sup> Troponin can be measured along with NT-proBNP (N-terminal pro-brain natriuretic peptide) and other clinical variables for risk stratification.<sup>179,180</sup>

Cardiac damage can be ischemic but not be due to overt epicardial coronary artery disease. For example, with left or right ventricular hypertrophy, there is often increased wall stress and a relative imbalance between oxygen supply and demand. This could be the cause of troponin elevations in patients with and without concomitant coronary artery disease who have hypertrophic obstructive cardiomyopathy, aortic stenosis, acute pulmonary embolism, chronic pulmonary hypertension and congestive heart failure. In addition, acute myocardial stretch from increased cardiac preload can result in proteolysis of troponin and cause its release.<sup>181</sup> This likely is part of the mechanism for troponin elevations in patients with renal disease and those with acute congestive heart failure and perhaps pulmonary embolism.

- **Pulmonary embolism:** Acute right ventricular strain secondary to increases in pulmonary arterial resistance is the cause of troponin elevations in pulmonary embolism.<sup>182</sup> Elevations usually resolve in 40 hours or less. Pulmonary embolism can cause right ventricular infarction.<sup>183,184</sup> Hypotension, hypertension and tachycardia could contribute with or without concomitant coronary artery disease. Troponin elevations are more likely to occur in patients with

shock<sup>185,186</sup> and clinical variables<sup>187,188</sup> associated with poor outcome. One might be able to measure troponin levels to determine which patients need more aggressive therapy.<sup>187,189</sup> Troponin elevations in pulmonary hypertension, likely due to a pathophysiology similar to that in pulmonary embolism, also have prognostic importance.<sup>190</sup>

- **Heart failure:** Elevations in cTnI and cTnT levels occur in patients with heart failure, in both the acute decompensated<sup>191,192</sup> phase and the stable phase.<sup>193,194</sup> Elevations are not solely due to coronary artery disease; patients with cardiomyopathy have elevations as well. These elevations have strong prognostic importance.
- **Subendocardial ischemia:** There is an association between increased troponin levels and left ventricular hypertrophy.<sup>195</sup> It is known that the subendocardium can have impaired perfusion due to increased wall stress, concomitant endothelial dysfunction and, often, increased myocardial oxygen demand. This is the mechanism for ischemia in patients with aortic stenosis, hypertrophic obstructive cardiomyopathy, and probably severe hypotension or hypertension with left ventricular hypertrophy. Catecholamines, which are released with stress and neurological insults, may also cause cardiac injury in this manner.
- **Endothelial dysfunction:** Recent data are clear that ischemia can be induced by endothelial abnormalities.<sup>196</sup> These can lead to cardiac injury and troponin release.

## Key points for clinical practice

- Cardiac isoforms of troponin are specific for the heart.
- Elevated troponin levels indicate cardiac injury but do not define the mechanism.
- In patients with acute coronary ischemia and elevated troponin levels, myocardial infarction should be diagnosed; treatment should be guided by the elevated troponin levels.
- In patients who do not have acute coronary ischemia, rule out other causes of troponin elevation.
- Patients with renal failure and elevated troponin levels should be evaluated initially for acute coronary syndromes. In the absence of an acute cause of the elevation, emergent treatment may not be required. If no urgent care is needed, subsequent troponin measurement is still indicated, since troponin elevations have prognostic importance.
- Know the 99th percentile of the troponin assay used.
- Elevated troponin levels imply an adverse prognosis. In some patients (e.g., those with acute coronary syndromes) troponin elevations may be short term and long term, and in other patients (e.g., dialysis patients and those having undergone vascular surgery) they may only be long term.
- Suspect a laboratory problem if the troponin values do not change or do not match the patient's presentation. Good laboratories can help to determine whether there are analytical issues confounding the results. The first approach is to repeat the assay after additional centrifugation to be sure to eliminate fibrin interference. Kits are available to correct for the presence of heterophilic and cross-reacting antibodies.<sup>197</sup>



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From the Cardiovascular Division and Division of Laboratory Medicine, Mayo Clinic and Mayo Clinic Graduate Medical School, Rochester, Minn.

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**Correspondence to:** Dr. Allan S. Jaffe, Cardiovascular Division, Gonda 5, Mayo Clinic, 200 First St. SW, Rochester MN 55905, USA; jaffe.allan@mayo.edu

## Canadian Medical Association



## Association médicale canadienne

### 2006 Special Awards – Call for Nominations

The Canadian Medical Association invites nominations for the 2006 special awards.

- Medal of Honour
- F.N.G. Starr Award
- Medal of Service
- May Cohen Award for Women Mentors
- Sir Charles Tupper Award for Political Action
- Award for Excellence in Health Promotion
- CMA Award for Young Leaders

Refer to the "Awards from CMA" section on [cma.ca](http://cma.ca) for detailed criteria on each of the awards or contact the awards co-ordinator at 800 663-7336 x2280.

Nominations should be submitted to:

**Chair, Committee on Archives and Awards  
c/o Committee Co-ordinator  
Strategic and Corporate Affairs  
Canadian Medical Association  
1867 Alta Vista Dr.  
Ottawa ON K1G 3Y6**

Closing date for receipt of nominations is Nov. 30, 2005.

### Prix spéciaux pour l'an 2006 – Appel de candidatures

L'Association médicale canadienne sollicite des candidatures à ses prix spéciaux pour l'an 2006.

- Médaille d'honneur
- Prix F.N.G. Starr
- Médaille de service
- Prix May-Cohen pour femmes mentors
- Prix Sir-Charles-Tupper d'action politique
- Prix d'excellence de l'AMC en promotion de la santé
- Prix des jeunes chefs de file de l'AMC

Voir «Prix et distinctions de l'AMC» sur le site [amc.ca](http://amc.ca) pour les critères détaillés de chaque prix ou contacter la coordonnatrice des prix au 800 663-7336, poste 2280.

Les candidatures doivent être soumises au :

**Présidente, Comité des archives et des distinctions  
a/s Coordonnatrice des comités  
Affaires générale et Stratégiques  
Association médicale canadienne  
1867, promenade Alta Vista  
Ottawa (Ontario) K1G 3Y6**

Les candidatures doivent être présentées au plus tard le 30 novembre 2005.