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CARDIOLOGY Rounds™

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Serum troponin in the risk stratification of acute coronary syndromes

BY DAVID FITCHETT, MD

The risk stratification of patients with chest pain and no ECG evidence of ST-segment elevation allows triage of patients to the most appropriate level of care. Elevated serum cardiac troponin T or I identifies patients with a three- to five-fold increase in the risk of adverse outcome, and it has a predictive value independent of clinical or electrocardiographic data. Cardiac troponin level, when combined with clinical observations and other investigations, has a promising role in identifying both low-risk patients who could be managed by conventional medical treatment and high-risk patients who might benefit from new and expensive medical treatment and/or revascularization.

The acute coronary syndromes of myocardial infarction and unstable angina are within a continuum, separated only by enzymatic evidence of acute myocardial infarction. Both conditions usually result from atherosclerotic plaque rupture and consequent coronary thrombosis that transiently or permanently occludes the vessel. A small proportion of patients with unstable angina has a minor increase of creatine phosphokinase (CK) to levels insufficiently elevated for diagnosis of myocardial infarction; they are more likely to have adverse outcomes than patients with no CK increase.[1,2] Detectable serum troponin in patients with chest pain and no ST elevation has recently been shown to be more consistently associated with cardiovascular complications than is a small increase in CK.[3] Comparison of troponin T, CK MB fraction, and myoglobin has also shown that troponin T is the only marker to predict future events.[15]

Cardiac troponin I and T are isoforms of a cardiac myofibrillar regulatory protein and are structurally and immunologically distinct from skeletal muscle troponins. Unlike CK, neither cardiac troponin T nor cardiac troponin I are normally detectable in human serum, and the "normal" reference levels are close to the minimum sensitivity of the assays. As a consequence, cardiac troponin as a marker of minor myocardial damage is more sensitive and specific than CK.

Although circulating troponin T and I have short half-lives, their dissociation from damaged myofibrils is slow. Troponins can therefore be found for more than 10 days after an event in the serum of patients with both myocardial infarction and severe myocardial ischemia. This is four times longer than for CK.

Mechanism of release in unstable angina

Circulating markers of myocardial cell injury can be present in patients with unstable angina due to ischemia-induced loss of integrity of the cell membrane and release of a small pool of cytosolic troponin,[5,6] and small areas of myocardial infarction not detectable by other techniques. In patients with unstable angina, microscopic infarction occurs due to small arterial occlusions from platelet emboli.[7]

Patients with unstable angina and non-Q-wave infarction are indistinguishable both clinically and electrocardiographically, and they belong within the spectrum of patients with acute coronary syn-

St. Michael's Hospital
30 Bond St., Suite 701A
Toronto, Ont. M5B 1W8
Fax: (416) 864-5330

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ST. MICHAEL'S HOSPITAL

UNIVERSITY OF TORONTO

dromes. Patients with unstable angina, detectable troponin levels, and no detectable CK might be considered to have had a mini non-Q-wave acute myocardial infarction (AMI) and thus to have a better prognosis than patients with a presumably larger non-Q-wave AMI. However, one study suggests that such patients have adverse outcomes similar to those of patients with non-Q-wave AMI and elevated CK.[8] It is probable that the presence of cardiac troponin in the serum of high-risk unstable angina patients is both a reflection of the severity of the episode of myocardial ischemia and an indication that the culprit coronary lesion is particularly active, with a high risk of reocclusion. Juralander et al[9] showed a good correlation between the presence of troponin T and the angiographic appearance of complex coronary artery stenosis morphology (i.e., ulceration, thrombus, plaque disruption) which, in itself, is predictive of an adverse outcome.

Cardiac troponin as a marker of adverse outcome

Studies summarized in Table 1 indicate that the detection of serum cardiac troponin T or I in patients with unstable angina is associated with a more than five-fold increase of death and/or myocardial infarction.[10–23] Although the majority of studies had follow-up periods of 21-42 days, others had observation times that varied from the time of discharge from hospital to 28 months. In all studies, 30%65% of patients had detectable serum troponin, that is, above the threshold level. For the studies with endpoints between discharge from hospital and 42 days,[10,12,15,18–20] the mortality rate for the patients with detectable troponin was 10.5%68.9%; for the group with sub-threshold troponin it was 1.6%61.7% ($p<0.04$, relative risk 6.6). In the same studies, the incidence of subsequent myocardial infarction in the troponin-positive group was 26.5%63.3%; for troponin-negative patients it was 3.3%62.0% ($p<0.02$, relative risk 8.0).

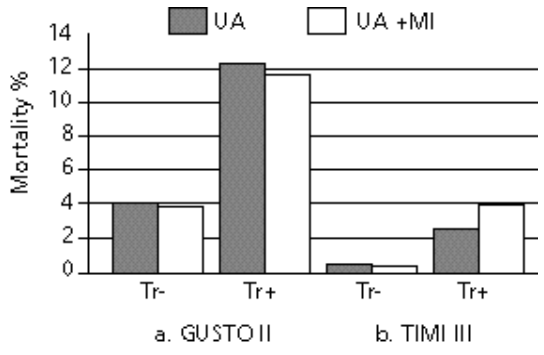
Three major studies (FRISC, GUSTO IIa, and TIMI IIIB.) of acute coronary syndromes have used sub-studies to examine the value of cardiac troponin as a predictor of adverse outcome.[15–17] Despite the high incidence of non-Q-wave AMI in the three studies (TIMI IIIB. 32%, FRISC 39%, and GUSTO IIa 72%), cardiac troponin T or troponin I, in TIMI IIIB. was predictive of mortality in the next 30-45 days in patients presenting with chest pain and no ST elevation, regardless of whether the frequency of non-Q-wave infarction was 30% or

Table 1: Cardiac troponin as a prognostic indicator in acute coronary syndromes

Study	No	Trop T or I	% Tp+	Follow–up	Death % Tp+/-	Death/MI or intervention % Tp+/-
Hamm et al 1992[10]	109	T	39	21 d	5/1	n/a
Ravkilde et al[11] 1995	124	T	20	28 mo	n/a	24/5.1
Wu et al 1995[12]	486	T	26	21 d	0/0	63/37
De Winter et al[13] 1996	128	T	23	6 mo	n/a	33/15
Stubbs et al[14] 1996	460	T	34	3 years	19/12	29/17
Antman et al[15] 1996	1404	I	41	42 d	3.7/1.0	n/a
Lindahl et al[16] 1996	976	T	77	5 mo	2.6/0	11.4/4.4
Ohman et al[17] 1996	855	T	36	30 d	12/4	n/a
Galvani et al[18] 1997	106	I	24	30 d	9./0	27.3/5.8
Cin et al 1996[19] (abstract)	72	T	34	hosp dc	25/4	n/a
Goldman et al[20] 1996 (abstract)	236	T	20	1 mo	19/1	15/6
Luscher et al[21] 1996 (abstract)	516	T/I	46	30 d	n/a	11.6/4.0
Ottari et al[22] 1996 (abstract)	74	T/I	24	30 d	n/a	17.5/8.5
Murphy et al[23] 1996 (abstract)	325	T	21	3 mo	12/3	51/11

n/a=not available, T=troponin-T, I=troponin-I, d=days, mo=months, Tp=troponin, hosp dc=hospital discharge, %Tp+=percentage of patients with increased troponin, MI=acute myocardial infarction (defined by recurrent chest pain and associated CK elevation.)

Figure 1: 30/42 day mortality in GUST0 IIa[17] and TIMI IIIB Trials[15] characterized by the presence (Tr+) or absence (Tr-) of troponin in patients with unstable angina (UA) and all patients entered into the trial (UA + MI)



70% (Figure 1). In addition, the GUSTO IIa study[17] demonstrated that troponin T detectable on admission in patients with ST elevation and Q-wave myocardial infarction was also predictive of an adverse outcome. Further analysis of these studies shows that troponin is probably a useful indicator for selecting patients who might benefit from the use of low-molecular-weight heparin[24] and the application of an early invasive strategy of coronary angiography and revascularization.

Independent and incremental prognostic value

Does an elevated serum cardiac troponin-T or -I level provide prognostic information beyond that of clinical information or findings on the baseline 12-lead ECG? The presence of elevated serum cardiac troponin, together with age, hypertension, number of antianginal drugs used, and ECG change at rest are independent predictors of outcome.[16] Patients with cardiac troponin T levels of <0.06 µg/L had a risk of death or myocardial infarction of 4.4% in comparison to 11.4% in those with troponin T at 0.06–0.18 µg/L and 14% in those with troponin T>0.18 µg/L.[16] For patients with a troponin T level <0.06 and no ECG ST/T-wave abnormalities, the risk was 3% compared to an 18% risk in patients with troponin >0.18 and ST/T-wave abnormalities.

A substudy of the GUSTO IIa trial[17] examined the relative values of the ECG and serum markers to predict 30-day mortality. The troponin T level, followed by the ECG, not only was the strongest predictor of mortality but also added prognostic information to that provided by the ECG.

In the TIMI IIIB study,[15] the predictive value of elevated troponin I persisted after adjustment for baseline variables associated with an increased risk of cardiac events, such as age and ECG-verified ST depression. The same study showed that the risk of death increased by 10% for every 1 ng of troponin I increase. For patients with a minimal elevation of troponin I (1.0–2.0 ng/ml), the risk of MI/death or need for revascularization is increased five-fold compared to patients with troponin I <1.0 ng/ml.[15]

Although a quantitative measure of serum troponin provides prognostic information, the detection of troponin above a predetermined threshold identifies patients at risk of adverse outcome. Point-of-care testing provides a rapid semiquantitative detection of serum troponin, allowing immediate triage of the patient. Later quantitative measure of troponin levels might provide additional prognostic information.

Timing of troponin determination

Most studies evaluated the prognostic value of the maximal troponin level from samples taken during the first 24 hours after admission. Serial sampling shows that by 12 hours from the onset of pain, 95% of troponin-positive patients will have an abnormal troponin level.[13]

The GUSTO IIa study[17] used one sample taken within two hours of admission, at a median time of 3.5 hours from the onset of symptoms, and it showed the troponin T level to be predictive of 30-day mortality above and in addition to the electrocardiographic findings. Furthermore, the predictive value of the earliest troponin sample was shown to be greater than that of troponin measurements taken at 8 and 16 hours after admission.

Elevated troponin I at the time of the patient's presentation in the emergency room was shown to be an indicator of increased mortality at 42 days, with a predictive value independent of high-risk clinical markers such as ST-segment depression and the age of the patient.[15] However, if the time from onset of chest pain to presention to the emergency department was under 8 hours, the presence or absence of serum troponin had no prognostic value. It is therefore suggested that blood samples be taken for troponin assay early after the patient's arrival in hospital and at a minimum of 6–8 hours from the onset of pain.

Troponin T or I?

The majority of studies assessing cardiac troponin as a prognostic indicator have used cardiac troponin T.[10–13,16,17,19,20,23] The TIMI IIIB study[15] found troponin I to be independently predictive of outcome, with a four-fold increase in 42-day mortality when troponin I was detectable in serum from a single sample taken at the time of the patient's enrollment into the study. Troponin T, CK mass, and CK isoforms might be

increased in the serum of patients with renal failure but no cardiac disease,[25] yet in the same patients troponin I remains in the normal range.

Direct comparison of troponin T and I in patients with unstable angina showed that the T and I subunits are elevated in the same proportion of patients (24%), yet only 10 of the 18 patients who were positive for either troponin I or T had both subunits detected.[26] A later study showed that 92% of patients had concordance between troponin T and I values.[27] Bedside testing of troponin-I, rather than troponin T, appears to be more sensitive in detecting early and minor myocardial injury, yet both tests gave similar positive and negative predictive values for any major cardiac event.[28] Thus it appears that both troponin T and I have similar diagnostic and prognostic value in patients with acute coronary syndromes.

Troponin and ER triage

The emergency department triage of patients with chest pain and no ST elevation, suggestive of Q-wave myocardial infarction, aims to recognize patients with high-risk unstable angina or non-Q-wave myocardial infarction who will benefit from intensive-care monitoring and potentially hazardous and expensive medical treatment/revascularization. Triage also should identify patients at lower risk of an adverse outcome who are unlikely to benefit from aggressive intensive-care-based management and can be discharged after a short period of observation.

De Winter et al[29] evaluated the use of myoglobin, troponin T, and CK MB mass to rule out the diagnosis of acute myocardial infarction in patients presenting to the emergency room with chest pain. Their gold standard for the diagnosis of AMI was the combination of history, electrocardiographic findings, and a typical curve for CK MB activity. The study showed that measuring CK MB mass had the highest sensitivity and specificity for rapidly ruling out myocardial infarction. Troponin T produced similarly high diagnostic success, but two to three hours later. A prospective study of the value of troponin I and T for the emergency room triage of patients with chest pain[28] showed that troponin I and T had 99% negative predictive values for any major cardiac event.

Clinician judgment can correctly identify 90% of patients presenting to the emergency department with chest pain who are at high risk of an adverse outcome.[30] Of the 10% of study patients not identified, half had positive troponin T levels and the other half had an increase in CK MB isoforms. Total CK MB was negative in all the 10% who were missed by clinical judgment. Thus clinical judgment is more sensitive than any biochemical marker in identifying high-risk patients, but biochemical markers enhance clinical judgment. When combined, clinical judgment and biochemical markers can identify correctly almost 100% of patients with chest pain at risk of an adverse outcome.

Conclusion

Serum cardiac troponin levels are useful indicators and predictors in several situations:

- In patients with unstable angina or non-Q-wave myocardial infarction, increased serum cardiac troponin T or I identifies those at high risk of an adverse outcome.
- Troponin T and I have equivalent diagnostic and predictive values.
- An elevated cardiac troponin level adds prognostic information to clinical and ECG findings, and it might indicate patients who could benefit from more aggressive medical and interventional treatment. The risk of an adverse outcome is directly related to the serum troponin I level.
- A single measurement of troponin taken early after admission, but at least 6–8 hours after the onset of pain, provides important prognostic information.
- The prognosis of a patient with unstable angina and positive troponin I might be similar to that of a patient with non-Q-wave infarction.
- Although troponin levels appear to be an ideal yardstick for optimizing emergency-department triage of patients with chest pain, there has been no prospective triage study that utilizes troponin and assesses its relative value. The upcoming study PACTS (Prognostic Accuracy of Cardiac Troponin Studies and Holter ST Monitoring) will provide some answers to these questions.

References

1. Armstrong PW, Chiong MA, Parker JO. The spectrum of unstable angina: prognostic role of serum creatinine kinase determination. *Am J Cardiol* 1982;49:1849–1853.
2. Murphy JJ, Connell PA, Hampton JR. Predictors of risk in patients with unstable angina admitted to a district general hospital. *Br Heart J* 1992;67:395–401.
3. Ravkilde J, Nissen H, Horder M, Thygessen K. Independent prognostic value of serum creatinine kinase iso-enzyme MB mass, cardiac troponin and myosin levels in suspected acute myocardial infarction. Analysis of 28 months follow up in 196 patients. *J Am Coll Cardiol* 1995;25:574–581.
4. Katus HA, Remppis A, Neumann FJ, et al. Diagnostic efficiency of troponin T measurements in acute myocardial infarction. *Circulation* 1991;83:902–912.
5. Feng YJ, Wu A, Ma L Lai T, Waters D Chen C. Serum troponin I is more sensitive for the detection of acute ischemic myocardial injury than serum myoglobin or CK MB. *J Am Col Cardiol* 1997.
6. Katus HA, Schoeppenthau M, Tanzeem A, et al. Intracellular compartmentation of cardiac troponin T and release kinetics in patients with reperfused and non-reperfused myocardial infarction. *Am J Cardiol* 1991;67:1360–1367.
7. Dominitz I, Boruchow IB, Hutchins G. Focal myocardial ischemic necroses associated with unstable angina pectoris. *J Am Col Cardiol* 1996;28:910–914.
8. Ravkilde J, Horder M, Gerhardt W, et al. Diagnostic and prognostic value of serum troponin T in suspected acute myocardial infarction. *J Clin Inv Scan* 1993;53:677–685.
9. Juralander B, Moliani MA, Balu. Serum troponin levels predict coronary findings in patients with unstable angina. *Circulation* 1995;92(8):I–679.
10. Hamm CW, Ravkilde J, Gerhardt W, et al. The Prognostic value of serum troponin T in unstable angina. *New Engl J Med* 1992;327:146–50.
11. Ravkilde J, Nissen H, Horder M, Thygsen K. Independent prognostic value of serum creatine kinase isoenzyme MB mass, cardiac troponin T and myosin light chain levels in suspected acute myocardial infarction. *J Am Col Cardiol* 1995;25:574–581.
12. Wu AHB, Abbas SA, Green, et al. Prognostic value of cardiac troponin T in unstable angina pectoris *Am J Cardiol* 1995;76: 970–972.
13. deWinter RJ, Koster RW, Schotveld JH, et al. Prognostic value of troponin T, myoglobin, and CK-mass in patients presenting with chest pain without myocardial infarction. *Heart* 1996;75:235–239.
14. Stubbs P, Collinson P, Mosely D, Greenwood T, Noble M. Prospective study of the role of cardiac Troponin T in patients admitted with unstable angina. *Brit Med J* 1996;313:262–264 .
15. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac specific troponin levels to predict the risk of mortality in patients with acute coronary syndromes. *New Engl J Med* 1996;335: 1342–1349.
16. Lindahl B, Venge P, Wallentin L, and the FRISC Study Group. Relation between troponin T and the risk of subsequent cardiac events in unstable coronary disease. *Circulation* 1996;93:1651–1657.
17. Ohman EM, Armstrong PW, Christenson RH, et al for the GUSTO IIa investigators. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. *New Engl J Med* 1996;335:1333–1341.
18. Galvani M, Ottani F, Ferrini D, et al. Prognostic influence of elevated values of cardiac troponin I in patients with unstable angina. *Circulation* 1997;95:2053–2059.
19. Cin VG, Gok H, Korkut B, et al. The prognostic value of serum troponin T in patients with unstable angina. *Eur J Cardiol* 1996;17(Abstr Supp:577).
20. Goldman BU, Hamm CW, Schneider JC, et al. The value of bedside troponin T testing in the emergency room for risk stratification in patients with chest pain after discharge from hospital. *J Am Coll Cardiol* 1996;27:359A.
21. Luscher M, Ravkilde J, Thygessen K, et al. Troponin T and Troponin I in detection of myocardial damage and subsequent cardiac events in 516 consecutive chest pain patients. A sub-study in the TRIM study. *Eur Heart J* 1996;17(Abstr Supp:31).
22. Ottari F, Galvani M, Ladenson J, et al. Direct comparison between elevations of cardiac troponin I and T in unstable angina pectoris. *Circulation* 1996;94(8):I–133.
23. Murphy JJ, Ramesh P, Murphy JM, Hooper RJ. Troponin T and risk assessment in patients with chest pain but without acute infarction *Eur Heart J* 1996;17(Abstr Supp:577).
24. Lindahl B, Venge P, Wallentin L. Troponin T identifies patients with unstable angina who benefit from long term anti thrombotic protection. Fragmin in Unstable Coronary Disease (FRISC study group). *J Am Coll Cardiol* 1997;29: 43–48.
25. Bhayana V, Gougoulias, Cohoe S, Henderson AR. Discordance between results for serum troponin T and troponin I in renal disease. *Clin Chem* 1995:41;312–317.
26. Ottani F, Galvani M, Laderson JH, et al. Direct comparison between elevations of cardiac troponin I and T in unstable angina pectoris. *Circulation* 1996;94;I–133.
27. Luscher M, Ravkilde J, Thygessen K, (for Heickendorf L for the TRIM study group). Concordance between troponin T and I values in 491 patients with unstable coronary syndrome. A TRIM substudy. *J Am Coll Cardiol* 1997:234A.
28. Hamm CW, Goldmann BU, Heeschen C, et al. A prospective study on the value of troponin I and T for emergency room triage. *Circulation* 1996;94.
29. De Winter RJ, Koster R, Sturk A, Sanders G. Value of myoglobin, troponin T, creatinine kinase MB mass in ruling out acute myocardial infarction in the emergency room. *Circulation* 1995;92:3401.
30. Green GB, Bessman ES, Dehlinger E, et al. A combined approach using multiple markers predicts adverse events among ED patients. *Circulation* 1996;941:I–134.

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Abstracts of Interest

In elective coronary artery bypass grafting preoperative troponin T level predicts the risk of myocardial infarction.

M. CARRIER, R. MARTINEAU, B.C. SOLYMOSS, L.C. PELLETIER, MONTREAL.

We studied the prognostic value of preoperative cardiac troponin T levels in 495 patients undergoing elective CABG at the Montreal Heart Institute between 1992 and 1995. Postoperative MI was defined by a new Q wave and/or by an increase in CK-MB levels >50 Iμ/L within 48 hours after surgery. Ninety-seven (97/495, 20%) patients had troponin T levels >0.02 μg/L before CABG. Although hospital mortality was similar (1%), 9 patients (9/97, 9.3%) with elevated levels of troponin T at baseline presented a myocardial infarction compared to 13 patients (13/398, 3.3%) with low levels at baseline (p=0.009, RR=2.8). Congestive heart failure occurred in 10 patients (10/97, 10%) with elevated baseline troponin T compared to 8 (8/398, 2%) patients with lower baseline values (p=0.0008, RR=5.2). Moreover, total cardiopulmonary bypass time (p=0.0005), intensive care unit (p=0.002) and hospital length of stay (p=0.008) were longer in patients with elevated troponin T levels at baseline. In logistic regression analysis, troponin T level at baseline was the variable most strongly related to myocardial infarction after surgery (p=0.0037), followed by redo bypass grafting (p=0.013).
Conclusion: Cardiac troponin T level at baseline, before elective CABG, is a powerful predictor of cardiac events after surgery. Preoperative troponin T stratification before CABG identifies a subgroup of patients with subclinical ischemic damage to the myocardium which significantly increases the risk of cardiac events after surgery.

Serial cardiac markers in unstable angina

M. LABINAZ, S.A. KEARNS, M.J. MADDOCK, L.A.J. HIGGINSON, D.S. OOI, OTTAWA.

Rapid triage of patients in chest pain evaluation clinics is facilitated by the use of serum cardiac markers. In order to determine the appropriate observation interval, we studied the temporal changes in serum creatine kinase (CK), CK-MB, myoglobin (MYC) and troponin I (TnI) in 65 unstable angina patients with total CK <400 U/L at presentation. Patients were categorized into those who developed AMI and those who required revascularization procedures during that admission (n=17), and those with uneventful hospital stays (n=48).
Results: Of 24 patients with ≥2 markers positive, 5 had infarction: 8 patients went on to revascularization procedures.
Number of patients showing abnormal results for the first time at the various sampling times and the total were:

Marker	0h	4h	8h	16h	24h	Total (%)
Patients with events:						
CK	4	0	1	0	0	5 (28)
CK-MB	0	3	3	0	2	8 (47)
MYO	1	1	0	1	0	3 (18)
TnI	4	4	4	2	0	14 (82)
Patients with no events:						
CK	3	1	2	0	2	8 (17)
CK-MB	1	1	0	2	0	4 (8)
MYO	0	2	0	1	2	5 (10)
TnI	2	5	5	4	4	20 (42)

Conclusion: Of the markers assessed, TnI was the most often positive. More than 50% of abnormal results occurred within 8 hrs. of presentation. In the group who had clinical events, 25, 33 and 14% CK-MB, MYO and TNI, respectively, developed abnormal values only.

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