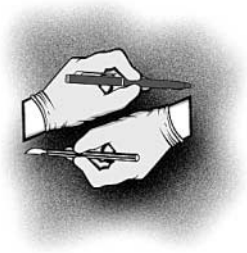

Qualitative troponin I estimation in the diagnosis of acute coronary syndromes in three rural hospitals

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Objective: To examine the utility of point-of-care qualitative troponin I (TnI) testing in patients with possible acute coronary syndromes (ACS).
Methods: A retrospective chart review of all patients undergoing qualitative TnI testing between September 2001 and February 2002 was conducted at the emergency departments of 3 rural hospitals in Alberta. We looked at the incidence of ACS, the comparison between TnI and creatine kinase (CK) testing and the timing of testing.
Results: Of the 235 patients tested, 8 had ST-elevation myocardial infarctions and 11 non ST-elevation infarctions. One patient had unstable angina with minimal myocardial damage. Qualitative TnI testing was positive in all 14 cases of infarction tested more than 6 hours after symptom onset, and CK elevation occurred in 15/17 cases (TnI sensitivity 1.0 [95% confidence interval (CI) 0.78–1.0], CK sensitivity 0.882 [95% CI 0.66–0.97]). There were 3 positive TnI tests and 33 raised CK levels in patients without evidence for ACS (TnI specificity 0.986 [95% CI 0.96–0.99], likelihood ratio [LR] 72.0 [95% CI 23.4–221.5]); CK specificity 0.847 [95% CI 0.79–0.89], LR 5.8 [95% CI 4.0–8.3]). In 44 patients (20.8%) TnI testing was inappropriately not repeated more than 6 hours after symptom onset.
Conclusion: Qualitative TnI testing appears highly sensitive and more specific than CK estimation in detecting myocardial infarction. Diagnostic algorithms must emphasize the importance of testing 6 or more hours after symptom onset.

Objectif : Étudier l'utilité du dosage qualitatif de la troponine I (TnI) au point de soin chez des patients possiblement atteints de syndromes coronariens aigus (SCA).
Méthodes : On a effectué une étude rétrospective des dossiers de tous les patients chez qui on a effectué un dosage qualitatif de la TnI entre septembre 2001 et février 2002 au service d'urgence de trois hôpitaux ruraux de l'Alberta. Nous avons étudié l'incidence de SCA, la comparaison entre les dosages de la TnI et de la créatine kinase (CK) et le moment où le test a eu lieu.
Résultats : Parmi les 235 patients examinés, 8 avaient eu un infarctus du myocarde avec élévation du segment ST, et 11 avaient eu un infarctus sans élévation du segment ST. Un patient avait une angine instable avec dommage minime au myocarde. Le dosage qualitatif de la TnI a donné un résultat positif dans tous les cas (14) d'infarctus chez lesquels on a effectué le dosage plus de 6 heures après l'apparition des symptômes et il y a eu hausse de la CK dans 15 cas sur 17 (sensibilité du dosage de la TnI, 1,0 [intervalle de confiance (IC) à 95 %, 0,78–1,0], sensibilité du dosage de la CK, 0,882 [IC à 95 %, 0.66–0,97]). Chez des patients qui ne présentaient pas de signes de SCA, on a obtenu des résultats positifs pour 3 dosages de la TnI et on a constaté des concentrations élevées de CK dans 33 cas (spécificité du dosage de la TnI, 0,986 [IC à 95 %, 0,96–0,99], rapport des vraisemblances [RV], 72,0 [IC à 95 %, 23,4–221,5]); spécificité du dosage de la CK, 0,847 [IC à 95 %, 0,79–0,89], RV, 5,8 [IC à 95 %, 4,0–8,3]). Chez 44 patients (20,8 %), le dosage de la TnI n'a pas été répété comme se doit plus de six heures après l'apparition des symptômes.
Conclusion : Les dosages qualitatifs de la TnI semblent très sensibles et plus spécifiques que l'estimation de la CK pour détecter l'infarctus du myocarde. Les algorithmes de diagnostic doivent mettre l'accent sur l'importance d'effectuer le test 6 heures ou plus après l'apparition des symptômes.

Introduction

Diagnosis of acute coronary syndromes (ACS) is often challenging. Although the typical ECG features of acute myocardial infarction are well known, such changes are apparent in only 50% of patients at the time of presentation.[1] The ECG in patients with unstable angina may be normal or show only subtle ST or T wave changes. It is important to identify these patients, as there is a significant risk of disease progression to acute infarction or death.[2,3]

Traditionally the diagnosis of acute myocardial infarction is confirmed by finding elevated serum levels of creatine kinase (CK) and, more specifically, elevated levels of the CK MB isoenzyme. Recently assays for new markers of myocardial damage such as troponin I (TnI) and troponin T have become available. As with CK MB, levels of these markers rise about 6 hours after the onset of infarction, but elevated troponin levels are more cardio-specific and correlate better with prognosis than do CK MB levels.[2–6] In addition, approximately 30% of patients with unstable angina have elevated troponin levels with a negative CK MB assay.[2,3] These patients, with minimal myocardial injury, are at increased risk of progression to myocardial infarction or death, and should be targeted for more aggressive medical therapy.[7,8] Elevated troponin levels may also occur outside the spectrum of ACS, in settings such as heart failure, pulmonary embolism, both myocarditis and pericarditis, renal failure, rhabdomyolysis and severe sepsis, probably reflecting minor degrees of cardiac injury.[9]

Rural hospitals face an additional challenge in making the diagnosis of myocardial infarction because many have limited laboratory facilities. Estimation of CK MB often requires transport of the blood sample to a distant laboratory for analysis, leaving the attending physician in a dilemma regarding patient management.

A point-of-care qualitative test for troponin I is now available; it has been evaluated in trials in larger urban hospitals.[10–12] Although the test would seem ideally suited for use in rural areas, reports are scanty, apart from a study reviewing patients presenting with chest pain to an emergency department in Newfoundland.[13] The paper neither demonstrated nor refuted the utility of the test, as the number of tests performed was low.

This retrospective study examines the use of this test in 3 rural hospitals, focusing on the utility and appropriateness of qualitative troponin I testing in patients with possible ACS. In particular, we wanted to determine whether the addition of point-of-care troponin I testing allowed more accurate diagnosis of ACS than ECG and CK estimation alone. We also wanted to ensure that the timing of testing was appropriate to rule out myocardial infarction.

Methods

A chart review was undertaken of all patients who had qualitative TnI estimation between September 2001 and February 2002 at 3 hospitals in rural Alberta. These 3 hospitals together have approximately 30 000 emergency department visits per year and are staffed by family physicians. Patients with ACS are typically admitted to the local hospital, with transfer to a tertiary care centre if unstable or if coronary artery imaging is required. The on-site laboratories provide quantitative estimation of CK, but estimations of the MB isoenzyme are referred out with a turn-around time of 12–24 hours.

In April 2001 qualitative TnI testing together with guidelines for appropriate use were introduced into the 3 hospitals. The guidelines recommended a baseline TnI test at presentation and then a repeat test at 6 hours after symptom onset. Positive samples are sent to the regional laboratory for quantitative TnI estimation, but these results are not available to clinicians for several days.

Patients were identified from laboratory records. We excluded patients referred from local medical clinics where no clinical information was available. The health records departments also identified records of all patients attending the emergency departments with diagnoses of acute myocardial infarction or unstable angina over the same time period, to ensure capture of all cases of ACS.

Information was abstracted from the records including the results of the qualitative troponin I assay and CK levels, together with quantitative troponin I and CK MB levels, if available. The time from symptom onset to the collection of the troponin samples was also calculated.

Cases with a diagnosis of myocardial infarction, positive results on TnI testing or elevated levels of CK, together with the cases identified by health records, were classified into diagnostic groups, using information from the clinical record, discharge summary, laboratory and ECG data, together with reports from hospitals to which patients had been transferred for further care. The classification rubric is shown in Table 1.

The Health Research Ethics Board at the University of Alberta granted ethical approval.

Laboratory methodology

Qualitative TnI testing was performed with Spectral Diagnostics Cardiac STATus™ (Spectral Diagnostics, Toronto). Exposure of blood or plasma containing TnI to antibodies embedded in a chromatographic matrix generates a coloured line. Laboratory staff performed all testing, as in a pilot study physician testers obtained unreliable results.

The Dade Behring Opus method was used for quantitative TnI testing. This test is considered positive for myocardial infarction if the recording exceeds 1.5 µg/L, and a blood level below 0.15 µg/L is reported as normal. Intermediate levels between 0.15 µg/L and 1.4 µg/L may represent unstable angina with minimal myocardial damage.

CK was measured using the J&J Vitros 250 analyzer (Ortho-Clinical Diagnostics). A blood level below 180 U/L is considered normal for men, with a blood level below 150 U/L normal for women. CK MB testing was performed with the Vitros 250 CK MB activity measurement. Results are interpreted as positive for myocardial infarction if both the CK MB exceeds 10 U/L and the ratio of CK MB/CK exceeds 10%.

Results

During the 6-month review the laboratory performed qualitative TnI testing in 235 patient encounters (1.6% of 14 396 emergency department visits). In all, 302 tests were performed (mean 1.29 tests per case; range 1–4). Health records identified 3 additional patients with possible ACS who had not undergone TnI testing, 2 of whom had no evidence for myocardial injury on chart review. Overall there were 8 ST-elevation myocardial infarctions and 10 non–ST-elevation infarctions. One case of unstable angina with minimal myocardial damage was detected. The diagnosis was indeterminate in one case and the remainder had no evidence of high-risk ACS.

Troponin testing

There were 17 positive TnI tests (Table 2): 12 were positive on initial testing and 5 only on repeat testing. Troponin testing was positive on 4/8 ST-elevation infarctions, 9/10 non–ST-elevation infarctions and the single case of unstable angina with minimal myocardial injury. In one case, where the diagnosis of infarction was obvious, no troponin testing was done. In the 4 cases of myocardial infarction with negative TnI, initial CK levels were within normal limits and repeat TnI estimations were not performed. In these cases the initial testing for cardiac markers was within 6 hours of the onset of symptoms. Three tests appeared to be false positives (Table 3). Quantitative testing on these samples showed borderline values in 2 cases (no. 4, no. 101). The final diagnosis for both was nonspecific chest pain. Neither patient had clinical features of other conditions associated with elevated troponin levels. The third patient (no. 117) presented with a cerebrovascular accident and had lain on the floor for several days. He had an elevated level of troponin and very high CK and CK MB, but the CK MB ratio was low. A pyrophosphate scan showed no evidence of acute infarction, and the final diagnosis was of rhabdomyolysis.

Creatinine kinase testing

Elevated creatinine kinase levels occurred in 49 of the 235 patients tested, 43 on initial testing and a further 6 on repeat testing. Thirty-three tests were classified as false positive and 2 as false negatives.

Table 1. Rubric for classification of acute coronary syndromes

Diagnosis	Clinical features	ECG findings	Markers (> 6 h)
STEMI	Appropriate	ST elevation	TnI / CK MB positive
NSTEMI	Appropriate	Normal or LBBB or ST depression or T inversion	TnI / CK MB positive
UAMMI	Appropriate	Normal or LBBB or ST depression or T inversion	TnI positive; CK MB negative
False positive test	Atypical	Normal or nonspecific changes	TnI positive or CK elevated; CK MB negative; quantitative TnI low
False negative test	Appropriate	ST elevation or LBBB or ST depression or T inversion	TnI negative or CK normal; CK MB positive

STEMI = ST-elevation myocardial infarction; NSTEMI = non–ST-elevation myocardial infarction; UAMMI = unstable angina with minimal myocardial injury; LBBB = left bundle branch block

(Table 3). There were no false positives in the 6 cases where initial CK was low and subsequently rose. CK testing was positive in 5/8 ST-elevation infarctions and 9/10 non–ST-elevation infarctions. The patient with unstable angina with minimal myocardial injury also had a minimal elevation of CK, but CK MB estimation was negative. In 2 ST-elevation infarction cases the patients were transferred before any repeat testing could be done. Review of the 2 false-negative cases showed that one had a positive troponin, left bundle branch block and a positive CK MB assay, and the other had a positive troponin and typical ST elevation, despite repeatedly normal total CK levels.

The final diagnosis was not clear in 1 case with elevated CK and a negative troponin. This patient, an elderly man, presented with transient atypical chest pain and a mildly raised CK (276 U/L.) Troponin was negative and his ECG was normal, but the CK MB was elevated. The attending physician's final diagnosis was non-cardiac chest pain.

Timing of testing

For 23 patients we were unable to determine if troponin testing was performed more than 6 hours after symptom onset because of missing or confusing documentation. Of the remaining 212 patients, 57 did not have TnI testing more than 6 hours after symptom onset. Repeat testing was not performed because of patient transfer (6), death (1), or because the initial early test was positive (2). Three were followed up with repeat CK testing rather than TnI, and 1 patient declined to stay for repeat testing. In 44 (20.8%) patients there was no documented reason for not repeating the test after 6 hours.

Discussion

The retrospective nature of the study does provide some limitations. The quality of documentation was variable, particularly with regard to timing of symptoms. We did not review the charts of all patients presenting with chest pain, so it is possible that we omitted patients with unrecognized myocardial ischemia who did not have troponin testing. Similarly, we cannot be sure that some of the patients discharged home, particularly those who were not tested 6 hours or more after symptom onset, did not have ACS. However we examined charts for evidence of later attendance at the emergency depart-

Table 2. Details of positive troponin I cases ranked by quantitative troponin I levels

Classification	Case no.	Quantitative troponin I (mcg/L)	Peak CK, U/L	CK MB	ECG findings
False positive*	101	0.2	74	Neg	Septal Q wave
False positive†	4	0.21	122	‡	Nonspecific ST changes
UAMMI	129	1.18	181§	Neg	Dynamic ST depression
NSTEMI	21	1.2	255§	‡	T changes
NSTEMI	61	1.5	1 089§	Pos	Normal
NSTEMI	147	2.4	283§	Pos	Normal
NSTEMI	126	2.88	295§	Pos	Nonspecific ST changes
STEMI	76	3.0	171	‡	ST elevation
NSTEMI	190	4.2	171	Pos	LBBB
STEMI	75	4.5	258§	Pos	ST elevation
NSTEMI	206	5.4	259§	Pos	LBBB
STEMI	128	5.86	586§	Pos	ST elevation
NSTEMI	110	9.9	762§	Pos	Nonspecific ST changes
False positive	117	11.2	20 752§	Pos¶	Inferior Q waves
NSTEMI	199	13.8	660§	Pos	ST depression
NSTEMI	200	19.0	832§	Pos	Nonspecific ST changes
STEMI	55	‡	2 982§	Pos	ST elevation

STEMI = ST-elevation myocardial infarction; NSTEMI = non–ST-elevation myocardial infarction; UAMMI = unstable angina with minimal myocardial injury; pos = positive; neg = negative
*Patient transferred, no evidence of ischemia.
†Repeat troponin testing negative.
‡Quantitative confirmation not performed.
§Indicates above reference range for CK: men >180 U/L, women >150 U/L.
¶CK MB elevated at 102 but ratio < 0.01.

ment, and did not find repeat attenders with missed infarction. Quantitative TnI testing was only performed if the qualitative test was positive. It is possible that some patients with minor myocardial damage could not be identified with this strategy. The classification of patients into diagnostic groups also has a subjective component and would be methodologically stronger if performed by a panel rather than a single physician.

Qualitative point of care troponin I testing appears to be a useful tool for the diagnosis of myocardial infarction in settings where CK MB testing is not available or delayed. Unlike CK estimation, TnI testing identified all definite cases of myocardial infarction in this series when testing was done 6 hours or more after symptom onset. Similarly the specificity of the test was significantly better than for CK. Availability of quantitative troponin testing would improve the specificity further, as 2 of the false positives had very low levels of troponin I on further analysis. Disappointingly, the test did not appear to identify a subset of patients with high-risk unstable angina that was not detectable by other means. All the patients with true-positive troponin testing had clearly ischemic ECGs and/or elevated CK levels. This may be a reflection of the small numbers of patients with ACS in our series.

It is of concern that over 20% of patients were not tested at an appropriate time interval. This is similar to the findings in Newfoundland, where 26% of patients were tested less than 6 hours after symptom onset.[13] For many patients it is probable that the clinical course of their symptoms dictated that a diagnosis of ACS was unlikely. However it raises the possibility that physicians may have incorrectly discharged patients on the basis of the negative early troponin test. We would recommend that troponin testing should not be performed until 6 hours after symptom onset. This would avoid the cost of testing in patients who clearly do not have an ACS and prevent the false reassurance of a premature negative test.

Table 3. Sensitivity and specificity of creatine kinase (CK) and troponin I (TnI) testing

Test	No. of patients with ACS (tested ≥6 hr)	No. of patients without ACS	Total
CK result			
Elevated	15	33	48
Normal	2	183	185
Total CK tests	*17*	*216*	*233*
TnI result			
Positive	14	3	17
Negative	0	213	213
Total TnI tests	*14*	*216*	*230*

Note:
CK specificity 0.847 (CI 0.79–0.89); sensitivity 0.882 (CI 0.66–0.97); LR 5.8 (CI 4.0–8.3).
TnI specificity 0.986 (CI 0.96–0.99); sensitivity 1.0 (CI 0.78–1.00; LR 72.0 (CI 23.4–221.5).
Exclusions from analysis: Two patients with normal CK levels and 4 with negative TnI testing ≤ 6 hours from symptom onset had confirmed ACS but did not have repeat testing. One patient with an indeterminate diagnosis had an elevated CK and a negative TnI.
ACS = acute coronary syndromes; CI = confidence interval; LR = likelihood ratio

Conclusion

This study suggests that point-of care qualitative troponin I testing could replace CK estimation for the initial diagnosis of ACS in rural hospitals. Results from qualitative TnI testing are highly sensitive and more specific for myocardial damage than CK levels. Positive tests should be verified by further quantitative analysis. In the interests of patient safety and cost effectiveness, cardiac marker testing should be deferred until at least 6 hours from symptom onset.

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