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Enzymes and Protein Markers

Correlation of Antemortem Serum Creatine Kinase, Creatine Kinase-MB, Troponin I, and Troponin T with Cardiac Pathology

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Background: **Spurious increases in serum troponins, especially troponin T, have been reported in patients with and without acute myocardial syndromes.**
Methods: **We studied 78 autopsied patients without clinical myocardial infarction (MI) and correlated histologic cardiac findings with antemortem serum creatine kinase (CK), its MB isoenzyme (CK-MB), cardiac troponin I (cTnI), and cardiac troponin T (cTnT).**
Results: **There was no significant myocardial pathology in 15 patients. Cardiac pathologies were in five groups: scarring from previous MI or patchy ventricular fibrosis (n = 9), recent MI (n = 27), healing MI (n = 7), degenerative myocyte changes consistent with congestive heart failure (CHF; n = 12), and other cardiac pathologies (n = 8). The median concentrations in the five groups were not significantly different for either CK or CK-MB. Compared with the no-pathology group, only the MI group was significantly different for cTnI, and the MI and other pathology groups were significantly different for cTnT. For patients with MI, 22%, 19%, 48%, and 65% had increased CK, CK-MB, cTnI, and cTnT, respectively; for CHF and other cardiac pathologies combined, the percentages were 28%, 17%, 22%, and 50%. For patients with increased cTnI, 72% and 28% had MI and other myocardial pathologies, respectively; patients with increased cTnT had 64% and 36%, respectively. Patients without myocardial pathology had no increases in CK-MB, cTnI, or cTnT.**
Conclusions: **All patients with increased serum CK-MB, cTnI, and cTnT had significant cardiac histologic changes. The second-generation cTnT assay appears to be a more sensitive indicator of MI and other myocardial pathologies than the cTnI assay used in this study.**

In recent years, serum troponins have been increasingly used in the diagnosis of acute coronary syndromes as studies have shown their greater clinical sensitivity over creatine kinase-MB (CK-MB)[4] *(1, 2)*. In patients with non-Q-wave myocardial infarction (MI) or unstable angina, serum troponins can provide risk stratification for short-term *(3–9)* and long-term *(9, 10)* cardiac events and mortality. This has been attributed mainly to the ability of serum troponins to detect microinfarcts, areas of necrosis too small to produce electrocardiographic changes or increased serum cardiac enzymes. Whereas increased short-term complications and mortality may understandably be explained by these microinfarcts, long-term events have also been attributed to complications of ischemia.

Additionally, a high percentage of end-stage renal failure patients show increased cardiac troponin T (cTnT) in the absence of acute cardiac ischemia *(11, 12)*. There have been suggestions that these represent spurious increases arising from re-expression of the cardiac isoform, the fetal form, in skeletal muscles of these patients *(13)*. We have observed a threefold increase in 1-year mortality in 172 hemodialysis patients with increased cTnT *(14)*, and although increases in cTnT may result from silent MIs that occur frequently in these patients, the temporal pattern of increases was not in keeping with acute ischemic events. This raised the possibility that increased cTnT in this group of patients was indicative of chronic disease processes that compromise survival.

There have been reports of similar increases in mortality associated with increased cTnT in congestive heart

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[4] Nonstandard abbreviations: CK-MB, creatine kinase-MB isoenzyme; MI, myocardial infarction; cTnI and cTnT, cardiac troponin I and T; and CHF, congestive heart failure.

failure (CHF) patients *(15–17)* and in patients with sepsis *(18)*. These findings led us to reexamine the basis of increased troponins, especially cTnT, within the context of subclinical myocardial pathology. We used histological examination of the heart at post mortem, which can indicate the extent and type of pathology present, to determine whether increased serum troponin concentrations can be explained by subclinical myocardial pathology.

Materials and Methods

SUBJECTS

Patients were selected from those undergoing postmortem studies at the Ottawa Hospital Civic Campus Department of Pathology and Laboratory Medicine. Patients with a clinical diagnosis of MI or patients in whom no suitable antemortem plasma samples were available were excluded from the study. A total of 78 patients were studied and included 6 from a study of chronic hemodialysis patients *(14)*.

ANTEMORTEM SAMPLES

Samples were routine clinical samples, drawn into evacuated tubes (PST® or SST®; Becton Dickinson) and processed in the routine manner. Sixty-four percent of samples were obtained within 7 days of death; samples from three dialysis patients and one cardiac patient were obtained >6 months before death. Most of the samples (88%) were frozen at −20 °C within 72 h. Twelve patients were studied retrospectively; serum markers were analyzed for clinical reasons in 6, and for a previous study on chronic hemodialysis patients in 6 *(14)*; 11 patients had only cTnT measurements, and one had CK and cTnT.

Creatine kinase was measured on the Boehringer Mannheim/Hitachi 917, using manufacturer's reagents, CK-MB and cardiac troponin I (cTnI) were measured on the AxSYM (Abbott Laboratories), and cTnT was measured on the Elecsys 1010 (Roche Diagnostics). The second-generation cTnT assay was used; this assay has no cross-reactivity with skeletal TnT. The cutoff values used in our laboratory are as follows: CK, 215 U/L for males and 160 U/L for females; CK-MB, 10 μg/L; cTnI, 2.0 μg/L; and cTnT 0.1 μg/L. The interassay imprecision (CV) for each assay is as follows: for CK, 2.3% at 245 U/L; for CK-MB, 12% at 20 μg/L and 8.7% at 124 μg/L; for cTnI, 7.0% at 3.3 μg/L and 7.9% at 34.2 μg/L; and for cTnT, 6.5% at 0.16 μg/L and 6.0% at 1.1 μg/L.

POSTMORTEM STUDIES

Gross and histological examinations of the heart were performed by a cardiac pathologist (J.P.V.) without knowledge of the serum marker values. Postmortem examinations were completed within 24 h of death in all patients.

Patients were classified as having recent MI if there was coagulative and contraction band necrosis <5 days old; healing MI if the infarct was >1 week old as evidenced by healed edges but without significant fibrosis; and old infarcts if there was prominent fibrosis. The other cardiac disorders seen were degenerative changes associated with CHF (myocytes characterized by clear cytoplasm and loss of myofilaments, often accompanied by pericellular fibrosis), inflammation, fibrosis, nonbacterial thrombotic endocarditis, sepsis changes, amyloid deposition, and infiltration by tumor.

STATISTICAL ANALYSIS

Means were compared using the Analysis ToolPak of Microsoft Excel, Ver. 7. χ^2 analysis and the Fisher's exact two-tailed test were performed. Odds ratios were calculated to determine the relationship between increased serum markers and the presence of cardiac pathology, using Epi Info, Ver. 6 (Department of Surveillance and Epidemiology, CDC) and InStat, Ver. 2.04 (GraphPad Software). Statistical significance was defined as $P < 0.05$ unless otherwise stated. Clinical sensitivities and specificities were calculated for all cardiac pathologies and for acute MI (recent and healing). For the latter diagnosis, patients with other cardiac pathologies were considered not to have disease.

Results

A summary of 66 patients for whom all cardiac markers were measured is shown in Table 1. A complete listing of the patient characteristics, clinical diagnoses, main cardiac histologic findings, and other significant vascular diseases is available as a supplement through the *Clinical Chemistry* Web site. The file can be accessed by a link from the on-line Table of Contents (http://www.clinchem.org/content/vol46/issue 3/). There was no myocardial pathology in 15 patients; there was old MI or ventricular fibrosis in 9, recent MI in 27 (11 microinfarcts), healing MI in 7, degenerative changes in 12, and miscellaneous pathology in 8 patients.

In the patients with no myocardial pathology, CK was increased in 3 of 15, and cTnI was just below the cutoff concentration (1.9 μg/L) in 1 patient. In patients with myocardial pathology, cTnT was most frequently increased. Although increases in CK were noted without increases in the other markers, increased CK-MB was associated with increased cTnI and cTnT in all patients. Similarly, all but one patient with increased cTnI had increased cTnT. The median concentrations and the percentages of patients with increased CK-MB, cTnI, and cTnT, but not CK, were higher in patients with myocardial pathology than for those with no myocardial pathology (Table 2 and Fig. 1). However, the odds ratio for the presence of acute MI was significant for cTnI and cTnT only, and the odds ratios for the presence of CHF changes and other cardiac pathologies were significant for cTnT alone. There was no significant difference between the groups with recent and healing MIs, nor did the size of the infarct appear to have any effect; hence, they were studied together. When all cardiac pathologies were con-

Table 1. Summary of patient and sample characteristics and pattern of increased serum markers in the 66 patients[a] with all four marker results available.

						No. (%) of patients with increased serum concentrations				
	n	Males, %	DM[b] and/or CRF, %	Sampled >6 days prior to death, %	Stored at 4° C >72 h, %	CK[c]	CK-MB, cTnI, and cTnT	cTnI and cTnT	cTnI only	cTnT only
No myocardial pathologies	14	36	50	14	29	3 (21)	0	0	0	0
Old MI or fibrosis	7	43	29	29	0	2 (29)	0	0	1 (14)	1 (14)
Recent MI	11	82	18	27	36	2 (18)	2 (18)	2(18)	0	2 (18)
Recent microinfarct	10	70	40	40	10	2 (20)	2 (20)	4(40)	0	2 (20)
Healing MI	6	67	50	33	17	2 (33)	1 (17)	2(33)	0	0
CHF	10	40	20	40	20	4 (40)	1 (10)	1(10)	0	1 (10)
Other myocardial pathologies[d]	8	50	50	38	25	1 (13)	2 (25)	0	0	3 (38)

[a] Detailed information on all patients, including significant medical history and cardiac findings at post mortem, is available as a supplement from the *Clinical Chemistry* Web site. The file can be accessed by a link from the on-line Table of Contents (http://www.clinchem.org/content/vol46/issue3/).

[b] DM, diabetes mellitus; CRF, chronic renal failure.

[c] Increase in CK occurred in isolation or in combination with another pattern group.

[d] Includes inflammation, necrosis, nonbacterial thrombotic endocarditis, and amyloid deposition.

sidered, the clinical sensitivities (95% confidence intervals) for CK, CK-MB, cTnI, and cTnT were 38% (25–52%), 26% (15–40%), 44% (31–59%), and 53% (41–65%), respectively. The specificity for CK was 80%, whereas the other markers showed 100% specificity. For acute MI, the specificities for CK, CK-MB, cTnI, and cTnT were 75% (59–87%), 92% (79–98%), 87% (73–96%), and 73% (57–85%), respectively. The clinical sensitivities for acute MI were 22% (9–42%), 19% (6–38%), 48% (29–68%), and 62% (44–78%), respectively. When we used only the samples collected within 6 days of death, the sensitivities changed marginally to 17% (4–41%), 22% (6–48%), 61%

Table 2. Median and range of serum concentrations in the five histologic groups, odds ratios of having abnormal pathology compared with no myocardial pathology, and the significance based on χ^2 analysis.

	No myocardial pathology	Old MI or patchy fibrosis	Recent/healing MI	CHF	Other myocardial pathologies
CK					
n	15	7	27	10	8
Median, U/L	55	73	49	82	47
Range, U/L	9–270	22–1085	10–478	10–304	23–421
Odds ratio	1.0	1.6	1.1	2.7	0.6
95% CI[a]		0.1–18.8	0.2–8.3	0.3–23.7	0.0–9.1
CK-MB					
n	14	7	27	10	8
Median, μg/L	1.2	2.7	2.5	3.1	2.2
Range, μg/L	0.5–4.0	0.0–5.3	0.9–75.7	0.9–15.9	1.0–18.4
Odds ratio	1.0	Undefined	3.2	4.6	11.2
95% CI			0.1–72.1	0.2–124.7	0.5–266.9
cTnI					
n	14	7	27	10	8
Median, μg/L	0.1	0.3	1.3	0.3	0.3
Range, μg/L	0.0–2.9	0.1–2.9	0.0–139.2	0.0–4.4	0.0–12.7
Odds ratio	1.0	6.7	27.0[b]	8.5	11.2
95% CI		0.2–187.4	1.5–498.5	0.4–199.6	0.5–266.9
cTnT					
n	15	9	34	12	8
Median, μg/L	0.02	0.03	0.13	0.07	0.26
Range, μg/L	0.00–0.07	0.01–0.15	0.00–13.11	0.0–1.41	0.03–0.62
Odds ratio	1.0	10.3	49.4[b]	22.7[b]	48.7[b]
95% CI		0.4–243.5	2.7–895.4	1.1–467.8	2.2–1102.7

[a] CI, confidence interval.

[b] Significance based on χ^2 analysis: $P < 0.01$ for two-tailed test.

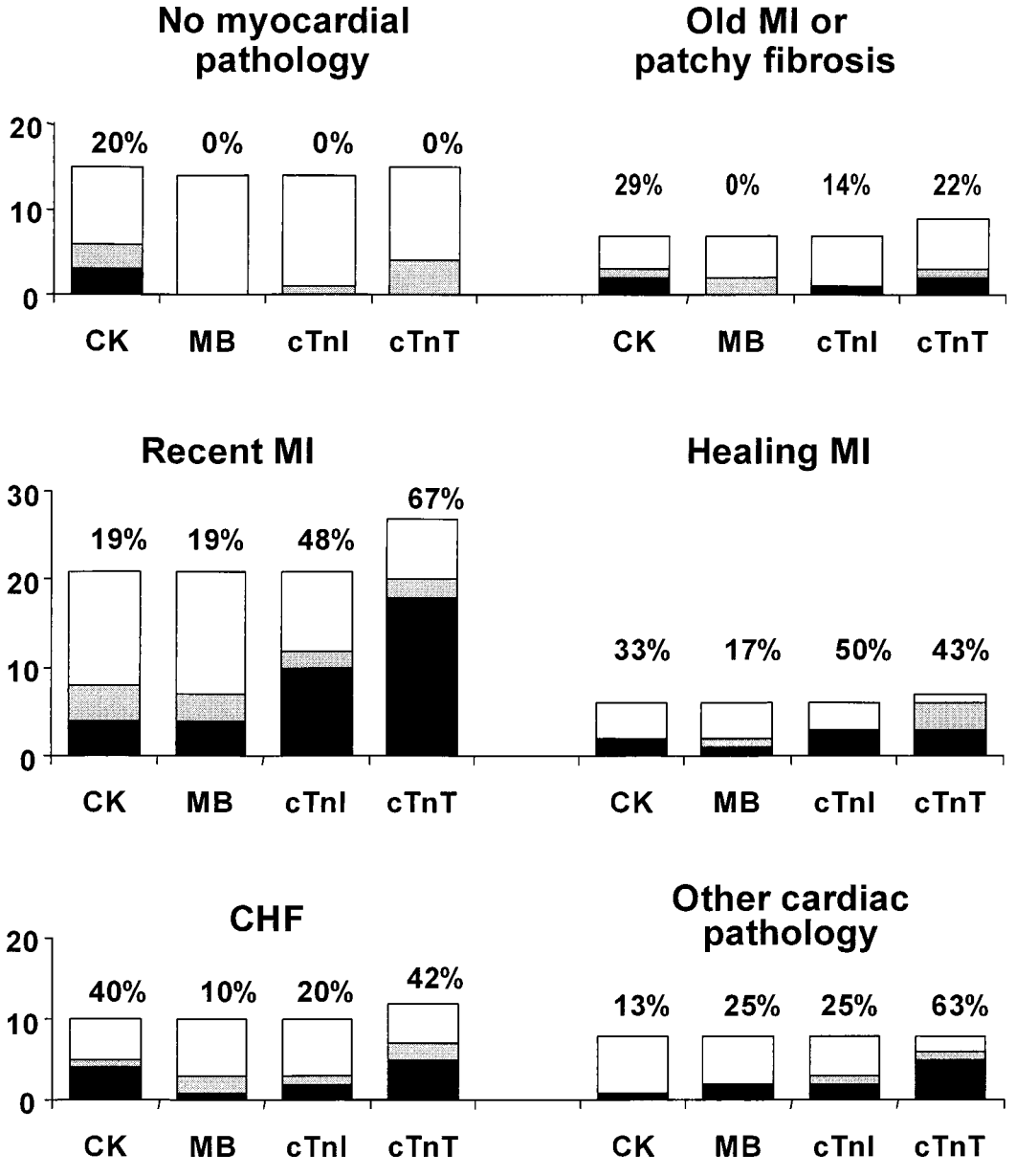

Fig. 1. Distribution of serum CK, CK-MB (*MB*), cTnI, and cTnT concentrations in the various groups.

Filled portions of the columns and *percentages* shown above the columns represent concentrations above the upper cutoff; *gray portions* represent marginal increases (values between cutoff and one-half the cutoff value); *open portions* represent no significant increases (below one-half the cutoff value).

(36–83%), and 70% (46–88%), respectively, and did not increase further when we restricted samples to within 3 days of death. For acute MI, the sensitivity of cTnT was not significantly different from that of cTnI, but it was significantly different from both CK-MB and CK. For cardiac pathologies other than acute MI, the sensitivity for cTnT over cTnI did not achieve statistical significance, with an observed difference of 21% and a SE of 12%.

Patients with diabetes mellitus had significantly lower CK-MB, cTnI, and cTnT; the median values for patients without and with diabetes were 2.5 vs 1.5 μg/L for CK-MB; 0.3 vs 0.2 μg/L for cTnI; and 0.08 vs 0.03 μg/L for cTnT. However, excluding the 11 diabetic patients from the analysis did not influence the findings. The medians for cTnI and cTnT were higher in patients with chronic renal failure than for those with normal renal function (1.6 vs 0.2 μg/L for cTnI and 0.20 vs 0.05 μg/L for cTnT), but the differences did not achieve statistical significance. Eliminating the 12 retrospective patients and studying only the 66 patients with results available for all markers yielded similar results.

The presence of acute myocardial ischemia was the most common cause of increased serum concentrations of

CK-MB, cTnI, and cTnT, contributing to >60% of increased values. Interestingly, patients with microinfarcts were just as likely to have increased values as patients with larger infarcts.

Discussion

The findings of this study confirm the increased clinical sensitivity of serum troponins over CK and CK-MB in acute coronary syndromes. Many of the patients with borderline increases in serum troponins had small MIs at postmortem. Because of the nature of this study, where a single plasma sample was used, the longer period of increased concentrations seen with serum troponins following an acute ischemic event *(19, 20)* may have contributed to the higher percentage of increased concentrations observed.

The important finding of this study was the presence of histologic changes in the hearts of almost all of the patients with increased serum CK-MB, cTnI, and cTnT. What had been considered as spurious increases, because of a lack of symptoms and clinical signs when currently available diagnostic modalities were used, is explained by diseased cardiomyocytes. Furthermore, there appears to be a difference between patients with acute ischemia and those with other myocardial disorders. In the former, the percentage of patients with increased cTnI is very similar to that for cTnT (50% vs 63%). The slightly higher positivity for cTnT can be explained by its longer half-life, which makes it more likely that a single random sample would have increased values. In patients with other myocardial pathologies, cTnT is increased more than twice as frequently as cTnI. This may explain the discordance seen between the troponins in end-stage renal failure patients but not seen in acute coronary syndromes. To explain this discrepancy, one could hypothesize that cTnT is more likely than the other markers to leak into circulation with minor pathologic changes. Approximately 6% of cTnT is present in the cytoplasm of cardiomyocytes *(21)* in contrast to 3% of cTnI *(22)*. Additionally, cTnT in serum exists mainly as free subunits, whereas cTnI exists complexed as a binary structure with troponin C, or as a ternary structure with both troponins C and T *(23)*, indicating that cTnI is released as a larger complex. Loss of cell membrane integrity could possibly allow selective leakage of cytosolic components into the circulation, with preferential leakage of cTnT when membrane damage is minor. With increasing destruction of the membrane architecture, larger cytosolic components may be leaked into circulation, leading to increases for both troponins.

Myocytes may die from several different processes, including necrosis (oncosis) and apoptosis, and it is recognized that these processes may be interrelated *(24, 25)*. Unlike necrosis, apoptosis proceeds through a genetically programmed series of biochemical and morphological steps designed to avoid the indiscriminate release of cytosolic contents and the ensuing inflammatory response. In apoptosis, the cell membrane remains intact, at least for some time. This would lead one to hypothesize that various myocyte cellular components appear in circulation at the different times of apoptotic and necrotic cell death.

The increased mortality seen with increased troponins, especially cTnT, in nonischemic settings supports our findings. We had been perplexed previously by the increased mortality associated with unexplained increases in cTnT in chronic hemodialysis patients *(14)*. Two recent studies *(26, 27)* in dialysis patients have shown similar associated mortality. In our study *(14)*, we were surprised to find that increased cTnT is a better predictor of mortality in patients without coronary artery or peripheral vascular disease and in non-diabetics, the groups traditionally considered at lower mortality risk for atherosclerosis. This now can be explained by cTnT reflecting subclinical myocardial pathology rather than acute coronary ischemia. Furthermore, we found a higher mortality risk associated with increased cTnT in the nonhypertensive group. Whereas systemic arterial hypertension is associated with atherosclerosis and mortality in most other diseases, in this group of patients, where hypertension occurs frequently either as the cause or the effect, the fall in blood pressure often denotes cardiac decompensation *(28)*. Increased cTnT in this group of patients therefore indicates the presence of cardiac disease and hence, not surprisingly, the poorer outcome.

Both patients with sepsis affecting the myocardium had increased cTnT, consistent with previous studies showing it to be a prognostic marker in sepsis *(18)*. Similar prognostic values in CHF patients have also been reported recently *(15–17)* and support our postulation that cTnT may be a useful prognosticator even in non-infarct-related cardiac disease. Such increases in cTnT may be indicative of non-infarct-related myocyte pathologies, as noted in our study.

With the use of serum troponins in acute coronary syndromes, there may be a need to reexamine the interpretation of the many risk-stratification studies of unstable angina and non-Q-wave MI patients *(3–10)*. These studies used mainly cardiac end-points, and an increased mortality generally was attributed to underlying ischemic disease. In light of our findings, one should consider the presence of other myocardial pathologies, in addition to the presence of microinfarcts, as contributing factors for mortality. Interestingly, a study of patients with low-grade or atypical angina showed a greater than twofold difference in event-free survival at 6 months between cTnT-positive and -negative groups despite very similar incidences of positive angiographic abnormalities (64% vs 47%) *(8)*. Increased troponins, especially cTnT, even in the absence of acute ischemia are indicative of compromised myocardium and carry a poor prognosis.

This study had several limitations. The nature of the study was such that samples could not be obtained from patients at a standard time before death. There also is the

issue of the quality of the samples, both plasma and histologic. Because of the retrospective nature of the study, the plasma samples used were those that had been stored following routine analysis. Most of the samples were frozen within the recommended 72 h for the cTnI assay *(29)*, and only 42% were frozen within the 24 h recommended for the cTnT assay *(30)*. The effect, if significant, would have produced even greater discrepancy between the two troponins. In addition, recent studies have shown that degradation of cTnI complexes, which is the predominant form in serum, and oxidation or phosphorylation of the cTnI molecule can produce changes in immunoreactivity, leading to increasing or decreasing concentrations with storage *(31)*. However, because only two patients with MI and one patient with sepsis were cTnT positive and cTnI negative, we do not think this had a major impact on our findings. Another limitation was that postmortem samples almost invariably show some autolysis, and more detailed studies, such as electron microscopy, were not possible. However, it would be ethically unacceptable at present to perform endomyocardial biopsies in patients to clarify the basis for increased serum troponins.

As data accumulate from clinical and laboratory studies, we need to reexamine the basis of increased troponins, especially cTnT, in patients without acute ischemia. The debate continues as to which troponin is superior. An important part of this debate is the poor specificity of cTnT in end-stage renal disease patients. Our findings imply that these increases, rather than being spurious, are indicative of underlying cardiac pathology. Although cTnI and cTnT are equal in the management of patients with acute coronary syndromes, cTnT is superior in detecting minimal cardiac disease and may be a better predictor of risk in certain groups of patients.

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