CARDIOVASCULAR MEDICINE

Troponin T concentrations 72 hours after myocardial infarction as a serological estimate of infarct size

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Heart 2002;**87**:520–524

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Accepted 9 January 2002

Background: After acute myocardial infarction, the structural protein T is released considerably longer than cytosolic creatine kinase (CK), CK MB isoenzyme (CK-MB), or lactate dehydrogenase (LDH) and late troponin T release (> 48 hours after onset of chest pain) appears to be less affected by early coronary reperfusion.

Objective: To investigate the precision of a single measurement of circulating troponin T concentrations 72 hours after onset of chest pain compared with standard scintigraphic and enzymatic estimates of myocardial infarct size.

Methods: Quantitative single photon emission computed tomography thallium-201 scintigraphy at rest was performed in 37 patients 2–3 weeks after myocardial infarction (group 1: 14 patients without early coronary reperfusion; group 2: 23 patients with early reperfusion achieved by thrombolytic therapy, by percutaneous transluminal coronary angioplasty, or by both).

Results: In both groups, the number of myocardial segments with abnormal thallium-201 uptake indicating the individual extent of irreversible myocardial damage correlated significantly with the troponin T concentrations 72 hours after infarction as well as with peak concentrations of CK, CK-MB, and LDH.

Conclusion: The data show that a single measurement of circulating troponin T 72 hours after onset of chest pain—independent of reperfusion—is superior for the estimation of myocardial infarct size to measurement of peak CK, CK-MB, or LDH, which require serial determinations and depend on coronary reperfusion.

After acute myocardial infarction (AMI), a patient's prognosis is closely related to the extent of irreversibly damaged myocardium.[1–3] In routine clinical practice, infarct size is estimated non-invasively by electrocardiography, imaging procedures (such as myocardial radionuclide imaging and echocardiography), and serological tests. Each of these methods, however, has its limitations.

The value of serum concentrations of cytoplasmic enzymes such as creatine kinase (CK), its myocardial isoenzyme CK-MB, and lactate dehydrogenase (LDH) for estimation of the extent of myocardial cell damage is limited by the requirement for serial determinations to identify peak or cumulative serum concentrations. The latter depends strongly on variable normal serum concentrations and the effects of coronary reperfusion.[4–6] Furthermore, specificity is relatively low since the expression of these enzymes is not restricted to the myocardium and increased serum concentrations can be observed as a result of other causes such as vigorous exercise and renal failure.[7 8]

In contrast to cytosolic markers, troponin T (TnT) is a structural protein of the contractile apparatus. After AMI, TnT is released continuously into the circulation for several days. TnT serum concentrations show a biphasic curve with one peak on the first day resulting from a release of the cytosolic TnT pool and a second "plateau" phase 3–4 days after the beginning of chest pain resulting from intramyocardial protein degradation.[9–12] Compared with cytosolic markers, the second peak of TnT seems to be almost unaffected by early coronary reperfusion.[13] In addition to its high sensitivity, TnT increase is also highly specific because TnT is expressed as skeletal isoforms and one highly cardiac specific isoform that is usually not detectable in patients without myocardial damage.[14]

Scintigraphic imaging with thallium-201, a potassium analogue, has a high sensitivity but lacks specificity because of its inability to distinguish between acute and prior infarction.[15 16]

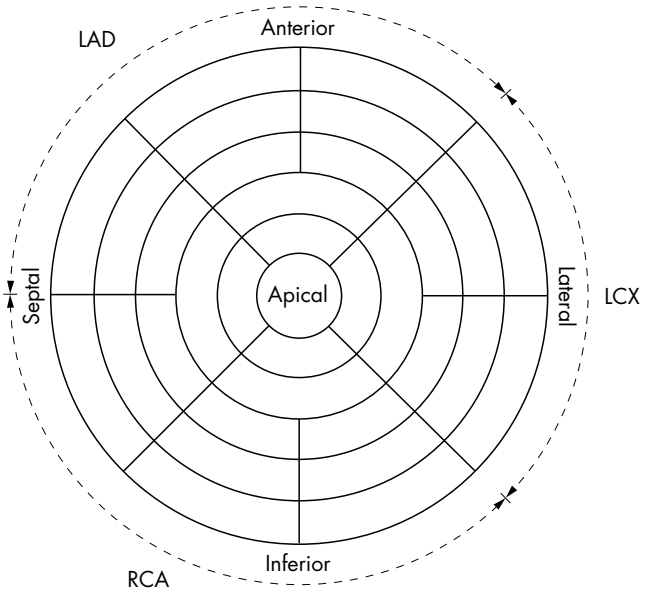

Figure 1 Polar map presentation of left ventricular thallium-201 uptake (33 segments).

In patients with a first myocardial infarction, however, thallium-201 scintigraphy is an accepted non-invasive method to estimate myocardial infarct size.

Abbreviations: CK, creatine kinase; CK-MB, creatine kinase MB isoenzyme; ELISA, enzyme linked immunosorbent assay; LDH, lactate dehydrogenase; SPECT, single photon emission computed tomography; TnT, troponin T

Table 1 Clinical data of non-reperfusion (group 1) and reperfusion (group 2) groups of patients

	Group 1 (n=14)	Group 2 (n=23)
Age (years)	65 (11)	60 (12)
Male sex	9 (64%)	17 (74%)
Infarct related vessel		
RCA	9 (64%)	13 (57%)
LAD	3 (22%)	6 (26%)
LCX	2 (14%)	4 (17%)

Data are mean (SD) or frequency.
LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery.

The aim of the present study was to investigate the reliability of TnT concentrations after 72 hours as a simple tool for the estimation of infarct size. For this purpose in patients with first AMI, myocardial infarct size was determined scintigraphically and then correlated with TnT serum concentrations 72 hours after the onset of symptoms, as well as peak and cumulative concentrations of CK, CK-MB, and LDH.

METHODS

Patients

Thirty seven consecutive patients with AMI were included. Exclusion criteria were chest pain lasting more than six hours at the time of admission and a history of prior myocardial infarction. Because of contraindications, no recanalisation was attempted in 10 patients and in an additional four patients recanalisation was not successful (group 1). Coronary recanalisation was achieved by intravenous thrombolysis, by percutaneous transluminal coronary angioplasty, or by both procedures in 23 patients (group 2). In all patients, coronary angiography was carried out either immediately after AMI or before being discharged from hospital.

Blood sampling

Blood samples were drawn every four hours during the first day, every eight hours on days 2 and 3, and then once daily until day 10. To allow clotting, the samples were kept at room temperature for 15 minutes and then centrifuged, and the serum was stored at −20°C until measurements were performed.

Cardiac enzyme measurements

CK and LDH activities were determined in a Chem 1 analyser (Technicon, Tarrytown, New York, USA) at 25°C, with reagents

Table 2 Scintigraphic and serological data

Patient	Infarct related vessel	Treatment	No of segments with <67% thallium-201 activity	TnT at 72 hours (ng/ml)	CKmax (IU/l)	CK-MBmax (IU/l)	LDHmax (IU/l)
Group 1							
1	RCA	Conservative	6	5.2	240	37	445
2	RCA	Conservative	5	4.2	273	40	323
3	LAD	Conservative	12	8.6	2031	215	1192
4	RCA	Conservative	6	14.2	1062	128	815
5	LAD	Conservative	15	15.4	978	84	997
6	RCA	Conservative	8	8.8	1700	190	1454
7	LCX	Conservative	5	3	210	19	384
8	RCA	Conservative	5	3	768	51	658
9	LCX	Conservative	9	9.8	1806	175	1218
10	RCA	Conservative	8	3.5	403	46	440
11	RCA	Unsuccessful PTCA	4	3.9	431	71	453
12	RCA	Unsuccessful PTCA	11	19	1116	114	791
13	LAD	Unsuccessful Sk lysis	1	1.8	245	24	325
14	RCA	Unsuccessful Sk lysis	1	4.6	589	61	332
Mean (SD)			6.9 (4.0)	7.5 (5.4)	847 (626)	90 (65)	702 (383)
Group 2							
1	RCA	PTCA	2	1.7	617	50	358
2	RCA	rtPA lysis	5	3.7	812	72	682
3	RCA	Sk lysis	9	8	855	114	761
4	RCA	rtPA lysis	6	5.3	998	63	462
5	LCX	Sk lysis	5	2.1	534	22	340
6	RCA	Sk lysis	8	6.8	1510	200	91
7	RCA	Sk lysis	8	6.4	1228	123	1086
8	LAD	Sk lysis	4	2.9	541	60	312
9	LCX	Sk lysis	4	6.2	920	96	626
10	LAD	rtPA lysis	7	6.8	1144	86	685
11	RCA	Sk lysis	9	6.9	643	78	601
12	RCA	rtPA lysis	11	7.3	1354	77	840
13	RCA	Sk lysis	1	3.0	670	61	405
14	RCA	rtPA lysis	10	11.0	1938	160	1190
15	LCX	rtPA lysis	5	1.5	253	25	224
16	LCX	rtPA lysis + PTCA	11	6.7	1480	144	863
17	LAD	Sk lysis	14	18.5	2045	189	1166
18	RCA	Sk lysis	2	6.1	780	72	456
19	RCA	Sk lysis	7	3.6	549	37	454
20	LAD	PTCA	1	2.6	668	74	518
21	LAD	rtPA lysis	3	4.1	837	55	501
22	LAD	Sk lysis	3	3.7	667	24	441
23	RCA	Sk lysis	6	3.2	904	67	731
Mean (SD)			6.1 (3.5)	5.6 (3.7)	954.2 (454.9)	84.7 (49.5)	635.1 (273.5)

CKmax, peak concentration of creatine kinase; CK-MBmax, peak concentration of creatine kinase MS isoenzyme; LDHmax, peak concentration of lactate dehydrogenase; PTCA, percutaneous transluminal coronary angioplasty; rtPA lysis, alteplase lysis; Sk-lysis, streptokinase lysis; TnT, troponin T.

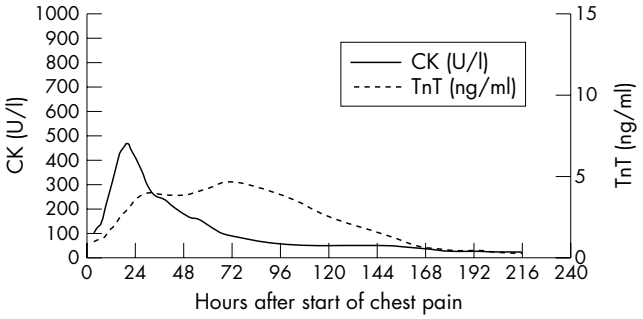

Figure 2 Time course of troponin T (TnT) and creatine kinase (CK) release in group 1 (non-reperfusion group, n = 14).

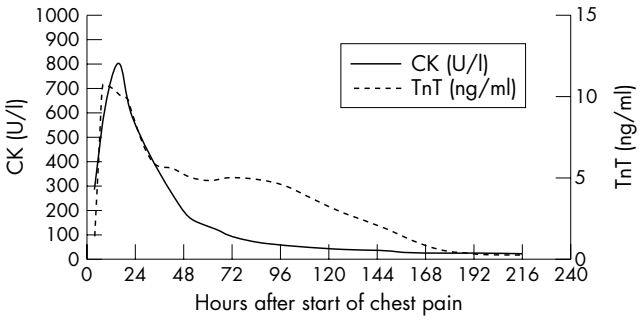

Figure 3 Time course of TnT and CK release in group 2 (reperfusion group, n = 23).

and protocols of the manufacturers. The upper limit of normal for total CK activity was 75 IU/l and for LDH 220 IU/l at 25°C.

The activity of the CK-MB isoenzyme was measured by an immunoinhibition assay (Boehringer Mannheim, Mannheim, Germany). The upper limit of normal was 10 IU/l or 6% of total CK activity, respectively.

Cardiac TnT was determined by a commercially available enzyme linked immunosorbent assay (ELISA) one step sandwich assay with streptavidin technology and two specific monoclonal antibodies developed by Katus and colleagues[14] (Enzymun-Test system, Boehringer Mannheim).

The measuring range for TnT in this test is 0.1–15 ng/ml. TnT concentrations > 0.5 ng/ml were considered to indicate myocardial cell damage. Cross reactivity with skeletal muscle isoforms of TnT is < 0.5%.

Thallium-201 scintigraphy

The extent of resting thallium-201 defects was determined by single photon emission computed tomography (SPECT). Ten to 18 days after myocardial infarction, each patient received 3.0 mCi thallium-201 intravenously at rest and was imaged 30 minutes later with a gamma camera (Siemens Orbiter ZLC 7500, Siemens AG, Erlangen, Germany) linked to a microcomputer (Elscint Microcomputer, Elscint, Wiesbaden, Germany). The camera was started from the right anterior oblique 30° projection and ended at the left posterior oblique 30° projection, collecting data from 32 views. Three dimensional polar maps were then displayed to evaluate the regional distribution of left ventricular thallium-201 activity (fig 1).[17] The scintigraphic estimation of infarct size was defined as the number of left ventricular segments with thallium-201 activity < 67% of maximum.

Table 3 Correlation coefficients between scintigraphic and serological determination of infarct size at peak concentrations of cardiac markers

	Group 1 (n=14)		Group 2 (n=23)	
Marker	*r*	p Value	*r*	p Value
TnT at 72 hours	0.718	<0.004	0.773	<0.001
CKmax	0.610	<0.021	0.737	<0.001
CK-MBmax	0.557	<0.039	0.669	<0.001
LDHmax	0.685	<0.007	0.765	<0.001

TnT was measured 72 hours after onset of chest pain.

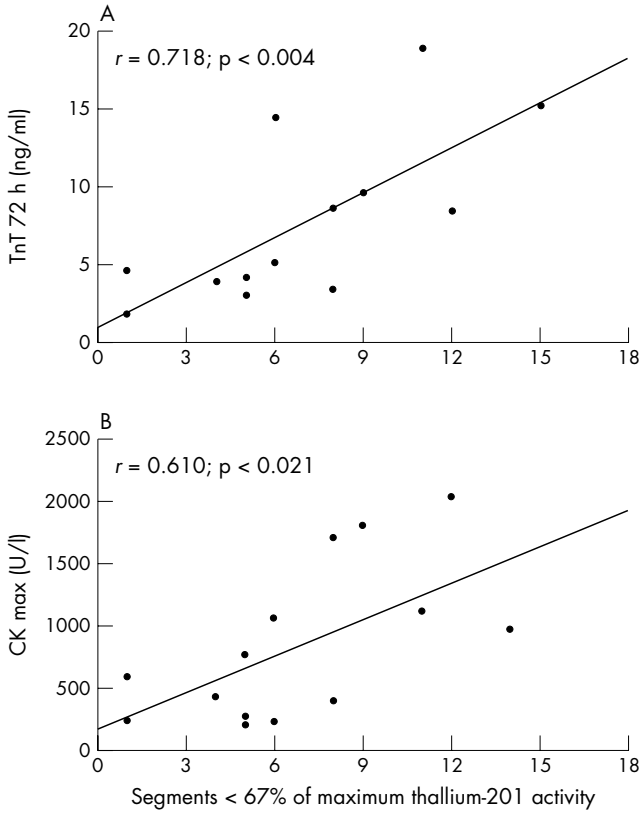

Figure 4 Correlation (A) between scintigraphic infarct size and TnT serum concentrations 72 hours after the onset of symptoms, and (B) between scintigraphic infarct size and maximal CK serum concentrations in group 1 (n = 14).

Statistical analysis

The defect size in tomographic thallium-201 myocardial scintigrams was compared with serological parameters by linear regression analysis. To compare the correlation coefficients, the method of Hotelling[18] was applied.

A probability value of $p < 0.05$ was considered significant. Continuous variables are shown as mean (SD).

RESULTS

Table 1 summarises the clinical data of the patients. Patients in the non-reperfusion (group 1) and reperfusion groups (group 2) were similar with regard to the infarcted coronary artery.

Mean age was non-significantly higher in group I than in group II (NS).

Serological estimation of infarct size

Peak and cumulative serum concentrations of TnT, CK, CK-MB, and LDH were obtained by serial determinations throughout the hospital stay. Table 2 shows individual data.

In both groups, TnT showed a biphasic curve with a brief peak within the first 24 hours and a second peak on the third to fourth day after the onset of chest pain. The first peak obtained in group 1 was lower than the second peak, whereas in group 2 the first peak clearly exceeded the second peak (fig 2, fig 3).

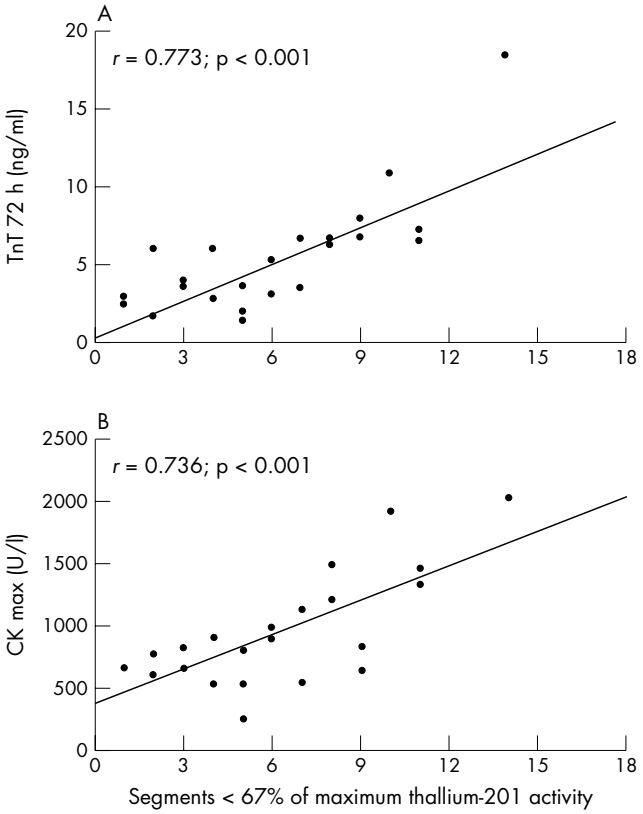

Figure 5 Correlation (A) between scintigraphic infarct size and TnT serum concentrations 72 hours after the onset of symptoms, and (B) between scintigraphic infarct size and maximal CK serum concentrations in group 2 (n = 23).

Thallium-201 imaging

"Scintigraphic infarct size" varied between 1 and 15 left ventricular segments with thallium-201 activity < 67% in group 1 (3–45%, mean 21%) and between 1 and 14 segments in group 2 (3–42%, mean 18%).

Correlation between scintigraphic estimation of infarct size and peak serum concentrations of cardiac markers

A significant linear correlation was obtained between scintigraphic infarct size and the peak serum concentrations of TnT, CK, CK-MB, and LDH (table 3).

Compared with cytosolic markers such as CK, CK-MB, and LDH, the TnT serum concentrations determined 72 hours after onset of chest pain reached the highest correlation coefficients with the scintigraphically estimated infarct size in both groups. Figures 4 and 5 show the correlation between scintigraphic and serological estimates of infarct size by TnT and CK.

Correlation between scintigraphic estimation of infarct size and cumulative serum concentrations of cardiac markers

Like the peak serum concentrations, the cumulative concentrations of all cardiac markers determined in this study correlated significantly with the scintigraphic infarct size, independent of coronary reperfusion (table 4).

Table 4 Correlation coefficients between scintigraphic and serological determination of infarct size at cumulative (cum) concentrations of cardiac markers

	Group 1 (n=14)		Group 2 (n=23)	
Marker	*r*	p Value	*r*	p Value
TnTcum	0.819	<0.001	0.780	<0.001
CKcum	0.655	<0.011	0.621	<0.003
CK-MBcum	0.623	<0.017	0.585	<0.003
LDHcum	0.603	<0.029	0.746	<0.001

Table 5 Correlation coefficients between cumulative CK concentration and cumulative concentrations of TnT, CK-MB, and LDH

	Group 1 (n=14)		Group 2 (n=23)	
Marker	*r*	p Value	*r*	p Value
TnTcum	0.684	<0.008	0.698	<0.001
CK-MBcum	0.943	<0.001	0.751	<0.001
LDHcum	0.856	<0.001	0.667	<0.001

Correlation between cumulative CK concentration and the cumulative serum concentration of other cardiac markers

The serological estimation of infarct size, determined by the cumulative concentration of CK, correlated significantly with the cumulative serum concentrations of TnT, CK-MB, and LDH (table 5).

DISCUSSION

Data obtained in the present study show that scintigraphic versus serological estimation of infarct size is significantly correlated for each serum marker tested, independent of coronary reperfusion. The highest correlation coefficients were achieved with serum concentrations of TnT determined 72 hours after the onset of chest pain and with its cumulative concentrations. The correlation coefficients for the cumulative concentrations of CK and the other cytosolic enzymes were slightly better than for cumulative CK and cumulative TnT. This may be explained by the different release kinetics of the cytosolic enzymes and the properties of TnT as a structural protein. Estimation of infarct size, however, is more precise with cumulative TnT concentrations than with cumulative cytosolic enzyme concentrations, according to the correlation coefficient between scintigraphic estimation of infarct size and cumulative concentrations of marker proteins (table 4).

As serological markers for the estimation of infarct size, serum concentrations of CK, CK-MB, and LDH are mostly used. The accuracy of this approach, however, is adversely affected by several factors: The normal range of serum enzyme activity ranges from 10–80 IU/l for CK, < 10 IU/l for CK-MB, and 140–290 IU/l for LDH. Compared with this normal variation, the serum concentration increase of these cytosolic enzymes after AMI is relatively low. For example, CK and LDH activities increase < 60-fold and < 10-fold, respectively.[19–21] Another disadvantage of cytosolic enzymes is their short persistence in the serum after AMI. CK and LDH serum concentrations decrease to normal concentrations within 3–6 days and 6–15 days, respectively.[22–25] Furthermore, these cytosolic enzymes are also present in non-cardiac muscular tissues and can therefore be increased for other reasons, independent of myocardial cell damage, such as renal failure, myopathies, trauma, or even after vigorous exercise or in chronic alcoholism.[7 8 26]

In contrast to cytosolic enzymes, the baseline concentration of TnT is below the detection limit of commercially available assays but may exceed 400 times the discriminating serum concentration in myocardial cell damage.[27] Compared with the cytosolic markers, TnT serum concentrations increase slightly earlier after the onset of symptoms at about 3.5 hours versus 4–8 hours (CK) and 6–12 hours (LDH).[21] Since cross reactivity with skeletal TnT is < 1%, the specificity and sensitivity of TnT are about 96% and 100%, respectively.[14]

Because of the release kinetics of cytosolic enzymes, which reach a single, brief maximal peak within the first 24–48 hours after AMI and decrease to normal concentrations rapidly

thereafter, serial blood sampling is mandatory to obtain the maximal or cumulative serum concentrations for estimation of infarct size. Prolonged TnT release over several days with a second peak on the third to fourth day allows a more precise estimation of infarct size over a longer period of time, even with a delay of several days after the onset of symptoms. When comparing the study groups in terms of peak serum CK concentration and infarct size estimated by scintigraphy (fig 4B, fig 5B), the gradient of the curve was greater in the reperfusion group than in the non-reperfusion group, reflecting a superincrease of maximal CK in the case of coronary reperfusion. In contrast with CK, the curve of TnT 72 hours after the onset of chest pain is not steeper in the reperfusion subgroup than in the non-reperfusion group (fig 4A, 5A); therefore, TnT 72 hours after the onset of chest pain seems to be almost unaffected by coronary reperfusion. The present study shows that a single blood sample 72 hours after the onset of symptoms allows a rather precise estimation of infarct size with serum TnT when compared with scintigraphic estimation. This result is supported by the findings of Kragten and colleagues.[28] In 22 patients with AMI, these authors also showed that the cumulative as well as the second TnT peak concentration correlated significantly with the cumulative release of cytoplasmic enzyme in reperfused myocardial infarctions; however, their results were not related to infarct size.[28]

Study limitations

In addition to the methodological considerations mentioned above, further limitations have to be taken into account. Using thallium-201 SPECT imaging, assessment of infarct size can be improved by correcting for variable left ventricular mass in the individual segments. Also, the differing absorption in anterior and posterior myocardial segments was not corrected.

Conclusions

According to the present results, a single measurement of circulating TnT 72 hours after the onset of symptoms is a simple and reliable tool for serological estimation of myocardial infarct size independent of early coronary reperfusion.

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