Non-invasive diagnosis of infarct artery patency after acute myocardial infarction by use of serial plasma troponin T concentrations: importance of measurement of peak levels

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Abstract

Objective—To confirm the validity of a previously described method for assessment of infarct artery patency involving serial measurements of creatine kinase activity by use of troponin T concentration as an independent plasma marker.

Design—Streptokinase (1.5×10^6 units) was given intravenously to 60 patients within 6 h of onset of prolonged chest pain and ST segment elevation, and blood was taken for measurement of troponin T concentration at baseline and at 1, 2, 3, 4, 8, 12, 16, 20, and 24 h after starting treatment. Coronary arteriography was performed at 2.6 (SD 0.3) h. Plasma troponin T concentration was assessed by two methods: (1) as the absolute rise between 0 and 3 h; and (2) as the proportion of the total rise (from baseline to peak) over the same period. Accuracy for prediction of infarct artery patency, assessed by receiver operating characteristic curves, was compared for both methods of assessment using troponin T and was in turn compared with previously reported results on the same patients using serial measurements of creatine kinase activity.

Results—Sufficient values for prediction of patency using troponin T were available in 53 patients. A rise in troponin T between 0 and 3 h to $\geq 9\%$ of peak concentration predicted angiographic patency with sensitivity of 94% and specificity of 100%. By contrast, at the optimum cutoff for absolute rate of rise (0.5 $\mu\text{g/l/h}$) sensitivity was only 66% and specificity 86%. Comparable figures for creatine kinase were 92% and 91% ($\geq 20\%$ of peak by 3 h) and 62% and 78% (150 IU/l/h). Receiver operating curves confirmed better predictive accuracy for proportions over absolute rates of rise for both markers ($P < 0.01$).

Conclusions—For accurate diagnosis of infarct artery patency using plasma markers it is necessary to express the rate of rise as a proportion of the peak level. Analysed in this way, both creatine kinase and troponin T are suitable for use in randomised trials of new thrombolytic or adjuvant drugs.

Keywords: troponin T; reperfusion; thrombolytic treatment

Early restoration of infarct artery patency is the major mechanism by which thrombolytic treatment reduces early mortality and preserves left ventricular function.¹ Infarct artery patency can be diagnosed non-invasively,²⁻⁴ and we have shown that early patency diagnosed by a rise in plasma creatine kinase (CK) activity of greater than 20% of the peak level at three hours after starting thrombolytic treatment was associated both with a lower 30 day mortality and reduced left ventricular dilatation in three-week survivors of anterior infarction.⁵ Confirmation of early infarct artery patency is clearly the most important test for efficacy of thrombolytic treatment and there are two main reasons why early patency should be determined. First, in patients whose condition is deteriorating, emergency revascularisation or angioplasty can be beneficial if the infarct related artery remains occluded after thrombolysis. Second, early infarct artery patency is an important end point for use in randomised clinical trials of new thrombolytic or adjuvant drugs. In the former case, patency or sustained occlusion must be diagnosed immediately, but in the latter information on patency can be obtained retrospectively.

In this report we aim to show that the proportion of the peak level of troponin T which appears in the plasma during the first three hours after starting thrombolytic treatment gives significantly greater predictive accuracy for diagnosis of early infarct artery patency than the slope of rise of the absolute value. This supports our earlier finding in the same patients using creatine kinase activity as the marker,⁵ and is shown by use of receiver operating characteristic curves.⁶ A major reason for the superiority for diagnosis of the three-hour proportions over the slopes of the absolute values is that patency of the infarct related artery of very small infarcts (probably reduced or prevented by thrombolytic treatment) is not diagnosed because a low peak level is necessarily accompanied by a small slope.

Methods

Our procedures for angiographic assessment of infarct artery patency and measurement of the activity of creatine kinase and its MM iso-

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Accepted for publication
10 November 1995

(Heart 1996;75:481-485)

forms have been described previously.^{5,7} Briefly, 60 patients (mean age 59, range 40–74, years) seen within 6 h of onset of continuous chest pain and with ST segment elevation of ≥ 1 mm in at least two leads of V4–V6, I, AVL, II, III, and AVF or ≥ 2 mm in leads V1–V3 of the electrocardiogram were given streptokinase 1.5×10^6 U intravenously over 30–60 min, and plasma creatine kinase activity was measured at 0, 1, 2, 3, 4, 8, 12, 16, 20, and 24 h after starting thrombolytic treatment. Thirty of the patients had ST elevation in the anterior leads of the ECG and 30 had elevation in the inferior leads; 46 developed pathological Q waves. Creatine kinase isoforms (CKMM1–3) were measured usually at baseline and at 3 h. At the time that these measurements were made, a method for measurement of troponin T concentration was not available to us, so that plasma was stored at -70°C for subsequent measurement of cardiac troponin T using an enzyme linked immunoassay method (Boehringer Mannheim).⁸ Coronary angiography was carried out at 2.6 (SD 0.3) h after starting thrombolytic treatment, after which a second thrombolytic drug (tissue plasminogen activator) was infused directly into the infarct related coronary artery if the arteriogram showed it to be occluded.⁹

We compared the troponin T measurements with the previously described creatine kinase data,⁵ and used receiver operating curves to compare the accuracy of the two markers to predict angiographic patency (thrombolysis in myocardial infarction study group grades 2 or 3¹⁰) at 2.6 (0.3) h after starting streptokinase infusion. Receiver operating curves were constructed by plotting sensitivity on the Y axis against 1-specificity on the X axis over a full range of possible cutoff points for judging the positivity or negativity of the test. Considering the resultant plot as a square, the corners of which are 0 and 100% sensitivity and 0 and 100% (1-specificity), the area below and to the right of the curve as a proportion of the total area of the square is a measure of the accuracy of the test. An area of 1.0 implies a “perfect” test and an area of 0.5 a “useless” test.^{11,12} The curves were used to compare both for troponin T concentration and creatine kinase activity the rate of rise of absolute activity or concentration over 3 h

(IU/l/h, $\mu\text{g/l/h}$; the slope) with the percent of total rise from baseline to peak levels over the same period (% of peak; the proportion). Areas under the receiver operating curves were compared using the method of Hanley and McNeil.¹²

Results

Plasma for measurement of troponin T was available from 53 of the 60 patients included in the earlier study.⁵ Comparisons are thus made between troponin T measurements on these 53 patients, 32 of whom had initially patent coronary arteries at arteriography (TIMI 3, $n = 30$; TIMI 2, $n = 2$) and creatine kinase levels on 60 patients in whom the infarct related artery was patent in 37 (TIMI 3, $n = 35$; TIMI 2, $n = 2$). As we described previously,^{5,9} patency was subsequently restored to 14 infarct related arteries (within 3–4 h in 13) by intracoronary infusion of tissue plasminogen activator.

The very large variation in peak levels of creatine kinase activity (and in the rate of rise between 0 and 3 h) which we had described previously⁵ was seen also for troponin T concentration (table 1). Variations in peak levels among patients of up to 100-fold for troponin T were, if anything, even greater than for creatine kinase. However, as with creatine kinase, there was a clear differentiation between the proportions of peak level which were released at the various sampling times when these were related to patency of the infarct related artery (fig 1).

A large part of the variation in peak creatine kinase levels had been due to the inclusion in the study of six patients whose levels had reached a peak which was less than twice the upper limit of normal for our laboratory (600 IU/l).⁵ These patients presented with typical symptoms of myocardial infarction and diagnostic ST segment elevation, but failed to

Table 1 Troponin T concentration ($\mu\text{g/l}$) compared with coronary patency assessed by arteriography. Values are mean (SD)

Time after thrombolytic treatment (h)	Artery patent (n = 32)	Artery occluded up to 3h (n = 21)	Artery initially occluded but patent after 3h (n = 13)	Artery remained occluded after 3h (n = 8)
0	0.2 (0.2)	0.3 (0.3)		
1	0.6 (1.0)	0.4 (0.4)		
2	2.5 (3.1)	0.6 (0.6)		
3	6.0 (6.5)	1.3 (1.0)		
4	9.6 (11.1)		3.6 (4.7)	2.0 (2.2)
8	18.7 (13.4)		24.0 (18.8)	18.3 (32.2)
12	19.9 (13.6)		26.3 (13.4)	22.5 (26.8)
16	16.5 (12.3)		25.5 (20.8)	22.6 (18.6)
20	12.8 (8.6)		15.9 (7.6)	17.6 (12.3)
24	10.5 (6.1)		14.8 (6.7)	34.1 (44.1)
Peak value	20.6 (15.0)		30.9 (23.1)	37.8 (44.7)
Time to peak (h)	12.1 (5.9)			18.3 (6.4)

Figure 1 The rise in troponin T expressed as a proportion of the peak concentration up until 24 h after starting streptokinase is shown for three groups of patients. Circles denote patients ($n = 32$) with open arteries at 2.6 (SD 0.3) h, while triangles denote those ($n = 8$) whose arteries were occluded throughout the period of observation. Squares denote patients ($n = 13$) whose arteries were recanalised within 3–4 h by intracoronary infusion of tissue plasminogen activator (see text). Bars indicated SEM.

Figure 2 Rise in troponin T concentration in patients showing respectively patent (empty circles) or occluded (filled circles) infarct related arteries at 2.6 (SD 0.3) h after starting streptokinase. The left hand plots show the rise in concentration from 0 to 3 h, while the right hand plots show the proportion of the total rise (peak level minus baseline level) from 0 to 3 h. The dotted line shows the optimal cut off point for the proportion of total rise.

Figure 3 Rise in creatine kinase activity using the same criteria as in fig 2. The dotted line shows the optimal cutoff point for the proportion of total creatine kinase rise.

Figure 4 Receiver operating characteristic curves for accuracy of troponin T (upper graph) and creatine kinase (lower graph) for prediction of infarct artery patency. The proportions of total area (0.97, 0.96) under the curves for per cent of peak release between 0 and 3 h are significantly greater ($P = 0.004$, $P = 0.0004$) than the proportions (0.80, 0.79) under the curves for slope.

develop pathological Q waves. Subsequent measurement of troponin T in five of these six patients showed more definite changes, the peaks rising to between three and 50 times the upper limit of normal ($0.2 \mu\text{g/l}$). The remaining patient showed only a small rise in troponin T concentration, which remained within the normal range.

Values for the slopes and proportions of troponin T and creatine kinase which appeared in the plasma between 0 and 3 h are shown in figs 2 and 3. Clearly the accuracy of both plasma markers for prediction of infarct artery patency was better for the proportions than for the slopes. This was because many patients with patent arteries had small slopes because the markers were rising to a low peak level; when the slopes were "normalised" to the peak levels the proportions became higher than the proportions for patients with occluded arteries. Receiver operating curves analysis (fig 4) confirmed the superiority of the proportions over the slopes for both markers, the difference being highly significant ($P = 0.004$ for troponin T; $P = 0.0004$ for creatine kinase).

Clearly there was no difference between the accuracy of troponin T and creatine kinase, either for the proportions or for the slopes. At the visually determined optimum cutoff values of $\geq 9\%$ for troponin T proportion and $\geq 20\%$ for creatine kinase proportion (figs 2 and 3), sensitivity and specificity were both better than 90% for both markers. By contrast, optimum values for troponin T slope were 66% and 86% at $0.5 \mu\text{g/l/h}$ and for CK slope

Table 2 Sensitivity and specificity of troponin T and creatine kinase as non-invasive markers of infarct artery patency. Values are per cent (lower 95% confidence limit)

	Predictive method	
	Proportion	Slope
Troponin T		
Sensitivity	94 (79)	66 (47)
Specificity	100 (84)	86 (64)
Creatine kinase		
Sensitivity	92 (78)	62 (45)
Specificity	91 (72)	78 (56)

were 62% and 78% at 150 IU/h. Values for sensitivity and specificity for the various methods, with their lower 95% confidence limits, are shown in table 2.

Discussion

We have shown a better than 90% sensitivity and specificity for prediction of infarct artery patency from measurements of plasma troponin T concentration made at 0 and 3 hours after starting thrombolytic treatment when expressed as a proportion of the peak concentration reached over 24 hours. Predictive accuracy (the percentage of cases correctly classified at the optimum cutoff point) was 51/53 (96%) compared with only 39/53 (74%) for the "uncorrected" slope of rise between 0 and 3 hours. This supports our previous findings which we reported on the same patients using creatine kinase; the predictive accuracy for the enzyme measurement was 55/60 (92%) using the proportions and 40/60 (68%) for the slopes (figs 2 and 3). Analysis by means of receiver operating curves (fig 4) showed that the predictive accuracy for the proportions of both markers was significantly higher than for the slopes. Thus for optimum predictive accuracy it was necessary to determine the peak of activity or concentration, which in practice required blood sampling from an indwelling venous line for 24 hours after the start of thrombolytic treatment. Diagnosis of infarct artery patency or occlusion was necessarily retrospective, making our method unsuitable for use in cases in which emergency revascularisation by "rescue" angioplasty or surgery is contemplated. Moreover our data relate to the use of streptokinase, which remains one of the most commonly used thrombolytic agents worldwide. Whether similar results would be obtained with an accelerated alteplase regimen will need to be evaluated in future studies.

Although early restoration of infarct artery patency is desirable for all patients,¹³⁻¹⁶ it is not feasible in the majority of hospitals to perform early angiography routinely in order to identify patients in whom thrombolytic treatment has failed. Development of more effective thrombolytic regimens is still necessary, however, because reduction in early mortality¹³⁻¹⁵ and improvement in left ventricular function^{15 16} depend on achievement of early infarct artery patency leading to tissue reperfusion.^{1 17} Several factors (inadequate recanalisation, intermittent patency, reocclusion, the no reflow phenomenon) can prevent adequate

reperfusion, leading to one estimate¹⁷ that with the best treatment presently available only 25% of myocardial infarcts are adequately reperfused. Clearly continuing trials to improve the efficacy of thrombolytic treatment are necessary. Moreover such trials should have the ability to detect those cases in which treatment has been most successful, that is, cases in which, despite prolonged chest pain and ST segment elevation, neither pathological Q waves nor ventriculographic evidence of infarction develops. Such cases have been well documented,^{5 15 16 18} and their number should increase as therapeutic strategies improve. The present method, in which the proportion of peak level rather than the slope of absolute rise is measured, is well suited for detection of these cases. Although creatine kinase levels rose to a peak less than twice "normal" in six patients (the left ventriculogram being normal in five of the six),⁵ peak levels of troponin T were raised from three- to 50-fold in all but one patient, confirming that myocardial necrosis had occurred. However, because of the low peak levels, these patients would all have been wrongly classified if the "uncorrected" slopes only had been considered.

Recent reports have in general found less satisfactory predictive value for creatine kinase and troponin T^{4 19-22} as markers of arterial patency, and the reason appears to be that absolute slopes, not proportions were used for prediction. Thus Zabel *et al*⁴ found areas under ROC curves to be 0.79 and 0.80 for creatine kinase and troponin T slopes respectively; these were similar to the areas for creatine kinase and troponin T slopes which we found, but less than the areas (0.96, 0.97) which we found for both of the corresponding proportions. Similarly Ohman *et al*²¹ found an area of 0.72 for creatine kinase slope, although this was improved to 0.85 by the addition of clinical variables.

Is non-invasive diagnosis of infarct artery patency desirable, and if so, what is the best method? The important prognostic and therapeutic implications mean that the answer to the first question must be in the affirmative. This being the case, both creatine kinase and troponin T appear to be of about equal value, although troponin T may be the more sensitive marker if the amount of myocardial necrosis is minimal. In this context it is of interest that raised levels of troponin T in the absence of increased creatine kinase activity predict infarction in patients with unstable angina.²³ Is non-invasive diagnosis more or less reliable than angiography? Despite the recent demonstration that differing grades of angiographic patency correlate with differing clinical outcomes¹ the probability that recanalisation does not equate with reperfusion²⁴ may mean that rapid protein washout from the infarct is more meaningful than angiographic patency of the infarct related artery. It is of interest that angiography of patients in the global utilization of streptokinase and tissue plasminogen activator (GUSTO) trial at three hours after streptokinase showed an open vessel (TIMI grades 2 or 3) in 74% of patients but complete

recanalisation (TIMI 3) in only 41%. The present data suggest a patency rate of approximately 60% at 2.5–3 hours after streptokinase. Reperfusion is not an all or none phenomenon, and arteries may open and close during thrombolytic treatment, rendering a single arteriographic "snapshot" potentially unreliable.²⁵ Further studies are necessary for clarification of the degrees of reperfusion which can be achieved by the use of thrombolytic treatment.

Supported by the Health Research Council and the National Heart Foundation of New Zealand. We are particularly grateful to the nursing staff of the Coronary Care Unit at Green Lane Hospital, without whose help this study would have been impossible.

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