Prospective study of the role of cardiac troponin T in patients admitted with unstable angina

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Abstract

Objective—To examine the prognostic significance and role in risk stratification of the biochemical marker troponin T in patients admitted with unstable angina.

Design—Single centre, blinded, prospective study of patients admitted with chest pain.

Setting—Coronary care unit of a district general hospital.

Subjects—460 patients admitted with chest pain and followed up for a median of three years. 183 patients had a final diagnosis of unstable angina.

Main outcome measures—Cardiac death, need for coronary revascularisation, or readmission with non-fatal myocardial infarction as first events.

Results—62 (34%) unstable angina patients were troponin T positive. This group had significantly increased incidence rates of subsequent cardiac death (12 cases (19%) v 14 (12%)), coronary revascularisation (22 (35%) v 26 (21%)), death or revascularisation (33 (53%) v 40 (33%)), and death or non-fatal myocardial infarction (18 (29%) v 21 (17%)) compared with the troponin T negative group. In multiple logistic regression troponin T status was a highly significant predictor for the end points coronary revascularisation and cardiac death or revascularisation as first events.

Conclusion—Troponin T in the serum of patients with unstable angina identifies a subgroup at higher risk of subsequent cardiac events

and its measurement aids in risk factor stratification. The increased risk extends to two years after admission. Prospective randomised trials are required to identify optimum therapeutic strategies for this subgroup.

Introduction

Unstable angina represents a critical phase of ischaemic heart disease and is associated with a significant risk of subsequent myocardial infarction or death.¹⁻⁷ A subset of patients with unstable angina have raised concentrations of the cardiac specific protein troponin T⁸⁻¹¹ in their serum early in the admission period. Detection of troponin T indicates minor myocardial damage and was associated with an excess of cardiac events both in inpatients⁹⁻¹¹ and on short term follow up.^{12 13} We evaluated the potential role of this marker in stratifying for risk patients with unstable angina admitted in routine clinical practice.

Subjects and methods

We conducted a single centre blinded study with follow up of patients admitted to a hospital coronary care unit with chest pain. Management decisions were based on clinical, electrocardiographic, and routine biochemical marker results (daily serum creatine kinase, aspartate transaminase, and hydroxybutyrate dehydrogenase activities). An additional sample was taken 12-24 hours after admission, when the cardiac troponin T concentration is at its most efficient for diagnosing myocardial damage in these patients.¹¹ All

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Fig 1—Kaplan-Meier cumulative hazard function curves for unstable angina according to troponin T status and end points †Mantel-Haenszel statistic. ‡Log rank statistic.

Table 1—Baseline demographic values. Except where stated otherwise figures are whole numbers (percentages) of subjects

Variable	Unstable angina		Significance†
	Troponin T positive (n = 62)	Troponin T negative (n = 121)	
Mean age (years) (SD)	62.8 (10.3)	59.9 (11.8)	0.089
Male sex	42 (68)	91 (75)	0.231
Hypertension	17 (27)	32 (26)	0.889
Diabetes mellitus	13 (21)	16 (13)	0.182
Current smoker	23 (37)	33 (27)	0.157
Previous myocardial infarction	20 (32)	46 (38)	0.444
Accelerated angina‡	27 (44)	49 (40)	0.692
Admission rest pain	44 (69)	80 (66)	0.507
Mean time to coronary care from worst pain (hours) (SD)	5.0 (6.5)	5.1 (8.9)	0.313
ST or T wave changes in admission electrocardiogram	31 (50)	49 (40)	0.162
Intravenous heparin	25 (40)	60 (50)	0.236
Nitrate therapy	36 (58)	65 (54)	0.644
β Blocker	21 (32)	32 (27)	0.492
Calcium antagonist	27 (45)	49 (40)	0.536
Pain as inpatient (>1)	17 (27)	25 (21)	0.305
Electrocardiographic changes with pain	10 (16)	13 (11)	0.230
Mean length of stay (days) (SD)	9.7 (4.5)	7.1 (5.1)	0.0001
Discharge aspirin	48 (77)	85 (70)	0.304
Mean No of discharge drugs	1.9	1.6	0.035

†Assessed by χ^2 for continuous variables and Mann-Whitney U for ordinal variables.

‡Increasing chest pain in 48 hours before admission.

Table 2—Multiple logistic regression analysis of variables for each end point

End point and variable	Significance†	Odds ratio	95% Confidence interval
Cardiac death			
Previous myocardial infarction	0.040	3.66	1.06 to 12.65
Troponin T status	0.507	1.50	0.43 to 5.41
Further pain or electrocardiographic changes, or both	0.765	1.20	0.36 to 4.03
Coronary revascularisation			
Accelerated angina‡	0.001	3.74	1.70 to 8.22
Troponin T status	0.007	3.18	1.37 to 7.37
Troponin T or accelerated angina, or both	0.0007	5.39	2.04 to 14.33
Further pain or electrocardiographic changes, or both	0.017	3.19	1.23 to 8.33
Cardiac death or revascularisation			
Troponin T status	0.008	2.55	1.28 to 5.08
Accelerated angina	0.038	1.98	1.04 to 3.79
Troponin T or accelerated angina, or both	0.0007	3.55	1.71 to 7.40
Further pain or electrocardiographic changes, or both	0.041	2.16	1.03 to 4.54
Cardiac death or non-fatal myocardial infarction			
Diabetes mellitus	0.007	4.56	1.51 to 13.7
Age	0.009	1.08	1.02 to 1.14
Previous myocardial infarction	0.037	2.83	1.06 to 7.57
Troponin T status	0.123	1.21	0.42 to 3.47
Further pain or electrocardiographic changes, or both	0.739	0.84	0.31 to 2.29

†Assessed by χ^2 .

‡Increasing chest pain in 48 hours before admission.

major coronary segment), a positive treadmill test result (>0.1 mV ST segment depression 80 ms after the J point), or detection of ischaemia on thallium radioisotope study. Patients with a final diagnosis of unstable angina were considered to be troponin T positive if the troponin T concentration was $\geq 0.2 \mu\text{g/l}$ 12–24 hours after admission.^{11 13}

Troponin T concentrations were measured by an enzyme linked immunosorbent assay (ELISA) with an ES-300 immunoassay analyser (Boehringer Mannheim, Lewes, Sussex).¹¹

Statistical analysis—Baseline demographic values were expressed as proportions of patients or means and standard deviations. Cumulative hazard curves were computed by the Kaplan-Meier method. End points were cardiac death, need for coronary revascularisation, death or revascularisation, and death or non-fatal myocardial infarction as a first event. Non-cardiac death was treated as a censored observation. End point statistical evaluation was performed with the log rank test and the Mantel-Haenszel test. All significant variables identified in univariate analysis and also indices that have been used to stratify unstable angina patients for risk^{2 16–20} were entered into a multivariate one step logistic regression model. Statistical analysis was by the SAS statistical software package (SAS Institute Inc, Cary, North Carolina; version 6.08).

Results

Troponin T measurements were available for 460 patients and this cohort was followed up for a median of 1032 days (lower quartile 858, upper quartile 1307, range 3–1607). A total of 183 patients had a final diagnosis of unstable angina. Table 1 summarises the baseline demographic details of these patients. Sixty two (34%) patients were positive for troponin T (serum concentrations 0.2–6.1 $\mu\text{g/l}$) and 121 (66%) negative for troponin T. Baseline demographic values in the troponin T positive and troponin T negative patients showed very little difference clinically between the groups (table 1).

Figure 1 shows the cumulative hazard curves for the unstable angina groups dichotomised according to troponin T status. All the curves separated early and continued to separate for about two years after the index admission. For cardiac death the curves began to converge after this period. Twelve (19%) troponin T positive patients compared with 14 (12%) troponin T negative patients died (log rank test, $P = 0.11$). This difference reached significance when allowance was made for coronary revascularisation by means of the Mantel-Haenszel statistic ($P = 0.035$; relative risk 2.58 (95% confidence interval 1.07 to 6.24)). Twenty two (35%) troponin T positive patients underwent revascularisation and only one (5%) died. By contrast, of the 40 troponin T positive patients who did not undergo revascularisation, 11 (28%) died (log rank test, $P = 0.028$). In the logistic regression model (table 2) only the association with previous myocardial infarction reached the conventional level of significance ($P = 0.04$).

Twenty two (35%) troponin T positive patients versus 26 (21%) troponin T negative patients underwent either coronary artery bypass grafting (14 (23%) versus 18 (15%) patients respectively) or percutaneous transluminal coronary angioplasty (eight (13%) versus eight (7%)) as first events (log rank test, $P = 0.032$; relative risk 2.09 (1.06 to 4.03)) (fig 1). In the regression model both accelerated angina (increasing chest pain in the 48 hours before admission) and troponin T status were highly significant for this end point (table 2).

Thirty three (53%) troponin T positive patients versus 40 (33%) troponin T negative patients either died or underwent revascularisation as a first event (log rank

management decisions were made without knowledge of the patient's troponin T status.

Full clinical details of each patient were recorded on a form. Follow up for cardiac events was by examination of hospital records, necropsy reports when available and death certificates, questionnaires, and telephone contact when required. Survival status and cause of death were established for all patients. Cause of death was classified according to American Heart Association criteria.¹⁴

Diagnostic classifications—Unstable angina was diagnosed retrospectively if the World Health Organisation criteria for myocardial infarction were not met.¹⁵ All enzyme measurements (serum creatine kinase, aspartate transaminase, and hydroxybutyrate dehydrogenase activities) were below twice the upper limit of the 95% reference range throughout the routine sampling period. Evidence of ischaemic heart disease was shown by either a cardiac event during follow up, a positive coronary angiogram (stenosis of 50% or more in a

Key messages

- Unstable angina represents a critical phase of ischaemic heart disease
- Stratifying patients with unstable angina for risk remains a difficult clinical problem
- A new cardiac specific protein, troponin T, can now be measured in serum
- The detection of troponin T 12-24 hours after admission identifies a high risk subgroup of patients with unstable angina
- Prospective trials are required to identify optimum therapeutic strategies for this subgroup

test, $P = 0.004$; relative risk 2.45 (1.30 to 4.61)) (fig 1). In the logistic regression model troponin T status was the most significant single variable predictor for this end point ($P = 0.008$; relative risk 2.55 (1.28 to 5.08)). Again the presence of either variable—that is, accelerated angina or troponin T status—was highly significant for this end point ($P = 0.0007$) (table 2).

Eighteen (29%) troponin T positive patients versus 21 (17%) troponin T negative patients either died or suffered a non-fatal myocardial infarction as a first event (fig 1) (log rank test, $P = 0.07$). This difference reached significance when allowance was made for coronary revascularisation by means of the Mantel-Haenszel statistic ($P = 0.042$; relative risk 2.16 (1.03 to 4.53)). In the logistic regression model patients with diabetes (table 2) had a significantly increased risk for this end point. The association with troponin T status did not reach significance ($P = 0.12$).

Comment

The overall finding from this study is that, though it should not be used as a sole discriminator of future risk, a serum troponin T concentration $\geq 0.2 \mu\text{g/l}$ measured 12-24 hours after admission will identify a subgroup of patients with unstable angina in routine clinical practice who are at increased risk of cardiac events on long term follow up. Prospective randomised trials are required to identify optimum therapeutic strategies for this subgroup.

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Characteristics of fatal methadone overdose in Manchester, 1985-94

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Deaths associated with methadone, a drug often prescribed for opiate addiction, are increasing.¹⁻³ We describe the recent experience in Manchester, particularly in relation to diverted methadone (methadone taken by someone other than the person to whom it was prescribed).

Subjects, methods, and results

We examined the records of the coroner for the City of Manchester (population around 400 000) from January 1985 to December 1994 and identified all fatal overdoses. Of 602 deaths associated with drug and alcohol toxicity, 90 were attributed wholly or partly to methadone. Another person died after developing gangrene of the arm from intravenous methadone injection. In 52 of the 90 cases methadone was the sole cause of death, the remaining deaths being caused by methadone

combined with other drugs or alcohol, or both. Victims' ages ranged from 2 to 50 years (mean 26.3 years; inter-quartile range 22 to 31 years); 79 were male. Eighteen of the victims were resident outside the city but died within its boundaries; the remainder had Manchester addresses, including one who died in Amsterdam but whose body was returned to Manchester for necropsy. Verdicts at inquest were misadventure (57), open (21), suicide (6), and accidental (1). Five inquests (on four children, aged 2 or 3 years, and one adult) were adjourned for criminal proceedings. Charges were brought in four, manslaughter being proved in two. In the remaining case the inquest was reopened and a verdict of unlawful killing recorded.

Evidence at inquest showed that 36 of the victims had taken methadone that had been prescribed to them; 32 had taken methadone prescribed to others (diversion), including four who bought methadone. In the remaining 22 cases the source was not recorded. The coroner usually records the prescription of methadone, so these cases probably also represent diversion of the drug.

Deaths associated with methadone rose steadily during the study, roughly in parallel with the rise in methadone prescription. In 1994 methadone accounted for 30.6% of all fatal overdoses in Manchester, and methadone associated deaths in Manchester accounted for 18.8% of the total in England and Wales in 1991 (table 1).

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