

SCIENTIFIC LETTERS

Symptom expectations and delay in acute myocardial infarction patients

The efficacy of the timely administration of thrombolytic treatment in the clinical management of acute myocardial infarction (MI) is well established. Large scale clinical trials have conclusively shown that the earlier the administration of such treatment, the greater the morbidity and mortality advantage.¹ The demonstration of this time dependent relation has prompted research into factors that contribute to the delay interval between symptom onset and hospital presentation. The failure of sociodemographic and clinical factors to be consistently related to pre-hospital delay² has recently focused attention on how patients make sense of their symptoms and determine whether they need urgent medical help.

Building on a recent study which found that patient delay was associated with a discrepancy between symptom experience and prior symptom expectation of MI,³ we extended the scope of this research by also investigating whether delay was related to having a family member present or to behaviours such as self medication before calling for help. We evaluated a consecutive sample comprising 47 participants with a confirmed diagnosis of acute MI (38 men and nine women with a mean (SD) age of 62 (13.4) years). Thirty eight per cent of the sample had a family history of MI and 15% of participants had experienced a previous MI.

Patients were required to recall both the symptoms experienced as part of their MI and the symptoms they expected using a list of 18 symptoms. Patients also rated the match between the symptoms experienced and the symptoms expected on a single visual analogue scale scored from 0 (no match) to 10 (exact match). Patients were asked what, if any, attempts at self treatment, such as resting or taking medication, they had made before reaching the decision to go to hospital. Patients were also asked whether an ambulance was called and if a doctor was consulted before arriving at hospital.

Differences in mean pre-hospital delay times were analysed using independent samples *t* tests and one way analyses of variance. In those instances where the data were

continuous, Pearson correlations were employed to test associations. A multiple regression analysis was used to examine which variables were most closely associated with pre-hospital delay time. All tests of statistical significance were two tailed and probability values of $p < 0.05$ were considered significant.

The majority of participants experienced their initial symptoms while at home (72.3%) and in the presence of another person (66%). Seventy four per cent of participants talked with someone following symptom onset. Consistent with previous studies⁴ the distribution of pre-hospital delay variable was highly positively skewed and required log transformation. The mean (SE) and median pre-hospital delay times were 15.3 (4.1) and 4.0 hours, respectively. Pre-hospital delay was unrelated to age, sex or the following clinical variables: site of MI, peak creatine kinase (CK) concentration, previous MI, family history of heart disease, current smoker, previously diagnosed diabetes mellitus, hypertension, and previous cardiac rehabilitation. However, shorter delay times were demonstrated in patients who experienced symptom onset in the presence of a family member (1.6 hours *v* 6.1 hours; $t(45) = 2.23$; $p = 0.03$) and who talked to another person (4.0 hours *v* 10.8 hours; $t(45) = 2.17$; $p = 0.04$) or a family member following symptom onset (2.2 hours *v* 6.5 hours; $t = 2.25$; $df = 45$; $p = 0.03$).

Eighty one per cent of the sample attempted to self treat their symptoms before seeking professional medical care, and this was associated with a significantly longer delay time ($t(45) = 2.07$; $p = 0.05$). An ambulance was called in the case of 66% of patients and this was associated with significantly shorter pre-hospital mean delay times (3.8 *v* 9.3 hours; $t(45) = -0.10$; $p = 0.04$). Fifty five per cent of the sample consulted a physician before hospital presentation and there was a trend for this to be associated with longer delay times (7.1 *v* 3.5 hours; $t(45) = 1.75$; $p = 0.09$).

The MI symptoms experienced and expected by patients are shown in table 1. The most common symptoms expected and experienced were chest pain, chest discomfort, loss of strength, fatigue, and radiating pain or shoulder pain. However, there was a discrepancy for many patients mostly in terms of symptoms they expected but were not experienced. The symptoms of collapse, dizziness, irregular heart beat, and loss of consciousness had significantly higher levels of expectation than experience. On the other hand, an upset stomach was expected by significantly fewer patients than in fact experienced the symptom.

The majority of the sample reported experiencing some degree of mismatch between experienced and expected symptoms, with only two participants reporting experiencing an exact match. As predicted, the degree of match was significantly correlated with delay ($r = -0.45$, $p = 0.002$), with a greater discrepancy between expectations and experience being associated with longer delays before reaching hospital. When patients were divided into three equivalent groups according to degree of match between expected and experienced symptoms, there was a highly significant effect for the length of pre-hospital delay ($F(2,44) = 108.5$; $p < 0.001$).

In order to determine the most important variables associated with pre-hospital delay, the factors significantly associated with delay in the univariate analyses were entered into a stepwise multiple regression model. Two variables entered the equation ($R = 0.45$, $F(2,44) = 8.64$, $p = 0.001$) with the majority of the variance (18%) being explained by the match between expected and experienced symptoms ($\beta = -0.43$, $p = 0.001$). Conversing with someone during symptom onset added an additional 6% of variance to the equation ($\beta = -0.28$, $p = 0.03$).

This study further highlights the role of symptom interpretation in determining the length of the pre-hospital delay time. We found none of the sociodemographic or clinical factors assessed to be significantly associated with pre-hospital delay times. Rather, delay was most closely related to the mismatch between expected and experienced symptoms. Conversation with someone about the symptoms during symptom onset also reduced delay. The importance of this finding is that, unlike previous studies that have focused on the clinical and demographic factors in delay, this newer approach provides a target for community education programmes and a way of evaluating the effectiveness of these interventions.

While the study is limited by the retrospective recall of symptoms, the data suggest that the reality for many patients in this study was that the onset of symptoms of MI were less dramatic than expected. Most patients had more dramatic expectations of symptoms of MI than actually occurred. These data suggest the need for public education to broaden the range of symptoms expected as part of the onset of an MI. Given that the role of another person seems to be critical in facilitating the decision to seek immediate help, intervention programmes targeted at widening the perception of symptom of MI onset should not just be restricted to those individuals at risk.

KATE PERRY
KEITH J PETRIE
CHRIS J ELLIS*
ROBERT HORNE†
RONA MOSS-MORRIS
Department of Health Psychology,
*Department of Medicine,
Faculty of Medical and Health Sciences,
The University of Auckland, Private Bag 92019,
Auckland, New Zealand
†Centre for Health Care Research,
University of Brighton,
Brighton, West Sussex, UK
kj.petrie@auckland.ac.nz

Table 1 Symptoms expected and experienced (%) as part of onset of myocardial infarction

Symptom	Expected	Experienced	<i>t</i> (46)	<i>p</i> Value
Breathlessness	59.6	51	0.850	0.400
Chest discomfort	85.1	87.2	-0.299	0.767
Chest pain	91.5	83.0	1.158	0.252
Collapse	36.2	19.1	2.226	0.031
Coughing	17	14.9	0.374	0.710
Dizziness	46.8	21.3	3.072	0.004
Fatigue	53.2	59.6	-0.724	0.473
Fever	19.1	27.7	-1.000	0.323
Headaches	19.1	17.0	0.330	0.743
Increased sweating	59.6	61.7	-0.240	0.811
Irregular heartbeat	72.3	31.9	5.15	0.000
Irritability	23.4	19.1	0.814	0.420
Loss of consciousness	42.6	17.0	3.072	0.004
Loss of strength	66	66	0.000	1.00
Nausea/vomiting	34	48.9	-1.854	0.070
Numbness	38.3	31.9	0.829	0.411
Radiating arm/shoulder pain	53.2	59.6	-0.684	0.497
Upset stomach	17	38.3	-2.871	0.006

1 Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. *Lancet*, 1994;343:311-22.

2 Gurwitz JH, McLaughlin TJ, Willison DJ, et al. Delayed hospital presentation in patients who

have had acute myocardial infarction. *Ann Intern Med* 1997;126:593-9.

- Horne R, James D, Petric K, et al. Patients' interpretation of symptoms as a cause of delay in reaching hospital during acute myocardial infarction. *Heart* 2000;83:388-93.
- Dracup K, McKinley SM, Moser DK. Australian patients' delay in response to heart attack symptoms. *Med J Aust* 1997;166:233-6.

Elevated concentrations of macrophage colony stimulating factor predict worse in-hospital prognosis in unstable angina

Macrophage colony stimulating factor (MCSF) is a haematopoietic growth factor released by the injured endothelium and can stimulate proliferation, differentiation, and maturation of monocytes and macrophages.¹ MCSF stimulates the synthesis of monocyte chemoattractant protein 1 and increases the adhesion of monocytes to endothelium. In addition, MCSF has been located in atherosclerotic lesions of humans and it has been proposed that it may contribute to the progression of atherosclerosis.

Elevation of MCSF has also been reported in unstable angina but few data exist regarding the prognostic value.² In the present study we evaluated whether admission concentrations of MCSF can predict prognosis in patients hospitalised with unstable angina.

We studied 122 patients (96 men and 26 women) aged 59 (10) years (range 38-75 years) admitted to our coronary care unit with severe unstable angina. Inclusion criteria were angina at rest with at least two attacks or one episode lasting > 20 minutes in the previous 24 hours with newly developed ≥ 0.1 mV ST segment depression in two or more contiguous leads. There was no elevation of creatine kinase (CK) on admission or six hours later. Exclusion criteria were recent myocardial infarction (< 3 months), coronary artery bypass graft, age > 75 years, left bundle branch block, and inflammatory disease.

Venous blood samples were obtained on admission for assessment of MCSF, interleukin 6 (IL-6), and C-reactive protein (CRP). CK was measured on admission and six hours later and those with increased concentrations were excluded. CK was also determined 12 hours after admission and then every day during hospitalisation to identify those with myocardial necrosis.

All patients received intravenous heparin, nitrates, aspirin, and a combination of β blockers and calcium antagonists according to the severity of symptoms. Patients were divided into two groups according to in-hospital outcome: group A comprised 70 patients with an eventful course, and group B comprised 52 patients without an event. An event was defined as the occurrence of death, non-fatal acute myocardial infarction, and the recurrence of angina requiring further titration of anti-ischaemic medication or early revascularisation.

Serum MCSF concentration was measured by quantitative sandwich enzyme immunoassay technique (R & D Systems) with a range from 31.2-2000 pg/ml. IL-6 was

measured with high sensitivity enzyme linked immunoassay (R & D Systems) with a range from 0.156-10 pg/ml. CRP was assayed by particle enhanced immunonephelometry (N Latex CRP mono, Dade-Behring) with a range from 0.175-1100 mg/l. The intra-assay and inter-assay coefficient of variation for MCSF and CRP measurements was < 5% and for IL-6 measurements < 12%.

MCSF, IL-6, and CRP values which were not normally distributed were expressed as medians. Differences between groups were analysed by Mann-Whitney U test. Spearman's rank correlation test was used for correlations. A logistic regression model was applied using outcome as dependent variable and MCSF, IL-6, CRP, age, sex, diabetes mellitus, hypertension, smoking, and body mass index as predictor variables. In this model logarithmic transformation was made on MCSF, IL-6, and CRP concentrations. A probability value of $p < 0.05$ was considered significant.

The two groups did not differ significantly with regard to age, sex, and risk factor distribution. During hospitalisation 70 of 122 patients (57.4%) had an eventful in-hospital course (group A). Of these, two died, 12 developed a myocardial infarction, and 56 had a recurrence of angina which in 31 patients did not respond to maximal medical treatment followed by urgent coronary angiogram. Fifty two of 122 patients (42.6%) responded entirely to medical treatment (group B).

MCSF, IL-6, and CRP concentrations were higher in group A compared to group B (table 1). MCSF concentrations were the most powerful predictor of outcome with an adjusted odds ratio for event during hospitalisation of 6.3 (95% confidence interval (CI) 1.9 to 21.2, $p = 0.003$). There was also a positive correlation between MCSF with IL-6 ($r = 0.37$, $p = 0.0001$) and CRP ($r = 0.52$, $p = 0.0001$) concentrations.

This study is the first to report that patients with unstable angina and clinical in-hospital deterioration have higher MCSF concentrations on admission than those with an uneventful course. In addition, MCSF concentrations were the most powerful predictor for short term prognosis. Recently, Saitoh and colleagues² showed that high MCSF concentrations predict cardiac events during a follow up period of 14 months in patients with stable and unstable angina.

Unstable angina is associated with an exaggerated inflammatory reaction and is characterised by a significantly larger amount of macrophage-rich plaques compared to stable angina. It has also been reported that MCSF is higher in patients with unstable than stable angina. These increased MCSF concentrations may not represent an epiphenomenon but may play a substantial role in activation and proliferation of macrophages. The precise signal of MCSF production in acute coronary syndromes is unknown. In vitro studies showed that minimally modified low density lipoprotein (LDL) induces the expression of MCSF,³ and therefore oxidised LDL could be a candidate inducer of MCSF production. It

has also been postulated that MCSF may initiate and prolong ischaemic episodes by increasing coronary tone, impairing vasodilatation, and promoting the formation of microthrombi.⁴ Therefore, the higher MCSF concentrations which predicted worse short term prognosis in our study may not only be a marker of ischaemia but may also play a role in triggering or worsening the ischaemia.

In our study admission IL-6 and CRP concentrations were also higher in patients with a complicated in-hospital course which is in line with previous studies.⁵ We also found a positive correlation of MCSF with IL-6 and CRP. The underlying mechanism of the interaction among MCSF, IL-6, and CRP is unclear. It is tempting to speculate that MCSF activated macrophages produce increased amounts of IL-6 which may lead to CRP production by hepatocytes.

This study suggests that increased admission concentrations of MCSF predict a worse short term prognosis in patients with unstable angina. MCSF may therefore play an active role in acute coronary events.

LOUKIANOS S RALLIDIS

KOSTAS P THOMADIS

MARIA G ZOLINDAKI*

AGGELIKI H VELLISARIDOU*

EVANGELOS G PASTERIADIS

Department of Cardiology and *Biochemistry

Laboratory General Hospital of Nikea,

Piraeus, Greece

rallidis@ath.forthnet.gr

- Roth P, Stanley ER. The biology of CSF-1 and its receptor. *Cur Top Microbiol Immunol* 1992;181:141-67.
- Saitoh T, Kishida H, Tsukada Y, et al. Clinical significance of increased plasma concentration of macrophage colony-stimulating factor in patients with angina pectoris. *J Am Coll Cardiol* 2000;35:655-65.
- Rajavashisth TB, Andalibi A, Territo MC, et al. Induction of endothelial cell expression of granulocyte and macrophage colony-stimulating factors by modified low-density lipoproteins. *Nature* 1990;344:254-7.
- Ikonomidis I, Andreotti F, Economou E, et al. Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. *Circulation* 1999;100:793-8.
- Biasucci LM, Liuzzo G, Fantuzzi G, et al. Increasing levels of interleukin (IL) -1Ra and IL-6 during the first 2 days of hospitalization in unstable angina are associated with increased risk of in-hospital coronary events. *Circulation* 1999;99:2079-84.

Use of cardiac rehabilitation among patients following coronary artery bypass surgery

Cardiac rehabilitation aims to facilitate physical, psychological, and emotional recovery for patients following coronary revascularisation, and evidence suggests that it improves short and long term prognosis.¹ Recently the *National service framework for coronary heart disease* has stated that by April 2002, 85% of eligible patients should be offered cardiac rehabilitation.¹ However, service provision for coronary artery bypass surgery (CABG) is far from optimal. Male sex and socioeconomic deprivation are associated with risk of cardiovascular disease and are also important factors in use of cardiac investigations, referral and waiting times for CABG itself.^{2,3} More recently this has been reconfirmed with the take up of cardiac rehabilitation among patients following myocardial infarction,⁴ but not in patients following CABG. We therefore examined determinants of uptake of cardiac rehabilitation in patients following CABG.

Table 1 Macrophage colony stimulating factor (MCSF), interleukin 6 (IL-6), and C-reactive protein (CRP) concentrations on admission in patients with eventful (group A) and uneventful (group B) in-hospital course

	Group A	Group B	p Value
MCSF (pg/ml)	477 (386 to 650)	309 (269 to 538)	0.0001
IL-6 (pg/ml)	9 (3.7 to 26)	4.5 (3 to 9)	0.01
CRP (mg/l)	9.3 (3.3 to 21)	2.9 (1.4 to 5.4)	0.0007

Values are expressed as median and 25th and 75th centile.

Between 1 November 1998 and 31 October 1999 we conducted an evaluation of patients' referrals for cardiac rehabilitation following CABG alone at one centre. Patients referred fell into the hospital catchment area which is not covered by a cardiac liaison service. All patients were invited by post or telephone to attend a seven week cardiac rehabilitation programme based at the hospital site. Patients are first invited to a pre-assessment clinic two weeks after discharge and a six week course on health education including supervised exercise and relaxation classes one month later. Patients who failed to attend were followed up by telephone. Data were abstracted on demographic details, cardiovascular risk factors, attendance, and reasons for non-attendance. Since the hospital site is centrally located with easy access, data on the mode of transport for patients invited for cardiac rehabilitation was not collected. The Carstairs index, derived from patients' post codes was used to measure socioeconomic deprivation,³ and was divided into three groups where category 1 denotes least deprived and 3 most deprived. Differences in patient characteristics between those attending and not attending were tested using *t* test and chi square (χ^2). Logistic regression was used to determine effects of independent variables on attendance and was reported as odds ratios and 95% confidence intervals (CI).

The referrals of 187 patients were reviewed and of these 111 (59%) attended at least one cardiac rehabilitation sessions. There were no significant differences in age, sex, previous myocardial infarction or CABG between patients attending or never attending cardiac rehabilitation (table 1). Non-attendance was associated with socioeconomic deprivation ($p = 0.01$) and smoking ($p = 0.005$). Using logistic regression to adjust for age, sex, and other risk factors, deprivation and smoking were both independently associated with non-attendance with odds ratios of 0.38 (95% CI 0.16 to 0.90) and 0.39 (95% CI 0.17 to 0.93), respectively. There was a significant trend to suggest that patients with more risk factors were less likely to attend cardiac rehabilitation ($p < 0.001$). Of the patients who did not attend 11/76 (15%) stated they were not interested, 7/76 (10%) felt fine, and 22/76 (29%) gave no reason. Of this patient group, 23/40 (58%) were least deprived and 10/40 (25%) most deprived. Of

the remaining non-attenders, 12/76 (17%) had multiple health problems, 6/76 (8%) work pressures, 3/76 (3%) had died, 3/76 (3%) could not speak English, and 12/76 (15%) could not be reached.

These results show a strong association between socioeconomic deprivation, smoking, and non-attendance of cardiac rehabilitation for patients following CABG. Forty one per cent of patients did not attend cardiac rehabilitation. Non-attendance was two thirds more likely if the patient smoked or lived in a deprived area and was significantly associated with having more cardiovascular risk factors than those attending. One third of patients invited for cardiac rehabilitation had previous myocardial infarction or CABG but the referral letters did not record whether this patient group had ever attended previous programmes. Recent evidence indicates that understanding and perceptions of patients having undergone coronary revascularisation of their disease may also affect attendance of cardiac rehabilitation.⁶ These factors require further investigation. Cardiac rehabilitation programmes may need to consider addressing the specific requirements for patients following CABG with greater risk factors and low socioeconomic status. These may include programmes which encourage the disinterested, and address issues of language barriers and work pressures. This is vital if the aims of the *National service framework for coronary heart disease*¹ are to be realised.

F C TAYLOR

J J VICTORY

G D ANGELINI

Bristol Heart Institute,

University of Bristol,

Bristol Royal Infirmary, Level 7

Marlborough Street,

Bristol BS2 8HW, UK

f.c.taylor@bristol.ac.uk

1 Department of Health. *National service framework for coronary heart disease*. London:HMSO, 2000

2 Pell J, Pell A, Norrie J, *et al*. Effect of socio-economic deprivation on waiting time for cardiac surgery: retrospective cohort study. *BMJ* 2000;320:15-19.

3 Ben-Shlomo Y, Chaturvedi N. Assessing equity to health care provision in the UK: does where you live affect your chances of getting coronary artery bypass graft? *J Epidemiol Community Health* 1995;49:200-4.

4 Melville M, Packham C, Brown N, *et al*. Cardiac rehabilitation: socially deprived patients are less likely to attend but patients ineligible for thrombolysis are less likely to be invited. *Heart* 1999;82:373-7.

5 Carstairs V, Morris R. *Deprivation and health in Scotland*. Aberdeen: Aberdeen University Press, 1991.

6 Cooper A, Lloyd G, Weinman J, *et al*. Why patients do not attend cardiac rehabilitation: role of intentions and illness beliefs. *Heart* 1999;82:234-6.

WEB TOP 10

www.heartjnl.com

These articles scored the most hits on *Heart's* web site during April 2001

1 Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials

PS Sanmuganathan, P Ghahramani, PR Jackson, E J Wallis, LE Ramsay
March 2001;85:265-71. (Cardiovascular medicine)

2 Joint British recommendations on prevention of coronary heart disease in clinical practice

December 1998;80(suppl 2):S1-29

3 Guideline for the management of patients with acute coronary syndromes without persistent ECG ST segment elevation

February 2001;85:133-42.

4 National Institute for Clinical Excellence guidance: too NICE to glycoprotein IIb/IIIa inhibitors?

C J Knight
May 2001;85:481-3. (Editorial)

5 Prosthetic valve endocarditis

C Piper, R Korfer, D Horstkotte
May 2001;85:590-3. (Education in Heart)

6 Cost effectiveness of ramipril treatment for cardiovascular risk reduction

IS Malik, VK Bhatia, J S Koerner
May 2001;85:539-43. (Cardiovascular medicine)

7 Diabetic heart disease: clinical considerations

AD Timmis
April 2001;85:463-9. (Education in Heart)

8 Radiofrequency catheter ablation of supraventricular arrhythmias

H Calkins
May 2001;85:594-600. (Education in Heart)

9 Survival with congenital heart disease and need for follow up in adult life

C Wren, J J O'Sullivan
April 2001;85:438-43. (Congenital heart disease)

10 Pulse pressure and prognosis

RS Khattar, J D Swales
May 2001;85:484-6. (Editorial)

Visit the Heart website for hyperlinks to these articles, by clicking on "Top 10 papers" www.heartjnl.com

Table 1 Patient characteristics of those attending and not attending cardiac rehabilitation

Patient characteristics	Attended or ever attended (n=111)	Never attended (n=76)	Statistical difference χ^2	
Age (mean)	63.4 (SD 8.84)	63.8 (SD 9.33)	0.74 (<i>t</i> test)	
Sex-female	23 (21%)	20 (26%)	p = 0.47	
Alive (mean 10 months)	110 (99%)	73 (96%)	p = 0.30	
Previous MI	24 (22%)	19 (25%)	p = 0.72	
Previous CABG	4 (4%)	4 (3%)	p = 0.71	
Carstairs				
1	64 (58%)	38 (50%)	p = 0.38	2 × 3 table p < 0.001
2	37 (33%)	20 (26%)	p = 0.33	
3	10 (9%)	18 (24%)	p = 0.01	
Risk factors				
Cholesterol (>5 mmol/l)	89 (80%)	58 (76%)	p = 0.65	
Hypertension*	76 (68%)	45 (59%)	p = 0.25	
Body mass index (> 30 kg/m ²)	49 (44%)	29 (38%)	p = 0.5	
Smoking (at discharge)	12 (11%)	21 (27%)	p = 0.005	
Alcohol intake†	8 (7%)	7 (9%)	p = 0.82	
Exercise (< than 3 times/week)	30 (27%)	20 (26%)	p = 0.76	
Diabetes	22 (20%)	14 (18%)	p = 0.89	
Family history of CHD	68 (63%)	53 (70%)	p = 0.3	
Number of risk factors				
0-2	41 (37%)	19 (25%)	p = 0.11	2 × 3 table p < 0.001
3-4	51 (46%)	34 (45%)	p = 0.098	
5+	19 (17%)	23 (30%)	p = 0.05	

* Systolic blood pressure > 140 mm Hg or diastolic blood pressure > 85 mm Hg.

† More than 21 units for men and less than 14 units for women.

CABG, coronary artery bypass graft surgery; CHD, coronary heart disease; MI, myocardial infarction.