European Heart Journal (1996) **17**, 1345–1349

Serum C-reactive protein concentration in acute myocardial infarction and its relationship to mortality during 24 months of follow-up in patients under thrombolytic treatment

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Objectives We studied the relationship between serum C-reactive protein and mortality in acute myocardial infarction.

Background Early recanalization of an infarct-related coronary artery is considered to be an essential prerequisite for reducing mortality by thrombolytic treatment in acute myocardial infarction. It also reduces the inflammatory reaction caused by acute myocardial infarction and is measurable by determination of serum C-reactive protein concentrations. We therefore studied the prognostic value of determining serum C-reactive protein in acute myocardial infarction.

Methods We measured serum C-reactive protein concentrations daily for 6 days and creatine kinase, as well as its MB isoenzyme concentrations twice a day, for 3 days after a myocardial infarct, in 188 consecutive patients selected for thrombolytic therapy and treated in the same University Hospital Coronary Care Unit. The highest serum concentrations were related to total mortality as well as to the causes of death 3, 3–6, 6–12 and 12–24 months after the onset of the myocardial infarction.

Results The highest serum concentrations of serum C-reactive protein were observed 2 to 4 days after the onset of myocardial infarction. The mean value of the highest serum concentration of C-reactive protein in patients who survived the whole 24-month study period was 65 $mg \cdot l^{-1}$, with the 95% confidence intervals for the mean ranging from 58 to 71. The corresponding values in those who died within 3, 3–6, 6–12 and 12–24 months were 166 (139–194), 136 (88–184), 85 (52–119) and 74 (38–111) $mg \cdot l^{-1}$, respectively. The values in those who died within 3 and 3–6 months of the infarction differed statistically significantly from the values in those who survived the whole period ($P<0{\cdot}001$ and $P<0{\cdot}05$, respectively). In patients who died due to congestive heart failure the mean highest serum C-reactive protein concentration was 226 (189–265) $mg \cdot l^{-1}$. In those who suffered sudden cardiac death and those who died from a new myocardial infarction or non-cardiac causes, the respective values were 167 (138–196), 64 (38–89) and 48 (10–86) $mg \cdot l^{-1}$. The values in those who died due to congestive heart failure and those suffering sudden cardiac death differed statistically significantly ($P<0{\cdot}001$) from the values of those who survived or died due to other causes. The highest serum concentrations of creatine kinase or its MB isoenzyme were not associated with mortality in this study.

Conclusions High serum C-reactive protein concentrations in acute myocardial infarction patients treated with thrombolytic drugs predict increased mortality up to 6 months following the infarction. Accordingly, reduction of inflammatory reaction by successful thrombolytic treatment may make an important contribution to the survival benefit of thrombolytic treatment of acute myocardial infarction.

(Eur Heart J 1996; 17: 1345–1349)

Key Words: Myocardial infarction, C-reactive protein, survival, congestive heart failure, sudden cardiac death.

Introduction

Thrombolytic treatment of acute myocardial infarction has led to a considerable decrease in mortality from this condition[1–5]. This is at least partially due to the capacity of reperfusion to reduce the size of an evolving infarction[6–9], and although the mechanisms are not

Revision submitted and accepted 7 February 1996.

This study was supported by a grant from the Finnish Heart Association.

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0195-668X/96/091345+05 $18.00/0

clear, early reopening of the infarct-related coronary artery may be of survival benefit beyond that achieved by limitation of infarct size[10,11]. One possible explanation for this phenomenon is that even large myocardial infarcts with an open infarct-related coronary artery are less prone to serious arrhythmias than similar infarcts with an occluded infarct-related coronary artery[11,12]. Modulation of the inflammatory reaction associated with myocardial infarction may also be involved[11].

C-reactive protein is an acute-phase reactant. Its serum concentration rises due to various inflammatory stimuli, including acute myocardial infarction[13–18]. We have previously shown that thrombolytic treatment of myocardial infarction leads to smaller rises in serum concentrations of C-reactive protein than expected from the size of the infarct[16]. Low serum C-reactive protein concentrations are found in myocardial infarct patients whose infarct-related coronary artery has undergone early opening[18]. We have also shown that if patients with an acute myocardial infarction have thrombolytic treatment, serum C-reactive protein concentrations correlate even better than infarct size with early cardiac failure[17].

In this study we sought to establish whether long-term mortality among acute myocardial infarct patients treated by thrombolysis is correlated with serum C-reactive protein concentrations. We found that those patients who died due to cardiac failure or sudden cardiac death within 6 months of the onset of acute myocardial infarct had higher serum C-reactive protein values than other infarct patients.

Patients and methods

We studied 188 consecutive myocardial infarct patients treated with thrombolytic drugs. Of the total number of patients, 124 were treated with streptokinase (Kabikinase or Streptase): 1·5 million units within 1 h, and 64 with alteplase (Actilyse): 10 mg bolus followed by 50 mg within 1 h and 40 mg within the subsequent 2 h. The mean age of the patients was 58 years with an SD of 9 years and range from 25 to 88 years. Males constituted 82% and females 18% of the patients.

Serum C-reactive protein was determined on admission and thereafter daily for 6 days as previously described[19]. In addition, the serum concentrations of creatine kinase and its MB isoenzyme were determined on admission and twice daily for 3 days[20–22]. The serum creatine kinase peak values were observed within the first 36 h of the onset of infarction and those of serum C-reactive protein between the 2nd and the 4th day. Two patients died before the peak serum values of total creatine kinase or creatine kinase MB were reliably determined, and five before the serum C-reactive protein peak value was known. Due to a complicating infection or for administrative reasons reliable peak serum concentrations of either creatine kinase or C-reactive protein were not obtained from 11 patients who were all alive after the 24-month study period.

We studied total mortality in the patients who lived long enough to allow a reliable determination of the peak serum values of C-reactive protein and creatine kinase and its MB isoenzyme. Mortality was determined at 3, 6, 12 and 24 months after the onset of acute myocardial infarction and compared with the highest serum C-reactive protein and creatine kinase values. We also studied the causes of death by dividing them into deaths due to cardiac failure with no new myocardial infarction, sudden cardiac deaths, deaths due to recurrent myocardial infarction and non-cardiac deaths. These causes were related to the C-reactive protein and creatine kinase values.

In statistical analysis we used the analysis of variance, Student's t-test and the calculation of confidence intervals. These were determined with the Statgraphics for Windows (version 1.4) statistical package.

Results

Overall, 28 (16%) of the patients died during the 2-year study period. Of these, 14 (8%) died during the 3-month period after the infarction. In these 14 patients with early deaths, nine could be reliably analysed for the peak serum value of C-reactive protein and 12 for creatine kinase and its MB isoenzyme. Only three patients (2%) died between 3 and 6 months, six (3%) between 6 and 12 months and five (3%) between 12 and 24 months after the infarction. Those patients who died within 6 months of the onset of acute myocardial infarction had had a higher C-reactive protein peak serum concentration than those who survived the whole study period or died later than 6 months after the onset of infarction (Fig. 1). The peak serum values of creatine kinase or its MB isoenzyme were similar in those patients who survived the whole study period as compared to those who died (Fig. 1).

When we studied the causes of death we found that in the cases of cardiac failure or sudden cardiac death the patients had higher serum C-reactive protein peak values than those who died due to other causes or survived the whole study period (Table 1). In the case of creatine kinase or creatine kinase-MB there was no relationship between the peak serum values and the causes of death.

Discussion

The low 2-year mortality in the present study confirmed that myocardial infarct patients who are selected for thrombolytic treatment have good short- and long-term prognosis. In this study we specifically sought to ascertain whether the outcome of those myocardial infarct patients who are treated with thrombolytic drugs could be predicted from the highest serum values of C-reactive protein and creatine kinase determined during the acute phase of myocardial infarction.

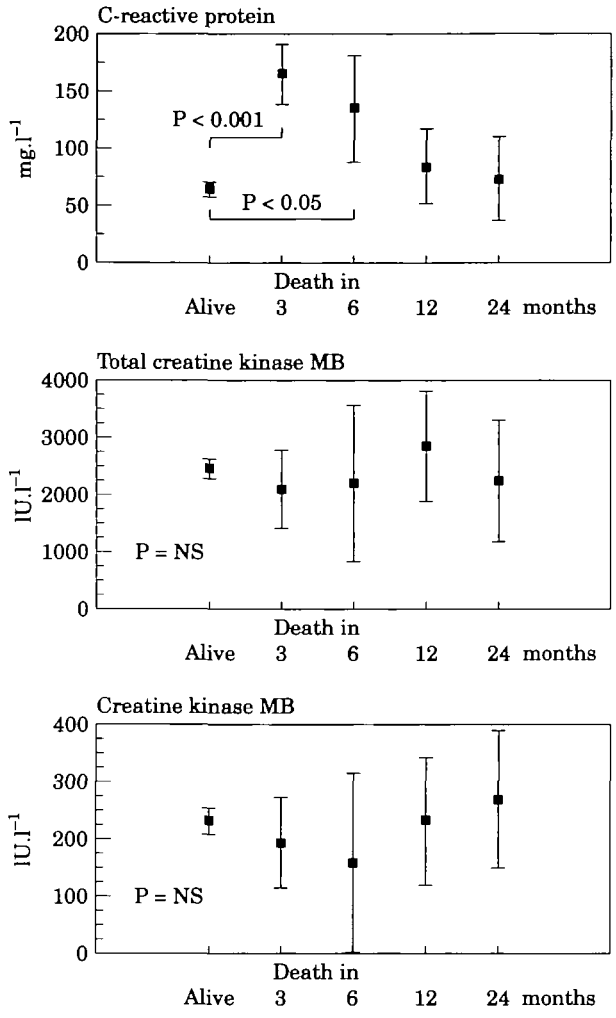

Figure 1 **Highest serum concentrations of C-reactive protein, total creatine kinase and creatine kinase MB (means ± 95% confidence intervals for the means) in patients who survived the whole 24 month study period (alive; 149 patients) and in those who died within 3 months (nine patients in the C-reactive protein group and 12 patients in the creatine kinase groups), 3–6 months (three patients), 6–12 months (six patients) and 12–24 months (five patients). The statistical significances were calculated by one-way analysis of variance followed by a multiple range test to reveal the groups which differed statistically from each other (Tukey HSD). Thereafter the exact statistical significance between these groups was calculated by Student's two tailed t-test. In addition to the statistical significances shown in the Figure, the C-reactive protein values in the patients who died within 3 months of the onset of infarction were significantly different from the values in patients who died 6–12 and 12–24 months after the infarction ($P<0.001$).**

The results showed that those patients who died during the first 6 months after the onset of infarction had higher peak serum C-reactive protein values than those who survived the whole 24-month study period or died later than 6 months after onset. Simes *et al.*[23] have shown that early patency of the infarct-related coronary artery is one of the most important predictors of survival in patients with acute myocardial infarction treated with thrombolytic drugs. According to our own earlier results[16,18] those patients who fail to reperfuse have high serum C-reactive protein values similar to those in patients not treated with thrombolysis. The present study confirmed that the association between early patency of the infarct related coronary artery and a low serum concentration of C-reactive protein in acute myocardial infarction, as found by us earlier, is also reflected in the survival prognosis of the patients. It may indeed be that a reduced inflammatory reaction due to successful reperfusion contributes to the survival benefit of thrombolytic treatment of myocardial infarction. No correlations between creatine kinase values and mortality were observed in this study.

The present results showed that, especially in cases of cardiac failure or sudden cardiac death, the patients had high serum values of C-reactive protein. In cases of death due to cardiac failure, our results accord with our previous finding of an association between the development of early cardiac failure and a high serum concentration of C-reactive protein in acute myocardial infarction[17]. Although infarct size has been shown to be the strongest prognostic indicator in acute myocardial infarction[24,25], we found no correlation between creatine kinase values and survival in this study. It may be that the determinations of creatine kinase, although frequent when compared to ordinary clinical practice, were too sparse to allow a reliable estimation of creatine kinase peak values. Furthermore, thrombolysis affects peak serum creatine kinase values in addition to infarct size. This emphasizes the importance of determining serum C-reactive protein when predicting the survival of myocardial infarct patients. A reliable estimate of its peak value is easily achieved by daily measurements[16], which are well suited to ordinary clinical practice.

Sager *et al.*[12] have shown that infarct patients who have developed a large myocardial infarction and have an obstructed infarct-related coronary artery are more prone to inducible ventricular tachycardia and sudden cardiac death than those who have an open infarct-related coronary artery. We have previously shown that the failure of thrombolytic treatment to reopen the infarct related coronary artery in acute myocardial infarction is associated with high serum C-reactive protein peak values[16,18]. Our present finding, of an association between high peak serum C-reactive protein concentration and sudden cardiac death in acute myocardial infarction is thus in accordance with the results of Sagar *et al.* Recently Berger *et al.*[26] have also shown that patients with a large myocardial infarction and a closed infarct-related coronary artery are more prone to ventricular fibrillation and sustained ventricular tachycardia than those with an equally large myocardial infarct but an open infarct-related coronary artery. It is not clear why an open infarct-related coronary artery diminishes the risk of serious arrhythmias in high-risk patients, or why even large myocardial infarcs result in only small C-reactive protein reactions

Table 1 Highest serum C-reactive protein concentration in the patients who survived the whole 24 month study period and in those who died due to different causes

Condition of the patient	Highest serum C-reactive protein concentration		Number of patients	Statistical significance*
	Mean value ($mg \cdot l^{-1}$)	95% confidence interval for the mean		
Alive	65	58–71	149	
Dead				
Cause of death				
New myocardial infarction	64	38–89	8	
Congestive heart failure	226	189–265	4	$P<0.001$
Sudden cardiac death	167	138–196	7	$P<0.001$
Other	48	10–86	4	

*The statistical significance was calculated by one-way analysis of variance followed by multiple range test (Tukey HSD) to reveal the groups which differed statistically from each other. Thereafter the exact statistical significance between these groups was calculated by Student's two-tailed t-test. The serum C-reactive protein peak concentrations in the patients who died due to congestive heart failure or who suffered sudden cardiac death differed statistically significantly ($P<0.001$ in all cases) from the corresponding values of the patients who remained alive or who died from new myocardial infarction or other causes.

if the infarct-related artery reopens. It may well be that the healing process in the infarcted myocardium is facilitated by reopening the infarct-related artery. This may lead to a diminished inflammatory reaction and eventually to a reduced risk of serious arrhythmias.

To conclude, the present study showed that those who have a high peak serum C-reactive protein concentration in the first days after an acute myocardial infarction treated by thrombolysis run an increased risk of dying of cardiac failure or suffering sudden cardiac death during the first 6 months after the infarction. Other studies have shown that the risk of dying as a result of these conditions can be reduced by treatment with ACE inhibitors[27,28] and possibly with amiodarone[29–31]. Determinations of serum C-reactive protein may thus help in selecting myocardial infarct patients for these therapies. Recently Liuzzo *et al.*[32] have reported that serum C-reactive protein concentrations may predict outcome in unstable angina pectoris. Hence the determination of serum C-reactive protein concentration may be valuable in all kinds of acute ischaemic syndromes.

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