| PublisherInfo | | |
|---|---|---|
| PublisherName | : | BioMed Central |
| PublisherLocation | : | London |
| PublisherImprintName | : | BioMed Central |

# TNF-α in AMI

| ArticleInfo | | |
|---|---|---|
| ArticleID | : | 4090 |
| ArticleDOI | : | 10.1186/ccf-1999-1421 |
| ArticleCitationID | : | 1421 |
| ArticleSequenceNumber | : | 27 |
| ArticleCategory | : | Paper Report |
| ArticleFirstPage | : | 1 |
| ArticleLastPage | : | 5 |
| ArticleHistory | : | RegistrationDate : 1999–8–23<br>OnlineDate : 1999–8–23 |
| ArticleCopyright | : | Current Science Ltd1999 |
| ArticleGrants | : | |
| ArticleContext | : | 130541111 |

Martin Phillips

## Keywords

Acute myocardial infarction, monoclonal antibody, tissue injury, tumor necrosis factor alpha

# Comments

While the ethics of the patient study are of some concern and the claims made by the authors in their discussion are dubious, this study is of interest to intensivists. There is considerable interest in the role of TNF-α in sepsis and septic cardiomyopathy. This study gives us more evidence that circulating TNF-α levels are of importance to cardiac function. In addition, the authors show that pretreatment with anti-TNF-α monoclonal antibody limits cardiac necrosis and cellular injury (indicated by less oxidative stress induced lipid peroxidation and reduced endothelial cell damage) in acute cardiac ischemia. As in the septic shock story, this is unlikely to be very useful clinically for patients presenting with acute chest pain. However, trials of anti-TNF-α monoclonal antibody may be worth consideration in the following circumstances: cardiac failure after AMI; pre-treatment in patients at high-risk of cardiac ischemia during major surgery; severe septic cardiomyopathy.

**Additional comment by paper report team leader:**

Although this paper may show interesting results, the ethics of this research must be seriously questioned as commented upon by our reporter. Thrombolysis was withheld in patients with AMI and no mention was made of whether thrombolysis was contraindicated in this group of patients, or that this treatment was unavailable, which seems extremely unlikely in view of the origin of the research and availability of other research materials. Withholding treatment known to have significant beneficial effects is difficult to justify for the sole purpose of research.

# Introduction

Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine present in many disease states and with a variety of functions, including the activation of neutrophils and monocytes. Activation leads to the release of other proinflammatory cytokines and adhesion molecules (which promotes neutrophil chemotaxis) and results in release of free radicals. These free radicals promote cellular injury to coronary artery and myocardial endothelial cells; TNF-α is particularly important in septic shock and inflammatory processes. TNF-α is also known to cause cardiac dysfunctions such as left ventricular dysfunction, cardiomyopathy, and pulmonary edema. Plasma levels of TNF-α have been shown to be elevated in acute myocardial infarction (AMI) and severe cardiac failure. Expression of TNF-α mRNA

is protein are markedly increased during myocardial ischemia, and, the use of an anti-TNF-α antibody has been shown to improve cardiac function after ischemia.

# Aims

To determine if myocardial injury in AMI is associated with a TNF-α release, and if treatment with monoclonal antibody to TNF-α can limit this injury.

# Methods

**Human study:**

Fourty two patients with AMI, confirmed by electrocardiogram, were studied (25 men, 17 women, age range 42-70 years). None received thrombolytic therapy. These patients were compared with 10 healthy controls (six men, four women, age range 36-62) without coronary artery disease. Blood samples were taken at 4, 8, 12, 24, 48, and 72 h after the onset of chest pain.

**Animal study:**

New Zealand white rabbits were anesthetized and a silk suture was tied around the Left Anterior Descending Artery (LAD) and occluded for 1.5 h. Thirty rabbits were used in four different groups. Group I underwent surgery but no LAD ligation; Group II had LAD ligation for 1.5 hours; Group III were given isotype-matched IgG antibody as a bolus 10 minutes before LAD ligation; Group IV were given anti-TNF-α monoclonal antibody (1 mg/kg) as abolus 10 minutes before LAD ligation. The dose of anti-TNF-alpha monoclonal antibody was determined from a preliminary study and completely neutralized the bioactivity of TNF-α *in vivo*. Infarct size was determined by injection of 10 ml 2% Evans blue dye into the left atrium at the end of the 1.5 hour ligation period. The area of myocardium at risk was thereby stained blue. The heart was then rapidly excised and prepared for histological examination. Blood was also removed at the end of the ligation period for measurement of isolated circulating endothelial cells, an indication of endothelial injury. These cells were confirmed by the presence of stainable von Willebrand's factor. Plasma malondialdehyde (MDA), a product of oxidative stress and lipid peroxidation, was measured by the thiobarbituric acid method. Plasma TNF-α was measured by radioimmunoassay.

# Results

Plasma TNF-α levels were elevated in patients with AMI, with peak levels (2-3 times those of controls) at 4 h after the onset of symptoms. After 48 hours TNF-α levels returned to control values. TNF-α levels correlated with creatinine kinase MB (CK-MB) in patients with AMI ($r = 0.65$, $P = 0.05$).

In the rabbit experiments, Group IV animals (who received anti-TNF-α monoclonal antibody) had significantly smaller areas of necrosis ($P < 0.01$) compared with Group II animals (ligation alone) or Group III animals (ligation and nonspecific IgG). TNF-α levels were increased in animals with LAD ligation compared to controls ($P < 0.01$). Anti-TNF-α monoclonal antibody (1 mg/kg) completely neutralized TNF-α release in animals with LAD ligation. MDA levels were also significantly increased in animals with LAD ligation compared with controls ($P < 0.01$). MDA levels were lower in anti-TNF-α antibody treated animals compared with Group II and III rabbits ($P < 0.01$) but were still markedly elevated compared with those in control group. Numbers of circulating endothelial cells were significantly higher in animals with LAD ligation ($P < 0.01$), lower in anti-TNF-α antibody treated animals as compared with Group II and IV rabbits ($P < 0.01$), but still markedly higher than in the control group ($P < 0.01$). There was correlation between TNF-α levels and area of necrosis, MDA levels, and numbers of circulating endothelial cells.

# Discussion

In this study, elevated levels of TNF-α, which correlated with CK-MB levels, were detected in the early phase of AMI. In the animal study, TNF-α levels correlated with areas of necrosis, markers of lipid peroxidation, and markers of endothelial cell injury. Treatment with anti-TNF-α monoclonal antibody significantly reduced all of these parameters in animals that underwent LAD ligation. Although many cell types are capable of releasing TNF-α, the most important are monocytes and macrophages. In the early phase of AMI, activated neutrophils and macrophages may be the most significant source of circulating TNF-α. Recent studies suggest that within 30 minutes of myocardial ischemia, expression of TNF-α mRNA and protein is stimulated, suggesting that the ischemic myocardium is also capable of TNF-α synthesis and release. The results of the clinical part of this study suggest that TNF-α is an early marker of the area of necrosis in AMI. TNF-α is an important mediator of tissue injury via the activation of inflammatory cells and endothelial cells. Correlation of TNF-α levels with CK-MB levels in patients with AMI suggests that TNF-α may directly injure cardiac myocytes. TNF-α levels were also higher in patients with poorer functional status, suggesting a negative inotropic effect of TNF-α. The correlation of TNF-α levels with the numbers of circulating endothelial cells suggests that TNF-α causes endothelial cell damage in myocardial ischemia.

Anti-TNF-α monoclonal antibody may have a therapeutic role in the treatment of patients with heart failure after AMI.

# References

1. Li D, Zhao L, et al: Kinetics of tumor necrosis factor α in plasma and the cardioprotective effects of a monoclonal antibody to tumor necrosis factor α in acute myocardial infarction. Am Heart J. 1999, 137: 1145-1152.