Increased plasma concentrations of interleukin-18 in acute coronary syndromes

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Objective: To examine the relation between plasma concentrations of interleukin-18 (IL-18), the interferon-γ inducing factor, and clinical instability of coronary artery disease.

Design and setting: Observational study in a university hospital.

Patients: 11 patients with unstable angina and negative troponin I, 21 patients with acute non-Q wave myocardial infarction (MI), 21 patients with acute Q wave MI, 9 patients with stable angina, and 11 controls.

Main outcome measures: Plasma IL-18 concentrations and their relation to clinical instability and myocardial dysfunction.

Results: Plasma concentrations of IL-18 were significantly increased in the unstable angina and MI groups in comparison with the stable angina and control groups (p < 0.01). No difference in IL-18 concentrations was found between patients with unstable angina, patients with non-Q wave MI, and patients with Q wave MI. Plasma IL-18 concentrations significantly correlated with decreased left ventricular ejection fraction (p = 0.01).

Conclusions: Plasma IL-18 concentrations are increased in patients with acute coronary syndromes and correlate with the severity of myocardial dysfunction.

Inflammatory mechanisms have an important role in the pathogenesis of atherosclerotic disease and the occurrence of acute ischaemic syndromes. However, because of our limited knowledge about the critical inflammatory pathways involved in the pathogenesis and progression of ischaemic heart disease in humans, no specific anti-inflammatory treatment can be advocated at this time. Interleukin-18 (IL-18), identified as the interferon-γ inducing factor, is produced by many cell types, particularly macrophages, and has direct proinflammatory activities in diverse cell types including inflammatory and vascular cells. We recently reported increased expression of IL-18 and its receptor in human atherosclerotic plaques, and Pomerantz and colleagues identified a deleterious role for IL-18 in an in vitro model of ischaemia–reperfusion injury. In addition, Setal and associates reported increased plasma concentrations of IL-18 in patients with acute myocardial infarction (MI), further supporting a role for IL-18 in this context. However, whether patients with other acute coronary syndromes have increased concentrations of IL-18 is unknown. In the present study, we examined the relation between plasma concentrations of IL-18 and the clinical instability of coronary artery disease. We also examined the relation between IL-18 concentrations and the extent of myocardial dysfunction.

METHODS
Patient characteristics
We studied 53 consecutive patients admitted to an intensive care unit for a chest pain syndrome at rest and ST segment modifications suggestive of myocardial ischaemia or necrosis. On the basis of serial serum troponin I measurements, the patients were classified as having had unstable angina (negative tests for troponin I, n = 11, 7 men and 4 women, mean (SEM) 69.9 (4.2) years old) or acute MI (positive troponin I tests, n = 42, 21 non-Q wave and 21 Q wave MI, 29 men and 13 women, 62.6 (1.9) years old). Patients with Q wave MI were admitted less than six hours after symptoms onset. Those with other ischaemic signs were admitted within 24 hours. To examine the association between IL-18 concentrations and plaque instability, we included a group of patients with documented stable coronary artery disease (n = 9, 6 men and 3 women, 65.8 (5.4) years old). Table 1 shows the patients’ characteristics and treatment during their hospital stay. In addition, five non-coronary patients (one with non-ischaemic chest pain, one with mitral stenosis, one with sinoauricular block, and two with acute pericarditis) and six healthy subjects formed the non-coronary control group (n = 11, 7 men and 4 women, 36.1 (4.0) years old). All patients and subjects gave informed consent.

Determination of plasma IL-18 concentrations
Blood samples were collected by venepuncture in 5 ml citrated tubes during hospitalisation between 6.00 and 8.00 am. The interval between admission and blood sampling for IL-18 ranged from 0–9 days with a median at 2 days. Plasma samples were prepared for determination of IL-18 concentrations using a commercially available enzyme linked immunosorbent assay (ELISA) kit (MBL, Nagoya, Japan).

Statistics analysis
Results are expressed as medians and ranges. Groups were compared by the Kruskal-Wallis and Mann-Whitney tests. Simple regression analysis was used to analyse the relation between plasma values of IL-18 and left ventricular ejection fraction or C reactive protein concentrations.

RESULTS
Figure 1 presents the data distribution. IL-18 concentrations were not associated with age, sex, risk factors, medications, or
The median IL-18 concentrations in control non-coronary subjects (46.8 pg/ml, range 34.2–68.2 pg/ml) were significantly different from those in patients with stable angina (85.7 pg/ml, range 56.0–157.7 pg/ml, p < 0.01), suggesting that IL-18 concentrations in patients with stable coronary disease may be associated with the presence of advanced coronary artery disease. In the group of patients with unstable angina, the median IL-18 concentrations (214.7 pg/ml, range 116.6–297.0 pg/ml) were significantly higher than those in the control group (p < 0.001) or the group with stable angina (p = 0.0012). In the group of patients with MI, the median IL-18 concentrations (164.6 pg/ml, range 53.6–602.5 pg/ml) were also significantly higher than those in the control group (p < 0.001) or the group with stable angina (p < 0.01). The IL-18 concentrations did not differ significantly between the group with unstable angina and the group with MI or between patients with Q wave and patients with non-Q wave MI.

Plasma IL-18 concentrations correlated significantly with the severity of myocardial dysfunction as assessed by the determination of ventricular ejection fraction ($r = -0.35$, p = 0.011) (fig 2). C reactive protein concentrations were available for 20 patients with unstable angina or MI (median 24.5 µg/ml, range 5.0–105.0 µg/ml). We found no correlation between IL-18 and C reactive protein concentrations (p = 0.38).

![Figure 1](https://www.heartjnl.com)  
**Figure 1** Distribution of plasma IL-18 concentrations in the patient groups.

![Figure 2](https://www.heartjnl.com)  
**Figure 2** Relation between left ventricular ejection fraction and plasma IL-18 concentrations ($r = -0.35$, p = 0.011) in patients with stable angina (black circles), unstable angina (white circles), or myocardial infarction (grey circles).
DISCUSSION

Two potentially important findings were observed in the present study. Firstly, plasma concentrations of IL-18 are increased in patients with acute coronary syndromes with or without myocardial necrosis. Secondly, plasma concentrations of IL-18 correlate with the severity of myocardial dysfunction.

Although these findings are preliminary and need confirmation in a large multicentre study, we believe that they should be considered seriously for several reasons. IL-18 has the potential to promote both atherosclerotic plaque instability and systemic inflammatory responses through activation of monocytes/macrophages, lymphocytes, and endothelial cells. Indeed, we have recently showed that in vivo activation of monocytes/macrophages, lymphocytes, and antiangiogenic cytokine heart disease. Finally, IL-18 is emerging as a potent cytokine that augments both innate and acquired immunity.

ACKNOWLEDGEMENTS

This study was supported by Action Concertée Incitative Jeunes Chercheurs, ACI 2000, Ministère de la Recherche, France.
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*Heart* 2002 88: 467-469
doi: 10.1136/heart.88.5.467

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