

SCIENTIFIC LETTER

Relation between circulating soluble Fas ligand and subsequent ventricular remodelling following myocardial infarction

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The Fas/Fas ligand (Fas-L) system has been established as one of the regulatory pathways of apoptotic cell death. Fas is a type I membrane protein which belongs to the tumour necrosis factor/nerve growth factor receptor family and mediates apoptosis.¹ A soluble form of Fas (sFas) found in sera of human subjects is thought to block apoptosis by inhibition of binding between Fas and the antibody to Fas on the cell membrane. Fas-L is a type II membrane protein in the tumour necrosis factor family, and human soluble Fas-L (sFas-L) apparently induces apoptosis of Fas expressing cells.¹ Recently, the occurrence of apoptotic death of cardiomyocytes has been demonstrated experimentally after injury caused by hypoxia, reperfusion, myocardial infarction, and coronary embolism. However, only two clinical reports assessing the concentrations of circulating sFas and sFas-L in patients with acute myocardial infarction (AMI) have been published.^{2,3} No study has evaluated the relation between these concentrations and left ventricular (LV) remodelling following AMI. Thus, in this study we measured the circulating concentrations of sFas and sFas-L in patients with AMI. We also investigated the relation of sFas and sFas-L to LV remodelling after AMI.

METHODS

Fifty two consecutive patients (41 men; mean age 64 years) who presented with their first episode of AMI within 24 hours of symptom onset and who underwent successful coronary angioplasty were studied. Patients with significant concomitant diseases, such as malignancy, pulmonary disease, autoimmune disease, thyroid disease, or concurrent viral infection were excluded from this study. The control group consisted of 36 age and sex matched patients (28 men; mean age 64 years) who presented with chest pain but were found to have no coronary artery stenosis.

Peripheral venous blood samples were obtained at the time of admission and on days 7, 14, and 21 in patients with AMI and on the day of cardiac catheterisation in control subjects. Blood samples were also taken from the coronary sinus (CS) in 20 patients on days 1 and 14 following AMI and from 18 control subjects. Serum concentrations of sFas and sFas-L were measured by enzyme linked immunosorbent assays with commercial kits (Medical & Biological Laboratories Co, Nagoya, Japan).

LV end diastolic volume index (EDVI) and LV ejection fraction were assessed by left ventriculography in subacute (two weeks) and chronic (three months) phases. Those included in the remodelling group ($n = 18$) had an increase in LV EDVI ≥ 5 ml/m² in the chronic phase relative to the baseline value from the subacute phase.

Comparison between the two groups was made by Student's *t* test. Differences in ratios were assessed by χ^2 test. The significance of changes in the time course of serum concentrations of sFas and sFas-L were evaluated by repeat measure analysis of variance and Bonferroni/Dunn test. A value of

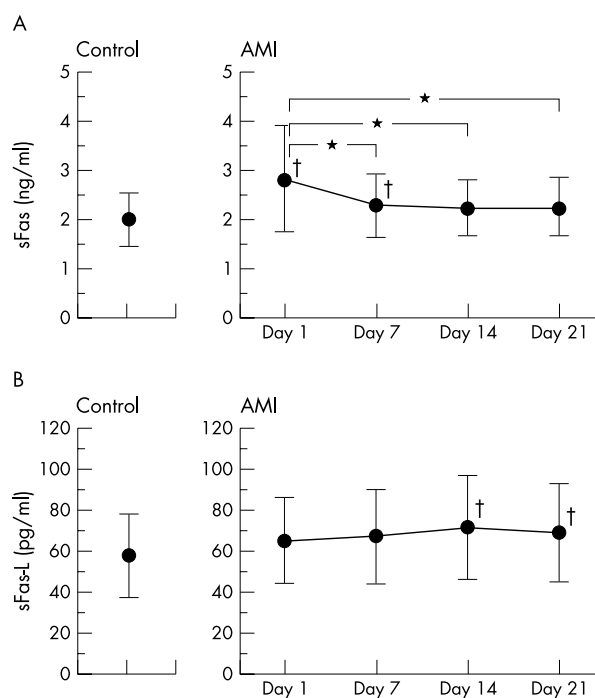


Figure 1 (A) Serial changes in serum sFas concentrations in patients with acute myocardial infarction (AMI). The serum concentration of sFas was higher at the time of admission in patients with AMI than in control subjects. Serum concentrations of sFas in patients with AMI were decreased by day 7 and further decreased to levels comparable to control values on day 14 following AMI. (B) Serial changes in serum sFas-L concentrations in patients with AMI. There was no significant difference in serum sFas-L concentrations between at the time of admission in patients with AMI and controls. Although the serum concentration of sFas-L did not change significantly throughout the course in patients with AMI, it was higher on days 14 and 21 in the AMI group than in the control group. * $p < 0.05$ v day 1; † $p < 0.05$ v control.

$p < 0.05$ was considered significant. All results are presented as mean (SD).

RESULTS

The serum sFas concentration on admission in patients with AMI was higher than in controls, whereas the serum sFas-L concentration was not different from control values. The serum sFas concentration was decreased by day 14, whereas

Abbreviations: AMI, acute myocardial infarction; CS, coronary sinus; EDVI, end diastolic volume index; LV, left ventricular

Table 1 Comparison of clinical characteristics and serum concentrations of sFas and sFas-L in patients with or without left ventricular remodelling

	Remodelling group	Non-remodelling group	p Value
n	18	34	NS
Male/female	13/5	28/6	NS
Age (years)	62 (12)	66 (10)	NS
Maximum CK (IU/l)	3266 (2438)	2694 (2213)	NS
PCWP (mm Hg)	16.2 (7.8)	14.4 (7.6)	NS
Cardiac index (l/min/m ²)	3.15 (0.87)	2.90 (0.87)	NS
LVEF (%)	49.2 (9.7)	59.8 (10.1)	p<0.01
IRCA			NS
LAD	9	16	
LCx	2	5	
RCA	7	13	
sFas (ng/ml)			
Day 1	2.9 (1.2)	2.8 (1.0)	NS
Day 7	2.3 (0.5)	2.3 (0.7)	NS
Day 14	2.3 (0.7)	2.2 (0.5)	NS
Day 21	2.1 (0.6)	2.3 (0.6)	NS
sFas-L (pg/ml)			
Day 1	71 (21)	61 (21)	NS
Day 7	73 (23)	63 (22)	NS
Day 14	87 (27)	63 (20)	p<0.01
Day 21	83 (25)	62 (21)	p<0.01

CK, creatine kinase concentration; IRCA, infarct related coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LVEF, left ventricular ejection fraction; NS, not significant; PCWP, pulmonary capillary wedge pressure; RCA, right coronary artery.

the serum sFas-L concentration did not change significantly following AMI (fig 1).

Mean (SD) serum sFas concentrations were significantly raised in the CS compared with that in the peripheral sample on day 1 in patients with AMI (CS 3.1 (1.1) ng/ml *v* peripheral vessel 2.9 (0.9) ng/ml, *p* < 0.05), whereas the concentration was not raised in the CS on day 14 in patients with AMI and control subjects (data not shown). In contrast, the serum sFas-L concentration in the CS was not different from that in the periphery on day 1 in patients with AMI and control subjects (data not shown), whereas it was elevated in the CS compared with that in the peripheral vessel on day 14 in patients with AMI (CS 73 (28) pg/ml *v* peripheral vessel 69 (23) pg/ml, *p* < 0.05).

Table 1 shows the comparison of clinical characteristics and serum concentrations of sFas and sFas-L in patients with or without LV remodelling. The groups were comparable with respect to sex distribution, age, maximum plasma creatine kinase concentrations, pulmonary capillary wedge pressure, cardiac index, and the anatomic distribution of infarction. The LV ejection fraction was lower in the remodelling group than in the non-remodelling group. Serum sFas-L concentrations on days 14 and 21 were higher in the remodelling group than in the non-remodelling group, whereas those on days 1 and 7 did not differ between the two groups. Serum sFas concentrations did not differ between the remodelling and non-remodelling groups on any day.

DISCUSSION

Only one previous investigation has evaluated the concentrations of circulating sFas in patients with AMI. Ohtsuka and colleagues² demonstrated that the serum sFas concentration increases in direct relation to the severity of haemodynamic impairment in 17 patients with AMI, but independent of infarct size. However, their study did not examine whether the increase in circulating sFas is a result of release from cardiac tissue. We have revealed that the sFas concentration in the CS was higher than that in peripheral blood in the acute phase of myocardial infarction, indicating that sFas found in serum is secreted primarily from the heart in patients with AMI.

Serum sFas-L concentrations on admission in patients with AMI were not different from those of control subjects, and these results are comparable to those of a previous report.³ In contrast to these results, however, another recent study demonstrated that plasma sFas-L concentrations were significantly raised on admission in 30 patients with AMI compared with 30 control subjects.³ This discrepancy may be caused by the small sample size used not only in this study but also in the previous studies.

Furthermore, in the present study, serum sFas-L concentrations on days 14 and 21 were higher in the remodelling group than in the non-remodelling group, whereas serum sFas concentrations did not differ between these two groups on any day. In experimental models, it has been reported that the mechanical load produced by myocardial infarction and ventricular failure may affect the regulation of Bcl-2 and Bax in viable myocytes, triggering programmed cell death and remodelling of the ventricular wall.⁴ In human hearts, it has been shown that the Bcl-2 protein is induced in salvaged myocytes during the acute phase of infarction, whereas the Bax protein, which may play an important role in the acceleration of apoptosis of myocytes after reperfusion, is overexpressed in later stages.⁵ These data support our hypothesis that enhanced secretion of sFas-L in the subacute phase of myocardial infarction may reflect induction of apoptosis related to ventricular remodelling.

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IMAGES IN CARDIOLOGY

Acquired supravalar type of left ventricular to right atrial communication following non-penetrating cardiac trauma caused by traffic accident

A 48 year old woman whose birth had been normal was administered to our hospital for examination of strong systolic heart murmur. She had been involved in a traffic accident three years previously, and a heart murmur had been detected since then.

Auscultation revealed a strong systolic murmur (Levine V/VI) with thrill at 3LSB. Transthoracic echocardiogram elucidated the shunt flow from left ventricle (LV) to right atrium (RA) associated with heart murmur. Transoesophageal echocardiogram revealed the shunt flow from LV to RA through the defect lying entirely on the RA side of the tricuspid valve during systolic phase (below). Cardiac catheterisation revealed O₂ step up at RA and left ventriculography demonstrated the shunt flow from LV to RA without ventricular septal defect (VSD) flow (right, upper panels). Qp/Qs calculated from Fick's law was 2.0, which is considered indicative of surgical closure of the defect. At open heart surgery, a defect at the membranous portion between the LV and RA with an intact

tricuspid valve was revealed (right, lower panels) and direct closure carried out. After the operation, the patient recovered uneventfully and has no residual heart murmur.

This case of an acquired LV to RA communication caused by non-penetrating chest trauma is very unusual. The acquired LV to RA communication is usually accompanied by tricuspid valve insufficiency along with ventricular

septal defect (subparavalvar LV to RA fistula). However, there has been no previous report regarding an acquired LV to RA communication with intact tricuspid valve (supravalar LV to RA fistula). Therefore, this is the first report of supravalar LV–RA fistula involved in non-penetrating cardiac injury.

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