Circulating Adhesion Molecules in a Ten-Year Follow-Up Study After Premature Myocardial Infarction

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Abstract: *Objectives*: The aim of the present study was to investigate the role of soluble circulating adhesion molecules (CAMs) in total and cardiac death in patients who had suffered premature myocardial infarction (MI).

Design: A prospective cohort study with 10 years follow-up. We measured concentrations of CAMs (intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and P-selectin) in stored plasma samples from series from 206 men and 56 women hospitalized for myocardial infarction.

Results: Concentrations of CAMs were significantly associated with one another, with other markers of inflammation, and with some classic coronary risk factors. ICAM-1 was the only significant predictor of death, but after adjustment for serum C-reactive Protein (CRP), ICAM-1 was no longer associated to mortality. The three other CAMs (VCAM-1, E-selectin and P-selectin) did not predict death or major cardiac events.

Conclusions: Our data indicate that the measurement of these adhesion molecules is unlikely to add significant predictive information to that provided by more established risk factors. However, the present study suggests an association between CAMs and between CAMs and traditional risk factors as total cholesterol, CRP and Lp(a) lipoprotein.

Keywords: Follow-up study, myocardial infarction, mortality, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, P-selectin.

INTRODUCTION

Adhesion molecules are expressed by endothelial cells, macrophages and smooth muscle cells in response to various inflammatory stimuli [1]. In this process, transient rolling of leucocytes along endothelium is mediated by selectins, including E-selectin and P-selectin, while stronger attachment of white cells to endothelium is mediated by intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [2]

The adhesion of monocytes and leukocytes to endothelial cells is regarded as an early event in the development of atherosclerotic lesions [3]. Cellular adhesion molecules (CAMs) are proteins associated with the vascular endothelium, and soluble forms of these proteins may be released into the circulation. Therefore, their increased plasma levels may indicate alteration in the functional state of endothelial cells.

Close correlations between endothelial dysfunction and number of cardiovascular risk factors have been reported [4]. Furthermore, association has been observed between high plasma concentrations of soluble adhesion molecules with atherosclerosis and coronary heart disease (CHD) [5-7].Some, but not all, prospective studies indicate that raised plas-ma concentrations of soluble adhesion molecules predict future cardiovascular death in patients with verified CHD [3, 6, 8].

It has been reported that the results of direct assessment of endothelial dysfunction by invasive procedures are strong predictors of disease outcome [9-10] and may provide valuable clinical informations. However, such approaches are limited by invasiveness of the procedure and are costly and time consuming.

On the other hand, several studies have reported prognostic impact of different markers after myocardial infarction (MI) in older populations, where concomitant conditions may have reduced the predictive value of the tests. Furthermore, some studies have only limited follow-up period or incomplete data on important covariables.

The aim of the present study was to explore the prognostic importance of soluble CAMs during a 10 years follow-up period among subjects with an earlier, premature MI. We searched both for evidence of endothelial activation and correlations among various CAMs, between CAMs and other known risk factors for CHD whose effects could be mediated through CAMs.

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MATHERIALS AND METHODOLOGY

Subjects

Between January 1986 and June 1989, 223 men ≤ 55 years and 61 women ≤ 60 years, all Norwegians, were hospitalized for MI at the Central Hospital of Akershus. In September 1989, the 206 men and 56 women (92.3%) still alive were invited to participate in a study and all but 13 men and 2 women (5.3%) were examined. The examination took place at least three months after the last MI and the mean time between last MI and baseline examination was 2.1 (±1.1) years. The median age at inclusion was 51 years (range 31-58) and 59 years (range 34-63) for men and women, respectively.

Diagnosis of Myocardial Infarction

MI was diagnosed according to WHO criteria at the time of inclusion (at least two out of three of the following criteria: chest pain, two-fold increase of creatinine kinase and /or ASAT or typical ECG findings)

Questionnaire

A self-administered questionnaire used at baseline had included questions related to health, smoking and alcohol consumption, use of drugs, physical activity, history of cardiovascular diseases, diabetes, or hypertension.

All patients included gave their informed consent.

Measurement of Ejection Fraction

Left ventricular ejection fraction had been measured routinely at hospital discharge following their MI using radionuclide ventriculography using a combination of stannous pyrophosphate !5 µg/kg and ^{99}TC-pertechnate (370-995 mEq) for *in vivo* labelling of red blood cells.

Blood Sampling

Blood had been drawn between 8.00 and 10.00 a.m. after an overnight fast. Plasma and serum samples were stored at -70° C. Measurements of lipids and other biochemical parameters were performed as described previously [11].

Measurement of CAMs

All the assays were performed with the investigators blinded to group.

Quantitative immunologic determinations of soluble ICAM-1 (sICAM-1), soluble VCAM-1 (sVCAM-1), and E-selectin were performed in plasma samples by enzyme-linked immunosorbent assay (ELISA) techniques with ELISA Parameter (R&D Systems, Minneapolis, Minn) kits. The procedural details recommended by the manufacturer were strictly followed. All determinations were done in duplicate. Intra-assay and interassay precisions were evaluated by calculating coefficients of variation with duplicates and triplicates of samples and control preparations. The intra-assay coefficients of variation were 4.4%, 5.9%, 4.4%, and 5.4 %, and the interassay coefficients of variation were 10.3%, 9.6%, 3.4%, 6.0% for sICAM-1, sVCAM, E-selectin, and P-selectin, respectively.

Endpoint Definition

Endpoints of the study were total, cardiac death and major cardiac events (combined endpoint of cardiac deaths, hospital verified MI or cardiac arrest). Cardiac deaths included ICD/9 codes 410-414. Time and causes of death were obtained from death certificates at Statistics Norway after having been granted permission from the Norwegian Data Inspectorate and Norwegian Board of Health.

Statistical Analyses

Continuous data are presented as mean (±standard deviation) for variables with normal distribution, or as median (interquartile range) for variables with skewed distribution. The distribution of CAMs was skewed but ln-transformed values exhibited a normal distribution and transformed values were used for analyses. Student's t-test was used to compare geometric means. Pearson´s correlation coefficient r was calculated to test for associations between continuous variables. Application of non-parametric tests (i.e. Mann-Whitney U test and Spearman rank correlation) gave essentially the same results. Differences among quartiles were assessed by the log rank test. Relative risks (RRs) and 95% confidence intervals (CIs) were assessed by univariate Cox proportional hazard regression. Bivariate and multivariate analyses were carried out to explore modifying effects of covariates for prognostic CAMs. We had a power of 89% to detect an RR of 2.5 between high and low CAMs values (beta=0.8, alpha=0,05). Area under the curve (AUC) was calculated from receiver operating curves (ROC) for all CAMs. All analyses were performed with the SPSS 11.0 statistical software.

Two-tailed values below 0.05 were considered statistical significant.

RESULTS

Characteristics of the cohort are presented in Table **1**. Almost every patient included had at least one established risk factor. Clustering of risk factors was common. In particular, a large proportion of the patients (~90%) was either current or previous smokers. The majority (73.1%) of the former smokers stopped smoking at the time of MI [12].

Fourty-four patients had died during 10 years of follow-up. Of these, 36 were classified as cardiac deaths, 6 as cancer deaths, and 2 as deaths from other causes. There were 70 major cardiac events. Furthermore, no patient was lost to 10 years follow-up, indicating a satisfactory completeness of the study. A new feature of the present study is that new indicators of prognosis after MI, such as CRP, could be included in multivariate analyses.

There were not significant differences between mean values of CAMs with respect to endpoints. When mean values of CAMs were analysed in subgroups of categorical covariables (results not shown), we found that levels of sICAM-1 and sVCAM-1 significantly differed with respect to gender and smoking pattern ($p<0.0001$).

Several highly significant correlations were observed by Pearson univariate correlation testing, as presented on Table **2**. ICAM-1 exhibited significant correlation with levels of

Table 1. Characteristics of Patients with Previous Premature Myocardial Infarction at the Baseline Examination (n=247)

Sex		
Males, n (%)	193	(78.1)
Females n (%)	54	(21.9)
Age		
Male, years, median (range)	51	(31-58)
Female, years, median (range)	59	(34-63)
Cardiac status		
Time since recent MI, years, mean (SD)	2.1	(1.1)
Ejection fraction, %, mean (SD) *(4)	49.8	(13.8)
Secondary diagnosis		
Hypertension, n (%)	91	(36.8)
Diabetes, n (%)	13	(5.3)
Lifestyle		
Non-smokers, n (%)	26	(10.6)
Ex-smokers, n (%)	130	(52.8)
Current smokers, n (%)	90	(36.6)
Biochemical variable		
TC, mmol/L, mean (SD)	6.9	(1.4)
TG, mmol/L, median (interquertile range)	1.6	(1.1,2.4)
Lp(a) lipoprotein, mg/dL,	10.5	(4.5,22.5)
Creatinine, µmol/L, mean (SD) *(6)	88.6	14.4
CRP, mg/L, median (interquartile range) *(4)	2.4	(1.2,4.1)
tHcy, µmol/L, median (interquartile range) *(1)	9.2	(7.7,11.2)
Fibrinogen, g/L, median (interquartile range)	3.4	(2.9,4.0)
Therapy at baseline (1989)		
Aspirin, n (%)	50	(20.2)
Warfarin, n (%)	50	(20.2)
Aspirin and Warfarin, n (%)	81	(32.8)
Beta-blocker, n (%)	120	(48.6)
Calcium antagonist, n (%)	33	(13.4)
Diuretics, n (%)	25	(10.1)
ACE inhibitors, n (%) *(1)	18	(7.3)
Oral nitrates, n (%)	42	(17.0)
Lipid lowering agents, n (%)‡	16	(6.5)

TC: Total cholesterol: MI: Myocardial infarction. TG: Triglycerides. CRP: C reactive protein, tHcy: total homocysteine.
* Missing values (number of missing values).
‡ Includes Lovastatin (n=11) and Colestyramin (n=4), or both (n=1).

total cholesterol (p=0.037), Lp(a) lipoprotein (p=0.013), CRP (p<0.0001), and levels of VCAM-1 and E-selectin (p<0.0001). ICAM-1 was the only CAM that correlated to time since recent MI (p=0.02), but this correlation was weak. Time since MI (in years) was not a predictor of prognosis in this cohort, neither when analysed as a continuous varible nor as quartiles (Q1: 0.3-1.3, Q2: 1.4-2.1, Q3: 2.2-3.0, and Q4: 3.1-3.4).

Table 2. Pearson Correlation Coefficient (r) of CAMs with Other Variables at Baseline

Variable	ICAM-1	VCAM-1	E-Selectin	P-Selectin
Ejection fraction	*0.08*	*0.08*	*-0.02*	*-0.05*
Age	*0.10*	*0.12*	*-0.07*	*0.02*
Time since MI	***0.16****	*0.09*	*0.1*	*0.01*
TG (mmol/L)	*0.03*	*-0.08*	*0.10*	***0.25****
TC (mmol/L)	***0.14****	***-0.18****	*-0.07*	*-0.01*
HDL-C (mmol/L)	*0.03*	*0.05*	*-0.05*	***-0.16****
Lp(a) (mg/dL)	***0.16****	*0.03*	*0.11*	*0.02*
CRP (mg/L)	***0.29****	*0.06*	*0.06*	*0.09*
tHcy (µmol/L)	0.13	0.05	**0.14***	**0.16***
Fibrinogen (g/L)	0.12	-0.10	0.02	0.10
ICAM-1		***0.23****	***0.32****	*0.08*
VCAM-1	***0.23****		*0.05*	*0.09*
E-selectin	***0.32****	*0.05*		***0.36****
P-selectin	*0.08*	*0.09*	***0.36****	

* p<0.05.
** p<0.01.

There were also found statistically significant correlations between VCAM-1 and total cholesterol levels (p<0.005); as well as between E-selectin and P-selectin (p<0.0001) and P-selectin and triglycerides and HDL-cholesterol (p<0.0001 and p=0.021, respectively).

Table **3** shows the number of endpoints and RRs with 95% confidence intervals according to quartile of each CAM. ICAM-1 was significantly associated to total death, and the association to cardiac death was of bordeline significance. However, when CRP (in quartiles) was forced into a bivariate analyses the associations of ICAM-1 to total and cardiac death disappeared, while the effect of CRP on mortality remained highly significant. When a stepwise multivariate analyses included other prognostic variables, such as smoking, hypertension (dochotomic variables), cholesterol, EF and age (in quartiles), ICAM-1 and the other CAMs were forced out of analyses (entry level 0.05, removal level 0.10, data not shown).

Area under the curve calculated for ICAM-1, VCAM-1, E-selectin and P-selectin were 0.56, 0.51, 0.53 and 0.55, respectively.

DISCUSSION

In this study of patients who had suffered from premature MI and reached a stable state, about 20% died during 10 years of follow-up. About 80% of these deaths were due to CHD. One should consider these results in the light of the sparse medical treatment these and probably many other post MI patients were offered at the time of inclusion compared

Table 3. Number of End-Points According to Quartiles (Q) of Different CAMs

Variable		Total Deaths		Cardiac Deaths		Major Cardiac Events	
		n	RR (95%CI)	n	RR (95% CI)	n	RR (95% CI)
ICAM-1 (ng/mL)							
Q1	22.4-166.2	5	1.0	4	1.0	8	1.0
Q2	166.3-195.8	14	2.7 (1.0-7.5)	13	3.1 (1.0-9.6)	24	3.3 (1.5-7.4)
Q3	195.9-258.6	8	1.6 (0.5-4.8)	6	1.5 (0.4-5.2)	16	2.1 (0.9-5.0)
Q4	285.7-732.2	14	3.9 (1.4-10.8)	12	4.2 (1.3-12.9)	20	2.8 (1.2-6.4)
VCAM-1 (ng/mL)							
Q1	61.0-281.1	9	1.0	8	1.0	20	1.0
Q2	281.2-354.8	10	1.1 (0.5-2.8)	8	1.0 (0.4-2.7)	12	0.6 (0.6-3.2)
Q3	354.9-427.3	9	0.9 (0.4-2.3)	9	1.0 (0.4-2.7)	18	0.9 (0.5-1.7)
Q4	427.4-1474.0	13	1.7 (0.7-4.0)	10	1.5 (0.6-3.7)	18	0.9 (0.5-1.7)
E-Selectin (ng/mL)							
Q1	12.0-29.9	6	1.0	4	1.0	11	1.0
Q2	30.0-38.4	12	2.1 (0.8-5.6)	10	2.6 (0.8-8.4)	16	1.5 (0.7-3.2)
Q3	38.5-50.5	13	2.1 (0.8-5.4)	11	2.6 (0.8-8.2)	20	0.9 (0.5-1.7)
Q4	50.6-158.2	11	1.9 (0.7-5.1)	10	2.6 (0.8-8.3)	19	1.9 (0.9-4.0)
P-Selectin (ng/mL)							
Q1	9.5-29.3	6	1.0	5	1.0	14	1.0
Q2	29.4-39.6	14	2.3 (0.9-6.2)	10	2.0 (0.7-5.9)	19	1.4 (0.7-2.8)
Q3	39.7-52.7	10	1.4 (0.5-3.9)	9	1.5 (0.5-4.5)	14	1.0 (0.9-2.1)
Q4	52.8-97.5	11	1.3 (0.5-3.6)	11	1.6 (0.6-4.6)	19	1.4 (0.7-2.9)

to standard treatment today. The relatively high survival rate could be due to their young age. The proportion of CHD deaths appears similar to older MI cohorts [13].

ICAM-1 was the only CAM associated to death in this study of relatively young MI patients, but the effect disappeared after adjustment for CRP. Both variables are markers of inflammation, but CRP appears superior to ICAM-1 as a predictor of mortality. This may reflect that inflammation is important for prognosis, and that CRP is a better and more sensitive marker of a low-grade inflammation. ICAM-1 correlated positively to time since recent MI, contradicting higher levels of ICAM-1 as a result of acute respons after MI. The other CAMs did not predict death. However, one cannot on basis of this study rule out that CAMs play an important role in the pathophysiological mechanisms following MI.

Expression of adhesion molecules on endothelial cells may promote the recruitment of inflammatory cells playing important roles in the atherosclerotic process [14]. The role of CAMs in various pathological processes including angiogenesis, thrombosis, apoptosis, cell migration & proliferation that can lead to both acute and chronic disease states are also well documented [14]. Therefore, the use of CAMs as potential diagnostic markers are increasingly utilized. However, soluble CAMs appear to add little predictive value to prognosis in a clinical setting.

Our study adds data to the reported information on vascular risk factors and concentrations of CAMs in people without CHD [5,6,15] and it confirms that these factors are generally associated with one another, and with other risk factors such as circulating CRP, cholesterol and Lp(a) lipoprotein.

Our results are not in agreement with previous observations [16, 17] who found that elevated plasma concentrations of VCAM-1, but not ICAM-1 and E-selectin, correlated with the extent of peripheral arterial disease and can predict an increased risk for subsequent cardiovascular events. In a case control study, Schumacher A *et al.* [18] reported significantly elevated circulating levels of sVCAM-1, sICAM-1, and P-selectin in the CHD patients (p for all <0.001). The correlations observed by us are in agreement with reported findings [15] on serum samples of 643 men with coronary heart disease and 1278 controls nested in a prospective study of 5661 men who were monitored for 16 years. This agree-

ment is present, even though their samples were derived from non-fasting subjects and were stored at -20^{0}C. They found significant associations of soluble CAMs with one another, with other markers of inflammation, and with some classic coronary risk factors, but concluded that soluble CAMs are unlikely to add much predictive information to that provided by more established risk factors.

A significant correlation ($p<0.001$) between raised concentrations of C-reactive protein and arterial endothelial ICAM-1 expression in endomyocardial biopsy samples from the prospective study of Labarrere *et al*. [19] was confirmed in our study. Moreover, we confirmed interaction between Lp(a) lipoprotein and ICAM-1 [20].

We do agree with recent reports [15, 21] that although endothelial dysfunction is important feature in early as well as in advanced stages of atherosclerosis, we can not advocate its routine assessment by measuring soluble CAMs. As suggested [21], certain aspects of laboratory limitations and costs need to be addressed as well. However, CAM's markers are already used to monitor the disease process they may be useful to control disease activity [22].

On the other hand, there is greater interest in evaluating markers of inflammation among individuals classified as having low-risk for cardiovascular disease [23]. There are proposals for trials that test whether patients with low LDL and high CRP levels benefit from statin therapy [24]. The possible value of CAMs markers in assessing the success of the therapy could be less certain as far as the relation of changes in these markers to cardiovascular risk remains unknown. As known, statin therapy may change the risk relation and, consequently, reduce the possible predictive value of CAMs [25], further making it difficult to assess the value of measuring changes in inflammatory markers [23]. Increased endothelial activation was suggested to be associated with increased long-term risk of death, myocardial infarction, or recurrent events, after adjusting for statin regimen [26], but further replication in independent samples is desirable.

CONCLUSION

Our data indicate that the measurement of CAMs is unlikely to add significant predictive information beyond that provided by more established risk factors.

However, the present study indicates that there is association between CAMs themselves, and between CAMs and risk factors such as total cholesterol, CRP and Lp (a) lipoprotein.

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