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Usefulness of Preoperative C-reactive Protein and Soluble Intercellular Adhesion Molecule 1 for Predicting Future Cardiovascular Events after Coronary Artery Bypass Grafting

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Abstract

High levels of C-reactive protein and soluble intercellular adhesion molecule 1 are associated with increased risk for cardiovascular events. No long-term data is available on predictive value of preoperative C-reactive protein and soluble intercellular adhesion molecule 1 on the outcome after coronary artery bypass grafting. We measured baseline C-reactive protein and soluble intercellular adhesion molecule 1 in preoperative serum stored at -80°C of 87 coronary artery diseased patients before undergoing isolated coronary artery bypass grafting. Follow up was performed after a mean duration of 7.6±0.1 years and all cardiovascular events were recorded. Data were analyzed by dividing the patients into two groups according to the median value of C-reactive protein and soluble intercellular adhesion molecule 1. During follow up 16 patients experienced a cardiovascular event. In patients with C-reactive protein above the median (1.9 mg/L) the cumulative cardiovascular event incidence was 29% compared to 9% in patients below the median (P=0.048). In Cox-regression analysis, corrected for age, gender and conventional risk factors, the adjusted relative risk of cardiovascular events of C-reactive protein above median was 3.9 (95% CI, 1.1 to 13.9; P<0.05). soluble intercellular adhesion molecule 1 level above the median (136µg/L) was associated with a cumulative cardiovascular event incidence of 21% versus 16% below the median (P=0.48). In conclusion, in patients undergoing coronary artery bypass grafting, elevated preoperative C-reactive protein levels, but not soluble intercellular adhesion molecule 1 levels, were associated with long term risk of cardiovascular events, independent of other cardiac risk factors.

Introduction

C-reactive protein has emerged as an important predictor of cardiovascular events in apparently healthy subjects[1;2], but also in patients with myocardial infarction[3], stable or unstable angina and after coronary conventional balloon angioplasty[4] or stent implantation.[5] Elevated levels of preoperative C-reactive protein has been associated with postoperative, in-hospital, outcome after coronary artery bypass grafting.[6] However, no data is available on long-term outcome after coronary artery bypass grafting. Cellular adhesion molecules, expressed on the endothelial membrane, facilitate the adhesion and subsequent transendothelial migration of circulating leukocytes. Soluble intercellular adhesion molecule 1 can be found in plasma and is considered to be surrogate markers of their true endothelial expression. Indeed, in healthy men, soluble intercellular adhesion molecule 1 has been associated with risk of future myocardial infarction.[1;7] However, the value of soluble intercellular adhesion molecule 1 in patients with established coronary artery disease remains to be determined. In this report, we analyzed the predictive value of preoperative C-reactive protein and soluble intercellular adhesion molecule 1 levels on long term incidence of cardiovascular events in patients undergoing coronary artery bypass grafting.

Methods and Results

From 1994 to 1997, 187 patients underwent elective coronary artery bypass grafting and participated in the QUO VADIS study.[8] Data on preoperative concentrations of C-reactive protein and soluble intercellular adhesion molecule 1 were available in 87 patients who form the basis of the present study.[9] Selection of the patients in the present study was solely based on the availability of serum (at -80°C) to determine preoperative C-reactive protein and soluble intercellular adhesion molecule 1. The institutional review board approved this study, and written informed consent was obtained from each subject. All laboratory measures were made in a core facility, and a validated assay was used for high sensitive C-reactive protein and soluble intercellular adhesion molecule 1.[9]

Long-term follow-up was performed by telephone contact. All cardiovascular events were validated by review of medical records. The outcome measure assessed was the time from coronary artery bypass grafting until the first occurrence of a component of the following: cardiovascular death, hospitalization for myocardial infarction, revascularization with percutaneous coronary intervention or re-coronary artery bypass grafting (if these procedures were performed at least 30 days after randomization), vascular surgery, and stroke as described previously.[10]

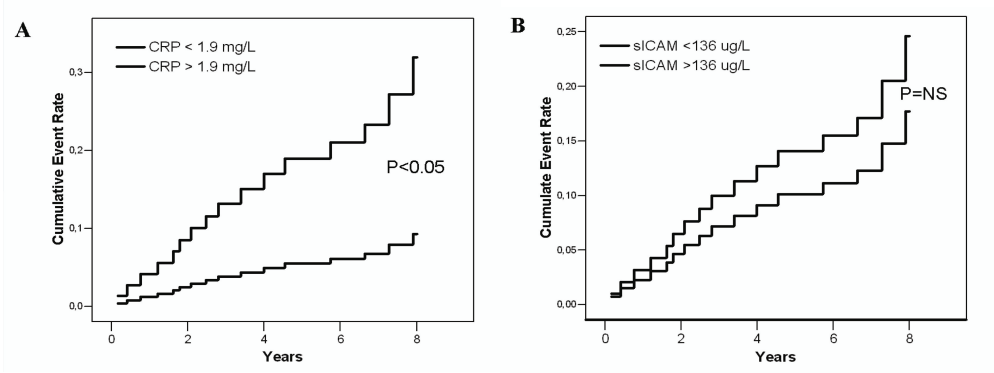
Data are expressed as mean±SEM. Statistical significance of differences in baseline characteristics was assessed by unpaired Student *t* test or χ^2 test when

Table 1. Distribution of baseline characteristics by baseline C-reactive protein and soluble intercellular adhesion molecule 1 concentrations

Variable	C-reactive protein			Soluble intercellular adhesion molecule 1		
	Low (n=44)	High (n=43)	*P*	Low (n=44)	High (n=43)	*P*
Age, (years)	62.9±1.5	62.9±1.2	1.0	62.3±1.4	63.5±1.3	0.53
Male/female	37/7	37/6	0.80	39/5	35/8	0.35
Body mass index (kg/m^2)	25.6±0.4	27.1±0.5	0.01	26.3±0.4	26.4±0.4	0.87
Hypertension	26	21	0.24	21	25	0.33
Diabetes Mellitus	3	6	0.28	3	6	0.28
Smoker			0.01			0.48
Never smoked	11	5		8	8	
Current smoker	4	12		6	10	
Number of coronary arteries narrowed			0.67			0.32
1	3	2		2	3	
2	12	11		10	13	
3	29	30		32	27	
NYHA class >II	23	23	0.90	22	24	0.40
Prior angina pectoris (past/current)	4/40	2/41	0.42	2/42	4/39	0.38
Prior myocardial infarction	17	19	0.60	16	20	0.34
Prior percutaneous coronary Intervention	6	5	0.78	8	3	0.12
Heart rate (bpm)	70.9±1.7	72.4±1.8	0.55	68.6±1.5	74.8±1.9	0.01
Blood pressure (mm Hg)						
Systolic	139.0±2.8	136.2±3.0	0.50	137.7±3.2	137.4±2.6	0.95
Diastolic	79.3±1.3	78.3±1.2	0.57	79.2±1.3	78.3±1.2	0.60
Lipid concentrations (mmol/l [mg/dl])						
Total cholesterol	6.28±0.22 [242±8]	6.23±0.18 [241±7]	0.85	6.05±0.20 [234±8]	6.46±0.20 [249±8]	0.15
Low-density lipoprotein Cholesterol	4.18±0.16 [161±6]	4.28±0.18 [165±7]	0.67	4.08±0.13 [158±5]	4.38±0.20 [169±8]	0.21
High-density lipoprotein Cholesterol	1.05±0.04 [41±2]	1.01±0.04 [39±2]	0.51	1.01±0.04 [39±2]	1.05±0.04 [41±2]	0.47
Triglycerides	2.12±0.25 [188±22]	2.06±0.18 [182±14]	0.86	1.96±0.20 [173±18]	2.23±0.23 [197±20]	0.37
Medication						
Quinapril	20	22	0.60	16	26	0.03
Aspirin	38	32	0.16	37	37	0.75
Lipid lowering	18	18	0.93	19	17	0.73
Follow-up time (years)	7.4±0.2	7.8±0.2	0.79	7.6±0.2	7.5±0.2	0.41

appropriate. Cox proportional hazards multivariate stepwise regression analysis was used to compute hazard ratios as estimates of relative risk of C-reactive protein and cardiovascular events during the follow-up period. Covariates entered in this regression model were age, sex, diabetes, hypertension, number of diseased coronary vessels, smoking status, body mass index, total cholesterol and high-density lipoprotein cholesterol. Statistical analysis was performed with SPSS statistical software (SPSS, Chicago, IL, USA). All P values were 2-tailed, and a value <0.05 was considered to indicate statistical significance.

Figure 1.



Cumulative cardiovascular event rate. Sex and age adjusted hazard ratios are shown for A) C-reactive protein (P<0.05) and B) soluble intercellular adhesion molecule 1 (P=NS) above and below its median value.

Of the 87 patients, 1 patient was lost to follow-up. Age at baseline was 62.9±0.9 years, and 13 (15%) were women. Before coronary artery bypass grafting, 41% of patients had a history of myocardial infarction, and 13% had previously undergone a percutaneous coronary intervention. At baseline, total cholesterol was 6.3±0.1 mmol/L (242 mg/dL), low-density lipoprotein cholesterol was 4.2±0.12 mmol/L (164 mg/dL), high-density lipoprotein cholesterol was 1.03±0.03 mmol/L (40 mg/dL), and triglycerides 2.09±0.15 mmol/L (195 mg/dL). Mean duration of follow-up was 7.6±0.14 years (median 7.7 years).
The median C-reactive protein was 1.9 mg/L (interquartile range 0.9 to 4.7 mg/L), the median soluble intercellular adhesion molecule 1 was 136 µg/L (mean 149±12). Baseline characteristics according to median C-reactive protein and soluble intercellular adhesion molecule 1 are presented in Table 1. High C-reactive protein was associated with higher body mass index and smoking (table 2). High soluble intercellular adhesion molecule 1 was only associated with a small increase in average heart rate.
During follow-up, 16 (19%) experienced a cardiovascular event, and 2 of these subjects had 2 events (Table 2). With C-reactive protein levels above the median (1.9 mg/L) the cumulative event incidence was 29% compared to 9% in patients below the median (P=0.048). C-reactive protein below median was associated with 69% fewer events (P<0.05). The relative risk for C-reactive protein above median was 3.1 (P<0.05). The age-, and sex-adjusted relative risk of cardiovascular events for C-reactive protein above median was 3.4 and after adjusting for conventional risk factors increased the relative risk to 3.8 (table 3). Figure 1 shows the 7.7 years age-, and sex-adjusted cumulative event rate for C-reactive protein and soluble intercellular adhesion molecule 1. When only the more objective events (cardiac death, myocardial infarction, and stroke) were considered, C-reactive protein above median remained a moderate predictor (relative risk 4.3 [95% CI, 0.75 to 24.55; P=0.10) with adjustment for age-, sex- and conventional risk factors.
With soluble intercellular adhesion molecule 1 levels above the median (136 ug/L) the cumulative event incidences were 21% and with soluble intercellular adhesion molecule 1 below median 16% (non-significant difference).

Table 2. Index of Cardiovascular Events During Follow-Up

Outcome	All patients	C-reactive protein			Soluble intercellular adhesion molecule 1		
		Low	High	P-value	Low	High	P-value
Cardiac death	1	1		0.617	1		0.414
Myocardial infarction	2		2	0.532	1	1	0.595
Percutaneous coronary intervention	2		2	0.138		2	0.138
Re- coronary artery bypass grafting	1	1		0.337		1	0.298
Stroke	8	2	6	0.108	4	4	0.905
Vascular surgery	4		4	<0.001	3	1	0.350
Total events	16	4	12	0.021	7	9	0.582

Discussion

In this 7.6 years study in coronary artery bypass graft patients, we studied the association between the inflammatory markers C-reactive protein and soluble intercellular adhesion molecule 1 with future cardiovascular events. Stratification according to preoperative soluble intercellular adhesion molecule 1 was not associated with an increase in cardiovascular events in our patients. However, we must be cautious in concluding lack of relation considering our sample size. In contrast to soluble intercellular adhesion molecule 1, cardiovascular event rate was significantly increased in patients with a preoperative C-reactive protein level above the median of 1.9 mg/L. Increased preoperative C-reactive protein was associated with 3-fold increased risk for cardiovascular events, even after adjustment for conventional risk factors.

Table 3. Relative risk of preoperative levels of C-reactive protein and soluble intercellular adhesion molecule 1 above median for cardiovascular events

	C-reactive protein			Soluble intercellular adhesion molecule 1		
	RR	95%CI	P-value	RR	95%CI	P-value
Univariate	3.14	1.01-9.86	0.048	1.43	0.53-3.84	0.48
Model 1	3.44	1.09-10.84	0.035	1.39	0.52-3.74	0.51
Model 2	3.84	1.04-14.2	0.043	1.59	0.53-4.77	0.41

Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex, diabetes, hypertension, number of diseased coronary vessels, smoking status, body mass index, total cholesterol, and high-density lipoprotein cholesterol.

The predictive value of C-reactive protein for recurrent cardiovascular events and death has been established previously in apparently healthy subjects[1;2] and in patients with acute coronary syndromes[11] or stroke[12], among patients in the stable phase after myocardial infarction[3], and among patients with documented coronary artery disease[13]. Our study suggests that even in a state of severe,

predominantly 3-vessel, coronary artery disease, in patients undergoing coronary artery bypass grafting, patients with increased C-reactive protein have an increased long-term risk of cardiovascular events. Previously, predictive value of C-reactive protein for in-hospital death after coronary artery bypass grafting was reported by others. Gaudino et al suggested that C-reactive protein >5.0 mg/L was not associated with in-hospital outcome in 113 coronary artery bypass graft patients[14]. However, Biancari et al reported a larger serie, involving 764 patients, in which they did find preoperative serum C-reactive protein levels of >1.0 mg/L to be associated with a significant increased risk of postoperative in-hospital death.[6] In addition, Milazzo et al reported that coronary artery bypass graft patients with preoperative serum C-reactive protein level of >0.3 mg/L had a significant increased risk to experience late ischemic events during a mean follow-up of 3.2 years.[15] Unfortunately, they did not correct for other risk factors. Preprocedural C-reactive protein has also been reported to predict cardiovascular events in other settings, including conventional balloon angioplasty[4] and coronary artery stent implantation[5]. Our median value of 1.9 mg/L is very close to the frequently used C-reactive protein cut-off value of 2.0 mg/L.[11;16] Our data suggests that preoperative C-reactive protein assessment might identify those at increased risk after surgery to experience another cardiovascular event.

Limitations of this study include its small sample size and will therefore require confirmation in larger prospective investigations. We studied only a limited number of patients and might have been underpowered to detect the prognostic importance of soluble intercellular adhesion molecule 1. Further work is needed to validate our findings in appropriate powered studies and to determine the appropriate values defining elevated C-reactive protein in this patient group.

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