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Patients with a history of stable or unstable coronary heart disease have different acute phase responses to an inflammatory stimulus☆

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Abstract

Increased levels of acute phase proteins (APP) in serum are associated with vulnerability of atherosclerotic plaques and acute manifestations of coronary heart disease (CHD). APP have been viewed as indexes of active vascular inflammation or as mediators of atherothrombosis. In the present study we tested the hypothesis that individuals who develop stable or unstable forms of CHD might have different innate responses to an inflammatory stimulus.

We compared changes in plasma C-reactive protein (CRP) and serum amyloid A (SAA) concentrations 48 h after a standardized inflammatory stimulus (adjuvanted influenza vaccination) in patients with quiescent CHD that had been manifested at onset as inducible myocardial ischemia (Group 1, $n = 26$) or as acute coronary syndromes (ACS) (Group 2, $n = 34$). Selected patients were free from inflammatory or other conditions that might affect the immune response.

CRP concentration increased significantly after vaccination in both groups (Group 1: 0.47 [0.21–0.86] to 0.56 [0.32–1.17] mg/L, $p = 0.005$; Group 2: 0.64 [0.21–1.09] to 0.75 [0.33–1.48] mg/L, $p = 0.003$), without significant differences between groups in absolute or percentage changes. By contrast, SAA did not change after vaccination in Group 1 (14.4 [8.9–19.5] to 14.8 [10.3–18.8] mg/L, $p = 0.88$) but increased significantly in Group 2 (16.9 [10.0–21.5] to 19.2 [11.3–29.1] mg/L, $p = 0.002$), with significant differences between the groups in absolute and percentage terms ($p = 0.015$ and 0.019, respectively). Changes in CRP and SAA, both absolute and percentage, were significantly correlated in Group 2 ($r = 0.60$ and 0.66, both $p < 0.001$). The responsiveness of plasma SAA to an inflammatory stimulus in Group 2 alone suggests a pro-inflammatory status in patients prone to acute coronary syndrome but not in those with inducible myocardial ischemia.

Keywords: Inflammation; C-reactive protein; Serum amyloid A; Coronary heart disease; Acute coronary syndrome

1. Introduction

The basis for the variability in expression of coronary disease between different individuals, ranging from a relatively benign and progressive flow-limiting stenosis associated with inducible ischemia to a life-threatening acute coronary syndrome (ACS), is not clear. Various sources of data indicate that inflammation plays a major role in the pathogenesis of atherosclerosis and particularly in the development of the vulnerable plaque, the main morphologic substrate of ACS [1–4]. Histological data demonstrate more signs of active

☆ After submission of this paper, a study was published showing a greater SAA response to influenza vaccination in men with versus without severe carotid artery disease [46]. This further suggests that the magnitude of the acute phase response to non-specific stimuli may relate to the individual susceptibility to atherosclerosis.

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inflammation in vulnerable or complicated than in stable stenotic plaques [5]. In vitro studies show that inflammatory cytokines [6,7] or acute phase proteins (APP) such as C-reactive protein (CRP) [8–11] or serum amyloid A (SAA) [12,13] promote changes associated with vulnerability to rupture or thrombogenicity of the atherosclerotic plaque. In addition, observational studies indicate that elevated blood levels of APP predict a first coronary event [14] and worsen the prognosis of patients with ACS [15,16].

However, there is no definitive explanation for the biological link between inflammation and ACS. A common view is that mediators released into the circulation during episodes of systemic infection or inflammation may promote arterial plaque vulnerability, which is supported by reports of frequent inflammatory episodes in different organs in the history of patients with ACS [17–19]. Alternatively, non-vascular inflammatory episodes and plaque vulnerability may be two independent expressions of a non-specific (genetically determined?) enhanced individual susceptibility to inflammation. So-called "pro-inflammation" may represent a common factor in the development of more inflamed plaques in arteries exposed to vascular risk factors and for enhanced inflammatory responses in other tissues exposed to non-specific noxious stimuli.

To test this hypothesis, we assessed the in vivo effect of a non-specific, non-vascular and standardized inflammatory stimulus on plasma levels of CRP and SAA, which provide a downstream integration of overall cytokine activation [2], in a selected population of patients with quiescent coronary heart disease (CHD) and a well-defined onset of coronary manifestations as either a stable disease or an acute coronary syndrome.

2. Methods

2.1. Patients

Sixty patients with clinically quiescent CHD attending the Atherosclerosis Prevention Unit of the Monzino Cardiology Center (Milan, Italy) were recruited for the study. Inclusion criteria were: male sex, 45–75 years of age, personal history of clinical and angiographic evidence of significant CHD (≥70% stenosis in one or more coronary arteries) manifested at onset as either exercise-inducible myocardial ischemia (Group 1) or ACS (Group 2), previous coronary artery bypass surgery, absence of coronary symptoms and exercise-inducible ischemia (confirmed by a negative treadmill test) in the past year, and clinical indication for influenza vaccination according to current national guidelines (Italian Ministry of Health).

Exclusion criteria were: indefinable clinical onset of CHD (e.g. undetected myocardial infarction, atypical angina, etc.), acute or chronic inflammatory or infective diseases, diabetes, renal disease (creatinine > 2 mg/dL or proteinuria > 500 mg/24 h), non-coronary vascular events or procedures in the preceding 6 months, major surgical interventions in the preceding 6 months, minor trauma in the last month (such as intramuscular injections or dental procedures), utilization of anti-inflammatory compounds (except aspirin at low doses as antiplatelet treatment) or immunosuppressive drugs, history of hypersensitivity to vaccine components, proteins from egg or chicken, polymixin B or neomycin, history of any serious adverse reaction to vaccines, autoimmune diseases and congenital or acquired conditions associated with immunodeficiency.

A pilot test was performed to assess the time-course of APP changes after influenza vaccination. After an overnight fast, five healthy male adults were subjected to influenza vaccination with Inflexal V®, 0.5 mL subcutaneous in the deltoid site. Venous blood was obtained at baseline and at 2, 4, 8, 24, 48 and 72 h after vaccination. As observed for other inflammatory stimuli [20,21], in this pilot study CRP and SAA blood levels peaked 48 h after influenza vaccination, which is in accordance with data from two studies reported while the present investigation was in progress [22,23]. Accordingly, venous blood was obtained at baseline and 48 h after vaccination to assess CRP and SAA changes in the coronary cohort. The local scientific and ethics committees approved the study and all the patients gave written informed consent.

2.2. APP determinations

Serum and EDTA-plasma samples were frozen at −80 °C until analyzed. Routine laboratory parameters were measured by standard methods. CRP was determined with high sensitivity in plasma and SAA was measured in serum by commercial ELISA methods (HYPHEN BioMed and Biosource, respectively). All the intra-assay and inter-assay coefficients of variation were < 6%.

2.3. Statistical analysis

Values are expressed as mean ± S.D. unless otherwise specified. CRP and SAA did not show a Gaussian distribution, so these variables are reported as medians [25th–75th percentiles]. Data were analyzed as absolute and percentage changes versus baseline. Non-parametric statistics were used to assess intra-group changes (Wilcoxon test) or inter-group differences (Mann–Whitney test) in CRP and SAA. Associations between changes in study parameters were assessed by Spearman correlation coefficients. The ability of changes in APP after vaccination to identify patients with a history of ACS was assessed by logistic regression; odds ratios and 95% confidence intervals (CI) as well as the area under the receiver operating characteristic (ROC) curve were determined. All analyses were two-sided and p values below 0.05 considered as statistically significant. All analyses were performed using SPSS 13.0.1 for Windows, Chicago, IL, USA.

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Table 1
Baseline characteristics of patients

	Group 1 ($n=26$) stable onset of CHD	Group 2 ($n=34$) ACS onset of CHD	p
Age at onset of CHD (years)	60.5 ± 5.9	55.2 ± 8.2	0.007
Age at vaccination (years)	64.5 ± 5.9 (45–73)	62.5 ± 6.3 (47–73)	0.22
Systolic blood pressure (mmHg)	135 ± 16	134 ± 13	0.79
Diastolic blood pressure (mmHg)	80 ± 7	81 ± 8	0.75
Cardiac rate (bpm)	61 ± 7	65 ± 6	0.08
Body mass index (kg/m^2)	26.4 ± 2.7	27.3 ± 2.7	0.20
Total cholesterol (mg/dL)	176 ± 27	179 ± 31	0.72
HDL-cholesterol (mg/dL)	47 ± 7	48 ± 10	0.71
LDL-cholesterol (mg/dL)	104 ± 25	106 ± 26	0.70
Triglycerides (mg/dL)	131 ± 72	123 ± 43	0.62
Creatinine (mg/dL)	1.0 ± 0.1	1.1 ± 0.2	0.93
Glucose (mg/dL)	96 ± 11	100 ± 10	0.20
CRP (mg/L)	0.47 [0.21–0.86]	0.64 [0.21–1.09]	0.26
SAA (mg/L)	14.4 [6.75–19.5]	11.0 [6.4–18.8]	0.76
Ex-smokers	50%	58%	0.28
History of hypertension	58%	64%	0.58
History of dyslipidemia	85%	88%	0.89
Previous influenza vaccination	65%	62%	0.77
Number of cardiovascular drugs	3.8 ± 1.1	4.0 ± 1.2	0.47
On aspirin	100%	100%	0.38
On statins	88.4%	85.3%	0.72

3. Results

Baseline variables including the number of cardiovascular drugs used, utilization of statins and aspirin, blood levels of glucose, creatinine, LDL-cholesterol, HDL-cholesterol, triglycerides, CRP and SAA were similar in the two Groups 1 ($n=26$) and 2 ($n=34$). None of the participants was a current smoker. Group 2 included 28 patients with onset of CHD as acute myocardial infarction and 6 as unstable angina. Age at onset of CHD was significantly lower in Group 2 but the age at the time of vaccination was similar in the two groups (Table 1).

A wide inter-individual variability of both CRP and SAA responses to influenza vaccination was observed (Fig. 1A and B). Fig. 2A shows that CRP significantly increased after vaccination in both groups (Group 1, 0.47 [0.21–0.86] to 0.56 [0.32–1.17] mg/L, $p=0.005$; Group 2, 0.64 [0.21–1.09] to 0.75 [0.33–1.48] mg/L, $p=0.003$), with no difference between the groups in either absolute or percentage changes.

In contrast (Fig. 2B), SAA showed no change after vaccination in Group 1 (14.4 [8.9–19.5] to 14.8 [10.3–18.8] mg/L, $p=0.88$) but increased significantly in Group 2 (16.9 [10.0–21.5] to 19.2 [11.3–29.1] mg/L, $p=0.002$), with significant differences between the groups. The absolute and percentage changes in both acute phase proteins were significantly correlated in patients with a history of ACS ($r=0.60$ and 0.66, respectively, both $p<0.001$) (Fig. 3).

By logistic regression analysis we calculated, using as a cut-off value the median SAA absolute change (1.15 mg/L), the odds ratio for an onset of CHD as an ACS to be 3.05 (95% CI 1.05–8.84, $p=0.039$), and the area under the ROC curve was 0.69 ± 0.07 ($p=0.015$).

4. Discussion

In vascular biology, acute phase proteins have been proposed as either direct causes of vascular damage or downstream "markers" or bystanders of active inflammation localized in atherosclerotic plaques [2,24].

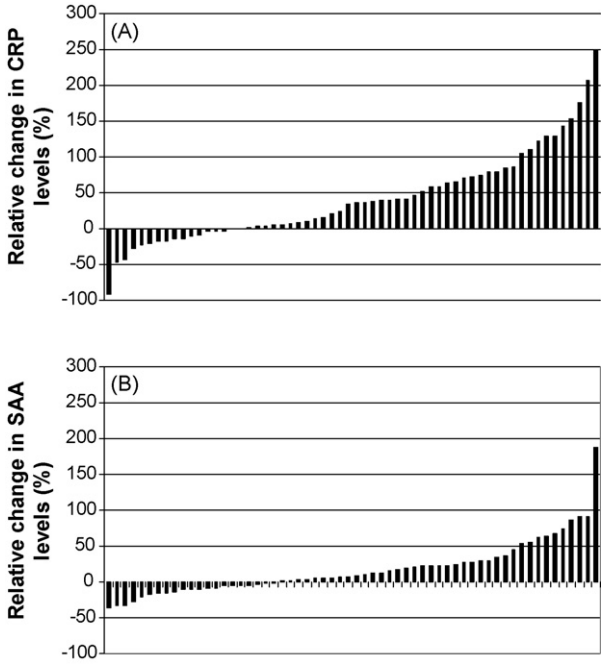

Fig. 1. Relative changes in (A) C-reactive protein and (B) serum amyloid A concentrations in response to influenza vaccination in individual coronary participants ($n=60$).

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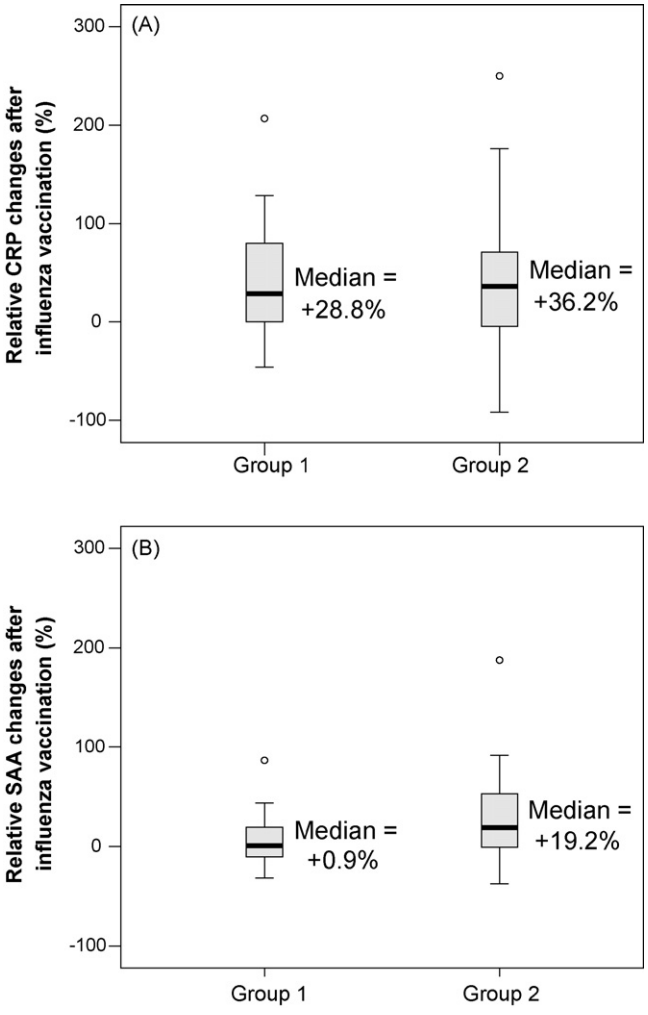

Fig. 2. Boxplots of the relative changes in (A) C-reactive protein and (B) serum amyloid A levels in response to influenza vaccination in coronary quiescent patients with a history of CHD onset as exercise-inducible myocardial ischemia (Group 1, $n = 26$) or as ACS (Group 2, $n = 34$). In each boxplot, the central thick line represents the median value, the lower and upper limits of the box represent the 25th and 75th percentiles of the distribution (interquartile range or IQR), the ends of the two lines extending from the IQR are the extreme values (within 1.5 times the IQR from the upper or lower quartile), and the open circles are potential outliers.

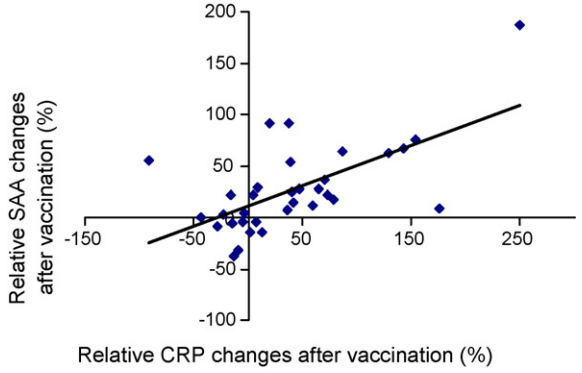

Fig. 3. Correlation between relative C-reactive protein (CRP) and serum amyloid A (SAA) changes in response to influenza vaccination in coronary quiescent patients with a history of CHD onset as ACS (Group 2, $n = 34$; $r = 0.66$, $p < 0.001$).

The present study investigated another hypothesis, namely that the association between increased APP levels and ACS reflects a "pro-inflammatory" individual precondition which determines, in parallel, the proneness of the arterial tissue to develop inflamed/vulnerable plaques (one cause of ACS), as well as the magnitude of the inflammatory response to non-specific stimuli in other tissues. Our new data support this hypothesis: they show that patients with a history of onset of CHD as an ACS display a significantly more intense SAA response to influenza vaccination, a non-vascular inflammatory stimulus, than patients with a history of onset of CHD as exercise-inducible myocardial ischemia.

Contrary to our expectations, CRP levels increased after influenza vaccination similarly in the two groups. One explanation of the different responses of SAA and CRP may be the higher sensitivity of the former to specific viral infections [25] and to other minor inflammatory stimuli [26]. Alternatively, the use of statins by 90% of our cohort could mask differences between the groups in the extent of the CRP response: earlier reports have shown statins to inhibit the response of CRP to different stimuli [27,28].

If our analysis is restricted to patients who were not on statins at the time of vaccination (data not shown), increases in CRP were found to be higher in Group 2 than in Group 1 (0.44 mg/L versus 0.18 mg/L, respectively), but the small number in each group (5 and 3, respectively) precludes formal statistical comparison.

Our results accord with previous observations from Liuzzo et al., who reported that coronary angioplasty or diagnostic coronary angiography increases blood levels of CRP and SAA in patients with unstable angina but not in those with stable angina [29], which again suggests an enhanced inflammatory response to non-specific stimuli in patients with unstable angina.

Unique characteristics of the present study design give further support to the theory of a pro-inflammatory disposition in determining lesion vulnerability. First, patients were classified according to their clinical manifestation at onset and not at recurrences of CHD, in an attempt to avoid any misclassification due to potential influences of cardiovascular drugs or interventions used on the clinical expression of coronary atherosclerosis. Secondly, the selection of patients with quiescent CHD at the time of vaccination allowed us to search for differences of the innate response in subjects with an immune system not boosted by inflammatory phenomena associated with atheroma rupture or myocardial ischemia [30]. Finally, the mean age at the time of the experimental stimulus, a factor that may significantly influence the intensity of the immune response [31], was similar in the two groups. Thus, unlike previous studies comparing features of inflammation in patients with ongoing acute or chronic coronary manifestations [32–34], the present research assessed the innate response in groups of similarly aged patients with currently quiescent CHD, well character-

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ized at onset as either exercise-inducible myocardial ischemia or ACS.

Vaccination has previously mostly been used to assess the innate response in humans using bacterial vaccines [35]. Recently, reported changes induced by a viral vaccination (against yellow fever) in plasma CRP levels of healthy subjects [36,37] showed wide inter-individual variability, a result analogous to that of CRP and SAA responses to influenza vaccination we observed. As previously mentioned, two groups have recently assessed the acute phase response to influenza vaccination in healthy subjects [22,23]; to the best of our knowledge, no previous investigations have been reported using influenza vaccination to investigate individual innate immune responses in coronary patients. Vaccination is an inflammatory stimulus, and systemic inflammation might theoretically promote arterial plaque vulnerability in patients with coronary atherosclerosis; however, influenza vaccination is recommended by current guidelines in patients with cardiovascular disease and other susceptible populations to reduce the risk of major complications of influenza should it be contracted, and a recent scientific statement from the American Heart Association recommends influenza immunization with inactivated vaccine as part of comprehensive secondary prevention in persons with coronary and other atherosclerotic vascular disease [38]. This is why we chose influenza vaccination as an experimental inflammatory stimulus for the present study as it is not only ethically acceptable, but desirable for these patients.

Although macroscopic signs of inflammation did not occur at the site of vaccination in any patient, subclinical variability in the extent of local leukocyte recruitment or cytokine production could account for the different SAA responses elicited in the two groups, as suggested by previous in vitro studies showing a higher IL-6 production by monocytes isolated from patients with recurrent unstable angina than from patients with stable angina or healthy controls [39]. We cannot exclude the possibility that pro-inflammatory cytokines released at the site of vaccination elicit a more intense SAA response by hepatocytes in patients with a history of ACS than in patients with one of stable CHD. We made no attempt to measure changes induced by influenza vaccination in cytokine levels or other upstream inflammatory events; thus, further studies are necessary to investigate which is/are the molecular mechanism/s underlying the different acute phase responses observed in the two coronary groups.

Polymorphism in genes involved in the pathway of innate immunity may affect the characteristics of the inflammatory response [40–43], and a recent study found significantly higher CRP levels in the offspring of patients with premature CHD than in controls [44]. These data suggest that the increased acute phase response in patients with a history of ACS observed in the present study may be genetically determined and that pro-inflammation associated with plaque vulnerability could be a heritable condition.

Beyond pathophysiological considerations, one of the main challenges in current clinical cardiology is the identification of individuals at risk of developing stable CHD as opposed to ACS, two circumstances with radically different prognosis and medical approach. As in previous studies [45], our baseline APP values were not different between the two groups with quiescent CHD. In contrast, the results of the logistic regression analysis showing a three-fold greater chance of starting CHD as an ACS in patients with higher changes of SAA after influenza vaccination indicate that this test may be able to distinguish patients with and without a history of ACS. More generally, our data raise the possibility that the APP response to a non-specific inflammatory stimulus could be a better marker than steady-state APP levels in identifying patients prone to ACS. Prospective studies are needed to establish the prognostic value of the CRP and SAA responses to influenza vaccination (or to other ethical and standardized inflammatory stimulus) in populations at high risk of CHD.

In summary, a non-specific inflammatory stimulus, such as influenza vaccination, elicits different innate responses in patients with a history of clinically distinct forms of CHD. Further studies may be warranted to substantiate the present results, to investigate the underlying molecular mechanisms and to corroborate the predictive value of pro-inflammation.

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