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## WIDESPREAD CORONARY INFLAMMATION IN UNSTABLE ANGINA

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### ABSTRACT

**Background** Inflammation within vulnerable coronary plaques may cause unstable angina by promoting rupture and erosion. In unstable angina, activated leukocytes may be found in peripheral and coronary-sinus blood, but it is unclear whether they are selectively activated in the vascular bed of the culprit stenosis.

**Methods** We measured the content neutrophil myeloperoxidase content in the cardiac and femoral circulations in five groups of patients: two groups with unstable angina and stenosis in either the left anterior descending coronary artery (24 patients) or the right coronary artery (9 patients); 13 with chronic stable angina; 13 with variant angina and recurrent ischemia; and 6 controls. Blood samples were taken from the aorta, the femoral vein, and the great cardiac vein, which selectively drains blood from the left but not the right coronary artery.

**Results** The neutrophil myeloperoxidase content of aortic blood was similar in both groups of patients with unstable angina (−3.9 and −5.5, with negative values representing depletion of the enzyme due to neutrophil activation) and significantly lower than in the other three groups ( $P < 0.05$ ). Independently of the site of the stenosis, the neutrophil myeloperoxidase content in blood from the great cardiac vein was significantly decreased in both groups of patients with unstable angina (−6.4 in those with a left coronary lesion and −6.6 in those with a right coronary lesion), but not in patients with stable angina and multiple stenoses, patients with variant angina and recurrent ischemia, or controls. There was also a significant transc coronary reduction in myeloperoxidase content in both groups with unstable angina.

**Conclusions** The widespread activation of neutrophils across the coronary vascular bed in patients with unstable angina, regardless of the location of the culprit stenosis, challenges the concept of a single vulnerable plaque in unstable coronary syndromes. (N Engl J Med 2002;347:5-12.)

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**T**HE hypothesis that inflammation of a vulnerable plaque is responsible for the development of acute coronary syndromes<sup>1-5</sup> is stimulating a variety of techniques for the detection and stabilization of vulnerable plaques.<sup>6-10</sup> Yet, it is unclear whether the inflammatory process is confined to a single vulnerable plaque or whether it is more widespread in the coronary vasculature.

The possibility of widespread inflammation of the coronary arterial bed is suggested by the recent report of multiple complex coronary plaques in patients with acute myocardial infarction<sup>11</sup> and by previous postmortem findings of multiple fresh thrombi in patients with unstable angina<sup>12</sup> and of multiple fissured, thrombosed plaques.<sup>13,14</sup> A widespread acute inflammatory process in the coronary arterial bed would have important implications for a clearer understanding of the pathogenesis, and eventually for the treatment and prevention, of acute coronary syndromes. By “widespread,” we mean involvement of more than one major coronary artery. By measuring leukocyte expression of CD11b and CD18 in aortic and coronary-sinus blood, Mazzone et al.<sup>15</sup> and de Servi et al.<sup>16</sup> demonstrated a transc coronary inflammatory activation of monocytes and neutrophils in patients with unstable angina. Such activation was not detectable in aortic blood. Unfortunately, these authors did not assess the correlation between activation and the location of the culprit coronary stenosis responsible for the angina.<sup>15,16</sup> Marked activation of neutrophils was also detected in the peripheral blood of patients with unstable angina, but not in those with stable angina or in controls. Activation was detected by

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measuring the neutrophil myeloperoxidase content, which is an index of more advanced inflammatory activation than that identified by measuring CD11b and CD18 expression.<sup>17,18</sup>

We ascertained whether the activation of neutrophils, presumably due to inflammation, in patients with unstable angina was confined to the vascular bed perfused by the vessel with the culprit coronary stenosis, or whether it also involved the vascular bed of angiographically normal or nearly normal arteries. We selected patients with coronary stenoses of either the left anterior descending or the right coronary artery. We simultaneously measured the neutrophil myeloperoxidase content in blood from the aorta, the femoral vein, and the great cardiac vein, which selectively drains blood from the left anterior descending coronary artery but not the right coronary artery.<sup>19</sup> Patients with stable angina and stenosis of the left anterior descending coronary artery, patients with variant angina and recurrent ischemia of the left anterior descending coronary artery, and patients without coronary disease (controls) were also studied.

## METHODS

### Patients

We studied a total of 65 patients, divided into five groups. Two of the groups consisted of the 33 patients who had Braunwald class IIIB unstable angina. Coronary angiography showed that the coronary stenosis responsible for the angina (the culprit stenosis) was in the left anterior descending coronary artery in 24 of these patients (the first group), and in the right coronary artery in the other 9 patients (the second group). The remaining three groups were made up of 13 patients with chronic stable angina and stenosis in the left anterior descending coronary artery; 13 patients with active variant angina and recurrent spasm in the left anterior descending coronary artery, which was documented by testing with ergonovine; and 6 control patients with mild mitral stenosis, atrial septal defect, or supraventricular tachycardia and a normal coronary angiogram.

Patients with a recent myocardial infarction (within three months), prior coronary interventions, an occluded coronary vessel, a culprit coronary stenosis in the circumflex branch, or intercurrent infective or inflammatory disorders were excluded from the study. No patients were taking antiinflammatory agents other than aspirin (up to 100 mg daily).

The protocol was approved by the ethics committee of the Catholic University of Rome, and all patients gave written informed consent.

### Protocol

Serum levels of C-reactive protein were measured on admission and used as a marker of systemic inflammation. Cardiac catheterization was performed within a mean ( $\pm$ SD) of  $2\pm 1$  days. Before the injection of a contrast agent, all patients underwent sampling of blood from the right femoral vein and simultaneous sampling of blood from the aorta and great cardiac vein for the measurement of neutrophil myeloperoxidase. In both groups of patients with unstable angina, in order to demonstrate that the great cardiac vein selectively drained blood from the left anterior descending but not from the right coronary artery, the blood oxygen saturation in the great cardiac vein was determined before and after the injection of 1.0 mg of isosorbide dinitrate into the left ante-

rior descending or the right coronary artery, according to the location of the culprit stenosis. The venous–arterial differences in neutrophil and leukocyte counts through the coronary and peripheral circulations were also determined.

The myeloperoxidase content was determined by using a hematologic analyzer (Bayer H\*1), which measures the differential leukocyte count as well as the cell count by automated flow cytometry, as previously described.<sup>17</sup> The H\*1 computer software calculates a myeloperoxidase index of the mean myeloperoxidase content in the neutrophil population. In healthy subjects, this index is close to 0. Positive values characterize neutrophils rich in myeloperoxidase, and negative values characterize neutrophils depleted of myeloperoxidase as a consequence of their activation. A lower myeloperoxidase index in blood from the great cardiac vein or the femoral vein, as compared with the aorta, was taken as an index of neutrophil activation through the coronary or femoral vascular bed. C-reactive protein levels were measured by a high-sensitivity, latex-enhanced immunonephelometric assay (Dade Behring BN II analyzer).<sup>20</sup> The working range of the assay was 0.175 to 1100 mg per liter, and the coefficient of variation was less than 5 percent.

### Statistical Analysis

Because the myeloperoxidase index did not have a normal distribution, nonparametric tests were used: the Mann–Whitney test and the Kruskal–Wallis test with multiple-comparison procedures (Dunn's method) for comparisons between groups, and the Friedman test and the Wilcoxon test with the Bonferroni correction for comparisons within groups. Correlations were determined with use of Spearman's rank-correlation coefficient.<sup>21</sup> The leukocyte and neutrophil counts had a normal distribution and were evaluated by analysis of variance for repeated measures with the Bonferroni correction. Chi-square statistics were used for categorical variables. A P value of less than 0.05 (two-tailed) was considered to indicate statistical significance. Data are reported as medians and ranges or as means  $\pm$ SD, as appropriate.

## RESULTS

The demographic, clinical, and angiographic characteristics of the patients are reported in Tables 1 and 2. Anginal symptoms before coronary angiography were similar in patients who had unstable angina with a left coronary lesion, those who had unstable angina with a right coronary lesion, and those who had variant angina (Table 1).

The blood oxygen saturation in the great cardiac vein markedly increased after injection of isosorbide dinitrate (1 mg) into the left anterior descending coronary artery of patients who had unstable angina with a left coronary lesion, but not after injection into the right coronary artery of patients who had unstable angina with a right coronary lesion ( $P=0.001$  by two-way analysis of variance). The median change in the blood oxygen saturation as a result of the isosorbide dinitrate injection differed significantly between the two groups (52.4 percent vs. 12.2 percent,  $P=0.04$ ), indicating that positioning the catheter in the great cardiac vein allowed for selective sampling of the blood draining from the vascular bed of the left anterior descending coronary artery. The leukocyte and neutrophil counts in the aorta, great cardiac vein, and femoral vein were similar; no differences were observed among groups (Table 1). Among patients who

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TABLE 1. CLINICAL CHARACTERISTICS OF THE STUDY PATIENTS.\*

CHARACTERISTIC	UNSTABLE ANGINA WITH A LEFT CORONARY LESION (N=24)	UNSTABLE ANGINA WITH A RIGHT CORONARY LESION (N=9)	CHRONIC STABLE ANGINA (N=13)	VARIANT ANGINA (N=13)	CONTROLS (N=6)
Male sex — no. (%)	19 (79)	7 (78)	10 (77)	9 (69)	2 (33)
Age — yr	63±10	60±9	61±9	57±4	55±12
Risk factors — no. (%)					
Diabetes	5 (21)	2 (22)	1 (8)	0	0
Hypertension†	15 (62)	6 (67)	4 (31)	2 (15)	0
Cholesterol >200 mg/dl‡	12 (50)	5 (56)	9 (69)	2 (15)	2 (33)
Smoking	7 (29)	4 (44)	2 (15)	1 (8)	1 (17)
Ischemic episodes during the 24-hr period before angiography					
Total no.	18	7	0	15	0
No. per patient	0.8±1.3	0.8±1.1	0	1.2±0.8	0
Total duration of ischemic episodes — min	13±20	10±18	0	23±14	0
No. of diseased vessels per patient§	1.41±0.51	1	1.45±0.82	0.29±0.49	0
Diameter of culprit stenosis — % of total	76±10	73±8	69±12	50±21	0
C-reactive protein — mg/liter¶					
Median	6.5	4.5	2.1	1.8	1.2
Range	0.1–24.8	0.9–30.6	0.1–5.7	0.08–5.6	0.04–3.2
White cells — per mm <sup>3</sup>	7265±1490	6930±1150	6570±1280	6507±1607	6336±1300
Neutrophils — per mm <sup>3</sup>	4215±1891	4328±2041	4740±1410	4097±1060	3673±1513
Myeloperoxidase index					
Femoral vein					
Median	-4.0	-5.2	1.9	-1.3	-0.1
Range	-13.7 to -0.5	-11.3 to -2.8	-4.6 to 8.3	-8.5 to 10.3	-8.7 to 0.7
Aorta**					
Median	-3.9	-5.5	0.1	0.1	-0.8
Range	-14.5 to -1.9	-12.7 to -2.1	-4.5 to 8.3	-6.9 to 10.5	-5.8 to 5.3
Great cardiac vein††					
Median	-6.4	-6.6	0.6	-0.4	-0.2
Range	-15.8 to -0.4	-13.9 to -4.0	-4.0 to 8.9	-9.4 to 11.0	-4.6 to 4.6
Great cardiac vein–aorta‡‡					
Median	-1.7	-1.5	0.3	0.5	0.6
Range	-5.8 to 0.6	-3.0 to 0.1	-2.3 to 1.5	-2.7 to 7.9	-1.9 to 1.5
Femoral vein–aorta§§					
Median	-0.2	0.2	0.1	0.2	1.5
Range	-3.5 to 7.3	-2.1 to 1.3	-2.3 to 2.7	-3.9 to 8.8	-4.6 to 1.4

\*Plus–minus values are means ±SD.

†P=0.02 for the comparison of patients with unstable angina with a left coronary lesion with patients with variant angina and with controls. P=0.01 for the comparison of patients with unstable angina with a right coronary lesion with patients with variant angina; P=0.04 for the comparison of patients with unstable angina and a right coronary lesion with controls.

‡P=0.02 for the comparison of patients with chronic stable angina with those with variant angina. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

§P=0.008 for the comparison of patients with unstable angina with a left coronary lesion with those with variant angina; P=0.05 for patients with unstable angina with a right coronary lesion versus those with variant angina; P=0.02 for patients with chronic stable angina versus those with variant angina.

¶P=0.003 for the comparison of patients with unstable angina with a left coronary lesion with those with chronic stable angina, P<0.001 versus those with variant angina, and P=0.008 versus controls; P=0.009 for the comparison of patients with unstable angina with a right coronary lesion with those with chronic stable angina, P=0.008 versus those with variant angina, and P=0.01 versus controls.

||P=0.01 for the comparison of patients with unstable angina with a left coronary lesion with those with chronic stable angina, P=0.04 versus those with variant angina, and P=0.05 versus controls. P=0.01 for the comparison of patients with unstable angina with a right coronary lesion with those with chronic stable angina, P=0.03 versus those with variant angina, and P=0.05 versus controls.

\*\*P=0.01 for the comparison of patients with unstable angina with a left coronary lesion with those with chronic stable angina, P=0.02 versus those with variant angina, and P=0.04 versus controls. P=0.01 for the comparison of patients with unstable angina with a right coronary lesion with those with chronic stable angina, P=0.03 versus those with variant angina, and P=0.04 versus controls.

††P<0.001 for the comparison of patients with unstable angina with a left coronary lesion with those with chronic stable angina, P=0.004 versus those with variant angina, and P=0.004 versus controls. P<0.001 for the comparison of patients with unstable angina with a right coronary lesion versus those with chronic stable angina, P=0.002 versus those with variant angina, and P=0.001 versus controls. For values in the great cardiac vein versus those in the aorta, P<0.001 for patients with unstable angina with a left coronary lesion and P=0.003 for those with unstable angina with a right coronary lesion.

‡‡P=0.004 for the comparison of patients with unstable angina with a left coronary lesion with those with chronic stable angina, P=0.01 versus those with variant angina, and P=0.03 versus controls. P=0.008 for the comparison of patients with unstable angina with a right coronary lesion with those with chronic stable angina, P=0.02 versus those with variant angina, and P=0.04 versus controls.

§§For the comparison of the difference in values between the great cardiac vein and the aorta and the difference in values between the femoral vein and the aorta, P=0.005 for patients with unstable angina with a left coronary lesion and P=0.04 for those with unstable angina with a right coronary lesion.

TABLE 2. PATTERN OF CORONARY DISEASE.

GROUP AND LOCATION OF STENOSIS	SEVERITY OF CORONARY STENOSIS (% OF TOTAL DIAMETER)				TOTAL >50	MEAN ( $\pm$ SD) EXTENT INDEX FOR LUMINAL IRREGULARITIES*
	30-50	>50 BUT <70	$\geq$ 70 BUT <90	$\geq$ 90		
	mean ( $\pm$ SD) no. of stenoses per patient					
Unstable angina with a left coronary lesion						
Left anterior descending coronary artery	0.53 $\pm$ 0.72	0.18 $\pm$ 0.73	0.88 $\pm$ 0.86	1.18 $\pm$ 0.81†	2.24 $\pm$ 1.25‡	1.41 $\pm$ 0.83§
Right coronary artery	0.33 $\pm$ 0.5	0	0.20 $\pm$ 0.58	0.07 $\pm$ 0.27	0.27 $\pm$ 0.73¶	1.02 $\pm$ 0.43
Unstable angina with a right coronary lesion						
Left anterior descending coronary artery	0.63 $\pm$ 0.74	0	0	0	0	0.63 $\pm$ 0.04**
Right coronary artery	0.13 $\pm$ 0.35	0	0.5 $\pm$ 0.76	1 $\pm$ 0.53††	1.5 $\pm$ 0.76‡‡	1.75 $\pm$ 0.9§§
Chronic stable angina						
Left anterior descending coronary artery	0.27 $\pm$ 0.47	0	1.1 $\pm$ 0.94	0.27 $\pm$ 0.47	1.36 $\pm$ 1.12	1.66 $\pm$ 0.91
Right coronary artery	0.2 $\pm$ 0.63	0.1 $\pm$ 0.32	0.1 $\pm$ 0.32	0.4 $\pm$ 0.52	0.6 $\pm$ 0.97	0.85 $\pm$ 0.41
Variant angina						
Left anterior descending coronary artery	0.29 $\pm$ 0.49	0	0.29 $\pm$ 0.49	0	0.29 $\pm$ 0.49	0.60 $\pm$ 0.46
Right coronary artery	0	0	0	0	0	0.98 $\pm$ 0.33
Controls						
Left anterior descending coronary artery	0	0	0	0	0	0.17 $\pm$ 0.15
Right coronary artery	0	0	0	0	0	0.14 $\pm$ 0.22

\*The extent of atherosclerosis was quantified by assigning a score of 0 to 3 per segment of the left anterior descending and right coronary arteries, as previously described.<sup>22</sup> An extent score of 0 indicates no luminal irregularities; 1, <10 percent of a segment's length appeared narrowed, irregular, or both; 2, 10 to 50 percent of a segment's length was abnormal; and 3, >50 percent of a segment's length was abnormal. The extent index was the extent score divided by the number of segments that could be properly visualized by antegrade flow.

†P=0.008 for the comparison with patients with chronic stable angina.

‡P=0.08 for the comparison with patients with chronic stable angina, and P<0.001 for the comparison with those with variant angina.

§P=0.03 for the comparison with patients with unstable angina with a right coronary lesion, P=0.32 versus those with chronic stable angina, P=0.04 versus those with variant angina, and P<0.001 versus controls.

¶P=0.003 for the comparison with patients with unstable angina with a right coronary lesion, and P=0.36 versus those with chronic stable angina.

||P=0.38 for the comparison with patients with unstable angina with a right coronary lesion, P=0.49 versus those with chronic stable angina, P=0.32 versus those with variant angina, and P=0.008 versus controls.

\*\*P=0.03 for the comparison with patients with unstable angina with a left coronary lesion, P=0.009 versus those with chronic stable angina, P=0.89 versus those with variant angina, and P=0.02 versus controls.

††P=0.008 for the comparison with patients with unstable angina with a left coronary lesion, and P=0.07 versus those with chronic stable angina.

‡‡P=0.003 for the comparison with patients with unstable angina with a left coronary lesion and P=0.03 versus those with chronic stable angina.

§§P=0.38 for the comparison with patients with unstable angina with a left coronary lesion, P=0.83 for the comparison with patients with chronic stable angina, P=0.14 versus those with variant angina, and P=0.005 versus controls.

had unstable angina with a right coronary lesion, the territory of the left anterior descending coronary artery had no wall irregularities in three patients, wall irregularities alone in three patients, and stenosis of 30 to 50 percent of the luminal diameter in the remaining three patients. Therefore, the atherosclerotic involvement was much smaller than that observed in patients who had unstable angina with a left coronary lesion and those who had chronic stable angina (Table 2).<sup>22</sup>

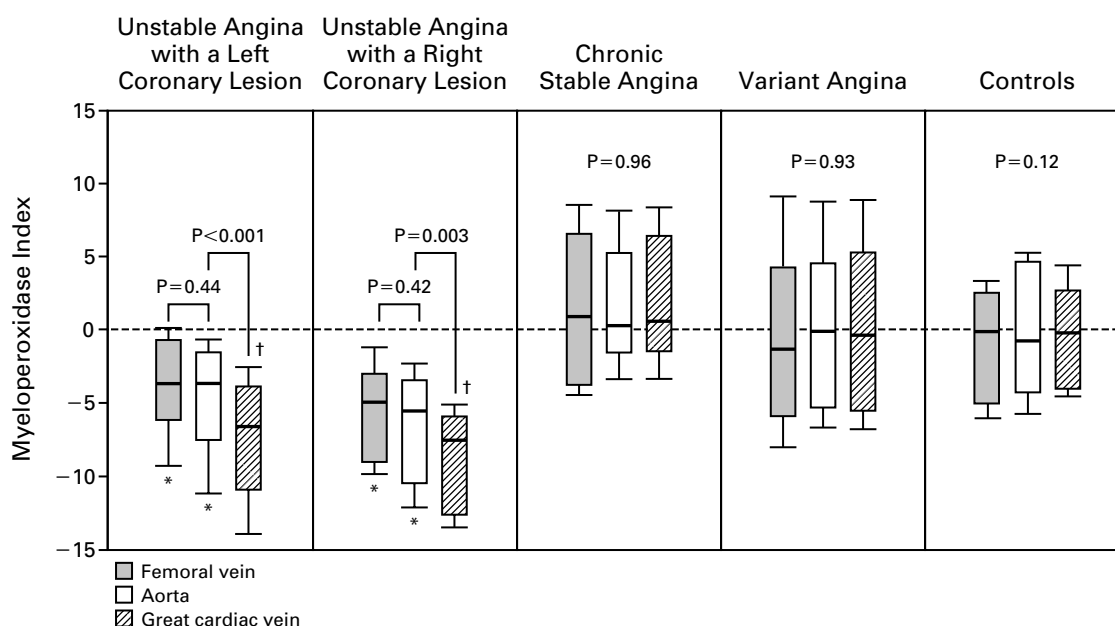
#### Neutrophil Activation in the Systemic Circulation

The median aortic myeloperoxidase indexes did not differ significantly between patients who had unstable angina with a left coronary lesion ( $-3.9$ ) and those who had unstable angina with a right cor-

onary lesion ( $-5.5$ , P=0.21), but they were significantly lower than those observed in patients with stable angina ( $+0.1$ ), patients with variant angina ( $+0.1$ ), and controls ( $-0.8$ ) (P<0.05 for all comparisons). The ranges for all values are reported in Table 1 and illustrated in Figure 1.

#### Neutrophil Activation through the Coronary and Femoral Circulations

In patients who had unstable angina with either a left or a right coronary lesion, a significant transcoronary decrease in the neutrophil myeloperoxidase index was observed. The median values in blood from the aorta and the great cardiac vein were  $-3.9$  and  $-6.4$ , respectively, for those with a left-coronary-artery lesion (P<0.001) and  $-5.5$  and  $-6.6$  for those with a



**Figure 1.** Neutrophil Activation, as Indicated by the Change in the Myeloperoxidase Index in Blood from the Femoral Vein, Aorta, and Great Cardiac Vein.

Patients with angina had stenosis of either the left anterior descending coronary artery or the right coronary artery. Data are presented as medians, with 25th and 75th percentiles (boxes) and 10th and 90th percentiles (I bars). Significantly lower values for myeloperoxidase in the aorta and the femoral vein were observed in both patients with unstable angina with a left coronary lesion and those with unstable angina with a right coronary lesion than in the other groups. In patients with unstable angina, but not in patients in any of the other groups, a further decrease in myeloperoxidase content was observed in blood from the great cardiac vein, not only when the neutrophils traversed the coronary vascular bed perfused by the culprit stenosis and thus subjected to recurrent ischemia (unstable angina with a left coronary lesion), but also when there was no coronary stenosis or any plausible cause of ischemia in the vascular bed draining into the great cardiac vein (unstable angina with a right coronary lesion). No neutrophil activation was detectable through the femoral circulation in any of the five groups studied. The asterisk indicates  $P < 0.05$  for the comparisons of the groups with unstable angina with a left coronary lesion and unstable angina with a right coronary lesion with the group with chronic stable angina, the group with variant angina, and controls. The dagger indicates  $P < 0.01$  for the comparisons of the groups with unstable angina with a left coronary lesion and unstable angina with a right coronary lesion with the group with chronic stable angina, the group with variant angina, and controls.

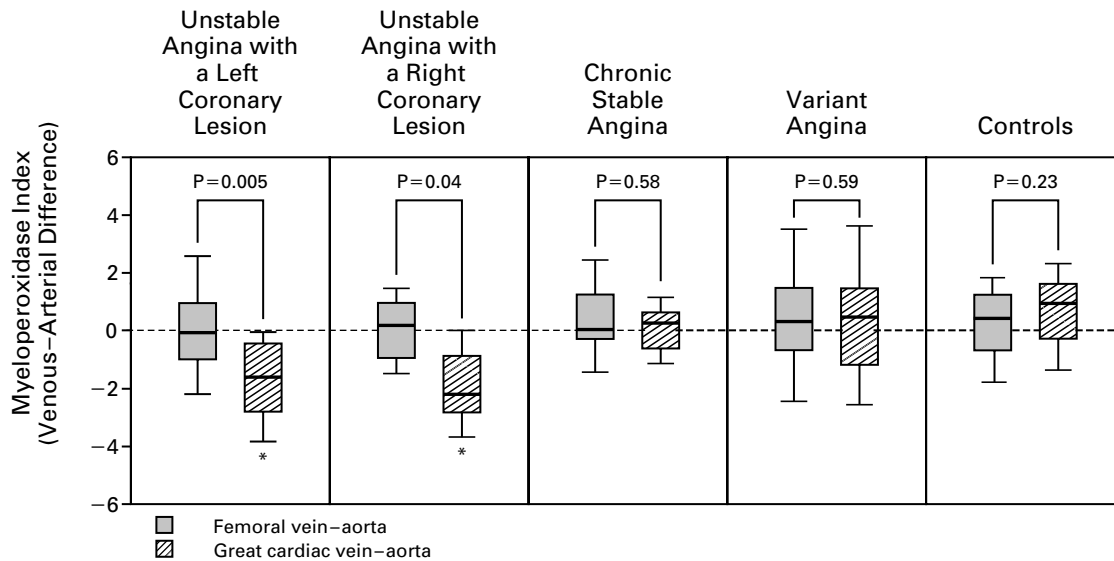
right-coronary-artery lesion ( $P = 0.003$ ). Conversely, no statistically significant transcoronary decrease in neutrophil myeloperoxidase content was observed in any of the other three groups; the myeloperoxidase values in blood from the great cardiac vein were  $+0.6$  in patients with stable angina,  $-0.4$  in those with variant angina, and  $-0.2$  in controls ( $P < 0.01$  for all the comparisons of patients with stable angina, patients with variant angina, and controls with both patients with unstable angina with a left coronary lesion and those with unstable angina with a right coronary lesion) (Table 1 and Fig. 1). No significant differences between the neutrophil myeloperoxidase contents of aortic and femoral venous blood were observed in any of the five groups (Table 1 and Fig. 1).

The change in neutrophil myeloperoxidase content across the coronary circulation was significantly greater in both patients with unstable angina with a

left coronary lesion and those with unstable angina with a right coronary lesion than in those with stable angina, those with variant angina, and controls (Table 1 and Fig. 2). The change in neutrophil myeloperoxidase content across the coronary circulation was significantly greater than the difference in neutrophil myeloperoxidase content between aortic and femoral venous blood in both patients with unstable angina with a left coronary lesion and those with unstable angina with a right coronary lesion, but not in any of the other three groups (Table 1 and Fig. 2).

#### Correlation between Levels of C-Reactive Protein and Myeloperoxidase

The median plasma levels of C-reactive protein were similar in patients with unstable angina with a left coronary lesion (6.5 mg per liter) and those with



**Figure 2.** Venous–Arterial Differences in Myeloperoxidase Content across the Femoral and Coronary Vascular Beds.

Data are presented as medians, with 25th and 75 percentiles (boxes) and 10th and 90th percentiles (I bars). The difference in myeloperoxidase content across the coronary circulation was significantly greater in both patients with unstable angina with a left coronary lesion and those with unstable angina with a right coronary lesion than in patients with chronic stable angina, patients with variant angina, and control patients. The difference in myeloperoxidase content across the coronary vascular bed was significantly greater than that across the femoral vascular bed in both patients with unstable angina with a left coronary lesion and those with unstable angina with a right coronary lesion, but not in any of the other three groups. The asterisk indicates  $P < 0.05$  for the comparison of the group with unstable angina with a left coronary lesion and unstable angina with a right coronary lesion with the group with chronic stable angina, the group with variant angina, and controls.

unstable angina with a right coronary lesion (4.5 mg per liter,  $P = 0.76$ ) and were significantly higher than the levels in patients with stable angina (2.1 mg per liter), patients with variant angina (1.8 mg per liter), and controls (1.2 mg per liter;  $P < 0.01$  for all comparisons) (Table 1).

Overall, in the five groups, a significant correlation was found between systemic levels of C-reactive protein and the aortic neutrophil myeloperoxidase content ( $r = -0.45$ ,  $P = 0.03$ ), as well as between systemic levels of C-reactive protein and the neutrophil myeloperoxidase content in blood from the great cardiac vein ( $r = -0.41$ ,  $P = 0.01$ ) (Fig. 3).

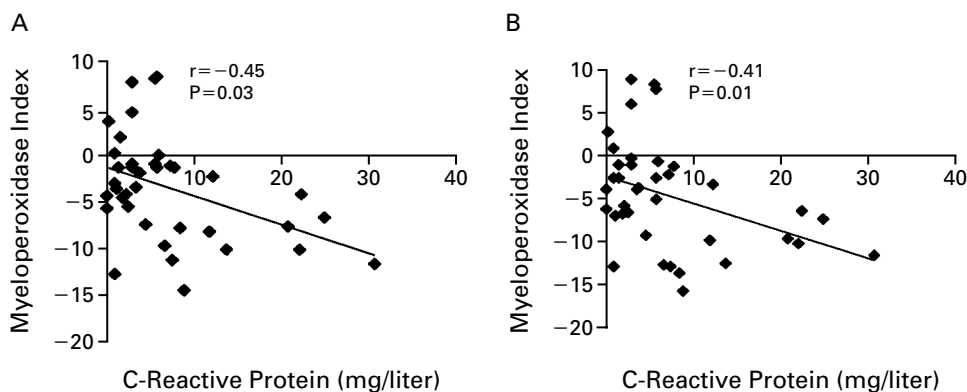
## DISCUSSION

Our findings confirm previous reports that in patients with unstable angina, leukocytes become activated as they traverse the coronary vascular bed,<sup>15,16</sup> and that such activation may be detectable systematically.<sup>17,23,24</sup> In addition, we found no significant increase in neutrophil activation in the great cardiac vein in controls, in patients with stable angina and documented left anterior descending coronary stenosis, or in patients with active variant angina and recurrent

ischemia in the territory of the left anterior descending coronary artery. Moreover, there was no detectable increase in neutrophil activation through the femoral circulation in any of the five groups studied.

In patients with unstable angina, transcortical neutrophil activation was not confined to the vascular bed perfused by the artery in which the culprit stenosis was located and thus subjected to recurrent ischemia. In fact, neutrophil activation occurred to a similar extent in patients in whom the left anterior descending coronary artery was not the site of the culprit stenosis. Patients with unstable angina and a culprit lesion in the right coronary artery had only minimal atherosclerotic involvement of the left anterior descending coronary artery, which was angiographically normal in three patients, had only luminal irregularities in three patients, and had stenosis of less than 50 percent of the diameter in three patients.

In animal models, neutrophil activation has been observed after 15 minutes of coronary occlusion–reperfusion.<sup>25</sup> However, our findings cannot be explained simply on the basis of an ischemia–reperfusion mechanism, in view of the fact that transcortical neutrophil activation was not observed in patients



**Figure 3.** Correlation between Systemic Values for C-Reactive Protein and the Change in the Myeloperoxidase Content in Blood from the Aorta and the Great Cardiac Vein.

C-reactive protein values were significantly and inversely correlated with the myeloperoxidase content of blood from the aorta (Panel A) and the great cardiac vein (Panel B). The diagonal lines are the regression lines.

with active variant angina, spasm of the left anterior descending artery, and a total ischemic burden similar to that of patients with unstable angina.

In patients with unstable angina, inflammatory-cell infiltrates are commonly found in most atherosclerotic plaques at postmortem examination<sup>1</sup> and in endarterectomy specimens.<sup>2,26</sup> Multiple fissured, thrombosed coronary plaques seem to be a common finding in acute coronary syndromes. Falk et al. reported 103 fissured, thrombosed plaques in 47 patients,<sup>13</sup> and Davies and Thomas reported 111 fissured, thrombosed plaques in 76 patients.<sup>14</sup> Neither of these reports discussed the possible clinical significance of the simultaneous rupture of multiple plaques. Multiple plaques with inflammatory-cell infiltrates and with a high content of proinflammatory cytokines were reported by Arbustini et al.<sup>12</sup> Finally, multiple complex lesions were reported by Goldstein et al.<sup>11</sup> The possibility that multiple plaque fissures and thrombi develop simultaneously at different sites merely as a result of mechanical stress seems rather unlikely. It would appear more reasonable to speculate that a multifocal or widespread inflammatory activation of the endothelium could change the characteristics of the interface between the blood and the vessel walls from anticoagulant and vasodilative to prothrombotic and vasoconstrictive, while at the same time activating the metalloproteases and collagenases responsible for endothelial-cell detachment and lysis of the plaque capsule at the sites where it is weakest.

Whether neutrophils become activated by interacting with the surface of sparse inflamed plaques or as a result of more widespread contact with a diffusely inflamed coronary endothelium is not known. De

Servi et al. detected no activation of monocytes and neutrophils across the culprit coronary stenosis in patients with unstable angina.<sup>16</sup> Conversely, the possibility of widespread coronary inflammation is suggested by the reports of alterations in coronary flow<sup>27,28</sup> and [<sup>18</sup>F]deoxyglucose uptake<sup>29</sup> in myocardial territories perfused by arteries without stenosis or culprit lesions in patients with recent infarctions and in those with unstable angina. Finally, in 10 percent of patients with unstable angina, inflammatory red streaks were observed along nonstenosed coronary arteries at the time of bypass surgery.<sup>30</sup>

The reported prevalence of systemically detectable inflammatory markers in acute coronary syndromes varies. Serum levels of C-reactive protein and of proinflammatory cytokines such as interleukin-6 are elevated in about 70 percent of patients with severe unstable angina on admission,<sup>31,32</sup> in 50 percent of such patients at discharge, and in 45 percent of such patients at six months of follow-up.<sup>20</sup> These increased levels are associated with recurrent instability and acute infarction. Accordingly, elevated levels of C-reactive protein and interleukin-6 are found before the appearance of markers of myocardial necrosis in nearly all patients in whom infarction is preceded by unstable angina, but in less than 50 percent of patients with myocardial infarction not preceded by unstable angina.<sup>31,33</sup> Therefore, the triggers of coronary thrombosis and vasoconstriction are not necessarily the same in all patients with acute coronary syndromes.

The activation of neutrophils as they traverse the coronary circulation of patients with unstable angina is a marker of a widespread inflammatory process occurring in the coronary vasculature. When the inten-

sity of the inflammatory stimuli varies, such a process may lead to waxing and waning of thrombosis and vasoconstriction. The possibility of widespread coronary inflammation has important implications for research and therapy. It challenges the widely accepted hypothesis that a single vulnerable plaque is responsible for the development of coronary instability — a hypothesis that is currently stimulating the development of techniques for the detection and stabilization of such plaques.

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