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Intracellular Neutrophil Myeloperoxidase Is Reduced in Unstable Angina and Acute Myocardial Infarction, but Its Reduction Is Not Related to Ischemia

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Objectives. **This study sought to assess neutrophil activation in acute coronary syndromes and its relation to ischemic episodes.**

Background. **Neutrophil activation has been reported in unstable angina and acute myocardial infarction; however, it is not clear whether it is related exclusively to ischemia–reperfusion injury.**

Methods. **We measured the index of intracellular myeloperoxidase in 1) patients with unstable angina, myocardial infarction, variant angina and chronic stable angina and in normal subjects (protocol A); and 2) in patients with unstable angina and acute myocardial infarction during the first 4 days of the hospital period (protocol B). To assess whether neutrophil activation was triggered by ischemia, the myeloperoxidase intracellular index was analyzed before and after spontaneous ischemic episodes and before and after ischemia induced by an exercise stress test in 10 patients with chronic stable angina. In 11 patients with unstable angina, we also compared values of the myeloperoxidase intracellular index at entry with those after waning of symptoms.**

Results. **In protocol A, the myeloperoxidase intracellular index was significantly reduced in patients with unstable angina and acute myocardial infarction compared with patients with stable and variant angina and normal subjects ($p < 0.01$). In protocol B, the myeloperoxidase intracellular index did not change over time in patients with unstable angina and myocardial infarction. However, in 11 patients with waning symptoms, the myeloperoxidase intracellular index was significantly higher after symptoms had waned ($p < 0.05$). In patients with unstable angina, 23 ischemic episodes were studied; no changes in the myeloperoxidase intracellular index were observed. In 10 patients with chronic stable angina and positive exercise stress test results, no significant differences in the myeloperoxidase intracellular index were observed after stress-induced ischemia.**

Conclusions. **Our study confirms that neutrophils are activated in acute coronary syndromes but suggests that their activation may not be only secondary to ischemia–reperfusion injury.**

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A growing body of evidence suggests that inflammation may play a role in unstable angina and acute myocardial infarction. Evidence of inflammation in acute coronary syndromes has been provided not only by a high prevalence of inflammatory cells in unstable coronary plaques (1–7) and by the presence of activated circulating lymphocytes, monocytes and macrophages (8–10), but also by the elevation of serum acute-phase proteins in unstable angina and acute myocardial infarction (11–14) and by increased urinary elimination of leukotriene B_4 (15) and thromboxane A_2 metabolites, in spite of the blockade of cyclooxygenase$_1$ by aspirin (16).

Neutrophil activation has been demonstrated in unstable angina and acute myocardial infarction (10,17–19) and, following coronary reperfusion, in experimental animals (20,21). The release of the content of granules may lead to endothelial damage and enhanced procoagulant activity, but it is not known whether neutrophil activation is caused by myocardial ischemia-reperfusion events in unstable angina or whether it is an independent, primary event. Myeloperoxidase is the major constituent of primary azurophil granules in neutrophils and is promptly discharged after activation by different agonists (22). To assess neutrophil activation and its time course in unstable angina and acute myocardial infarction in relation to the development of ischemic episodes and necrosis, we used a blood cell counter capable of extensive cytochemical analysis of leukocytes and quantification of intraneutrophil myeloperoxidase content. We also studied patients with active variant angina and spontaneous episodes of transmural ischemia and patients with chronic stable angina and effort stress test induced ischemia to assess whether episodes of myocardial ischemia having a pathogenetic mechanism different from that in unstable angina could lead to a similar neutrophil activation.

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JACC Vol. 27, No. 3
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Table 1. Clinical Characteristics of Study Patients

	UA (n = 30)	CSA (n = 40)	AMI (n = 16)	VA (n = 7)
Male gender	24 (80)	31 (77)	14 (87)	5 (62.5)
Age (yr)				
Mean ± SD	57.8 ± 8.3	59 ± 8.9	58 ± 9	55.5 ± 7.7
Range	43–74	42–79	41–72	44–68
History				
Previous MI	9 (30)	14 (35)	4 (25)	0
Previous CSA	10 (34)		10 (34)	0
Risk factors				
Current smoker	16 (53)	19 (47)	10 (62.5)	4 (50)
Hypertension	15 (50)	12 (30)	7 (44)	3 (37.5)
Cholesterol >200 mg/dl	7 (23)	20 (50)	4 (25)	5 (62.5)
Diabetes	6 (20)	5 (12.5)	2 (12.5)	0
Family history of CHD	8 (27)	13 (32.5)	5 (31)	2 (25)
Coronary angiography	n = 23	n = 25	n = 8	n = 7
3-vessel disease	6 (26)	6 (24)	1 (12.5)	0
2-vessel disease	8 (35)	6 (24)	0	0
1-vessel disease	6 (26)	13 (52)	8 (75)	1 (14)
No significant stenosis	3 (13)	0	3 (12.5)	6 (86)

Data presented are number (%) of patients, unless otherwise indicated. AMI = acute myocardial infarction; CHD = coronary heart disease; CSA = chronic stable angina; MI = myocardial infarction; UA = unstable angina; VA = variant angina.

Methods

Patients. We studied three groups of patients and two groups of control subjects. The patient groups included 30 patients with unstable angina, defined as rest angina with two ischemic episodes at rest or at least one ischemic episode of long duration (≥20 min) occurring within the last 24 h and demonstrating diagnostic electrocardiographic ST and T changes; 16 patients with acute myocardial infarction admitted to our coronary care unit within 6 h from the onset of symptoms with persistent ST segment elevation and small or no Q waves and no creatine kinase (CK) elevation on admission; and 7 patients with active variant angina demonstrated by positive ergonovine test results (23). The control groups included 40 patients with chronic stable angina and coronary heart disease demonstrated by coronary angiography and 26 blood donors from the hematology transfusion department. Between March 1993 and January 1994, 110 patients were admitted to our coronary care unit with a diagnosis of unstable angina and 102 patients with a diagnosis of acute myocardial infarction. Patients were excluded from the study if they had evidence of infective or inflammatory diseases, chronic disease, known thrombotic disorders other than coronary artery disease, recent (<1 month) acute myocardial infarction, operation or major trauma. Patients who were excluded included 38 with unstable angina because the last ischemic episode occurred >24 h before admission, 5 for CK or troponin T elevation within 6 h after admission, 15 for evidence of an ongoing inflammatory process, 4 for malignancy and 3 for left bundle branch block. Fifteen patients were not enrolled because one of the investigators was unavailable for the sampling procedure or for the analysis. Fifty-five patients with acute myocardial infarction were excluded because of chest pain lasting >6 h or elevated CK at entry, or both, 15 for evidence of an ongoing inflammatory process, 3 for a chronic disease, 4 for malignancy, 3 for evidence of other thrombotic disorders and 6 because one of the investigators was unavailable for the sampling procedure or for the analysis. Patient characteristics were homogeneous and are reported in Table 1.

Study design. To assess the prevalence and time course of neutrophil activation in acute coronary syndromes and the temporal relation between ischemic episodes and neutrophil activation, we designed two different protocols.

Protocol A. We compared the values of the myeloperoxidase index at the time of coronary care unit admission in patients with unstable angina, acute myocardial infarction and variant angina with those of patients with chronic stable angina and normal subjects.

Protocol B. We assessed the activation of the neutrophils during the initial 4 days of coronary care unit admission by taking blood samples as soon as possible after admission and, subsequently, in unstable angina every 6 h for the first 24 h and between 8 AM and 10 AM on days 2 (48 h) and 3 (72 h) and at hospital discharge, and in acute myocardial infarction 6 h after admission and between 8 AM and 10 AM on days 2 and 3 after admission. Sampling was interrupted when the addition of heparin or urgent revascularization (coronary angioplasty or bypass surgery) was clinically indicated. Of 30 patients with unstable angina, 13 had refractory angina, 1 had an acute myocardial infarction, 1 died, and 4 underwent elective bypass surgery or coronary angioplasty. To compare values of the myeloperoxidase intracellular index at entry (active unstable angina) with those after waning of symptoms (resolving unstable angina), we also took blood samples 1 week after symptoms had waned in the 11 patients in the unstable angina group without major coronary events or revascularization.

Troponin T and CK—specific and sensitive markers of myocardial cell necrosis—were also measured serially to assess their possible relation with neutrophil activation. All patients in the unstable angina group underwent Holter monitoring for 24 h and remained in the coronary care unit under electrocardiographic (ECG) monitoring of the lead with the most striking ischemic ST changes until completion of the study. The nurses were instructed to recognize and annotate each ST segment change from the monitors. Coronary angiography was performed in 23 of 30 patients (6 excluded because of waning of symptoms and negative stress test results, 1 because of death) within 5 days of admission because of the severity of symptoms. The angiograms were reviewed by an expert angiographer who was unaware of the patients' clinical and analytic data. To assess whether neutrophil activation was enhanced by ischemic episodes, the myeloperoxidase intracellular index and neutrophil count were analyzed both before and after a spontaneous ischemic episode (n = 23) and before and after an exercise stress test positive for ischemia in 10 patients with chronic stable angina (Protocol B1).

Materials. Samples were taken in 1:9 ethylenediaminetetraacetic acid (EDTA) solution and quickly analyzed. The

myeloperoxidase content was determined using a Bayer H*1 hematology analyzer that measures leukocyte differential count, as well as blood cell count, using automated cytochemistry in flow. Leukocytes containing myeloperoxidase, such as neutrophil and eosinophil granulocytes, reduce hydrogen peroxide in water and free oxygen, which oxidates 4-chloro-1-naphthol to a dark intracellular precipitate. Using a tungsten optical method, the H*1 measures the scattering and absorption of light produced by leukocytes while passing in single file through a well collimated light beam. The measurement of scattered light is proportional to the cell size, as in most flow cytometers, whereas the amount of absorbed light is a function of cell staining intensity (i.e., of myeloperoxidase activity). The H*1 computer software calculates an index, named the myeloperoxidase intracellular index, which quantifies the mean myeloperoxidase activity of the whole neutrophil population (24). The myeloperoxidase intracellular index is an index that expresses in arbitrary units the mean absorption of light of the neutrophil population of each sample. In normal subjects this index is about 0. Positive values appear when the neutrophils are rich in myeloperoxidase, and negative values appear when the neutrophils are depleted of myeloperoxidase, which typically happens after neutrophil activation.

Statistical analysis. The myeloperoxidase intracellular index was found not to have a normal distribution, thus nonparametric tests were used to analyze the data. We used the Kruskal-Wallis analysis for comparison among different groups and, when appropriate, Wilcoxon's test. Friedman's statistic was used for comparison within the same group. Spearman's rank test was used for correlations. Neutrophil counts were found to have a normal distribution, and the analysis was carried out by means of analysis of variance with Bonferroni correction. A p value <0.05 was accepted as significant. All tests are two-tailed.

Results

Protocol A. The myeloperoxidase intracellular index was reduced significantly in patients with unstable angina and acute myocardial infarction compared with those with chronic stable and variant angina and normal subjects ($p < 0.01$). The median myeloperoxidase intracellular index was −1.3 (range +5.5 to −7) in normal subjects, +7.4 (range +20 to −18.7) in patients with chronic stable angina, −4 (range +5 to −15) in patients with unstable angina and −7.8 (range +2 to −25) in patients with acute myocardial infarction. The myeloperoxidase intracellular index in patients with variant angina was similar to that in patients with chronic stable angina because the myeloperoxidase intracellular index at entry was +5 (range −1 to +9.8) (patients with chronic stable and variant angina vs. normal subjects, $p < 0.01$) (Fig. 1), although patients with variant angina had more ischemic episodes and longer total ischemic burden (even with episodes lasting >10 min) than patients with unstable angina (Table 2).

In patients with acute myocardial infarction, but not those with unstable angina, this reduction in the myeloperoxidase intracellular index was associated with an increase in the number of neutrophils, which measured 4,900 ± 1,060 cells/mm^3 in normal subjects, 4,490 ± 1,675 cells/mm^3 in patients with unstable angina, 3,275 ± 1,502 cells/mm^3 in patients with chronic stable angina, 8,655 ± 1,820 cells/mm^3 in patients with acute myocardial infarction and 3,730 ± 980 cells/mm^3 in patients with variant angina ($p < 0.01$, patients with acute myocardial infarction vs. those with unstable and stable angina and normal subjects) (Fig. 2).

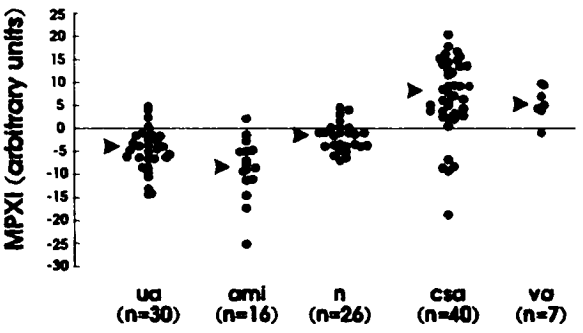


Figure 1. Myeloperoxidase intracellular index (MPXI) values in patients with unstable angina (ua) (median −4 [range +5 to −15]), acute myocardial infarction (ami) (median −7.8 [range +2 to −25]), chronic stable angina (csa) [median +7.4 [range +20 to −18.7]) and variant angina (va) (median +5 [range −1 to +9.8]) and in normal subjects (n) (median −1.3 [range +5.5 to −7]). Median values are shown as **arrowheads**. Negative values appear when the neutrophils are depleted of myeloperoxidase, as typically happens after neutrophil activation. $p < 0.01$, patients with unstable angina and acute myocardial infarction versus patients with chronic stable and variant angina and normal subjects.

Protocol B. During the study, the myeloperoxidase intracellular index did not change significantly over time in patients with unstable angina or acute myocardial infarction (Fig. 3). However, in 11 patients with waning of symptoms, the myeloperoxidase intracellular index was significantly higher 1 week after symptoms had waned (+7.1, range, −1.5 to +15.1) than on admission (−3 [range, −12 to +11]) (Fig. 4). In patients with acute myocardial infarction, no correlation was found between CK peak and the myeloperoxidase intracellular index. The CK and troponin T levels were normal in all samples in patients with unstable angina.

Protocol B1. In patients with unstable angina, 23 ischemic episodes (12 symptomatic, 11 asymptomatic) were observed during the first 24 h. Blood samples were taken within 6 h (2 ± 2 h) of each ischemic episode. No changes in the myeloperoxidase intracellular index were observed before or after the ischemic episodes compared with entry values (−4.5 at entry [range −13.1 to 4.7], −4.7 before ischemia [range −13.1 to 4.5], −3.5 after ischemia [range −11.4 to 1.2]) (Fig. 5). The myeloperoxidase intracellular index did not correlate with time from the ischemic episode or with length of the episode (7 ± 4 min).

Twenty-four patients with chronic stable angina underwent an exercise stress test according to the Bruce protocol: 14 of 24 had negative test results with no signs or symptoms of ischemia

JACC Vol. 27, No. 3
March 1, 1996:611–6

Table 2. Ischemic Episodes During 24-h Holter Monitoring in Patients With Unstable Angina and Variant Angina

	Unstable Angina	Variant Angina	p Value
No. of episodes	23	42	< 0.01
Mean [±SD] episodes/pt	0.9 ± 1.5	5 ± 2	< 0.01
Median episode length (range) (min)	10 (2–40)	5 (1–13)	< 0.05
Mean ± SD total ischemic burden (min/pt)	12.7 ± 21.5	31 ± 28	< 0.05

pt = patient.

(test duration 11 ± 2 min; rate-pressure product 37.500 ± 1.400), and 10 of 24 patients had myocardial ischemia during the exercise stress test (test duration 6 ± 4 min; rate-pressure product 17.000 ± 1.100; time of ischemia 6 ± 3 min). Significant differences in the myeloperoxidase intracellular index were not observed either before or after exercise stress test induced ischemia, or were they observed in patients with positive or negative test results (Table 3).

Discussion

Our study demonstrates that circulating neutrophils in patients with acute myocardial infarction and unstable angina have a low myeloperoxidase content, indicative of a significant release of myeloperoxidase from neutrophils related to their activation, which is in agreement with previous studies. In patients with resolving unstable angina, neutrophil myeloperoxidase content returned to levels similar to that in patients with chronic stable angina and normal subjects, suggesting that neutrophil activation was confined to the active phase of unstable angina. However, no further decrease in myeloperoxidase content in neutrophils in patients with unstable angina was detected after spontaneous ischemic episodes, and no decrease in neutrophil myeloperoxidase content was detected during ischemia induced by exercise stress test in patients with chronic stable angina and even after multiple, prolonged, spontaneous episodes in patients with variant angina.

Previous studies. In previous studies, neutrophil activation was observed and related to ischemia-reperfusion. In experimental animals it was observed as a component of reperfusion injury after 3 h of coronary occlusion (20) or 90 min of low flow perfusion with 20 min of reperfusion (21). Neutrophil activation has also been demonstrated in unstable angina and acute myocardial infarction by Mehta et al. (17), who observed in

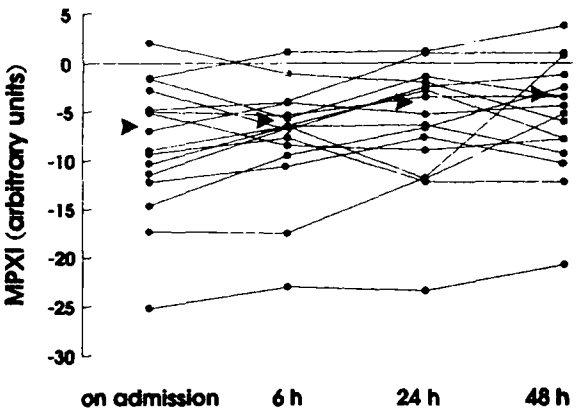


Figure 3. Myeloperoxidase intracellular index (MPXI) in patients with acute myocardial infarction during the 48-h study. Median values on admission (−7), after 6 h (−6.5), 24 h (−5.3) and 48 h (−4.4) are shown as **arrowheads**. Negative values appear when the neutrophils are depleted of myeloperoxidase, as typically happens after neutrophil activation. p = NS.

Figure 2. Number of neutrophils (PMN) in patients with unstable angina (ua) (4,490 ± 1,675 cells/mm^3), acute myocardial infarction (ami) (8,655 ± 1,820 cells/mm^3), chronic stable angina (csa) (3,275 ± 1,502 cells/mm^3) and variant angina (va) (3,730 ± 980 cells/mm^3) and in normal subjects (n) (4,900 ± 1,060 cells/mm^3). Median values are shown as **arrowheads**. p < 0.01, patients with acute myocardial infarction versus those with unstable and stable angina and normal subjects.

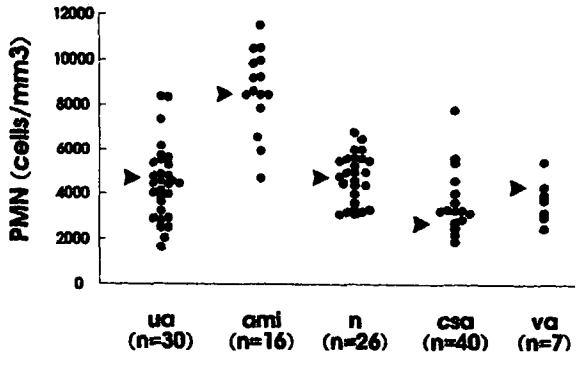
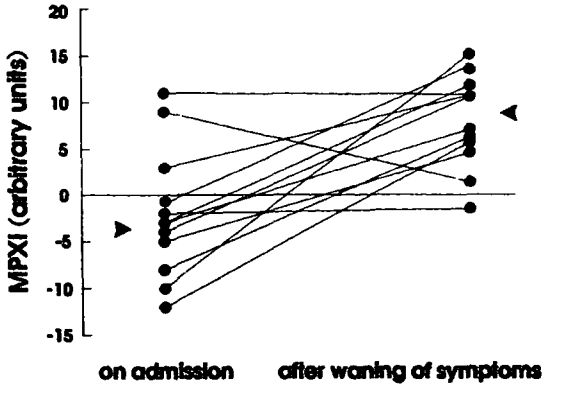


Figure 4. Myeloperoxidase intracellular index (MPXI) on admission (median −3 [range −12 to +11]) and after waning of symptoms (median +7.1 [range −1.5 to +15.1]) in 11 patients with unstable angina. Median values are shown as **arrowheads**. Negative values appear when the neutrophils are depleted of myeloperoxidase, as typically happens after neutrophil activation. p < 0.01, myeloperoxidase intracellular index after symptoms waned versus myeloperoxidase intracellular index on admission.



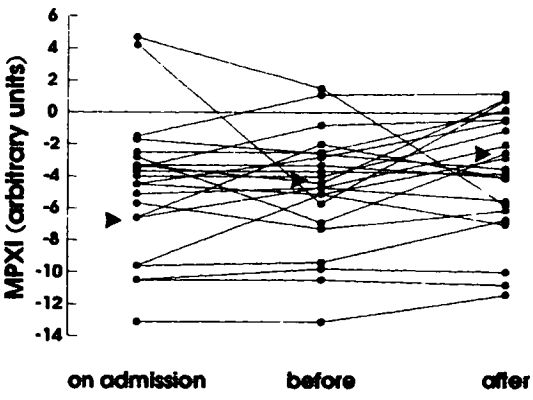


Figure 5. Myeloperoxidase intracellular index (MPXI) values on admission (median −4.5 [range −13.1 to 4.7]) and before (median −4.7 [range −13.1 to 4.5]) and after ischemic episodes (median 3.5 [range 11.4 to 1.2]) in patients with unstable angina after ischemia. Negative values appear when the neutrophils are depleted of myeloperoxidase, as typically happens after neutrophil activation. p = NS.

unstable angina a 15-fold increase in levels of peptide b-beta, a marker of elastase release and a constituent of primary granules such as myeloperoxidase, and by Mazzone et al. (10), who showed significant transcardiac expression of CD11b/CD18 integrins in neutrophils in unstable angina patients. However, these studies did not assess the time course of neutrophil activation and did not relate it with the occurrence of ischemic episodes.

Neutrophil activation in myocardial infarction. The lack of significant changes in the release of primary granules from neutrophils during the first 72 h in acute myocardial infarction compared with the entry values is in agreement with the findings of Dinerman et al. (18), who also found a steady level of neutrophil activation, measured as plasma levels of elastase, after hospital admission for acute myocardial infarction, and no correlation with CK. At variance from Dinerman et al., we studied all acute myocardial infarction patients within 6 h of symptom onset and before any detectable increase of plasma levels of CK and troponin T. However, we could not rule out the possibility that the increased number of granulocytes and their degranulation in acute myocardial infarction may be secondary to the ongoing necrosis or to transient episodes of reperfusion not detectable clinically. The finding that no further decrease of the myeloperoxidase intracellular index was observed after thrombolysis in patients with acute myocardial infarction suggests that neither prolonged periods of ischemia and reperfusion nor thrombolytic agents or thrombus remodeling are sufficient to cause a profound reduction in the neutrophil myeloperoxidase intracellular index in the periphery.

Neutrophil activation in unstable angina. Similarly, the cause of granulocyte degranulation in unstable angina, which is of the same magnitude as that observed in acute myocardial infarction, is not clear. Our findings seem to suggest that myocardial ischemia and reperfusion may not be the only stimuli responsible for neutrophil activation. This possibility is strengthened by the observation that active variant angina, a human model of ischemia, not associated with plaque instability or thrombus formation, does not result in activation of peripheral circulating neutrophils, which is in agreement with the lack of rise in C-reactive protein levels in spite of numerous prolonged episodes (25). It is possible that short episodes of ischemia may not be sufficiently strong to cause myeloperoxidase release in a large enough number of neutrophils to allow detection of the phenomenon in peripheral blood, or, alternatively, activated neutrophils may be rapidly sequestered (10,19).

Neutrophil activation in unstable angina may also result from inflammatory mediators such as the complement system, aggregated immunoglobulins or immune complexes, or from inflammatory cytokines and fibrin degradation products (22,25,27). Thus it is possible that the observed neutrophil activation depends on thrombus formation. However, the lack of decrease in the myeloperoxidase intracellular index after ischemic episodes in our study suggests that thrombus formation may not be the cause of neutrophil activation, and is in agreement with preliminary data showing that inflammation may precede activation of the coagulation system in unstable angina (28).

The observation that patients with variant or chronic stable angina had a myeloperoxidase intracellular index significantly

Table 3. Myeloperoxidase Intracellular Index Before and After Exercise Stress Test

	Negative Exercise Stress Test Results	Positive Exercise Stress Test Results
No. of pts	14/24	10/24
Test duration (min)	11 ± 2	6 ± 4
Rate-pressure product	37,500 ± 1,400	17,000 ± 1,100
Duration of ischemia (min)		6 ± 3
MPXI before test (AU)	4.4 (−9.2–18.3)	5.6 (−8.6–15.6)
MPXI after test (AU)	5.3 (−10.8–19.9)	4.8 (−11.1–15.9)
	p = NS (MPXI before vs. after)	p = NS (MPXI before vs. after)

Data presented are mean value ± SD, number of patients or median (range). AU = arbitrary units; MPXI = myeloperoxidase intracellular index; pts = patients.

higher than normal subjects is also intriguing, but because we did not address our study specifically to this point, we have no definitive explanation to account for it. However, it is possible to speculate that the membrane-stabilizing properties of the calcium antagonist drugs widely used in these two groups of patients might be responsible for the higher myeloperoxidase intracellular index in patients with variant angina and stable angina than in normal subjects.

Conclusions. Our study confirms activation of neutrophils in patients with unstable angina and acute myocardial infarction. We also demonstrate that no neutrophil activation occurs in patients with variant angina, suggesting that this phenomenon may occur independently of ischemic episodes and that ischemia-reperfusion events may not be the exclusive cause of neutrophil activation in acute coronary syndromes. Our findings and the growing evidence that inflammation plays a major role in unstable angina suggest that neutrophil activation may be related to the inflammatory component of unstable angina.

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