

## Correlation Between Biochemical Markers and Coronary Angiography in Patients with non-ST Elevation Acute Coronary Syndromes

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### OBJECTIVE

Investigate the correlation between biochemical markers (TNI, CRP and fibrinogen) and anatomical coronary angiographic findings in patients with non-ST elevation acute coronary syndromes (NSTEMI-ACS).

### METHODS

One blood sample was obtained to test for markers, and coronary angiography was performed within the first 72 hours after hospitalization. Univariate analysis was used to search for correlations between the 3 markers and the angiographic findings in the group of patients with an identified ischemia-related artery (IRA), and multivariate analysis was performed to investigate the correlation between these markers and the presence of unstable atherosclerotic lesions solely in the group with a coronary obstruction >50%.

### RESULTS

Prospective study conducted with 84 patients, 65.5% of whom were men. In the IRA-identified group, blood levels of the three markers were higher than in the groups with no IRA-identified or with normal coronary arteries. The analysis used to evaluate the IRA-identified group showed significant correlations between TIMI flow and TN-I ( $p = 0.006$ ), unstable atherosclerotic lesions and TN-I and fibrinogen ( $p = 0.02$  and  $p = 0.01$ , respectively), and multivessel disease and CRP ( $p = 0.0005$ ). The multivariate analysis showed that CRP, fibrinogen and TN-I were independent predictors of unstable atherosclerotic lesions ( $p = 0.002$ ;  $p = 0.003$  and  $p = 0.007$ , respectively).

### CONCLUSION

In NSTEMI-ACS patients, TN-I, CRP and fibrinogen blood levels within the first 10 hours after hospitalization correlated with coronary angiographic findings.

### KEY WORDS

Acute coronary syndromes, inflammation, thrombosis, myocardial injury.

The detection of high blood levels of inflammatory-activity markers in patients with acute coronary syndrome has confirmed the importance of inflammation in the process of atheroma plaque destabilization.

There is evidence in medical literature of a correlation between clinical presentation and serum elevation of biochemical markers (of inflammation, thrombosis and myocardial injury) in patients with non-ST acute coronary syndromes. Likewise, a relationship has also been demonstrated between clinical aspects and coronary anatomy in this group of patients<sup>1</sup>.

The objective of this study is to investigate the correlation between serum levels of inflammation, thrombosis and myocardial biochemical markers (titrated C-reactive protein, fibrinogen and troponin I, respectively) and anatomical findings on coronary angiography in a group of non-ST ACS patients admitted to the emergency department.

## METHODS

After approval by the Research Ethics Committee, consecutive patients with unstable angina (UA) or non-ST acute myocardial infarction (non-ST AMI) admitted to the emergency department were prospectively enrolled from November 1999 to July 2001. Patients fulfilled the following criteria for inclusion: 1) Male or female, 18 years of age, minimum; fertile women should have a negative HCG blood test before being enrolled in the study. 2) Chest pain suggestive of myocardial ischemia, with up to 24 hours of progression that: a) occurs at rest or with minimum exertion, is prolonged (> 20 minutes) or recurrent (> two episodes of at least five minutes each during the last 24 hours); or b) is progressive (angina episodes that become more frequent, more severe, last longer and/or are precipitated by minimum effort).

1) Angina symptoms associated with at least one of the following conditions: a) electrocardiogram showing ST segment depression greater than or equal to 0.5 mm, in at least two consecutive leads; or transient ST segment elevation (< 20 minutes) of no more than 1 mm in at least two consecutive leads; or T-wave inversion greater than or equal to 3 mm (or pseudonormalization > 1 mm above or below the isoelectric line) in at least three consecutive leads; or b) evidence of previous myocardial infarction documented by electrocardiogram; or c) previous coronary angiography showing at least one large coronary artery with a minimal occlusion of 50% of the luminal diameter; or d) previous myocardial revascularization documented with transluminal coronary angioplasty (balloon, directional coronary atherectomy or stent) or coronary artery bypass graft (CABG); or e) increase in enzyme levels: creatine kinase MB fraction (CK-MB mass) > 5.3 ng/mL and/or myoglobin > 70 ng/mL.

Patients with conditions that interfere with the interpretation of the ST segment on the electrocardiogram,

such as a pacemaker rhythm, were excluded. Likewise, patients with angina secondary to non-cardiac causes, systemic inflammatory processes and regular users of anti-inflammatory drugs were excluded.

Patients underwent one single peripheral venous blood sampling for laboratory tests. Venipuncture was performed in one of the upper extremities, according to international standard guidelines<sup>2</sup>, between 6 and 10 hours (average 8 hours) after hospital admission to determine: a) concentrations of titrated CRP (by nephelometry), reference value up to 0.5 mg/dL; b) TN-I (by immunofluorometry – Opus Bhering), reference value up to 0.5 ng/mL; c) Fibrinogen (CLAUSS – automated methodology that measures thrombin consumption), reference value 200 to 400 mg/dL.

Creatine kinase MB (CK-MB mass - reference value up to 5.3 ng/mL) and myoglobin (reference value up to 70 ng/mL) were also measured in the same sample using the automated chemiluminescence method. Such enzymes were also measured at hospital admission as part of the emergency room protocol.

All patients underwent coronary angiography during hospitalization and, invariably, up to 72 hours (average 24 hours) after hospital admission.

Each angiography was analyzed by two separate experienced examiners blinded as to the other parameters analyzed, with the exception of the electrocardiogram and the echocardiogram, tools used to help identify the ischemia-related artery. The two examiners disagreed as to which angiographic group ten patients should be assigned (see description below), so a third examiner analyzed the angiographies in order to determine the parameter. The two examiners reached a consensus about the other angiographic differences.

The ischemia-related artery (IRA) was defined as the one with a lesion greater than or equal to 90% of the vessel lumen, with corresponding segment alteration on echocardiogram or electrocardiogram related to this vessel and/or instability of the atherosclerotic lesion.

To define the presence of an unstable atherosclerotic lesion at least one of the following three criteria had to be fulfilled: a) IRA TIMI flow <3; b) IRA intracoronary thrombus (defined as intracoronary vascular filling defect); c) Ambrose type II eccentric atherosclerotic lesion in IRA (this isolated criterion was used only if the occlusion was greater than or equal to 90% of the vessel lumen).

Patients were broken down into three groups, according to coronary angiographic findings: 1) Group I: patients with identification of the ischemia-related artery; 2) Group II: patients without identification of the ischemia-related artery; 3) Group III: patients with normal coronaries or an atherosclerotic occlusion < 50 % of the vessel lumen.

The following parameters were analyzed for Group I: identification of IRA and distal flow (TIMI); presence of an intracoronary thrombus; presence of IRA occlusion;

presence of an unstable atherosclerotic lesion; number of arteries with an occlusion greater than 75% of the vessel lumen; and classification of the lesion responsible for the ischemia, according to Ambrose et al<sup>3</sup>.

For Group II, the number of arteries with an occlusion greater than 75% of the vessel lumen and the presence of an unstable atherosclerotic lesion were analyzed.

TN-I, CRP and fibrinogen serum values were measured for the three angiographic groups, and the laboratorial definition for infarction was characterized by myoglobin > 70 ng/mL and/or CK-MB mass > 5.3 ng/mL at hospital admission or at the second measurement (on average 8 hours after admission). It is worth mentioning that for this paper the laboratory definition of acute myocardial infarction based solely on the increase of serum troponin levels was not used, as patients started to be enrolled before the American and European Heart Associations had published their agreement about the redefinition of the disease. We chose not to alter the diagnoses of patients whose changes in enzyme levels were restricted exclusively to TN-I > 0.5 ng/mL, in order to preserve the original methodology.

For the IRA-identified group (Group I), values for TN-I, CRP and fibrinogen correlated with the type of ischemia-related artery, TIMI flow, presence of thrombus and/or occlusion in the ischemia-related artery, presence of an unstable atherosclerotic lesion and the number of vessels with lesions > 75% of the lumen.

Finally, a multivariate analysis was conducted aiming to investigate the three biochemical markers (TN-I, CRP and fibrinogen) as independent predictors of unstable atherosclerotic lesions.

As such, Group III patients (normal coronaries or atherosclerotic occlusion < 50% of the vessel lumen) were excluded, and patients belonging to Groups I and II were analyzed as a whole and subdivided into two subgroups according to whether or not they had unstable atherosclerotic lesions.

It should be mentioned that, for the purpose of this analysis, positive TN-I values were considered as those greater than 0.5 ng/mL, and negative TN-I values were those smaller than or equal to 0.5 ng/mL.

The statistical analysis was done according to the following design: 1) Sample description with presentation of categorical and continuous variables distribution by means of central tendency and dispersion measurements. 2) Graphic representation of the continuous variables and their distribution in the groups using box plots. 3) Univariate analysis using Mann-Whitney and Kruskal-Wallis tests, as needed. 4) A generalized linear model with binomial distribution and a logit link function was used for the multivariate evaluation of the three markers, with cross validation and forward stepwise regression for the selection of variables according to the likelihood ratio.

5) The whole statistical analysis was planned with a 5% significance level and 80% statistical power.

## RESULTS

This study was carried out with eighty-four patients. Table 1 shows the characteristics of the patients enrolled in the study.

Table 2 shows the distribution of the biochemical markers analyzed. The ischemia-related artery (IRA) was identified in 69% of the patients analyzed. Table 3 shows that fifteen patients had coronary occlusion greater than 50% of the vessel lumen but it was not possible to identify the IRA, and eleven patients had normal coronaries.

In all three angiographic groups the main diagnosis was unstable angina and Group I had the largest proportion of non-ST AMI patients, as shown in Table 4. Table 5 displays the angiographic characteristics of Groups I and II.

When comparing the three groups, a few significant differences were observed. As to troponin I, it is important

**Table 1 – Sample characterization**

Sample characteristics		N	%
Patients enrolled		84	100.0
Mean age (years)		61.4	-
Gender	Male	55	65.5
	Female	29	34.5
Race	White	72	86.0
	Black	12	14.0
Previous AMI		25	29.8
Previous TCA		17	20.2
Previous MR		3	3.5
RF for atherosclerosis	Hypertension	60	71.4
	Sedentarism	54	64.3
	Dyslipidemia	39	46.4
	Family history	22	26.2
	Smoking	22	26.2
Diagnosis	Diabetes mellitus	17	20.2
	Unstable angina	55	65.5
	Non-ST AMI	29	34.5
Admission ECG	ST segment depression	30	35.7
	T wave inversion	24	28.6
	Normal	19	22.6
	ST segment depression + T wave inversion	11	13.1
Treatment	TCA	34	40.5
	Only clinical (treatment)	34	40.5
	MR	13	15.5
TCA + MR		3	3.5
In-hospital AMI		4	4,8
In-hospital death		5	6

RF – Risk factors; ECG – Electrocardiogram; TCA - Transluminal coronary angioplasty; MR – Myocardial revascularization; AMI – Acute myocardial infarct

Table 2 – Biochemical markers

Marker	Mean	Median	First quartile	Third quartile	Standard deviation
Troponin I (ng/mL)	3.6	0.7	0.5	2.4	7.4
CRP (mg/dL)	1.5	0.8	0.5	1.9	2.5
Fibrinogen (mg/dL)	347.5	339.5	259.5	438.0	133.9

Table 3 – Distribution according to angiographic group

Angiographic group	Number of patients	%
I	58	69.0
II	15	17.9
III	11	13.1

Table 4 – Distribution of angiographic groups according to diagnosis

Angiographic group	Unstable angina	Non-ST AMI
I	34 (58.6 %)	24 (41.4 %)
II	13 (86.7 %)	2 (13.3 %)
III	8 (72.7 %)	3 (27.3 %)

Table 5 – Angiographic characterization of groups I and II

		Group I (58 pts) N (%)	Group II (15 pts) N (%)
IRA	LCB	2 (3.4)	-
	LAD	24 (41.4)	-
	LCX	17 (29.3)	-
	RCA	15 (25.9)	-
IRA TIMI	0/1	13 (22.4)	-
	2	25 (43.1)	-
	3	20 (34.5)	-
IRA thrombus	yes	29 (50.0)	-
	no	29 (50.0)	-
IRA occlusion	yes	11 (19.0)	-
	no	47 (81.0)	-
Unstable atherosclerotic lesion	yes	49 (84.5)	0 (0)
	no	9 (15.5)	15 (100.0)
Number of arteries with lesions >75% vessel lumen	<3	42 (72.4)	10 (66.7)
	3 or + or LCB	16 (27.6)	5 (33.3)
IRA Ambrose	Concentric stenosis	3 (6.4)	-
	Type I eccentric	10 (21.3)	-
	Type II eccentric	32 (68.0)	-
	Multiple irregularities	2 (4.3)	-

IRA – ischemia-related artery; GI – angiographic group I; GII – angiographic group II; LCB – left coronary branch; DA – LAD; LCX – circumflex artery; RCA – right coronary artery

to note that Group I had a mean TN-I value greater than the other two groups ( $p = 0.03$ ). Moreover, Groups II and III had similar mean values ( $p = 0.47$ ). CRP values appeared in decreasing order in Groups I, II and III, respectively, with statistical significance ( $p = 0.001$ ), and the same decreasing distribution was observed in the analysis of fibrinogen values among the three groups, also statistically significant ( $p < 0.0001$ ).

The analysis of the statistical correlation between angiographic variables and serum values of biochemical markers in Group I showed the following results: there was no correlation between the type of ischemia-related artery and the serum values of the biochemical markers analyzed, not even when patients were allocated to only two subgroups, right and left coronaries ( $p = 0.36$ ;  $p = 0.10$  and  $p = 0.10$  for TN-I, CRP and fibrinogen, respectively).

When Group I patients were subdivided into two subgroups according to TIMI flow in the ischemia-related artery (TIMI 3 or TIMI <3), significantly greater TN-1 values were observed in the subgroup with IRA TIMI flow < 3 ( $p = 0.006$ ). Such a difference was not observed for CRP and fibrinogen values ( $p = 0.09$  and  $p = 0.20$ , respectively).

Considering the presence or absence of a thrombus in the ischemia-related artery, no statistically significant difference was observed for TN-I, CRP and fibrinogen ( $p = 0.08$ ;  $p = 0.20$  and  $p = 0.08$ , respectively).

As to the presence or absence of occlusion in the ischemia-related artery, no statistically significant difference was observed either for levels of TN-I, CRP, and fibrinogen ( $p = 0.37$ ;  $p = 0.36$  and  $p = 0.28$ , respectively).

In the subgroup of patients with unstable atherosclerotic lesions, a significant difference for TN-I and fibrinogen values (greater values) was observed as compared to patients in Group I with no unstable lesion ( $p = 0.02$  and  $p = 0.01$ , respectively). However, no significant difference was observed among the subgroups as to CRP values ( $p = 0.38$ ).

Regarding the presence of multiarterial lesions (three or more arteries or LCB with lesions  $> 75\%$  of vessel lumen), the CRP values observed were significantly greater than those for the subgroup of patients with less than three arteries with lesions  $> 75\%$  of the vessel lumen ( $p = 0.0005$ ). For TN-I and fibrinogen, there was no significant difference between these two subgroups ( $p = 0.8176$  and  $p = 0.6911$ , respectively).

Group I and II patients were pooled and classified according to the presence of an unstable atherosclerotic lesion, and 67.1% of them were found to have such a lesion instability. Group III patients were not included in this analysis since they had normal coronaries (Table 6).

**Table 6 – Breakdown of patients from Groups I and II according to the presence of unstable atherosclerotic lesions**

Unstable atherosclerotic lesion	Number of patients	%
Yes	49	67.1
No	24	32.9

It should be mentioned that the group with no unstable atherosclerotic lesions consisted of the fifteen Group II patients and nine Group I patients who did not have unstable atherosclerotic lesions. The 49 patients with unstable atherosclerotic lesions were part of the group with an identified IRA.

Multivariate analysis was used to examine CRP, fibrinogen and TN-I in order to identify which were prognostic markers of unstable atherosclerotic lesions.

This multivariate analysis showed that serum levels of CRP and fibrinogen, and whether or not TN-I is positive, are independent factors of atherosclerotic lesion, i.e., the greater the levels of CRP and fibrinogen, the greater the probability of unstable atherosclerotic lesions; and when TN-I is positive ( $> 0.5$  ng/mL), there is a greater probability of unstable atherosclerotic lesions as compared to a negative TN-I (less than or equal to 0.5 ng/mL) ( $p = 0.002$ ; 0.003, and 0.007, respectively).

## DISCUSSION

In this paper, the diagnosis of unstable angina (UA) at hospital admission was more frequent than that of non-ST elevation acute myocardial infarction (non-ST AMI); this data are consistent with the findings of a study by Zebrack et al<sup>4</sup>, who observed 58% of patients with UA and 42% with non-ST AMI from a total of

1,360 patients with non-ST ACS. Such percentages are similar, since the cases described are prior to the year 2000 when acute myocardial infarction was redefined, and patients with TN-I values greater than the reference value, formerly seen as high-risk UA patients, started to be diagnosed as having a non-ST AMI, making this diagnosis more prevalent<sup>5,6</sup>.

Berk et al<sup>7</sup>, observed in their study that 90% of 37 patients with UA had CRP levels greater than 0.6 mg/dL at hospital admission. Another author conducting a study of patients with UA also described that 73% of them had serum CRP levels greater than 0.3 mg/dL<sup>7</sup>. In the present study, 53 patients (63%) had serum levels of this marker greater than 0.5 mg/dL. The mean and median values for CRP and fibrinogen were also similar to the results observed by other authors in their analyses of patients with non-ST ACS<sup>4,7,8,9,10,11</sup>.

In the coronary angiographic analysis, specifically the percentage of patients with an identifiable IRA, there were differences between this study and the results observed by Benamer et al<sup>6</sup> and Ambrose et al<sup>3</sup>, whose percentages were 53 % and 60 %, respectively. However, those authors enrolled only patients with unstable angina which would explain the greater value observed in the present paper (69%) that also enrolled patients diagnosed with non-ST AMI, an illness with a higher prevalence of identification of the ischemia-related artery<sup>12,13</sup>.

Fifty percent of Group I patients had an intracoronary thrombus, a percentage higher than that observed by Benamer et al<sup>6</sup> and Dangas et al<sup>14</sup> (18% and 14%, respectively). As mentioned earlier, those authors analyzed only UA patients, whereas in this study, 34.5% of the sample consisted of patients diagnosed with non-ST AMI. Literature reports that angiographic findings of intracoronary thrombus are more frequent among non-ST AMI patients, compared to UA, as well as in early coronary angiographic studies performed within the first 24 hours of hospitalization. This would explain the high percentage found in the cases of patients here analyzed, as coronary angiography was performed on average within 24 hours after hospital admission<sup>15</sup>. In the cases described by Benamer et al<sup>6</sup>, all coronary angiographies were performed after 24 hours of hospitalization (on average, five days post-admission), which might explain the 18% percentage of intracoronary thrombus observed.

Heeschen et al<sup>16</sup>, when analyzing 853 patients with refractory UA by coronary angiography within the first 24 hours after treatment onset, observed a higher prevalence of intracoronary thrombus (14.6%) in patients with a serum T troponin level (TN-T) greater than 0.1 mcg/L defined as TN-T positive (30.9% of the sample). In the present study, the high percentage of thrombi (50%) observed seems to be also associated with the high prevalence of TN-I positive patients (51%) in the sample.

The definition of an unstable atherosclerotic lesion in

these cases was based on the presence of an intracoronary thrombus, Ambrose II type eccentric lesion or IRA TIMI flow < 3. Other authors have also taken into consideration data such as the presence of a thrombus, coronary occlusion, TIMI flow and type II lesion eccentric as per Ambrose's classification to characterize atherosclerotic lesion instability<sup>3,6,8,17</sup>. It is worth mentioning that the distribution of the patients analyzed in the present study according to the type of stenosis based on such a classification followed a distribution similar to that described by the authors in 1985, when 54% of the stenoses were Ambrose type II eccentric lesions in groups of patients with unstable angina<sup>11</sup>. Another author described a 66% percentage of Ambrose type II eccentric stenoses among 88 patients with UA, which is a value similar to the one found here (68%)<sup>18</sup>.

In 1996, Chen et al<sup>19</sup>, investigated the presence and progression of angiographically complex lesions (irregular borders, ulcerated lesions and presence of a thrombus) in patients with stable and unstable angina pectoris. These authors observed 64% and 32% of complex lesions in the two groups, respectively. Moreover, they observed that the progression of these lesions had a greater prevalence in the unstable angina group, within a period of eight months. Medical literature reports that the complex stenoses observed in patients with stable angina, although angiographically similar to those of the unstable angina group, seem to differ in "activity", according to a multifactor parameter that includes inflammation, thrombogenic activity and vessel-reactivity<sup>20</sup>, corroborating the conclusions of Chen et al<sup>19</sup>.

Other authors report the presence of unstable lesions in more than 70% of patients with acute coronary syndromes<sup>21</sup>, reaching 80% in the study by Benamer et al<sup>6</sup>. Such data are consistent with those described here: 84.5% of unstable atherosclerotic lesions in the group with ischemia-related artery identified, and in 67.1% of Groups I and II combined, i.e., in those patients with a coronaropathy defined as an occlusion greater than 50% of the vessel lumen. It should be mentioned that no patient in Group II had an unstable atherosclerotic lesion, since this characteristic was one of the criteria used to identify the IRA.

In the present sample, the TN-I highest mean value was observed in Group I, as compared to the other groups. Such data reinforce the results by Benamer et al<sup>6</sup>, in which serum TN-I elevation within the first twelve hours of hospital admission was an independent predictor of IRA identification on coronary angiography. Moreover, patients with high TN-I levels had a higher prevalence of complex coronary stenoses (presence of thrombi or vessel occlusion) as compared to those with normal serum TN-I levels<sup>22,23,24</sup>.

CRP values were also significantly higher in Group I patients compared to the other groups. In the study by Benamer et al<sup>6</sup> there was no significant difference in CRP

values among the groups with and without an identified IRA on coronary angiography; however, the authors did not include in their analysis patients whose coronaries had no significant atherosclerotic lesions and, consequently, with a smaller potential for coronary inflammation.

Fibrinogen values were also significantly higher in Group I patients. Such finding may be correlated with the high prevalence of intracoronary thrombi in this group (50%), as this biochemical marker is associated with inflammatory-thrombotic phenomena<sup>11</sup>. Also, as mentioned previously, Group I consists of a higher percentage of patients with non-ST AMI as compared to the other two groups in which serum fibrinogen values are greater than those of UA patients, as shown in the TIMI IIIb study<sup>11</sup>.

No statistically significant correlation was found between the TN-I, CRP and fibrinogen values and the type of artery responsible for the ischemia in Group I. This finding is consistent with two articles published that analyzed patients with non-ST ACS<sup>6,11</sup>. Likewise, there was no significant correlation between biochemical markers and TIMI flow, except the TN-I values that were greater in the subgroup with a TIMI of less than three, reinforcing the concept that the serum elevation of this enzyme is related to an arterial flow not sufficient enough to prevent myocardial injury<sup>6,23,25</sup>. In a group of 1,161 patients with non-ST ACS, Lindhal et al<sup>24</sup> demonstrated an inverse relation between TN-T levels and IRA TIMI flow, i.e., the highest TN-T levels were detected in those patients with the smallest IRA TIMI flow.

No significant correlation was observed between biochemical markers and the presence of thrombi in the IRA. However, when this variable was analyzed together with others that were part of the definition of an unstable atherosclerotic lesion, such as type II Ambrose eccentric lesion and TIMI flow < 3, a significant association with TN-I and fibrinogen serum levels was observed in the univariate analysis. It is possible that, with the inclusion of a greater number of patients, this variable may have isolated significance.

Furthermore, in a study conducted with 1,150 non-ST UA and AMI patients during the period from October 1989 to June 1992, Antman et al<sup>26</sup>, did not detect a correlation between the presence of a coronary thrombus and TN-I serum elevation either.

Lindhal et al<sup>24</sup>, however, demonstrated a direct relationship between TN-I serum elevation and the presence of intracoronary thrombi, angiographically complex lesions and unfavorable TIMI flow in non-ST ACS patients.

The connection between the CRP serum level and the presence of thrombi on coronary angiography in patients with non-ST ACS has not yet been demonstrated. It is known that the elevation of this marker is associated with the worst clinical progression for patients, but is not necessarily correlated with anatomical complexity at the

coronary level<sup>6</sup>. In a study conducted with one hundred patients with UA, no association was found between systemic inflammation (elevation of plasma CRP) and the anatomical complexity of an atherosclerotic lesion in the IRA<sup>6</sup>.

Similarly, clinical studies with non-ST ACS patients suggest a connection between serum fibrinogen level and ischemic cardiovascular events since this marker is directly involved in the thrombotic process. However, no relationship between elevation of plasma fibrinogen and the presence of intracoronary thrombus has yet been demonstrated by coronary angiography<sup>11</sup>.

In the present study, no correlation was found between TN-I, CRP, and fibrinogen values and the presence of occlusion in the IRA. Benamer et al<sup>6</sup> did not observe either any association between TN-I elevation and occlusion of the vessel mentioned. As mentioned before, these authors have not demonstrated a correlation between serum CRP elevation and occlusion of the IRA either. As to fibrinogen, a marker for recent thrombosis, the lack of correlation may be associated with the presence of collateral circulation or non-thrombotic occlusion.

Correia et al<sup>10</sup> described greater values of CRP in patients with multiarterial coronariopathy hospitalized with diagnoses of UA or non-ST AMI. This finding is consistent with the results of this study in which merely the CRP value was significantly higher in Group I patients with multiarterial coronariopathy, supporting the concept that TN-I is a marker of the presence of a vessel responsible for the ischemia and not of the number of vessels with atherosclerotic disease observed on coronary angiography<sup>6</sup>.

In the present study, patients with unstable atherosclerotic lesion were analyzed according to two different approaches.

Univariate analysis evaluated the correlation between serum levels of biochemical markers and the presence of lesion instability only for the group with identified IRA (Group I). The analysis detected significantly higher values of TN-I and fibrinogen in patients with lesion instability, a result similar to that of other authors for whom the elevation of these two biochemical markers was also associated with high angiographic complexity and signs of instability in the IRA (based on the Ambrose classification, in the presence of thrombi and with abnormal TIMI flow)<sup>6,21,25</sup>. The analysis of CRP values, however, did not show any difference between the values detected in groups with and without unstable lesions.

The exact relationship between inflammation and atherosclerosis has yet to be fully defined, and there is not enough information available to determine if unstable coronary disease is due to a single vulnerable plaque or to diffuse vascular inflammation. The recent work by Buffon et al<sup>27</sup> suggests that individuals at increased risk of

acute coronary events, indicated by serum CRP elevation, supposedly have multiple vulnerable lesions in their coronary anatomy, i.e., vulnerable lesions in arteries other than those responsible for the ischemia, confirming the association between the serum levels of this inflammation marker and diffuse coronariopathy<sup>9,10</sup>.

Multivariate analysis investigated the relationship between the serum level of the three biochemical markers and the presence of atherosclerotic lesion instability in patients from Groups I and II combined, i.e., in all patients with obstructive coronariopathy with a block greater than 50% of the vessel lumen, subdivided according to the presence or absence of unstable lesions. In this analysis, besides TN-I and fibrinogen, CRP was also an independent predictor of the presence of unstable atherosclerotic lesions.

In 2000, Goldstein et al<sup>28</sup>, analyzed 253 patients diagnosed with acute myocardial infarction who had undergone coronary angiography, and observed that 60.5% of them had one single complex atherosclerotic plaque (with thrombus, ulceration, irregular surface, insufficient flow and an obstruction of more than 50% of the vessel lumen), whereas 39.5% had multiple complex plaques, supporting the recent concept that ACS patients have diffuse coronary inflammation that generates higher blood CRP levels. At the European Congress in 2003, Arroyo et al<sup>29</sup> described a correlation between the serum level of CRP measured at admission and the number of complex coronary stenoses in 125 UA patients. Thus, the association found in this study between the serum CRP level and the presence of unstable lesions can be justified by the existence of more than one complex plaque, added to an extensive and diffuse coronary inflammatory process in the group of patients with unstable lesions in the IRA, since none of the patients from Group II had unstable lesions and only nine patients (15.5%) from Group I did not have unstable lesions.

Sano et al<sup>30</sup> recently analyzed ninety patients with infarction who had undergone coronary intravascular ultrasound during the first six hours of the onset of symptoms, and suggested that the elevation of serum CRP may be linked with atherosclerotic plaque rupture when there is intense inflammatory activity. This conclusion also justifies the greater CRP values in the group of patients with unstable lesions.

Therefore, differences in the results of the uni- and multivariate analyses can have two explanations: A) The populations studied were different, with possible reflections on the significance of the variables analyzed. B) Group I patients, despite having an IRA identified on coronary angiography, possibly had anatomical diffuse coronary inflammatory processes which led to the elevation of serum CRP, including the nine patients of this angiographic group who did not have unstable lesions but

had a high prevalence of three-artery disease (34%), and none of which had an obstruction of less than 75% of the vessel lumen.

On the other hand, in patients from Group II (comprising 62.5% of the subgroup without an unstable lesion in the multivariate analysis), the inflammatory process at the coronary level was not as exuberant, since 60% of patients in this group had merely moderate atherosclerotic occlusions (between 50% and 75% of the vessel lumen) and none of them had unstable lesions, which explained the smaller serum CRP level.

In 1999, Lagrand et al<sup>31</sup> described CRP as a marker that reflects inflammation associated not only with the extension but also with the severity of the atherosclerotic occlusion, corroborating the results reported here.

It is important to emphasize that the precise relationship between serum levels of biochemical markers and coronary angiographic findings in patients with non-ST ACS will still be the subject of investigation in many other clinical studies, and continue today as a challenge to be documented and accompanied by paradigm changes.

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