Plasma Viscosity and NLR in Young Subjects with Myocardial Infarction: Evaluation at the Initial Stage and at 3 and 12 Months

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ABSTRACT: In the “Sicilian study on juvenile myocardial infarction,” we had evaluated plasma viscosity (PV) and neutrophil/lymphocyte ratio (NLR) in subjects with acute myocardial infarction (AMI) at the age of <45 years. Now, we examined the relationship between these 2 parameters in 120 subjects (109 men and 11 women) aged <45 years with recent AMI. The patients were classified according to the number of cardiovascular risk factors, the electrocardiographic criteria (ST-segment elevation myocardial infarction [STEMI] or non-ST-segment elevation myocardial infarction [NSTEMI]), and the extent of coronary stenosis, evaluated with coronary angiography. On fasting venous blood, we measured PV at the shear rate of 450 s⁻¹ and NLR. The control group included 50 healthy subjects (mean age = 55.1 ± 7.8 years). At the initial stage, PV and NLR were significantly increased in comparison with controls. Subdividing AMI patients according to the median value of NLR, in the group with high NLR PV was significantly higher, whereas subdividing the patients according to the PV median value, NLR was not different between the 2 groups; and at 12 months after AMI, we observed only a significant decrease in NLR. Only PV was discriminant regarding the cardiovascular complications registered during an 18-month follow-up. The evaluation of PV may be of prognostic value in juvenile AMI.

KEYWORDS: plasma viscosity, neutrophil lymphocyte ratio, juvenile myocardial infarction

Introduction

Neutrophil to lymphocyte ratio (NLR) has been examined in cardiovascular disorders, and it has been suggested as a prognostic factor in coronary artery disease (CAD). NLR was negatively correlated with myocardial perfusion and positively correlated with CAD severity. In a group of subjects with stable chronic CAD, NLR was an independent predictor of cardiac death, in most cases referable to acute myocardial infarction (AMI). NLR level was an indicator of all-cause mortality and of major adverse cardiac events in patients undergoing angiography or cardiac revascularization after AMI. In patients with ST-elevation myocardial infarction (STEMI), the maximum level of NLR was found at 12 to 24 hours after hospitalization and was correlated with mortality increase. A growing rate of in-stent thrombosis, nonfatal myocardial infarction, and cardiovascular mortality has been associated with higher levels of NLR. Some studies have shown an association between an increased NLR and a higher prevalence of no-reflow after percutaneous coronary intervention (PCI) in STEMI patients. In non-STEMI (NSTEMI) patients, higher NLR was associated with a greater prevalence of atrial fibrillation and heart failure, a lower left ventricular ejection fraction, and greater rates of coronary artery bypass grafting (CABG). Other authors demonstrated that the NLR value after hospitalization was an independent predictor of 1 year reinfarction and mortality in diabetic subjects with AMI.

Plasma viscosity (PV) is a major determinant of blood rheology and plays a pivotal role, together with erythrocyte deformability and platelets, in microcirculatory blood flow. Plasma viscosity is due especially to plasma protein content, although the contribution to viscosity of the different protein fractions significantly differs. Albumin, in fact, is responsible of only 36% of the difference in viscosity between water and plasma (both Newtonian fluids), while it represents 60% of the total plasma proteins. Fibrinogen only corresponds to about 4% of the total plasma proteins, while its contribution to PV is about 22%. The difference may be explained by the molecular size and shape of different proteins. Plasma viscosity has a remarkable interindividual stability although it changes in several clinical conditions. Plasma is generally considered a Newtonian fluid, so its viscosity is assumed not to be dependent on the shear rate. High-shear-rate PV is considered to be the true Newtonian PV. This parameter influences microvascular flow resistance, which regulates the vascular tone and maintains a functional capillary density.

Plasma viscosity seems to be an independent risk factor for cardiovascular events. Some studies showed a link between PV and the risk of cardiovascular diseases, as well as a relationship between PV and the severity of CAD. Plasma viscosity was associated with the incidence of cardiovascular and noncardiovascular death during the long-term follow-up of a male population. Plasma viscosity seems to have a prognostic value in patients with unstable angina, transmural myocardial
infarction, and no-reperfusion STEMI patients who have undergone PCI.

Considering the aforementioned evidence, the aim of this study was to evaluate the trend of NLR and PV and especially their intercorrelations in subjects with juvenile myocardial infarction (JMI) at the initial stage and after 3 and 12 months. Previously, we have separately examined these parameters in the same population of patients with JMI. This article is a part of the scientific project identified as ‘Sicilian study on juvenile myocardial infarction’. Myocardial infarction occurring at a relatively young age (45 years is the age limit generally accepted) has peculiarities in the pattern of risk factors and coronary lesions, which can justify its definition as a separate clinical condition.

Subjects
In this study, we examined 120 young subjects (109 men and 11 women, aged <46 years) with recent AMI. The time interval between the AMI onset and the investigation was 13 ± 7 days. The diagnosis of AMI was carried out on the basis of clinical picture, electrocardiography, blood parameters (creatinine kinase, troponin, and myoglobin), and echocardiography. The localization of infarction was anterior in 60 patients (50%), inferior in 59 (49.2%), and indefinite in 1 (0.8%). Subjects were admitted either from the A&E department of our university hospital or were transferred from other hospitals in western Sicily. In each subject, we examined the presence of the main cardiovascular risk factors, including smoking habits, family history of CAD, hypercholesterolemia, arterial hypertension, and diabetes mellitus. According to the number of cardiovascular risk factors, the young AMI subjects were subdivided into 3 subgroups: 39 of them had 0 to 1 risk factor, 39 had 2 risk factors, and 42 had 3 to 5 risk factors. Coronary angiography was performed only in 103 subjects. In the other cases, the subjects declined their consent or the angiographic evaluation was not carried out because of the long distance between the hospital in which the AMI was diagnosed and the angiographic unit of the university centre. The 103 subjects in which coronary angiography was performed were subdivided into 3 groups on the basis of the extent of coronary lesions: 23 subjects did not have any significant coronary lesions, 46 had a single-vessel disease (defined as a stenosis >70% in 1 coronary artery) and 34 had a multi-vessel disease, that is, a stenosis >70% in at least 2 coronary vessels. A revascularization procedure was performed in 68 patients (a PCI in 60 and a CABG in 8). The interval between the revascularization and the study was at least 5 days. The 12 patients with significant coronary lesions who did not undergo any revascularization procedure were among those recruited in the first 12 months of the study (April 2001–March 2002), when the organization of interventional cardiology in Sicily was much less advanced than it would become in the following years. Seven of the patients refused their consent to the ‘new’ procedure; in 5 cases, it was not proposed due to ‘technical reasons’. Of the patients with no revascularization, 4 were lost at follow-up, 1 had reinfarction, 1 developed heart failure, and 6 had no events during the follow-up period.

Table 1. Means ± SD of NLR and PV in control subjects and AMI patients.

|                | CONTROL SUBJECTS | AMI PATIENTS      | P      |
|----------------|------------------|-------------------|--------|
| NLR            | 1.817 ± 0.711    | 2.376 ± 0.873     | <.0001 |
| PV 450 s⁻¹ (cP)| 1.259 ± 0.125    | 1.519 ± 0.108     | <.0001 |

AMI, acute myocardial infarction; NLR, neutrophil/lymphocyte ratio; PV, plasma viscosity.

Of the young subjects with AMI, 83 were also investigated at 3 months and 66 at 12 months. The study was approved by the Ethical Committee and each subject gave informed consent.

Methods
Blood samples were collected by venous puncture from the ante-cubital vein and immediately transferred to glass tubes anticoagulated with ethylenediaminetetraacetic acid (EDTA)-K3. The following parameters were evaluated:

- Neutrophil/lymphocyte ratio (NLR): white blood cells, neutrophil, and lymphocyte counts were obtained by using an automated blood cell counter and the NLR was calculated.
- Plasma viscosity (PV): this parameter was measured at the shear rate of 450 s⁻¹ using the cone-and-plate viscometer Wells–Brookfield mod. ½ LVT (Middleboro, MA).

The same parameters were examined in a group of normal subjects comparable to AMI subjects for age and sex, without any sign of acute or chronic vascular disease (clinical history, physical examination, laboratory, and instrumental tests).

Statistical Analysis
Data were expressed as mean ± SD; the statistical difference between normal controls and young AMI subjects at baseline, between STEMI and NSTEMI, and between AMI patients with and without cardiovascular events at follow-up was examined according to the Student t test for unpaired data. The comparison between the groups of young AMI subjects subdivided on the basis of the number of cardiovascular risk factors and the number of involved coronary vessels was performed using the one-way analysis of variance model. We also performed the Bonferroni post-test for each pair of groups. As for the distribution of risk factors and stenosed coronary vessels according to NLR and PV, the chi-square test was employed. The difference between NLR and PV at the initial stage of AMI and at 3 and 12 months was explored using the Student t test for paired data. The statistical correlation between NLR and PV was examined using linear regression.

Results
At the initial stage, NLR and PV were significantly higher in young AMI subjects compared with normal controls (Table 1). Neither of these parameters distinguished STEMI from
NSTEMI (data not shown). Subdividing young AMI subjects according to the number of cardiovascular risk factors (Table 2) and to the number of involved coronary vessels (Table 2), no difference in NLR or PV was observed among the 3 respective subgroups.

Subsequently, we subdivided the entire group of young AMI subjects according to the median value of NLR, and in the 2 subgroups, no statistical difference was found concerning the risk factors (Table 3) or the involved coronary vessels (Table 3). Taking the same approach, we subdivided the total group of young AMI subjects according to the median value of PV, and also, in these 2 subgroups, no difference was observed concerning the risk factors (Table 4) or the involved coronary vessels (Table 4). We observed an increase in PV in the subgroup with higher NLR, but no difference in NLR was evident between the subgroups with higher and lower PV (data not shown).

We also examined the behaviour of the 2 parameters after 3 and 12 months, in comparison with the initial stage. This investigation showed that at both times, only a decrease in NLR was evident (Table 5).

During the follow-up, 24 subjects developed cardiovascular complications; 6 patients developed heart failure, 15 a new ischemic event: stable angina in 2, unstable angina in 9 (6 underwent PCI, 3 CABG), and reinfarction in 4 (3 underwent PCI, 1 CABG); 3 patients developed heart failure and also had an ischemic event: 1 stable angina, 1 unstable angina, and 1 reinfarction; the acute coronary syndromes underwent revascularization through PCI. None of the ischemic events happened less than 3 months before hematological re-evaluation.

We compared the initial NLR and PV values in AMI subjects who did or did not subsequently developed cardiovascular complications, and it emerged that only PV was discriminant, even though at a low level of statistical significance (Table 6).

At the initial stage and at 3 and 12 months after AMI, we examined the statistical correlation between NLR and PV, not only in the entire group, but also in the subgroups obtained subdividing AMI subjects for risk factors or involved coronary vessels. From this analysis, it was observed that only after 12 months, there was a significant positive correlation between the 2 parameters and only in the whole group (data not shown).

**Discussion**

Acute myocardial infarction (AMI) at a young age is generally considered a rather infrequent event in medical practice, nevertheless it accounts for 2% to 10% of all cases of AMI, as demonstrated by different surveys.25,26
The 2 parameters we simultaneously examined, NLR and PV, even though not statistically correlated, initially seemed to have a parallel course, not influenced by cardiovascular risk factors nor by the angiographic picture. On the contrary, the evaluation of NLR and PV at 3 and 12 months after AMI showed a different behaviour of the 2 parameters. In fact, NLR decreased significantly at follow-up, whereas PV did not. The persistent increase, unique to PV, was contrary to expectations because both NLR and PV can be part of the reaction to an acute ischemic condition. However, studying the genetic pattern in the same population of young AMI patients, we observed a higher prevalence of pro-inflammatory polymorphisms and a lower prevalence of anti-inflammatory polymorphisms. Unlike NLR, PV could be a marker of such genetic alteration.

The difference in the initial PV values between AMI subjects with and without cardiovascular complications during follow-up suggests a predictive role of this hemorheological parameter. This observation conforms to the findings from a large prospective study, recently published, which enrolled 3386 men and women (aged 30–74 years) and examined blood and plasma viscosity as predictors of cardiovascular disease and total mortality. During an average follow-up of 17 years, it clearly emerged that only PV had a significant predictive role for both cardiovascular events and total mortality.

In this regard, a limitation to our study was the early interruption of follow-up. Such interruption, as mentioned in a previous paper on the same topic, was due to the distance between our university centre and the place of origin of many of these young AMI subjects.

### Conclusions

Our study, besides showing the predictive value of PV as a cardiovascular risk factor also in subjects who have AMI at a relatively young age, gives evidence of a persistent alteration of this parameter.

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**Table 4.** Distribution of risk factors and stenosed coronary vessels in AMI patients subdivided according to PV.

| RISK FACTOR | PV ≤ MEDIAN VALUE (1.510) | PV > MEDIAN VALUE (1.510) | P  |
|-------------|---------------------------|----------------------------|----|
| 0-1 risk factor | 22 (36%) | 17 (28.8%) | .6575 |
| 2 risk factors | 18 (29.5%) | 21 (35.6%) |  |
| >2 risk factors | 21 (34.5%) | 21 (35.6%) |  |

| STENOSED CORONARY VESSELS | PV ≤ MEDIAN VALUE (1.510) | PV > MEDIAN VALUE (1.510) | P  |
|---------------------------|---------------------------|----------------------------|----|
| No coronary lesions | 11 (22%) | 12 (22.6%) | .9638 |
| 1 stenosed vessel | 23 (46%) | 23 (43.4%) |  |
| 2-3 stenosed vessels | 16 (32%) | 18 (34%) |  |

AMI, acute myocardial infarction; NLR, neutrophil/lymphocyte ratio; PV, plasma viscosity.

**Table 5.** Means ± SD of NLR and PV in AMI patients at baseline and after 3 months and at baseline and after 1 year.

| BASELINE AND AFTER 3 MONTHS (N=83) | BASELINE | AFTER 3 MONTHS | P  |
|----------------------------------|----------|---------------|----|
| NLR | 2.363 ± 0.833 | 2.038 ± 0.701 | .0009 |
| PV 450 s⁻¹ (cP) | 1.492 ± 0.097 | 1.466 ± 0.119 | .0667 |

| BASELINE AND AFTER 1 YEAR (N=66) | BASELINE | AFTER 1 YEAR | P  |
|----------------------------------|----------|--------------|----|
| NLR | 2.358 ± 0.822 | 2.113 ± 0.932 | .0460 |
| PV 450 s⁻¹ (cP) | 1.492 ± 0.097 | 1.475 ± 0.009 | .1371 |

AMI, acute myocardial infarction; NLR, neutrophil/lymphocyte ratio; PV, plasma viscosity.

**Table 6.** Means ± SD of NLR and PV in AMI patients with and without cardiovascular events during follow-up.

| AMI PATIENTS WITHOUT EVENTS | AMI PATIENTS WITH EVENTS | P  |
|-----------------------------|--------------------------|----|
| NLR | 2.293 ± 0.806 | 2.535 ± 0.761 | .1987 |
| PV 450 s⁻¹ (cP) | 1.500 ± 0.107 | 1.555 ± 0.094 | .0295 |

AMI, acute myocardial infarction; NLR, neutrophil/lymphocyte ratio; PV, plasma viscosity.
rheological parameter in the follow-up of these patients. We did not observe a similar persistence of NLR, that is, another marker of acute phase reaction. It is not possible to exclude that in many young subjects with AMI, the increase in PV is genetically determined, then pre-existent and even contributing to the pathogenesis of AMI.

Author Contributions

All the authors contributed to the research design, the drafting of the article and the revision process. MM performed the laboratory testing. RLP performed the statistical analysis.

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