Relation Between Platelet Response to Exercise and Coronary Angiographic Findings in Patients With Effort Angina

Gaetano Antonio Lanza, MD; Alfonso Sestito, MD; Sonia Iacovella; Laura Morlacchi; Enrico Romagnoli, MD; Giovanni Schiavoni, MD; Filippo Crea, MD; Attilio Maseri, MD; Felicita Andreotti, MD, PhD

Background—Platelet reactivity is increased by exercise in patients with obstructive coronary artery disease (CAD) but not in patients with syndrome X. In this study, we prospectively investigated whether the platelet response to exercise might help distinguish, among patients with angina, those with obstructive CAD from those with normal coronary arteries (NCAs).

Methods and Results—Venous blood samples were collected before and 5 minutes after exercise from 194 consecutive patients with stable angina. Platelet reactivity was measured by the platelet function analyzer (PFA)-100 system as the time for flowing whole blood to occlude a collagen-adenosine diphosphate ring (closure time). Coronary angiography showed CAD in 163 patients (84%) and NCA in 31 patients (16%). Baseline closure time was shorter in NCA patients (78.0±16 versus 95.5±23 seconds, $P<0.0001$). With exercise, closure time decreased in CAD patients (−15.5 seconds; 95% confidence limits [CL], −13.0 to −18.0 seconds; $P<0.0001$), but increased in NCA patients (12.5 seconds; 95% CL, 7.4 to 17.7 seconds; $P=0.0004$). An increase in closure time with exercise ≥10 seconds had 100% specificity and positive predictive value for NCAs. Similarly, a decrease ≥10 seconds had 100% specificity and positive predictive value for CAD. A closure time change (increase or decrease) ≥10 seconds allowed a correct classification of 55% of all patients.

Conclusions—Among patients with stable angina, the response of platelet reactivity to exercise was predictive of normal or stenosed coronary arteries at angiography. Specifically, an increase in closure time with exercise ≥10 seconds was invariably associated with the presence of NCA. **(*Circulation*. 2003;107:1378-1382.)**

Key Words: platelets ■ coronary disease ■ syndrome X ■ tests

Previous studies have shown that exercise increases platelet reactivity in patients with obstructive epicardial coronary artery disease (CAD).[1–4] This can occur even at low workloads and independently of whether myocardial ischemia is induced or not during exercise.[5] In a recent study, we found that in contrast to well-matched CAD patients, those with cardiac syndrome X (effort angina, positive exercise test, and angiographically normal coronary arteries) display a decrease in platelet reactivity after exercise.[6] These findings suggested that the platelet response to exercise might help distinguish, among patients with anginal pain, those with significant stenoses from those with normal coronary arteries (NCAs) at angiography. To address this question, we measured platelet reactivity at baseline and after exercise in a prospective cohort of consecutive, unselected patients referred for diagnostic coronary angiography because of stable anginal chest pain.

Methods

Patients

A consecutive cohort of patients who fulfilled the following inclusion criteria were enrolled: (1) stable pattern of angina for >6 months; (2) documented ST-segment depression and/or typical angina during exercise testing; (3) referral to our institute for coronary angiography; (4) absence of hemodynamically significant stenoses in extracardiac arterial districts on the basis of clinical history and physical examination; and (5) informed consent to take part in the study. A careful clinical history, including risk factors for CAD and drug therapy, was recorded from each patient. Patients with any of the following conditions were excluded: (1) myocardial infarction or unstable angina in the previous 6 months; (2) anticoagulant therapy; (3) previous coronary angiography; (4) previous revascularization procedures (surgical or percutaneous); and (5) variant angina.

Exercise Testing

All patients performed an exercise test in the morning, in the fasting state, according to a symptom/sign-limited standard Bruce protocol. Leads II, V_2, and V_5 were monitored continuously; a 12-lead ECG was printed at the end of each stage or when clinically indicated and at 1-minute intervals in the recovery phase. Blood pressure was measured at baseline, at peak exercise, and during the last minute of each stage. The test was stopped in case of (1) physical exhaustion, (2) ST-segment depression ≥3 mm, (3) progressive angina (Borg scale ≥6), or (4) relevant clinical events (eg, dyspnea, hypotension, or arrhythmias). ST-segment depression was considered significant if it was horizontal or downsloping and ≥1 mm at 0.08 seconds from the J point.

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From the Istituto di Cardiologia, Università Cattolica del Sacro Cuore, Roma, Italy.

Correspondence to Gaetano A. Lanza, MD, Istituto di Cardiologia, Università Cattolica del S. Cuore, L.go A. Gemelli, 8, 00168, Roma, Italy. E-mail g.a.lanza@inwind.it

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Blood Sampling

Blood samples of 5 mL were drawn from all patients before and 5 minutes after the exercise test through a clean puncture of an antecubital vein by minimal hemostasis. The samples were transferred to plastic tubes that contained 0.106 mol/L trisodium citrate (blood:citrate 9:1) and kept at room temperature. A 1-mL aliquot was used to assess platelet function within 1 hour of sampling.

Platelet Reactivity

Platelet reactivity was measured with the platelet function analyzer (PFA)-100 system (Dade Behring, Milan, Italy). The tests were performed by 2 experienced technicians who were totally blinded to the patients' clinical history, the results of coronary angiography, and the time of blood sampling.

Briefly, 800 μL of anticoagulated whole blood is added to a standardized cartridge and incubated at 38.5°C. The blood is then aspirated under arterial shear rates (5000 s^{-1}) through a ring coated with collagen (2-μg equine type 1) and ADP 50 μg. Platelets in the sample adhere to the ring, are activated, and form an aggregate that ultimately occludes the opening. The time to reach occlusion (closure time) is taken as a measure of platelet reactivity (adhesion and aggregation), with shorter times indicating greater reactivity. In normal subjects, we previously found the method to have a good reproducibility (r=0.89 for duplicate measures) and the results to be independent of sex and age.[7,8] Finally, because collagen and ADP are used as platelet agonists, the measure is virtually unaffected by aspirin use.[9]

Coronary Angiography

Diagnostic left and right coronary angiograms were performed by the standard Judkins' technique. Significant CAD was defined as a ≥50% reduction in lumen diameter of ≥1 major epicardial artery.

Statistical Analysis

Differences in continuous variables between groups were assessed by t test, whereas proportions were compared by χ^2 test with Yates' correction. Two-way ANOVA, with a 1-factor repeated-measure design, was used to compare baseline and postexercise closure time. In case of global statistical significance, multiple comparisons were done by Scheffé tests. Statistica for Windows version 4.0 software (Statsoft, Inc) was used for the analyses. Data are mean±SD. Differences were considered significant at $P<0.05$.

Results

Baseline Characteristics

Overall, 194 consecutive patients with a clinical history of chronic stable angina were included in the study. Coronary angiography revealed significant CAD in 163 patients (84%) and normal epicardial coronary arteries in 31 patients (16%). None of the patients showed subcritical (<50%) focal coronary stenoses or aspects that suggested diffuse coronary atherosclerosis. The main clinical findings of the 2 groups of patients are shown in Table 1. Compared with NCA patients, those with CAD were slightly older (P=0.01) and more often male (P=0.0001). Diabetes mellitus was more frequent in CAD patients, but other cardiovascular risk factors and drug therapy did not differ significantly between the 2 groups. There were 73 patients with a history of previous myocardial infarction, all of whom showed significant CAD at angiography. A previous history of admission to a coronary care unit because of unstable angina was present in 45 patients, 35 of whom showed significant stenoses at angiography (P=0.28 versus NCA patients). Platelet count was similar in the 2 groups, whereas hematocrit was slightly higher in CAD patients. Antiplatelet agents were taken by 141 patients (aspirin by 131 and ticlopidine by 10 patients). No patient was taking a combination of antiplatelet drugs.

TABLE 1. Main Clinical Findings of the 2 Groups of Patients

	NCA (n=31)	CAD (n=163)	P
Clinical data			
Age, y	56.6±9	61.7±13	0.01
Sex (males/females)	13/18	135/28	0.0000
Current/ex-smokers	4/11	30/81	0.11
Hypertension	16	77	0.80
Hypercholesterolemia	14	78	0.94
Diabetes mellitus	...	23	0.05
Family history of CAD	13	72	0.97
Previous unstable angina	10	35	0.28
Previous MI	...	73	0.002
Drug therapy			
β-Blockers	8	60	0.33
Ca^{2+} channel blockers	18	78	0.40
Nitrates	10	65	0.55
Aspirin	19	112	0.55
Ticlopidine	2	8	0.69
Lipid-lowering drugs	4	29	0.69
ACE inhibitors	4	40	0.24
Platelet count, $10^3 \times mm^{-3}$	198±47	211±64	0.28
Hematocrit, %	40.2±4.2	41.8±3.8	0.03
Coronary angiography			
1-Vessel disease	...	72	...
2-Vessel disease	...	57	...
3-Vessel disease	...	34	...

MI indicates myocardial infarction.

Exercise Results

The main results of exercise testing are reported in Table 2. There were no significant differences between the 2 groups in exercise duration and rate-pressure product at peak exercise.

TABLE 2. Main Exercise Test Results in the 2 Groups of Patients

	NCA (n=31)	CAD (n=163)	P
Before exercise			
Heart rate, bpm	76±14	75±14	0.70
Systolic BP, mm Hg	126±19	133±20	0.37
RPP, bpm × mm Hg	9549±2228	10 018±2474	0.33
Peak exercise			
Heart rate, bpm	122±21	121±22	0.92
Systolic BP, mm Hg	164±19	175±23	0.04
RPP, bpm × mm Hg	20 163±5122	21 447±5664	0.24
Exercise duration, s	398±159	411±149	0.67
ST depression, No. of patients	25	117	0.42
ST depression, mm	1.0±0.4	1.3±0.6	0.02
Angina, No. of patients	10	45	0.76

BP indicates blood pressure; RPP, rate pressure product.

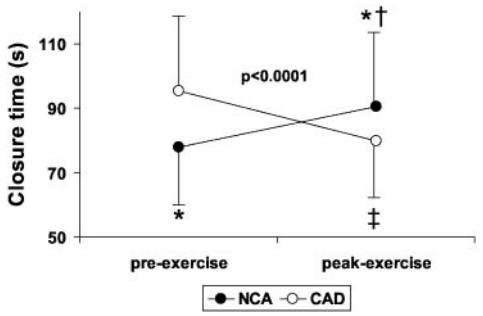

Figure 1. Mean (±SD) values of closure time at baseline and after exercise in 2 groups of patients. *$P<0.0001$ vs CAD; †$P=0.0004$ and ‡$P<0.0001$ vs preexercise.

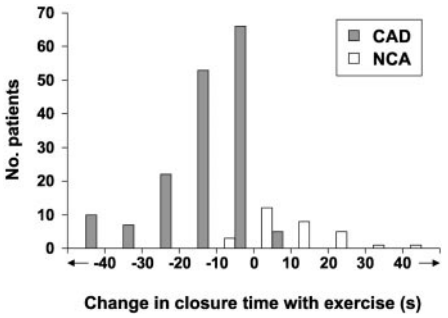

Figure 2. Distribution of change in closure time with exercise in 2 groups of patients.

The frequency of ST-segment depression and angina was also similar in the 2 groups, although the entity of ST-segment depression was slightly greater in CAD patients.

Platelet Reactivity

Average closure times at baseline and after exercise in the 2 groups of patients are shown in Figure 1. At baseline, mean closure time was shorter in NCA patients (78.0±16 versus 95.5±23 seconds, $P=0.0001$). After exercise, closure time increased in patients with NCAs (to 90.6±22 seconds; average increase 12.5 seconds; 95% confidence limits [CL], 7.4 to 17.7 seconds; $P=0.0004$), whereas it decreased in CAD patients (to 80.0±16 seconds; average decrease, −15.5 seconds; 95% CL, −13.0 to −18.0 seconds; $P<0.0001$). The difference in platelet response to exercise between the 2 groups was highly significant ($P=0.0001$) in the whole population and in various subgroups of patients considered, including males or females, patients younger or older than 65 years, those without diabetes mellitus, those treated with different forms of anti-ischemic drugs, and those taking or not taking aspirin (data not shown; $P<0.001$ for all comparisons).

Among CAD patients, the platelet response to exercise did not differ significantly according to history of previous myocardial infarction ($P=0.20$). In patients with 1-vessel versus those with 3-vessel disease, closure time values were similar, both at baseline (93.8±21 versus 94.4±17 seconds, respectively, $P=0.91$) and after exercise (80.2±17 versus 83.1±15 seconds, respectively, $P=0.15$), with similar degrees of change with exercise ($P=0.29$). CAD patients with and without diabetes also had similar closure time values at baseline (93.8±21 versus 94.4±17, respectively, $P=0.65$) and after exercise (80.2±17 versus 83.1±15 seconds, respectively, $P=0.99$), with similar degrees of change with exercise ($P=0.34$).

Predictive Value of the Platelet Response to Exercise

Figure 2 shows how the changes in closure time (from baseline to after exercise) were distributed in the present cohort of patients. An increase in closure time with exercise ≥10 seconds had a 100% specificity and a 100% positive predictive value for NCAs at angiography, although the sensitivity was only 48% (Table 3). Similarly, a decrease ≥10 seconds had a 100% specificity and a 100% positive predictive value for significant CAD at angiography, although the sensitivity was again quite low (56.4%; Table 3). Thus, sufficiently large changes in closure time after exercise (ie, either a decrease or an increase ≥10 seconds) allowed a correct classification of 55% of all patients (15 NCA, 92 CAD).

Discussion

Our data show that among patients with stable anginal chest pain, the platelet response to exercise, assessed by the PFA-100 method with collagen/ADP as platelet agonists, may help predict the presence or absence of significant coronary stenoses at angiography. Specifically, an increase in closure time with exercise ≥10 seconds was virtually diagnostic for the presence of NCAs. These findings have clinical and pathophysiological implications.

Clinical Implications

ST-segment depression and typical angina during exercise are believed to indicate the presence of significant coronary artery stenoses at angiography. The ECG exercise test, however, is far from being an optimal tool for the diagnosis of CAD. In particular, a significant proportion (≈20%) of unselected patients who undergo angiography for a history of chest pain and for ST-segment depression and/or typical angina on exercise are found to have NCAs.[10,11] A number of these patients are classified as having cardiac syndrome X,[12] the majority of whom are women.[13,14] False-positive results on the exercise ECG often lead to invasive investigations, which increase medical costs and expose patients to a definite, although small, risk of complications. Thus, improving the diagnostic accuracy of exercise testing would have relevant clinical, and even financial, implications.

Several approaches have been proposed to this end, including extended ECG lead recording,[15] analysis of other ECG

TABLE 3. Predictive Value of the Platelet Response to Exercise for the Presence of NCAs or of Significant CAD

	Sensitivity	Specificity	PPV	NPV
Predictivity for NCA				
CT increase ≥10 s	48.4%	100%	100%	91.1%
Predictivity for CAD				
CT decrease ≥10 s	56.4%	100%	100%	30.4%

PPV indicates positive predictive value; NPV, negative predictive value; and CT, closure time.

parameters,[16] more sophisticated methods of ST-segment analysis,[17,18] and multivariate scores.[19,20] Several of these methods, however, require very accurate ECG recordings for computerized analyses and/or have a less than optimal diagnostic accuracy. Noninvasive imaging (eg, radionuclide and echocardiographic) stress tests have been proposed.[21,22] Even these, however, may lack adequate sensitivity and specificity and may be rather expensive. The response of exercise ECG to nitrates may help identify, among anginal patients, those who are likely to have NCAs.[23,24] However, large studies on the predictive accuracy of this finding are lacking, and the assessment requires highly reproducible exercise results[23] and repeated exercise testing, which can be impractical and time consuming.

In the present study, a measure of platelet reactivity by a simple operator-independent method (PFA-100) was able to identify, among patients referred for coronary angiography for stable angina, those who were very unlikely to have significant atherosclerotic coronary lesions at angiography. Indeed, despite the enhanced platelet reactivity at baseline, patients with NCAs exhibited a significant reduction in platelet reactivity after exercise, whereas CAD patients, in agreement with previous studies,[1–5] showed a significant increase.

Specifically, a lengthening of closure time by ≥10 seconds from baseline to 5 minutes after exercise was diagnostic of NCAs, with a 100% specificity and positive predictive value. Conversely, a reduction of closure time by ≥10 seconds at peak exercise was highly predictive of CAD, with a positive predictive value of 100%. Admittedly, however, only 55% of the entire population showed sufficiently clear-cut results (ie, changes in closure time ≥10 seconds after exercise) to allow a correct classification (15 NCA and 92 CAD patients).

Another possible clinical implication deserves consideration. Several studies have suggested that strenuous exercise may increase the risk of coronary events.[25–27] It is possible that by facilitating thrombosis, the increase in platelet reactivity induced by exercise in patients with epicardial coronary stenoses may contribute to such events. On the other hand, patients with angina and NCAs have been demonstrated to have a low occurrence of cardiac events,[13,28] and the reduction of platelet reactivity under stressful conditions might be a protective factor in such patients.

Pathophysiological Considerations

Interestingly, platelet reactivity by the PFA-100 method, which reflects both platelet adhesion and aggregation, was increased at baseline in NCA patients compared with CAD patients. This does not appear to be a random finding, because significantly shorter closure times were observed in another series of syndrome X patients compared with well-matched CAD patients or healthy subjects.[6] The cause of the increased baseline platelet reactivity in anginal NCA patients remains to be ascertained. In these patients, a coronary microvascular dysfunction has been reported,[29,30] with several abnormalities potentially capable of promoting platelet activation, including endothelial dysfunction (with possible impaired NO production[31–33] and increased endothelin release[34,35]), abnormal autonomic function,[36] increased sodium-hydrogen exchanger activity,[37,38] and oxidative stress.[39]

On the other hand, during stress conditions, an enhanced myocardial release of adenosine, the main metabolic regulator of coronary blood flow, has been hypothesized to occur in patients with syndrome X and to have a major role in determining the main pathophysiological features of the syndrome.[40] Because adenosine is also a powerful antiplatelet agent,[41–43] we recently investigated whether adenosine might be involved in the reduction of platelet reactivity that occurs with exercise in these patients. In fact, we found that the intravenous administration of theophylline, a well-documented platelet adenosine receptor antagonist,[41,42,44] prevented the exercise-induced prolongation of closure time in syndrome X patients but induced no significant changes in healthy controls, thus supporting our hypothesis. Although adenosine is also released during myocardial ischemia in CAD patients, in these patients, the concomitant presence of strong proaggregant factors (eg, high shear and impaired antithrombotic endothelial function) may ultimately predominate, resulting in increased exercise-induced platelet reactivity.[6,45,46]

Study Limitations

In this unselected consecutive population of patients with anginal symptoms, only those with either significant coronary artery stenoses or normal epicardial arteries were casually included, most likely as a result of chance. Although we do not know how platelet reactivity is modified by exercise in patients with only subcritical stenoses, this should not change the main result of the present study, ie, that an increase of ≥10 seconds in closure time after exercise is evidence against the presence of angiographically significant CAD.

We did not attempt to investigate in this study the mechanisms of the reduction of platelet reactivity with exercise in syndrome X. We previously showed that enhanced adenosine release may be responsible for this finding.[6] However, other potential mechanisms, involving endothelial function, platelets, or other circulating substances, may play a role, and these aspects need to be adequately investigated in future studies.

Conclusions

Our results show that platelet response to exercise, assessed by the PFA-100 method with ADP and collagen as agonists, can predict the presence of NCAs or significant CAD at angiography. Specifically, in the present study, an increase of ≥10 seconds in closure time with exercise was always associated with evidence of NCAs, which suggests that in these cases, further diagnostic investigations, with their attending costs and risks, can be avoided.

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