Effect of Amlodipine on Exercise-Induced Platelet Activation in Patients Affected by Chronic Stable Angina

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Summary

Background: Literature concerning exercise-induced platelet activation in chronic stable angina is somewhat confusing. The reason lies in the type of exercise as well as in methodological problems. A powerful, recently introduced procedure to detect platelet activation is flow cytometry. Platelet response to activating factors is mediated by calcium uptake; however, calcium antagonist effect on platelet activity is still unclear.

Hypothesis: The study was undertaken to investigate exercise-induced platelet activation before and after treatment with amlodipine in chronic stable angina.

Methods: Twenty patients with chronic stable angina were entered into the study. Each subject underwent a symptom-limited cycloergometer stress test following a washout period of 2 weeks. Blood samples were collected before and immediately after exercise. All subjects were then randomized into two groups of 10 patients each, with Group 1 and Group 2 taking amlodipine 10 mg/day, and placebo for 4 weeks, respectively. They subsequently underwent a second exercise stress test, and blood samples were obtained before and immediately after exercise. Flow-cytometric evaluation of platelet activity was performed in order to recognize GMP-140 expression on platelet membrane.

Results: Strenuous exercise induced a significant increase in platelet activation in all subjects prior to therapy. No signif-

icant differences were observed in platelet activity at rest between Groups 1 and 2, whereas a significant decrease in exercise-induced platelet activation was demonstrated in Group 1 compared with Group 2.

Conclusion: Our data provide evidence of the favorable effect of amlodipine on exercise-induced platelet activation in patients affected by chronic stable angina.

Key words: amlodipine, platelet activity, exercise, chronic stable angina

Introduction

There is much and increasing evidence that platelet activation is involved in atherogenesis as well as in coronary vasoconstriction.^{1,2} Primary and secondary prevention trials provided evidence that antiplatelet agents may be effective in reducing morbidity and mortality in coronary artery disease (CAD).³⁻⁵ Platelets, once activated in response to the aggregatory effect of various factors, can be aggregated and release potent vasoactive agents, leading to coronary vasoconstriction.⁶⁻⁸ Nevertheless, it is less clear whether chronic stable angina may be related to platelet activation. Interest in the pathophysiologic role of platelets in exercise-induced myocardial ischemia in patients with stable CAD is considerable, although several studies report unchanged or even reduced platelet activity following exercise.⁹⁻¹⁵ Goudevenos *et al.*¹⁴ reported a significant increase in platelet response to the aggregatory effect of platelet activating factor (PAF) at rest in patients with CAD and exercise-induced myocardial ischemia, whereas patients with CAD and negative exercise stress test exhibited the same response to the PAF aggregatory effect at rest as did those of the control group. The confusion presumably relates to the intensity, duration, and type of exercise, as well as to the choice of platelet function methodology. Platelet aggregation can be studied in whole blood *in vitro* by various cell-counting procedures or by filtagometry *ex vivo* or *in vitro*. A new specific technique has been recently introduced for a better evaluation of platelet activity in

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vivo: the "flow-cytometric evaluation," which evaluates single platelets in the sample and may detect sensitization of the platelets by, for example, exercise, providing a detailed analysis of the single platelet receptor exposure. Kestin *et al.*¹³ observed a significant increase in platelet activation using flow cytometry in untrained healthy subjects. Based on increasing evidence of the role of platelets in atherogenesis and the development of thrombotic complications of atheroma, the effect of antianginal drugs on platelet activity has been investigated.^{11, 15–20} Most of the platelet response to activation depends on changes in intracellular calcium concentrations. Whether different calcium antagonists may affect platelet function is still unclear.^{21–23} The majority of studies to date failed to provide definite results,^{24–27} reflecting the inadequacy of isolated in vitro testing of drugs as well as the methodological problems of measuring platelet activation in vivo.

The aim of our study was to assess whether strenuous exercise may determine an increase in platelet activity in chronic stable angina and to evaluate the effect of amlodipine, a 1,4-dihydropyridine class calcium-antagonist of well-documented efficacy in the treatment of chronic stable angina,^{28–30} on platelet activation due to physical exercise.

Methods

Patients

Twenty consecutive patients (mean age 58 ± 8 years; range 48–66; 13 men) affected by chronic stable angina entered the study. Diagnosis was supported by clinical evaluation, cycloergometer exercise stress test, and myocardial perfusional stress scintigraphy. All subjects gave written informed consent to entering the study. The protocol was approved by the Ethical Committee of the University. Patients affected by diabetes mellitus and hypertension were excluded. None of the patients had either previous myocardial infarction, coronary artery bypass graft, or angioplasty. They were in New York Heart Association (NYHA) class I–II, and none of them presented with hemodynamically significant valvular lesions. All patients were in sinus rhythm, no bundle-branch block present.

Study Protocol

A double-blind study divided into two parts was performed. In the first part, each subject underwent a 2-week run-in period. Any preceding therapy (including antiaggregants) was withdrawn during the 2 weeks. After this washout period, every subject underwent a symptom-limited cycloergometer exercise test with increasing load steps of 25 W every 2 min. A 12-lead electrocardiogram (ECG) and blood pressure were recorded at rest, at the end of each step, at peak exercise, and during the recovery phase. Criteria for exercise interruption were fatigue, chest pain or other limiting symptoms, and ST-segment depression ≥ 2 mm. To avoid the reported increase in platelet activity between 6:00 and 9:00 A.M.,³¹ all tests were performed after 9:30 A.M.

In the second part of the study, after the run-in period, all patients were randomized into two groups of 10 patients each. Patients in Group 1 were instructed to take amlodipine 10 mg/day for 4 weeks, to be taken at 8:00 A.M. Patients in Group 2 were treated with placebo. No significant differences were present with regard to severity of CAD, heart rate, blood pressure, antianginal medications, or preexisting disease between the two groups. At the end of the treatment period, all subjects underwent a second symptom-limited cycloergometer exercise stress test. The exercise test was performed not less than 2 h after the last consumption of the medication.

Blood Sampling and Procedures

Blood samples were obtained from an antecubital vein under minimal stasis before and immediately after exercise by means of a 19-gauge butterfly needle with no tourniquet in an attempt to minimize platelet activation during blood collection. The second venipuncture was made distal to the initial site to avoid any traumatic activation of platelets. After the first 2 ml of blood were discarded, 4–5 ml of blood were collected into a plastic syringe containing 200 μ l of 1% glutaraldehyde solution and ethylenediaminetetraacetate (EDTA) (5 mM final concentration). Platelet-rich plasma (PRP) was obtained by centrifugation of blood at 100 g for 15 min. Further centrifugation of PRP at 1200 g for 15 min gave a platelet-containing pellet which was washed and resuspended in Dulbecco's phosphated buffered saline (PBS), pH 7.4.

We performed flow cytometry to evaluate platelet activation.³² Analysis was performed on 1 ml platelet suspension containing 5×10^6 cells. This suspension was incubated in the dark with 20 μ l of anti GMP-140 (PADGEM) (IgG1, mouse) (Immunotech, Marseille, France) FITC-labeled monoclonal antibody for 30 min at room temperature. At the end of incubation, platelets were washed three times in PBS. Nonspecific binding of monoclonal antibody was assessed by incubating platelets with FITC-labeled anti CD13 monoclonal antibody (a mouse IgG1 isotypic antibody). The fluorescence of samples was analyzed in a flow cytometer (Becton-Dickinson, Rutherford, N.J.). All measurements were monitored following excitation of cells passing through the beam of an air-cooled Argon ion laser (488 nm excitation, 15 mW output). Parameters collected included forward angle light scatter, 90° light scatter, and 530 nm green fluorescence. A gate was set around the platelets and 5,000 cells were analyzed for FITC fluorescence to quantitate the amount of platelet-bound monoclonal antibody. Control platelets were incubated with FITC-coupled nonbinding isotype-matched mouse antibody with the same fluorochrome protein ratio and concentration as the specific IgG. Results were expressed as percent positive platelets, defined as those with a fluorescence intensity exceeding that of 98–99% of the control platelets.³³

Statistical Analysis

A Package Software SPSS 6.0 for Windows (SPSS Inc., Chicago, Ill., USA) was used to perform statistical analysis.

TABLE I Exercise stress test parameters

	Pretreatment group	Group 1	Group 2
Max HR (beats/min)	140 ± 34	133 ± 28 ^a	138 ± 32
Watts achieved	107 ± 25	117 ± 22 ^b	104 ± 27
Exercise duration (min)	9 ± 1.1	10.4 ± 1.3 ^b	9.2 ± 1.1
Mean BP at rest (mmHg)	113 ± 15	98 ± 14 ^b	109 ± 11

Group 1 = after amlodipine. Group 2 = after placebo.

^a = NS between Groups 1 and 2.

^b = $p < 0.05$ between Groups 1 and 2.

Abbreviations: HR = heart rate, BP = blood pressure, NS = not significant.

The Kolmogorov-Smirnov test was used to verify the homogeneity of Groups 1 and 2. The analysis of histograms of the intensity of fluorescence was performed using the Kolmogorov-Smirnov two-sample test.³⁴ Only values of alpha < 0.001 were considered significant. Wilcoxon's rank sum W test was employed to analyze the difference of GMP-140 expression on platelets between the two groups. The Wilcoxon matched-pairs signed-rank test was used to evaluate the intraindividual differences. For analysis of exercise test parameters, unpaired *t*-test was used. *P* values < 0.05 were considered statistically significant. All data are shown as mean $\pm$ standard deviation.

Results

No side effects of amlodipine were recorded except for two cases of mild perimaleolar edema. All patients completed the study.

TABLE II Platelet activity at the end of the run-in period

	At rest ^a	After exercise ^a
Pretreatment group (n = 20)	17 ± 5	32 ± 10
	$p = 0.0002$	

^a = Percentage of fluorescent platelets positive to antibody anti-GMP-140.

Data are expressed as means $\pm$ standard deviation.

The cardiovascular parameters obtained from exercise stress test are shown in Table I. The mean percentage (85%) of predicted maximum heart rate achieved was similar in the two groups.

In the first part of the study, we observed a statistically significant increase in platelet activity due to strenuous exercise after the run-in period, as expressed by the elevation of the percentage of fluorescent platelets interacting with anti-GMP-140 antibodies (Table II) (Fig. 1). This phenomenon was highly evident in all patients prior to therapy (Fig. 2).

Platelet activation after strenuous exercise resulted in a significant difference between patients following therapy with amlodipine when compared with those taking placebo, while no difference was found in platelet activity at rest between the two groups (Table III). The percentage changes of fluorescent platelets positive to anti-GMP-140 antibodies in single patients in the two groups before and after exercise are shown in Figure 3.

Discussion

There is a complex relation between exercise and coronary ischemic disease. The clinical observation that physical exer-

FIG. 1 Example of flow-cytometric profile before (A) and after (B) exercise in a patient in the pretreatment group. An increase of percent positive platelets was observed in the quadrant number 2 of (B).

FIG. 2 Platelet activity of single patients before and after exercise in the pretreatment group. ■ = At rest, ▨ = after exercise.

cise can precipitate myocardial ischemia forms the basis for the widespread use of exercise stress test as a means of provoking ischemia for diagnostic or prognostic purposes.

As the role of platelets in atherogenesis and coronary vasoconstriction is well accepted, exercise-induced platelet activation has been investigated by flow cytometry and reported¹³ to be significantly increased in sedentary healthy subjects compared with physically active subjects. Platelets normally circulate in the resting state and can form platelet thrombi only when activated after exposure to an appropriate agonist. Thus, platelet behavior might be different in patients with CAD whose endothelium dysfunction may result in altered platelet responsiveness even at rest. Recently, Furman, using the flow-cytometric evaluation of platelet activity, found it significantly increased at rest in patients with CAD.³⁵ The literature concerning platelet activation by physical exercise is somewhat confusing. The reason for most of the actual controversies presumably lies in methodological problems. Platelet behavior in vivo may be quite different from that in vitro. Moreover, most of the employed procedures (venopuncture and isolation) may lead to spontaneous activation (alteration and degranulation of platelet surface membrane). In our study, platelets were collected directly into a fixative, without prior anticoagulation or centrifugation, thus maintaining the morphologic and biochemical properties of the circulating state.³² Once activated, platelets release potent vasoactive mediators such as serotonin and thromboxane, both involved in vasoconstriction (Folts model in dog).³⁶ By the assay of binding to platelets a fluorescein-labeled monoclonal antibody that recognizes GMP-140, we demonstrated the platelet exercise-induced activated state in patients affected by chronic stable angina. GMP-140 is an integral membrane glycoprotein with a molecular weight of 140 kD, present in human megakaryocytes, in vascular endothelial cells, and in platelets. This protein, localized in alpha-granule membranes of unstimulated platelets, becomes a component of the external plasma membrane during activation and secretion; it is, therefore, a good

TABLE III Platelet activity after treatment

	Group 1 ^a	Group 2 ^b	p Value
At rest ^c	15 ± 4	18 ± 7	NS
After exercise ^c	18 ± 5	29 ± 7	0.002

^a = Patients in therapy with amlodipine.

^b = Patients receiving placebo treatment.

^c = Percentage of fluorescent platelets positive to antibody anti-GMP-140.

Data are expressed as means ± standard deviation.

marker for platelet degranulation. Furman *et al.* demonstrated that an increase in circulating degranulated platelets is accompanied by monocyte-platelet aggregates formation.³⁵ It can then be reasonably concluded that the increased exercise-induced platelet activity that we observed in CAD may reflect a major risk for the genesis of platelet thrombi. Large therapeutic trials of antiplatelet agents support the concept of an association between platelets and cardiovascular ischemia: antiplatelet agents have been shown to reduce the incidence of cardiovascular ischemic events. Nevertheless, protection with aspirin, the primary agent assessed to protect patients from the mentioned platelet-mediated thrombotic events, has not been as complete as desired. Previous studies³⁷⁻³⁹ observed that aspirin does not interact with the platelet GMP-140 surface expression that is independent from the arachidonic acid pathway. One possible problem with aspirin has been suggested: human platelets studied *ex vivo* and inhibited with aspirin can be reactivated with epinephrine, particularly when catecholamine levels are elevated, such as in sympathetic stimulus.⁴⁰ Assuming that the effect of epinephrine is to enhance calcium uptake by the platelet, Folts²⁷ found that the epinephrine effect on aspirin-treated platelets of stenosed canine coronary arteries was blocked by the second generation

FIG. 3 Platelet activity of single patients before and after exercise in Group 1 (after amlodipine) and Group 2 (after placebo). ■ = At rest, ▨ = after exercise.

dihydropyridine calcium-channel blocker amlodipine. Calcium antagonists are among the most prescribed medications for hypertension and CAD. Due to their action on intracellular calcium concentration, they might be expected to have an effect on platelet activity. Against this hypothesis, at the usual therapeutic doses, the calcium blockers nifedipine, verapamil, and diltiazem inhibit *ex vivo* platelet aggregation only moderately. Many of the conflicting results are probably due to the different methodological procedures employed to detect platelet activity. Knight *et al.*,²⁰ using the flow-cytometry assay, observed an unexpected increase in platelet activation after amlodipine administration. This effect was also observed in a small number of young healthy subjects with no endothelium functional incompetence and after only 1 week of therapy. In our study, we used, for the first time, flow cytometry to evaluate the effect of therapy on platelet activity in patients with stable CAD. No difference in platelet activity at rest was found between the two groups (amlodipine and placebo) after 4 weeks of treatment; nevertheless, we demonstrated a statistically significant reduction in platelet activity after strenuous exercise in the amlodipine group. Our data confirm that physical exercise can lead to platelet activation in patients with stable CAD, presumably acting as a sympathetic stimulus resulting in platelet degranulation. Moreover, this effect has been shown to be inhibited by amlodipine, which can affect internal and external calcium mobilization from platelets as previously reported from experimental models. This inhibitory effect on exercise-induced platelet activation seems not to be necessarily related to impairment of exercise performance. Although previous studies documented the efficacy of amlodipine in reducing ischemic episodes in chronic stable angina,^{28–30} further investigation is required to evaluate whether this antithrombotic effect may be effective in reducing the progression of atherosclerotic disease.

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