The Effect of Low Dose Acetylsalicylic Acid on Platelet Aggregation in Patients with Coronary Heart Disease at Rest and During Physical Exercise Testing

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Abstrak

Aktivitas trombosit yang meningkat pada penderita penyakit jantung koroner (PJK) waktu melakukan aktivitas fisik ataupun mengalami stres akan menerangkan terjadinya kejadian koroner akut pada keadaan tersebut. Asam asetil salisilat (AAS) dosis rendah adalah salah satu jenis obat antitrombotik yang akan menghambat agregasi trombosit dengan jalan menghambat ensim siklo-oksigenase di dalam trombosit. Untuk membuktikan hal tersebut, tahap pertama diperiksa agregasi trombosit secara invitro dengan menggunakan ADP 5 Umol pada 30 penderita laki-laki infark miokard lama dan 15 orang laki-laki normal sebagai kelola yang dilakukan uji latih jantung dengan beban (ULJB). Kemudian tahap kedua secara acak dan tersamar ganda 15 orang penderita PJK diberikan AAS 100 mg/hari sedangkan 15 orang lagi diberikan plasebo sebagai kelola selama 7 hari dan setelah itu pemeriksaan agregasi trombosit serta ULJB diulang kembali. Pada keadaan istirahat sebelum ULJB tidak ada perbedaan yang bermakna antara rata-rata nilai agregasi trombosit (NAT) kelompok penderita dengan kelompok orang normal. Pada kelompok penderita, segera setelah ULJB terlihat rata-rata NAT meningkat bermakna ($p < 0,001$), dan ini lebih tinggi bermakna dibandingkan kelompok orang normal ($p < 0,05$). Tiga puluh menit kemudian turun kembali bermakna ($p < 0,05$) dibandingkan segera setelah ULJB dan tidak berbeda bermakna ($p > 0,05$) dibandingkan sebelum ULJB. Pada kelompok AAS ternyata terdapat penurunan rata-rata NAT yang bermakna setelah pemberian obat pada sebelum ULJB ($p < 0,05$), segera setelah ULJB ($p < 0,001$) dan 30 menit kemudian ($p < 0,05$). Sedangkan pada kelompok plasebo tidak ada perubahan yang bermakna ($p > 0,05$). Bila dibandingkan antara kedua kelompok setelah pemberian obat, ternyata pada kelompok AAS rata-rata NAT ini lebih rendah bermakna baik sebelum ULJB ($p < 0,05$), segera ($p < 0,05$) ataupun 30 menit setelah ULJB ($p < 0,05$). Dari hasil penelitian diatas dapat disimpulkan bahwa pada penderita PJK, aktivitas fisik akan meningkatkan kemampuan trombosit untuk beragregasi. Pemberian AAS dosis rendah (100 mg/hari) dapat menurunkan peningkatan agregasi tersebut.

Abstract

Platelets play an important role in the pathogenesis of acute coronary events. Low dose acetylsalicylic acid (ASA) is one of the antithrombotic drugs used on patients with coronary heart disease (CHD) to inhibit platelet aggregation. In order to prove its efficacy, first platelet aggregation was measured in vitro with 5 µMol Adenosine diphosphate (ADP) at rest, immediately and 30 minutes after treadmill exercise in 30 male patients with old myocardial infarction and in 15 normal male control subjects. At rest and prior to exercise there was no significant difference in mean platelet aggregation between CHD patients and control subjects. Immediately after exercise the mean platelet aggregation was significantly increased in CHD patients ($p < 0.001$) and had significant higher value than the normal subjects ($p < 0.05$). Thirty minutes after exercise, mean platelet aggregation was significantly lower again ($p < 0.05$). Secondly, a double blind and placebo-controlled randomized study of ASA 100 mg daily for 7 days was conducted in all CHD patients (15 received ASA and 15 placebo). Thereafter platelet aggregation studies and the exercise test were repeated. In the ASA group after therapy, the mean platelet aggregation was significantly lower at rest ($p < 0.05$), immediately ($p < 0.001$) and 30 minutes after exercise ($p < 0.05$), while in the placebo group there was no significant difference ($p > 0.05$). Comparing the 2 groups after therapy, it was found that the ASA group had significant lower platelet aggregation than the placebo group at rest as well as immediately or 30 minutes after exercise ($p < 0.05$). It is concluded that low dose ASA (100 mg daily) inhibits the increased tendency towards platelet aggregation in patients with CHD during physical exercise.

Keywords : *Coronary heart disease, Platelet aggregation, Exercise stress test, Acetyl salicylic acid.*

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INTRODUCTION

Platelets play an important role in the pathogenesis of atherosclerosis and coronary heart disease (CHD). Platelet thrombi in the coronary artery can obstruct coronary blood flow, and Thromboxane A2 (TxA2) released by platelets may induce coronary vasospasms. These factors explain the occurence of acute coronary events, such as unstable angina, myocardial infarction, and sudden death.[1,2] This theory is supported by the evidence of increased platelet activation in CHD patients, especially during acute myocardial ischemia or infarction.[3,4,5] Coronary thrombus was also found in CHD patients, both from surgery on early acute myocardial infarction as well as in autopsies following sudden cardiac ischemic death.[6,7]

When a CHD patient undergoes physical exercise or stress, the enhanced plasma cathecolamine level, vascular endothelial damage, and turbulent blood flow due to atherosclerotic stenosis, are assumed to be the cause of increased platelet activation. Furthermore, the thrombus formed and TxA2 released by platelets, are regarded as the cause of failure to enhance myocardial blood supply. Several investigators have reported this increase of platelet activation in CHD patients during physical exercise[8,9,10] or stress.[11,12]

Thus secondary prevention against acute coronary events in CHD patients, especially during physical exercise or stress, is very important. Based on evidence showing the important role of platelets in the pathogenesis of CHD, the use of antithrombotic drugs has been developed. Acetylsalicylic acid (ASA), one of the oldest, most readily available, and inexpensive drugs, has recently been used widely as an antithrombotic agent[13,14]. In view of the considerable side effects and the long term nature of its usage, the lowest optimal ASA dose should be sought. The dose should still inhibit cyclooxygenase in platelets, while only slightly influencing cyclooxygenase in the blood vessel wall. The formation of TxA2, an aggregator and vasoconstrictor, will therefore be inhibited, while prostacyclin (PGI2), an antiaggregator and vasodilator, will not change significantly.[13,14,15]

The purpose of this study was to assess the administration of low dose ASA (100 mg daily) to decrease platelet aggregation in CHD patients at rest or after physical exercise testing, was hope, that low dose ASA will be effective as secondary prevention in CHD patients.

MATERIALS AND METHODS

Subjects

CHD patients, registered from November 1985 through March 1987 at the National Cardiac Centre (NCC) in Jakarta, volunteered to participate in a controlled double-blind study. The study was carried out in 2 parts, from March - July 1987.

The inclusion criteria were, male patients with a previous acute myocardial infarction at least 3 months prior to the study, with no other cardiovascular disease, and without coronary risk factors, such as hypertension, hyperlipidemia, diabetes melitus, overweight or smoking. Previous acute myocardial infarction was determined from medical records by the fulfilment of 2 out of 3 criteria, respectively, a history of typical chest pain, characteristic ECG and serial cardiac enzyme changes.

The exclusion criteria were, inability to perform the exercise test, or contraindication of exercise testing. Those with hypersensitivity to ASA, a history of gastroduodenitis, peptic or duodenal ulcer, or bleeding disorders, were also excluded. Subjects, presenting difficulties or technical errors in obtaining blood samples, were also excluded.

For the first part of the study, the control group consisted of 15 normal male age-matched volunteers. Each subject in this group was a non smoker, with no history of any heart disease, not taking any medication, and was found healthy on physical examination, with normal ECG, chest X ray and laboratory results. The results of exercise testing in this group were negative.

Study design

All subjects were informed of the nature of the study and gave informed consent. Drugs such as antithrombotics, anticoagulants, calcium antagonists, and beta blockers, except nitrates were discontinued 2 weeks prior to the study. Throughout the study, both groups were instructed not to change their daily dietary habits.

The first part of the study was conducted on all subjects, with the normal group as control. Platelet aggregation and platelet count were examined at rest, after an overnight fast of minimally 12 hours. These examinations were repeated immediately and 30 minutes after exercise testing.

In the second part of the study, only the CHD patients were included in a randomized, double-blind,

and placebo-controlled study. A daily dose of 100 mg ASA and placebo were administered for 7 consecutive days. The procedure in the first part of the study was repeated on the 8th day. Drug compliance was checked every 2 days. Each patient was given more than the amount required and the remaining capsules were tallied at the end of the study.

Exercise test protocol

The exercise test was conducted using a treadmill, according to the Bruce protocol. Exercise was terminated in the CHD group at the onset of chest pain, and ECG changes such as ST segment depression of more than 3 mm or serious ventricular arrhythmia. If there was no ischemic response, all subjects were required to achieve 85 % of maximal predicted heart rate to insure a controlled standard hemodynamic stress and qualify for inclusion in the study.

The exercise test was considered positive if there was a horizontal downsloping or upsloping ST segment depression of 1.5 mm, 0.08 seconds from J point, with or without chest pain. It is considered negative if at least 85 % of the maximal predicted heart rate was achieved without significant symptoms or ST segment changes on ECG recording.

Platelet aggregation and platelet count examination

The blood samples from different veins were taken before as well as immediately and 30 minutes after the exercise test, using a syringe and 21-gauge needle. With a single venipuncture and as little manipulation as possible, 11 ml of blood was withdrawn. No tourniquet was used to occlude venous blood flow, since such intervention might influence certain platelet function parameters. In case of failure, the procedure was repeated with another syringe and on another vein. The first 1 ml of blood was discarded, then 1 ml was put in a polypyrene bottle containing 1.5 mg disodium EDTA for platelet count, while the remaining 9 ml was put in a polypyrene tube containing 1 ml 3.8 % sodium citrate for platelet aggregation examination.

The platelet aggregation was measured in vitro according to the Born method, which is based on light transmission.[16] Adenosine diphosphate (ADP) of 5 uM was used as an aggregating agent. Measurement was made with a PA-3210 Aggrecorder (Daichi-Japan) in the Clinical Pathology Laboratory of the Faculty of Medicine, University of Indonesia / Dr. Cipto Mangunkusumo Hospital, Jakarta. Ten ml of citrated blood was centrifuged at 160 G for 10 minutes at room temperature, in order to obtain platelet rich plasma (PRP). This supernatant was then centrifuged again at 2000 G for 10 minutes, in order to obtain platelet poor plasma (PPP). PRP and PPP were then used to measure platelet aggregation. The change in light transmission due to platelet aggregation was recorded for 5 minutes on recording paper. The maximum aggregation was expressed as a percentage. The whole procedure must be completed within a period of less than 2 hours after blood collecting.[16] Quality control on the laboratory apparatus was conducted.

The platelet count was performed on EDTA-blood with the model 8201/2 AL-Cell Counter in the NCC Laboratory. Quality control was also conducted on this laboratory apparatus.

Each procedure, both blood sample collecting and laboratory tests, was carried out by the same technician.

Statistical Analysis

Data were analyzed using the Student's test for paired and unpaired values. A probability (p) value of < 0.05 was considered statistically significant.

RESULTS

The CHD group consisted of 30 male patients with an average age of 56.40 $\pm$ 6.33 years (range 40 - 67 years). Fifteen normal volunteers with an average age of 54.67 $\pm$ 3.58 years (range 50 - 61 years) made up the control group. Average age, resting blood pressure, fasting blood sugar, total plasma cholesterol, and triglyceride levels between the two groups did not differ significantly ($p > 0.05$) (table 1). Twenty patients in the CHD group showed positive exercise test results.

Effect of physical exercise on platelet aggregation

Mean heart rate during blood sample collecting immediately after exercise testing, did not differ significantly from the mean maximal heart rate reached at the peak of exercise testing. In the CHD group it was 143.23 $\pm$ 8.34 / minute and 144.17 $\pm$ 8.05 / minute, while in the normal group it was 143.33 $\pm$ 16.55 / minute and 147.8 $\pm$ 6.26 / minute, with $p > 0.05$.

Table 1. Clinical data of CHD patients and normal subjects

Group	Age (year)	Fasting blood sugar (mg/dl)	Total cholesterol (mg/dl)	Triglycerides (mg/dl)	Resting SBP (mmHg)	Resting DNP (mmHg)
CHD patients (n = 30)	56.40 ± 6.33	90.93 ± 8.94	212.97 ± 28.18	128.30 ± 24.72	130.00 ± 14.86	82.67 ± 6.39
normal subjects (n = 15)	54.67 ± 3.58	86.27 ± 9.88	201.27 ± 30.23	119.33 ± 22.76	128.00 ± 8.62	84.00 ± 5.07

Values are mean ± standard deviation.
Abbreviations : CHD = coronary heart disease, SBP = sistolic blood pressure, DBP = diastolic blood pressure

There were no significant differences between the two groups for mean platelet counts taken at rest as well as immediately and 30 minutes after exercise testing ($p > 0.05$). Comparison of mean platelet counts at rest as well as immediately and 30 minutes after exercise showed differences in both groups, although the differences were not significant, with $p > 0.05$ (table 2).

The mean platelet aggregation values in the normal group at rest (50.18 ± 24.55 %), immediately after exercise testing (53.67 ± 28.11 %), and 30 minutes later (49.45 ± 25.75 %) did not differ significantly ($p > 0.05$) (figure 1). In the CHD group, mean platelet aggregation value at rest was 62.58 ± 23.78 %. This value increased significantly to 71.70 ± 24.59 % immediately after exercise testing, with $p < 0.001$.

Thirty minutes later, it had decreased significantly to 66.05 ± 24.92 %, with $p < 0.05$. This last value was not significantly different from the mean platelet aggregation measured at rest, with $p > 0.05$ (figure 1).

The mean platelet aggregation in CHD patients with positive exercise test did not differ significantly from that of patients with negative test. The values were respectively, 63,36 ± 26,11 % and 61.02 ± 19.44 % at rest ($p > 0.05$), 73,21 ± 28,72 % and 68,69 ± 13,84 % immediately after exercise ($p > 0.05$), and 67.19 ±29.41 % and 63.79 ± 12.86 % 30 minutes later ($p > 0.05$).

There was no significant difference in the mean platelet aggregation measured at rest between the 2 groups, with $p > 0.05$. But immediately after exercise testing, the CHD group showed a significantly higher mean platelet aggregation value compared with the normal group, with $p < 0.05$. Thirty minutes after exercise testing, there was a decrease in mean platelet aggregation values in both group, even though the CHD group still showed a significantly higher value, with $p < 0.05$ (figure 2).

Effect of ASA administration

In the CHD group, the mean heart rate recorded during blood sample collecting immediately after exercise testing, did not differ significantly ($p > 0.05$) from the mean maximal heart rate attained at the peak of the exercise test. The values were respectively, 143.23 ± 8.34 / minute and 144.17 ± 8.05 / minute before drug administration, and 144.17 ± 8.37 / minute and 145.23 ± 8.94 / minute after drug administration.

There were no significant differences ($p > 0.05$) in mean platelet counts taken at rest or immediately and 30 minutes after exercise testing, for both ASA and placebo groups (table 2).

In the ASA group, a significant decrease in mean platelet aggregation was achieved after drug administration. At rest, the value decreased from 62.18 ± 26.40 % to 48.97 20.63 % ($p < 0.05$). Immediately after exercise, the decrease was from 69.49 ± 29.21 % to 50.45 ± 24.40 % ($p < 0.001$), and 30 minutes later from 59.77 ± 27.71 % to 51.09 ± 21.97 % ($p < 0.05$) (figure 3). No significant differences ($p > 0.05$) in mean platelet aggregation were found in the placebo group after drug administration at rest or immediately and 30 minutes after exercise testing (figure 3).

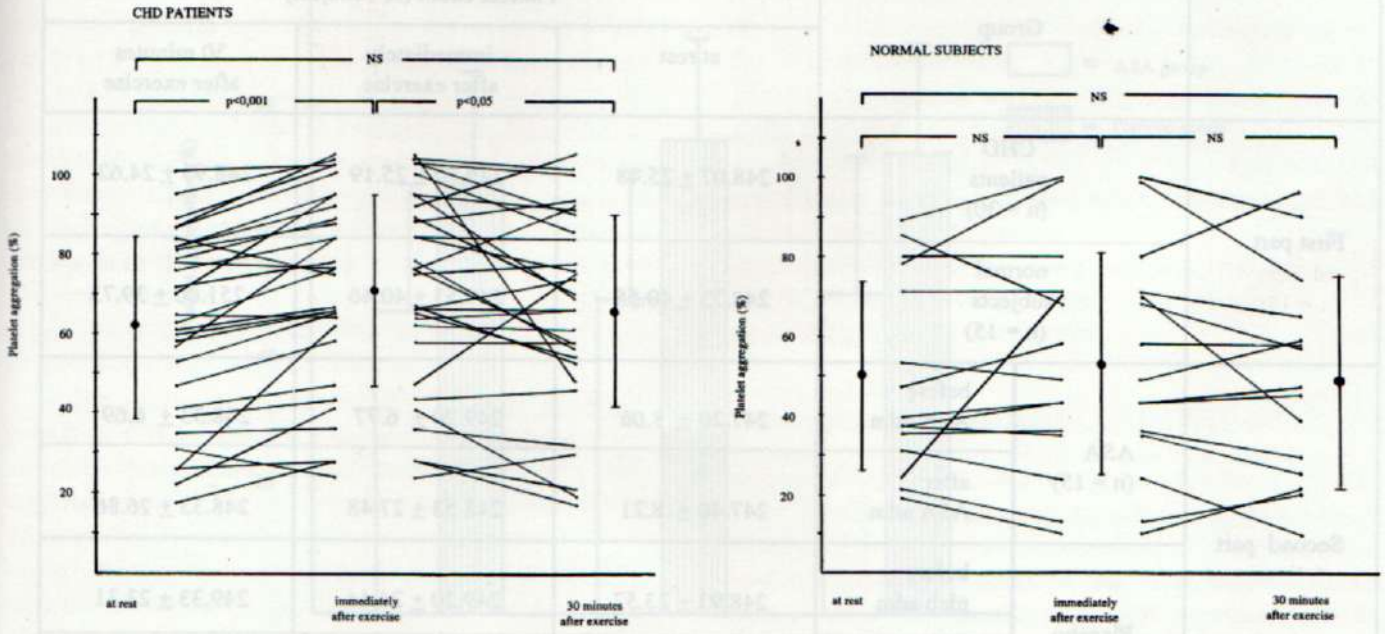

Figure 1. Platelet aggregation values at rest, immediately and 30 minutes after exercise testing in coronary heart disease (CHD) patients and normal subjects. Only the CHD patients had a significant increase in mean platelet aggregation during exercise.

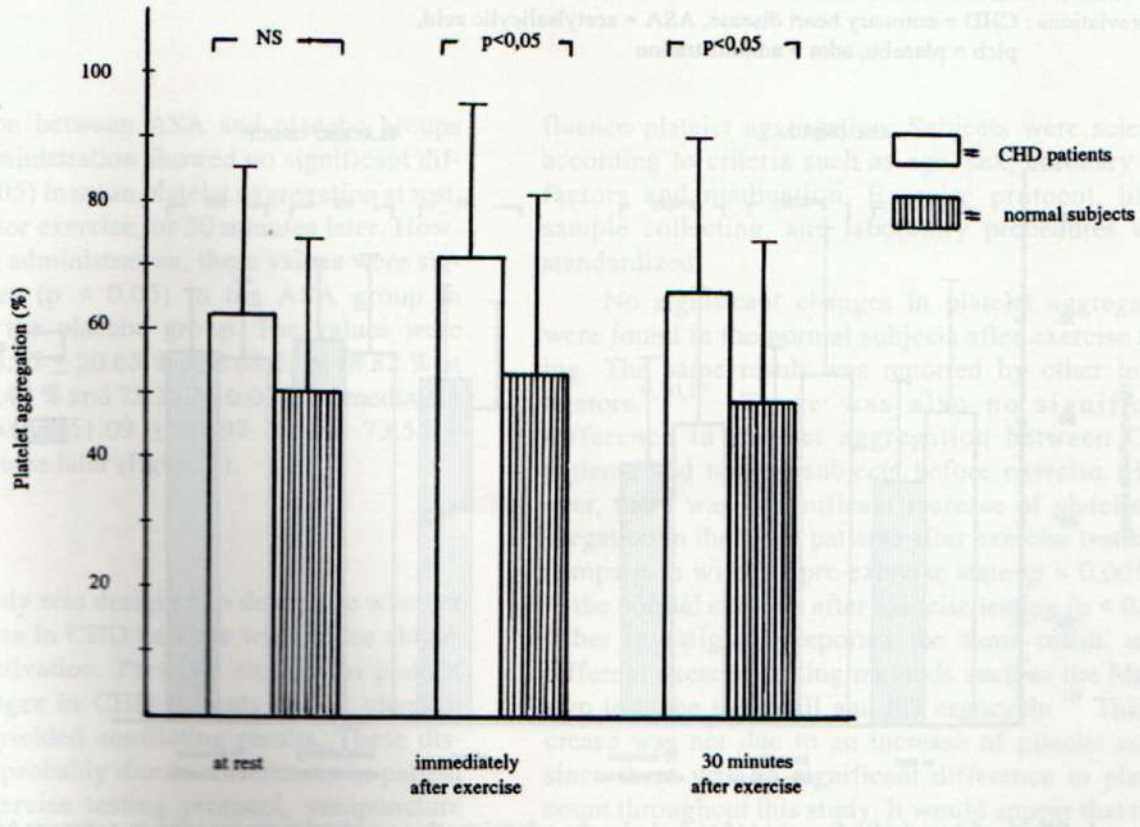

Figure 2. Mean platelet aggregation at rest, immediately and 30 minutes after exercise testing in coronary heart disease (CHD) patients and normal subjects. Immediately and 30 minutes after exercise the mean platelet aggregation was significantly higher in CHD patients.

Table 2. Mean platelet count in CHD patients and normal subjects (first part of the study), and in CHD patients before and after ASA or placebo administration (second part of the study).

	Group		Platelet count (X 1000/ml)		
			at rest	immediately after exercise	30 minutes after exercise
First part	CHD patients (n = 30)		248.07 ± 25.48	249.20 ± 25.19	248.93 ± 24.62
	normal subjects (n = 15)		248.73 ± 40.55	249.53 ± 40.46	251.00 ± 39.73
Second part	ASA (n = 15)	before ASA adm	247.20 ± 8.06	249.20 ± 6.77	248.53 ± 6.69
		after ASA adm	247.40 ± 8.21	248.53 ± 27.48	248.33 ± 26.86
	Placebo (n = 15)	before plcb adm	248.93 ± 23.57	249.20 ± 24.44	249.33 ± 23.31
		after plcb adm	248.20 ± 24.25	248.67 ± 24.24	249.27 ± 25.03

Values are mean ± standard deviation.
Abbreviations : CHD = coronary heart disease, ASA = acetylsalicylic acid, plcb = placebo, adm = administration

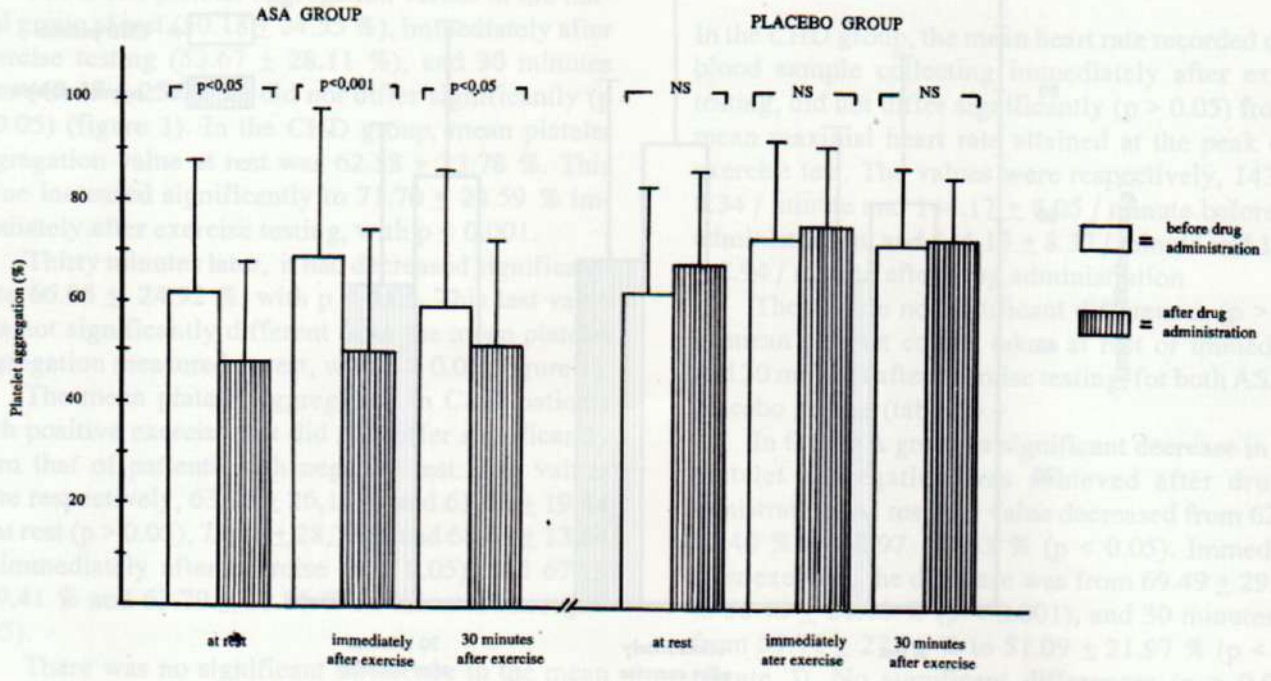

Figure 3. Effects of Acetylsalicylic acid (ASA) and placebo administration on platelet aggregation in coronary heart disease (CHD) patients at rest, immediately and 30 minutes after exercise testing. Only the ASA group had a significant decrease in mean platelet aggregation after drug administration.

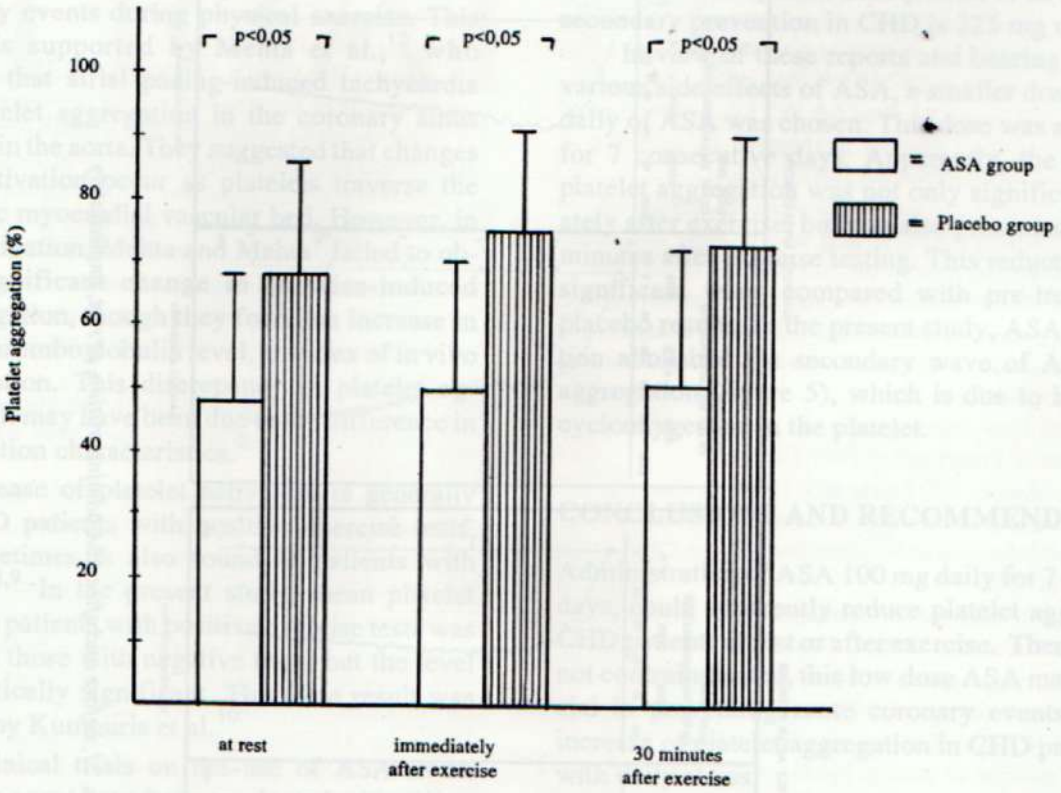

Figure 4. Mean platelet aggregation in the acetylsalicylic acid (ASA) and placebo group after drug administration at rest and after exercise testing. The ASA group had a significant lower in mean platelet aggregation than the placebo group as well as at rest, or after exercise.

Comparison between ASA and placebo groups before drug administration showed no significant differences ($p > 0.05$) in mean platelet aggregation at rest, immediately after exercise, or 30 minutes later. However, after drug administration, these values were significantly lower ($p < 0.05$) in the ASA group in comparison to the placebo group. The values were respectively, 48.97 ± 20.63 % and 68.22 ± 18.82 % at rest, 50.45 ± 24.40 % and 75.15 ± 16.01 % immediately after exercise, and 51.09 ± 21.97 % and 73.55 ± 17.62% 30 minutes later (figure 4).

DISCUSSION

The present study was designed to determine whether physical exercise in CHD patients will induce abnormal platelet activation. Previous studies on platelet activation changes in CHD patients during physical exercise have yielded conflicting results. These discrepancies are probably due to differences in patient population, exercise testing protocol, venipuncture technique or blood processing methods. This present study attempted to minimize factors that might influence platelet aggregation. Subjects were selected according to criteria such as age, sex, coronary risk factors and medication. Exercise protocol, blood sample collecting, and laboratory procedures were standardized.

No significant changes in platelet aggregation were found in the normal subjects after exercise testing. The same result was reported by other investigators.[9,10,17] There was also no significant difference in platelet aggregation between CHD patients and normal subjects before exercise. However, there was a significant increase of platelet aggregation in the CHD patients after exercise testing in comparison with the pre-exercise state ($p < 0.001$) or in the normal subjects after exercise testing ($p < 0.05$). Other investigators reported the same result, using different exercise testing methods such as the Master step test, the treadmill and the ergocycle.[10] This increase was not due to an increase of platelet count, since there was no significant difference in platelet count throughout this study. It would appear that there was a hyperactive platelet state, causing a tendency to aggregate more easily, in CHD patients. This may

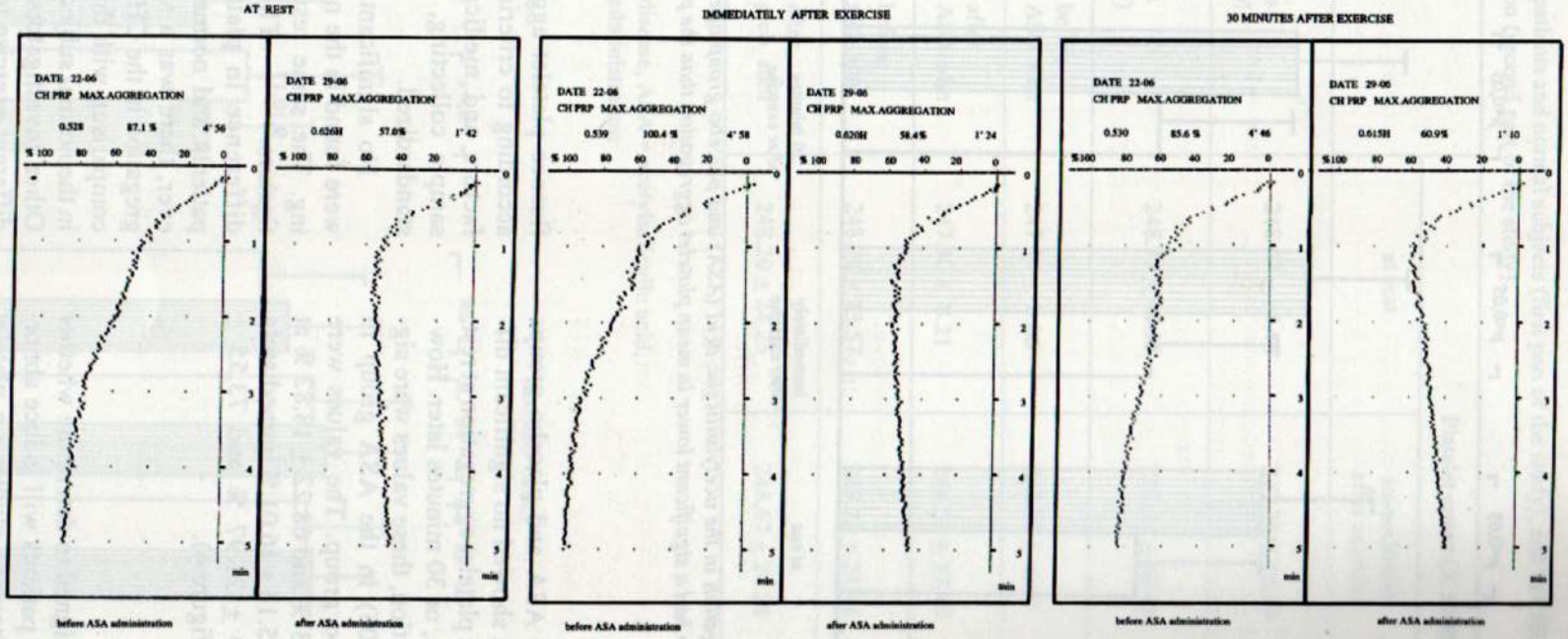

Figure 5. Platelet aggregation in coronary heart disease (CHD) patient no. 21, before and after ASA administration, at rest, immediately and 30 minutes after exercise testing.

explain the pathophysiology of myocardial ischemia or acute coronary events during physical exercise. This assumption is supported by Mehta et al.,[12] who demonstrated that atrial pacing-induced tachycardia increases platelet aggregation in the coronary sinus blood and not in the aorta. They suggested that changes in platelet activation occur as platelets traverse the atherosclerotic myocardial vascular bed. However, in another investigation, Mehta and Mehta[9] failed to observe any significant change in exercise-induced platelet aggregation, though they found an increase in plasma beta-thromboglobulin level, an index of in vivo platelet activation. This discrepancy in platelet aggregation result may have been due to the difference in patient population characteristics.[9]

The increase of platelet activation is generally found in CHD patients with positive exercise tests, although sometimes is also found in patients with negative test.[8,9] In the present study, mean platelet aggregation in patients with positive exercise tests was higher than in those with negative tests, but the level was not statistically significant. The same result was also reported by Kumpuris et al.[10]

Many clinical trials on the use of ASA as an antithrombotic agent have been conducted with differing dosages. According to Masotti et al.[18], 2-5 mg/kg body weight is the most appropriate dose that can induce maximum inhibition of TxAa formation without significantly affecting PGI2. Weksler et al.[19] demonstrated, that low doses ASA of 40, 80 and 325 mg, could inhibit in vitro platelet aggregation by reducing TxA2 production 77, 95, and 99 % respectively, while only reducing PGI2 production by 35, 38, and 75 %. A dose of 100 mg as reported by Patrono et al.[20] can also inhibit platelet aggregation and TxA2 formation by more than 95 %.

Several investigations have reported the effect of ASA on CHD patients subjected to stress induced by exercise or atrial pacing. Kumpuris et al.[10] reported the ability of ASA to decrease platelet aggregation in CHD patients during exercise testing. However, large doses were used, 4 x 600 mg daily for 2 weeks and 1300 mg daily for 10 days, respectively. Mehta et al.[12] also found a decrease of TxA2 production and platelet aggregation in atrial pacing-induced tachycardia, 30 minutes after orally administering of 650 mg ASA.

The role of ASA in the secondary prevention of myocardial infarction incidence and coronary mortality has been thoroughly investigated in various longitudinal studies. The beneficial effect of ASA on post-myocardial infarction, although apparent, is not statistically significant; but the effect on unstable angina is statistically succesful.[21,22,23,24,25] It seems, that the lowest optimal dose proved to be beneficial in secondary prevention in CHD is 325 mg daily.[24]

In view of these reports and bearing in mind the various side effects of ASA, a smaller dose of 100 mg daily of ASA was chosen. This dose was administered for 7 consecutive days. Apparently, the decrease in platelet aggregation was not only significant immediately after exercise, but was also present at rest and 30 minutes after exercise testing. This reduction was still significant when compared with pre-treatment and placebo results. In the present study, ASA administration abolished the secondary wave of ADP-induced aggregation (figure 5), which is due to inhibition of cyclooxygenase in the platelet.

CONCLUSIONS AND RECOMMENDATIONS

Administration of ASA 100 mg daily for 7 consecutive days, could apparently reduce platelet aggregation in CHD patients at rest or after exercise. Therefore, when not contraindicated, this low dose ASA may be beneficial in preventing acute coronary events caused by increase of platelet aggregation in CHD patients faced with daily stress.

Extensive longitudinal studies of the effect of 100 mg of ASA on secondary prevention and its side-effects should be undertaken.

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