PLATELET AGGREGATION STUDIES IN PATIENTS WITH ANGINA PECTORIS

—Relationships to Types of Angina and Coronary Pathoanatomy—

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Platelet aggregation was studied in patients with angina pectoris in whom coronary sclerosis was found by arteriography. The subjects consisted of 20 patients with stable angina pectoris, 12 with unstable angina pectoris and 4 with variant form of angina pectoris. Fifteen healthy subjects served as controls. ADP- and collagen-induced platelet aggregations were estimated during resting conditions before and immediately after an exercise test.

In patients with unstable angina pectoris, ADP-induced as well as collagen-induced platelet aggregations during resting conditions were significantly less than those in normal subjects. After exercise, however, they significantly increased. In stable angina pectoris, they did not differ from those in the control group and their responses to exercise were also not significant.

In general, platelet aggregation during resting conditions was accelerated in relation to an increase in the number of coronary arteries involved.

The results demonstrate that examination of platelet aggregation during resting conditions and following exercise aids in a more accurate evaluation of the types and the stages of patients with angina pectoris.

PLATELET function has been known to play an important role in the pathogenesis of ischemic heart disease, but there are still uncertain results concerning the relationship of the enhanced platelet aggregation to its pathogenesis. Several studies on platelet aggregation in patients with ischemic heart disease have been reported,¹⁻³ but little attention has been given to the types or phases of ischemic heart disease. This lack of attention may be a significant reason for the different results which have been obtained concerning the platelet function in ischemic

heart disease. The present study was designed to evaluate platelet aggregation during resting conditions and its responsiveness to exercise with special emphasis on the types of angina pectoris, i.e., stable or unstable, and the number of coronary arteries involved.

MATERIALS AND METHODS

Selection of Patients

Thirty-six patients with a mean age of 54.2 years, ranging from 32 to 76, were studied. All patients had been hospitalized due to chest pain or chest oppression. Twenty had stable effort angina (A1), 12 had unstable effort or spontaneous angina (A2), and the remaining had variant angina (A3). No patients had taken aspirin or

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any other agents known to alter platelet function for at least 2 weeks before the study. Fifteen healthy volunteers with a mean age of 40.0 years, ranging from 28 to 51, served as the control subjects. None of them had ever had abnormal ECG findings either at rest or after exercise, symptoms attributable to heart disease or major risk factors for coronary artery disease.

Quantification of Coronary Pathology

Coronary angiography was performed using Sones' technique on 36 patients. The occurrence and severity of coronary angiographic lesions, assessed by at least 6 projections, was expressed by the following definition: minimal changes = absence or minimal changes of coronary angiographic lesion; SVD = occurrence of one lesion of greater than 50% cross-sectional luminal narrowing in a single coronary artery; DVD = two or more lesions in two major coronary arteries; TVD = those in the three major coronary arteries.

Exercise Test

Graded multi-staged treadmill exercise testing according to the modified Bruce's protocol was performed and analyzed using a computer-assisted system for exercise (CASE, Marquette). The exercise test was terminated at the onset of severe chest pain, exhaustion, or upon obtaining at least 85% of the maximal predicted heart rate, significant ST depression or drop of blood pressure. Exercise testing in the patients with intractable angina pectoris was performed after achieving remission by medical treatment.

Measurement of Platelet Function

Blood samples taken from the cubital vein in a fasting state were collected into plastic tubes containing 3.8% sodium citrate with a ratio of 9 to one before and immediately after exercise. From these samples, platelet rich plasma (PRP) was obtained by centrifugation at $200 \times g$ for 10 min at room temperature. All platelet aggregation studies were performed between 60 and 75 min after the sampling. A platelet aggregation meter (MODEL 169, Evans Electroselenium Ltd., Halstead, Essex, England) was employed. Platelet aggregation was measured at a stirring speed of 800 rpm. The platelets were counted visually with a bright-line hemacytometer and a phase contrast microscope. The aggregate-stimulation agents included ADP ($1 \mu\text{M}$) and collagen ($1 \mu\text{g/ml}$). Light transmission through the platelet poor plasma (PPP) was set at 100%, then an

intensity of PRP was obtained. The results for each determination were expressed as the following ratio:

$$\text{platelet aggregation rate} = \frac{\text{maximum detection of optical density of PRP measured from base line}}{\text{optical density of PPP measured from base line}} \times 100$$

Statistical Analysis

Statistical examination was carried out according to the following conventional methods. A Student's *t*-test for paired and unpaired data and an independent variable test were used to determine the significance level of the difference between control subjects and patients with stable or unstable angina. Values were given as mean $\pm$ standard deviation (SD), and probability (*p*) value of less than 0.05 was considered statistically significant.

RESULTS

Control Studies

In control subjects, mean platelet aggregation induced by ADP was 78.0 ± 7.0 at rest and 75.6 ± 7.2 after exercise. Collagen-induced platelet aggregation was $80.4 \pm 9.8\%$ at rest and 79.3 ± 7.8 after exercise. Mean platelet counts was $212,000 \pm 52,000/\text{mm}^3$ at rest and $211,000 \pm 52,000$ after exercise. Previously we investigated the platelet aggregation in response to exercise in 18 ostensibly normal persons and confirmed that when it was expressed as percentile changes of the control value at rest, the normal range was less than 15% (Table I). Although some cases showed a decrease in platelet aggregation after exercise, we considered that a 15 percentile increase or more compared with platelet aggregation at rest was an abnormal hyperresponsiveness in such a study, because a decrease in platelet aggregation after exercise was considered to be a rather desirable effect from the viewpoint of a suppression of the platelet aggregation. No abnormal hyperresponsiveness was observed in either ADP- or collagen-induced aggregation in control subjects (Table II).

Platelet Aggregation during Resting Conditions in Patients with Angina Pectoris

Data from patients with stable and unstable angina pectoris is summarized in Tables III and IV. In group A1, mean platelet aggregations induced by ADP and collagen were 75.5 ± 12.6 and 79.7

TABLE I PLATELET AGGREGATION STUDIES AT REST AND AFTER TREADMILL EXERCISE TEST IN EIGHTEEN OSTENSIBLY NORMAL PERSONS

No. of Subjects	Age	Sex	Platelet counts ($\times 1,000/\text{mm}^3$)		ADP ($1 \mu\text{M}$)			Collagen ($1 \mu\text{g/ml}$)		
			At Rest	After Exercise	At Rest	After Exercise	% Change	At Rest	After Exercise	% Change
1	27	M	206	208	53	58	(9)	76	68	(-11)
2	27	M	210	221	49	44	(-10)	96	95	(-1)
3	27	M	269	308	84	85	(1)	84	86	(2)
4	60	M	196	232	58	56	(-3)	88	88	(0)
5	47	M	232	247	80	73	(-9)	86	81	(-6)
6	29	M	167	191	73	83	(14)	83	86	(4)
7	35	M	232	185	86	86	(0)	72	77	(7)
8	46	M	236	217	61	56	(-8)	55	57	(4)
9	28	M	250	237	78	76	(-3)	75	72	(-4)
10	47	M	217	235	79	72	(-9)	92	85	(-8)
11	51	M	166	186	77	79	(3)	76	85	(12)
12	21	F	217	220	81	82	(1)	80	80	(0)
13	51	F	241	181	83	80	(-4)	85	81	(-5)
14	58	F	253	226	68	67	(-1)	41	40	(-2)
15	39	F	292	275	70	72	(3)	70	73	(4)
16	44	F	136	146	79	85	(8)	73	82	(12)
17	41	F	193	179	72	69	(-4)	71	65	(-8)
18	58	F	192	165	81	88	(9)	88	82	(-7)
mean	40.9		217.0	214.4	72.9	72.8		77.3	76.8	
SD	12.0		37.7	38.5	10.7	12.1		12.9	12.6	

TABLE II PLATELET AGGREGATION STUDIES AT REST AND AFTER TREADMILL EXERCISE TEST IN CONTROL GROUP

No. of Subjects	Age	Sex	Platelet counts ($\times 1,000/\text{mm}^3$)		ADP ($1 \mu\text{M}$)			Collagen ($1 \mu\text{g/ml}$)		
			At Rest	After Exercise	At Rest	After Exercise	% Change	At Rest	After Exercise	% Change
1	51	F	241	181	85	76	(-11)	86	83	(-4)
2	44	F	136	146	73	82	(12)	79	85	(7)
3	41	M	238	202	82	73	(-11)	87	81	(-7)
4	41	M	223	217	84	79	(-6)	87	89	(2)
5	39	F	128	169	79	74	(-6)	77	76	(-1)
6	46	M	236	217	61	56	(-8)	55	57	(4)
7	35	M	232	185	86	72	(-16)	72	77	(7)
8	28	M	250	237	78	76	(-3)	75	72	(-4)
9	47	M	217	235	79	64	(-19)	92	85	(-8)
10	51	M	166	186	90	79	(-12)	85	76	(-11)
11	41	F	217	220	80	80	(0)	81	82	(1)
12	30	M	312	339	72	76	(6)	69	73	(6)
13	29	M	167	191	73	80	(10)	83	86	(4)
14	30	M	276	301	72	82	(14)	97	80	(-18)
15	47	M	138	135	76	85	(12)	81	87	(7)
mean	40.0		211.8	210.7	78.0	75.6		80.4	79.3	
SD	7.7		52.1	51.9	7.0	7.2		9.8	7.8	

TABLE III PLATELET AGGREGATION STUDIES AT REST AND AFTER TREADMILL EXERCISE TEST IN PATIENTS WITH STABLE ANGINA PECTORIS (GROUP A1)

No. of Patients	Age	Sex	CAD	Platelet counts ($\times 1,000/\text{mm}^3$)		ADP ($1 \mu\text{M}$)			Collagen ($1 \mu\text{g/ml}$)		
				At Rest	After Exercise	At Rest	After Exercise	% Change	At Rest	After Exercise	% Change
1	64	F	M	186	149	83	82	(-1)	78	88	(13)
2	54	M	M	258	279	63	80	(27)	83	70	(-16)
3	44	F	M	190	154	95	98	(3)	90	80	(-11)
4	62	M	M	176	165	70	77	(10)	74	67	(-10)
5	52	M	S	141	155	68	39	(-43)	70	70	(0)
6	74	M	S	200	227	71	61	(-14)	88	93	(6)
7	51	M	S	316	290	65	65	(0)	73	84	(15)
8	57	M	S	116	127	50	—	(—)	98	97	(-1)
9	49	M	S	174	174	86	74	(-14)	40	71	(78)
10	63	M	S	222	176	70	55	(-21)	98	93	(-5)
11	45	F	S	177	143	76	82	(8)	85	90	(6)
12	53	M	D	208	238	74	80	(8)	64	77	(20)
13	57	M	D	157	177	74	88	(19)	76	84	(11)
14	40	M	D	124	192	91	73	(-20)	98	90	(-8)
15	38	F	D	155	175	96	94	(-2)	91	95	(4)
16	58	M	D	156	166	56	40	(-29)	52	58	(12)
17	63	M	T	218	237	70	77	(10)	69	81	(-17)
18	76	M	T	210	196	90	82	(-9)	95	97	(2)
19	32	M	T	124	141	91	91	(0)	74	85	(15)
20	66	M	T	215	206	70	72	(3)	97	96	(-1)
mean	54.9			186.2	188.4	75.5	74.2		79.7	83.3	
SD	11.2			47.0	44.1	12.6	15.8		15.5	11.1	

Abbreviations: CAD = coronary artery disease, M = minimal change, S = single vessel disease, D = double vessel disease, T = triple vessel disease

TABLE IV PLATELET AGGREGATION STUDIES AT REST AND AFTER TREADMILL EXERCISE TEST IN PATIENTS WITH UNSTABLE ANGINA PECTORIS (GROUP A2)

No. of Patients	Age	Sex	CAD	Platelet counts ($\times 1,000/\text{mm}^3$)		ADP ($1 \mu\text{M}$)			Collagen ($1 \mu\text{g/ml}$)		
				At Rest	After Exercise	At Rest	After Exercise	% Change	At Rest	After Exercise	% Change
1	60	F	M	345	301	59	85	(44)	70	88	(26)
2	60	M	S	243	205	18	75	(317)	76	84	(11)
3	50	M	S	197	198	39	55	(41)	26	67	(158)
4	65	F	S	112	92	37	30	(-19)	53	40	(-25)
5	44	F	S	101	155	48	82	(71)	68	77	(13)
6	53	M	D	208	238	35	70	(100)	10	74	(640)
7	62	M	D	235	179	48	99	(106)	41	74	(80)
8	51	F	D	220	220	73	90	(23)	77	79	(3)
9	58	F	T	228	238	68	90	(32)	75	75	(0)
10	48	M	T	206	191	62	94	(52)	81	83	(2)
11	50	M	T	330	318	83	97	(17)	87	74	(-15)
12	38	M	T	196	200	15	50	(233)	23	75	(226)
mean	53.3			218.4	211.3	48.8	76.4		57.3	74.2	
SD	7.6			68.2	57.8	20.2	20.6		24.9	11.6	

Abbreviations are the same as in Table III.

TABLE V PLATELET AGGREGATION STUDIES AT REST AND AFTER TREADMILL EXERCISE TEST IN PATIENTS WITH VARIANT FORM OF ANGINA PECTORIS (GROUP A3)

No. of Patients	Age	Sex	CAD	Platelet counts ($\times 1,000/\text{mm}^3$)		ADP (1 μM)			Collagen (1 $\mu\text{g}/\text{ml}$)		
				At Rest	After Exercise	At Rest	After Exercise	% Change	At Rest	After Exercise	% Change
1	52	M	S	150	159	55	65	(18)	89	50	(-44)
2	62	M	D	229	226	57	67	(17)	71	84	(18)
3	76	M	D	240	298	63	65	(3)	71	71	(0)
4	36	M	M	214	225	76	81	(7)	75	86	(15)
mean	56.5			208.3	227.0	62.8	69.5		76.5	72.8	
SD	14.6			34.9	49.2	8.2	6.7		7.4	14.3	

Abbreviations are the same as in Table III.

Fig.1. Incidence of abnormal response of ADP-induced platelet aggregation to exercise.

Abbreviations: A1 = stable angina pectoris, A2 = unstable angina pectoris. Statistically significant difference was present between stable and unstable angina ($\chi^2 = 18.75$, $p < 0.005$).

$\pm 15.5\%$ respectively. Mean platelet count was $186,000 \pm 47,000/\text{mm}^3$. No significant difference was found as compared to those of the control group. On the other hand, in group A2 mean ADP- and collagen-induced platelet aggregations at rest were 48.8 ± 20.2 and $57.3 \pm 24.9\%$ respectively. Mean platelet count was $218,000 \pm 68,000/\text{mm}^3$. ADP- and collagen-induced platelet aggregations were significantly lower than those of group A1, and even than those of the control group. In group A3, ADP-induced aggregation at rest showed a tendency to decline below the normal range (Table V).

Platelet Aggregation Response to Exercise

In group A1, ADP- and collagen-induced platelet aggregations did not respond significantly to exercise in most cases. In group A2, on the contrary, aggregation was significantly accelerated by exercise (Fig. 1). In group A3, platelet aggregation was between groups A1 and A2.

In group A2, 92% of the patients exhibited an abnormal hyperresponsiveness to exercise. On the other hand, only 11% exhibited an abnormal hyperresponsiveness in group A1.

Platelet Aggregation with Reference to the Severity of Coronary Arterial Lesions

In group A1, ADP-induced platelet aggregation at rest was $77.6 \pm 12.3\%$ in patients with minimal changes on a coronary arteriogram, 69.4 ± 10.1 in single vessel disease, 78.2 ± 14.2 in double vessel disease and 80.3 ± 10.3 in triple vessel disease (Table VI). Thus, ADP-induced platelet aggregation at rest was accelerated in accordance with an increase in the number of the coronary arteries involved. However, in the case of collagen-induced platelet aggregation such a tendency was not apparent. In group A2, ADP-induced platelet aggregation was also accelerated in accordance with an increase in the number of the coronary arteries involved (Table VII). No significant correlation was found in group A3.

DISCUSSION

Method for Evaluating Platelet Aggregation

Platelet aggregation has been evaluated by various devices such as the optical density method^{4,5} the filtration pressure method⁶ and the quantitative detection method of platelet aggregates in circulating blood.⁷ Each method has its merits and demerits respectively for analysing the platelet function. In the present investigation we measured the maximum platelet aggregation using the optical density method because of its reasonably established reproducibility, sensitivity and manageability.

It is also claimed that platelet aggregation is

TABLE VI PLATELET AGGREGATION STUDIES IN STABLE ANGINA PECTORIS WITH REFERENCE TO CORONARY ARTERIOGRAM (GROUP A1)

		ADP (1 μ M)		Collagen (1 μ g/ml)	
		At Rest	After Exercise	At Rest	After Exercise
Minimal Change	Mean	77.6	82.3	81.3	76.3
	$\pm$ SD	12.3	8.1	6.0	8.3
SVD	Mean	69.4	62.7	78.9	85.4
	$\pm$ SD	10.1	13.7	18.8	10.1
DVD	Mean	78.2	75.0	76.2	80.8
	$\pm$ SD	14.2	18.9	16.9	12.9
TVD	Mean	80.3	80.5	83.8	89.8
	$\pm$ SD	10.3	7.0	12.4	6.9
Total Cases	Mean	75.5	74.2	79.7	83.3
	$\pm$ SD	12.6	15.8	15.5	11.1

Abbreviations: SVD = single vessel disease, DVD = double vessel disease, TVD = triple vessel disease

TABLE VII PLATELET AGGREGATION STUDIES IN UNSTABLE ANGINA PECTORIS WITH REFERENCE TO CORONARY ARTERIOGRAM (GROUP A2)

		ADP (1 μ M)		Collagen (1 μ g/ml)	
		At Rest	After Exercise	At Rest	After Exercise
Minimal Change	Mean	59	85	70	88
	$\pm$ SD				
SVD	Mean	31.3	53.3	49.7	63.7
	$\pm$ SD	9.5	18.4	22.9	18.1
DVD	Mean	52.0	86.3	42.7	75.7
	$\pm$ SD	15.8	12.1	27.4	2.4
TVD	Mean	57.0	82.8	66.5	76.8
	$\pm$ SD	25.4	19.1	25.5	3.6
Total Cases	Mean	48.8	76.4	57.3	74.2
	$\pm$ SD	20.2	20.6	24.9	11.6

Abbreviations are the same as in Table VI.

markedly affected by the various conditions for estimation.^{8,9} In this study we measured all platelet aggregation 60 to 75 min after blood withdrawal with a stirring speed of 800 rpm, making the final concentrations of 1 μ M of ADP and 1 μ g/ml of collagen, respectively.

Concentration of ADP for Platelet Aggregation

Although most investigators have used high concentration of ADP (2–5 μ M),^{1,8} we adopted a final concentration of 1 μ M of ADP and could observe characteristic findings on platelet aggregation in patients with stable and unstable angina pectoris, like Mehta et al.¹⁰ Nagakawa⁸ claimed that the most suitable concentration of ADP for analyzing platelet aggregation in patients with ischemic heart disease was 2 μ M. However, in

our experience, there were no significant differences between 1 μ M ADP and 2 μ M ADP. This will be reported elsewhere.

Platelet Aggregation during Resting Condition

In the present study platelet aggregation at rest in patients with stable angina was not enhanced significantly. However, enhanced platelet aggregation has been described in some reports. For example, Frishman et al.¹ found significantly increased ADP-induced platelet aggregation at rest in patients with stable angina pectoris, while Steel et al.² did not find it. The latter was partially in accordance with our present result in patients with stable angina pectoris.

On the other hand, our results showed that platelet aggregation was lower in the unstable

angina group at rest than in the control group. Mehta et al.³ found that platelet aggregation in coronary venous blood in patients with coronary artery disease was significantly lower than that in the control group at rest and they postulated that the consumption or destruction of platelet might have occurred within the atherosclerotic coronary vasculature. This may support our finding.

Platelet Aggregation Response to Exercise

In the present study it was considered that a 15 percentile increase or more comparative platelet aggregation at rest was an abnormal hyperresponsiveness and an increase less than 15% or a decrease was a normal responsiveness. It was suggested that decrease in platelet aggregation after exercise was produced by the superior action of prostacyclin to that of thromboxane A_2 and these conditions were desirable to prevent an ensuing thrombi formation, which will be discussed in detail later.

In the present study no significant change of platelet aggregation was observed after treadmill exercise in stable angina pectoris and exercise enhanced platelet aggregation was demonstrated only in unstable angina pectoris. Frishman et al.¹¹ have reported no significant change after treadmill exercise, which supports our finding in stable angina pectoris, except for their higher values at rest than ours in which the values were within normal range. Yamazaki et al.¹² have reported that exercise (Master's test) enhanced ADP-induced platelet aggregation in all patients with angina pectoris but not in the normal control group, although they did not refer to the type of angina pectoris.

Some difference in platelet aggregation between patients with angina pectoris and those with myocardial infarction was found in our previous studies. In contrast, Levites and Haft¹³ found significantly higher platelet aggregation after exercise (double Master's two-step-test) in patients with stable angina pectoris and old myocardial infarction. However, our data indicated that platelet aggregation in patients with angina pectoris and myocardial infarction should be regarded separately.

Our significantly lower values in the unstable angina group than in the control group may be explained by a platelet consumption. Mehta et al.¹⁰ investigated the platelet aggregation in coronary artery disease during tachycardia stress induced by atrial pacing and found that platelet

aggregation appeared to increase during tachycardia stress and that platelet counts were lower in the coronary sinus blood sample than in the aortic one. Our data may be compatible with theirs, although a decrease of platelet count in the peripheral blood was not significant.

Type of Angina Pectoris and Platelet Aggregation

Our study showed that the variance in platelet aggregation was evident in patients with angina pectoris, namely in patients with unstable angina it was significantly accelerated after exercise. Recently thromboxane A_2 , which is a strong coronary vasoconstrictor and enhances platelet aggregation, has been noted in regards to the mechanism of myocardial ischemia.¹⁴ Lewy et al.¹⁵ found thromboxane B_2 , a metabolite of A_2 , increased by approximately 200% in coronary sinus and 130% in coronary artery immediately after pacing. They have postulated that thromboxane A_2 can play some role in responding to regional myocardial ischemia. On the other hand, Mehta et al.¹⁶ found that platelets in angina pectoris were significantly less sensitive to prostacyclin's antiaggregatory effects than those in the control subjects. A disturbed balance between vascular prostacyclin synthesis and platelet thromboxane A_2 production may be related to vasoconstriction and enhanced platelet aggregation, resulting in the syndrome of myocardial ischemia in some patients. The present data suggests that this balance is not disturbed in patients with stable angina but disturbed in patients with unstable angina pectoris.

Relation of Platelet Aggregation to Coronary Pathoanatomy

The present data indicates that in patients with angina pectoris, except for the variant form, platelet aggregation at rest was accelerated in accordance with an increase in the number of coronary arteries involved, in which a more than 50% narrowing of the lumen was regarded as a significant obstruction. Steele et al.², however, found an abnormally shortened platelet survival time in 11 out of 21 patients, but it did not significantly correlate to the site and number of coronary atherosclerosis.

The variant form of angina pectoris in the present series lacked such a relationship and may be related to coronary spasm^{17,18} which has been considered one of the causes of myocardial ischemia.

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