Clin. Cardiol. 5, 269 274 (1982)

Original Articles

Assessment of Diagnostic Value of Dipyridamole Testing in Angina Pectoris

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Summary: In order to assess the diagnostic value of dipyridamole (D) testing, we studied the responses of 34 patients with chest pain and 10 normal subjects. Blood pressure and 12-lead ECG were recorded during and after intravenous infusion of 0.6 mg/kg dipyridamole for 10 minutes. Coronary arteriography and maximal or symptom-limited exercise tests were performed in the 34 patients with chest pain. During infusion 13 patients presented ischemic ST changes and 5 with anginal pain only. The latter group had normal coronary arteries. Among the 13 patients with ischemic ST changes, 7 had at least two critical coronary stenoses and the remaining 6 had no coronary lesions. Dipyridamole tests showed poor sensitivity (44%) and specificity (39%) with respect to coronary arteriography. The relatively high number of positive responses in subjects with normal coronary arteries indicates that the coronary steal phenomenon is not the sole cause of "ischemic" response to the drug. Indirect indexes of myocardial oxygen consumption were higher in patients with a positive response to drug infusion than in those with a negative response; however the value of rate-pressure product at infusion end never reached that observed at ischemic threshold during exercise testing in the same patient. This suggests that neither can oxygen consumption increase be considered as entirely responsible for ischemic response to dipyridamole. In conclusion dipyridamole test cannot be proposed for predicting critical coronary stenoses.

Key words: Angina pectoris, dipyridamole test, exercise test

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Received: July 31, 1981
Accepted with revision: January 26, 1982

Introduction

Recent studies have reported that intravenous administration of dipyridamole provokes anginal pain with or without ischemic electrocardiographic changes in patients suffering from angina pectoris (Albro *et al.*, 1978; DeAmbroggi *et al.*, 1978; Slany *et al.*, 1977; Tauchert *et al.*, 1976; Tavazzi *et al.*, 1977). Therefore, the infusion of dipyridamole has been proposed as a diagnostic test in angina pectoris. However, the mechanism by which the drug may produce electrocardiographic changes and anginal pain is still not clearly understood (Afonso *et al.*, 1967; DePonti *et al.*, 1971; Famm *et al.*, 1968; Gould *et al.*, 1978; Hamilton *et al.*, 1972; Weiss *et al.*, 1972; Winbury *et al.*, 1970). The purpose of our investigation was to establish the diagnostic value of dipyridamole testing compared with the response to exercise testing and coronary angiography in patients with angina pectoris.

Methods

Thirty-four patients with chest pain, 17 males and 17 females, between 34 and 72 years (mean age 47.7±7.2

TABLE I Patient characteristics

Case	Age (years)	Sex	D Test	CCA	EX
1	42	M	+	+	+
2	41	M	+	+	+
3	46	M	+	+	+
4	43	M	+	+	+
5	37	F	+	+	+
6	40	F	+	+	+
7	58	F	+	+	−
8	56	F	+	−	+
9	50	F	+	−	A
10	34	M	+	−	+
11	44	F	+	−	+
12	48	M	+	−	+
13	53	F	+	−	+
14	52	F	A	−	+
15	53	F	A	−	+
16	63	F	A	−	A
17	37	F	A	−	+
18	53	F	A	−	+
19	51	M	−	+	+
20	39	M	−	+	+
21	48	M	−	+	+
22	47	F	−	+	+
23	55	M	−	+	+
24	55	M	−	+	+
25	43	F	−	+	A
26	34	M	−	+	−
27	44	M	−	+	−
28	52	M	−	±	+
29	50	M	−	±	+
30	52	F	−	±	+
31	48	F	−	±	−
32	57	F	−	−	+
33	56	M	−	−	+
34	43	M	−	−	−

Abbreviations: CCA = cine coronary angiography (+ = one or more coronary stenosis ≥75%; ± = one or more coronary stenosis <75%; − = normal coronary arteries); D test = dipyridamole test (+ = ST depression ≥0.1 mV; A = anginal pain without ischemic ST changes; − = negative test,; Ex = exercise text (+ = ischemic ST depression ≥0.1 mV; A = anginal pain without ischemic ST changes; − = negative test)

years) were studied (Table I). Effort angina was the presenting symptom in 7 patients, 11 had chest pain only at rest, and 16 patients had both rest and effort anginal pain. No medication other than nitroglycerin was administered during the week preceding the test.

Coronary arteriography was performed with the Sones technique: 35-mm cineangiograms were obtained at 40 frames/s in multiple views. Left ventriculography was also performed in the 30° right oblique projection. An M-mode echocardiogram was carried out with an Echoline 20 Smith and Kline instrument.

All the patients performed maximal or symptom-limited exercise tests in the supine position. The 12-lead ECG and blood pressure (BP) were recorded at rest, throughout the exercise, and during the recovery period. The dipyridamole test was performed by administration of 0.5–0.6 mg/kg of the drug intravenously over a period of 10 minutes. The 12-lead ECG and blood pressure were recorded in basal conditions, during the 10-minute infusion, and for at least 30 minutes after the end of infusion. Ischemic ST changes were defined as horizontal or downsloping ST depressions ≥0.1 mV.

Blood pressure was measured by a mercury sphygmomanometer.

A maximal exercise test and dipyridamole test were performed in a control group of 10 asymptomatic healthy males, aged 25 to 40 years, using the same protocol.

All studies were performed after at least a 10-hour period of abstinence from beverages or medications containing xanthine derivatives.

Informed consent was obtained from each patient and healthy volunteer.

Statistical analysis was made using the Student's *t* test for paired and unpaired data.

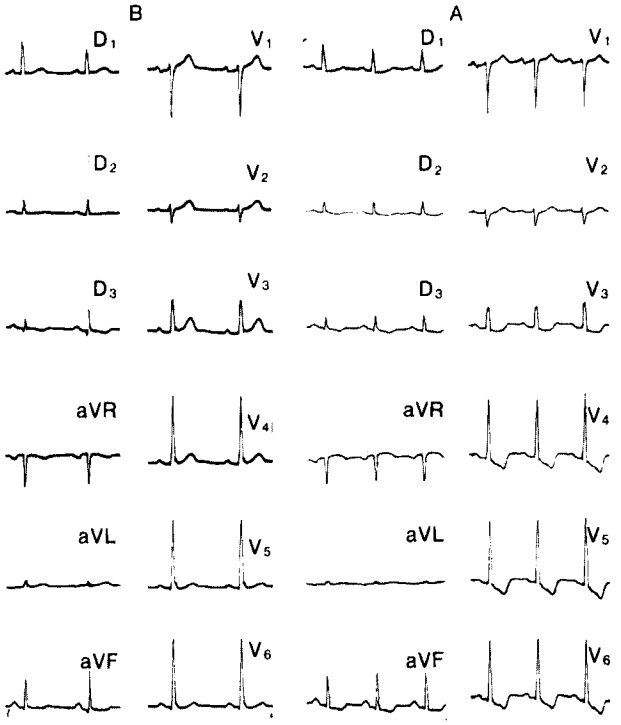

FIG. 1 Case No. 3 with effort angina and critical coronary stenosis. 12-lead ECG recorded before (B) and after (A) i.v. infusion of dipyridamole. Ischemic changes are evident on precordial leads.

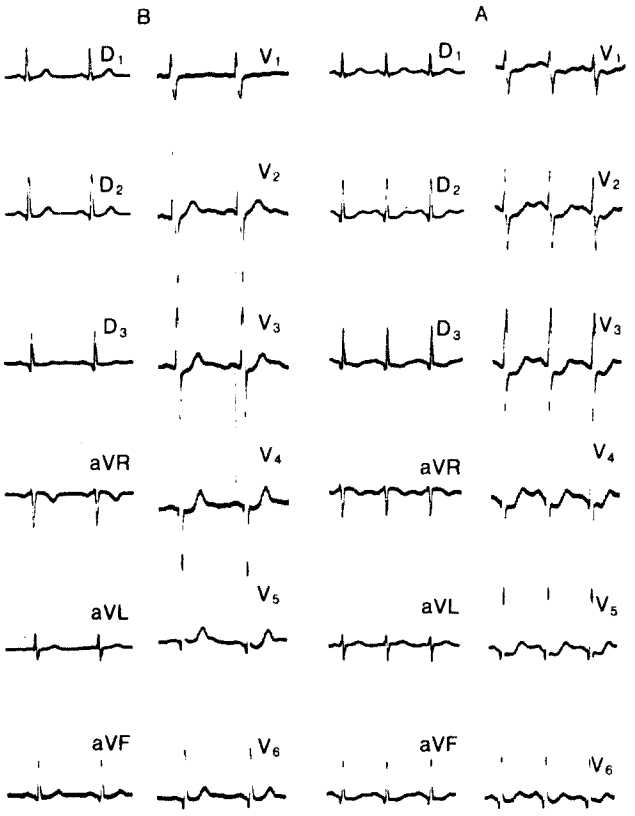

FIG. 2 Case No. 10 with spontaneous angina and normal coronary arteries. 12-lead ECG recorded before (B) and after (A) i.v. infusion of dipyridamole.

Results

Dipyridamole tests were positive in 18 patients. Ischemic ST depressions with chest pain were observed in 13 patients (Figs. 1 and 2), chest pain only in 5 (Table I). Anginal pain was always similar to previous attacks. Moreover in each case theophylline administration induced a regression of pain, as previously reported (Tauchert *et al.*, 1976).

Sixteen subjects had one or more coronary stenoses ≥75%, 4 had no critical abnormalities, while 14 had normal coronary arteries (Table I). Angiographic evidence of spontaneous coronary spasm was obtained in 2 patients, one of them had critical coronary stenoses.

On the basis of coronary arteriograms, 7 of the patients with a positive dipyridamole test were true positives (D+C+), while 11 were false positives (D+C−) (Table II). All 5 patients with chest pain belonged to the latter group. Nine patients had a false negative response to the test (D−C+), and 7 patients were true negatives (D−C−). The 2 patients with coronary spasm had negative responses.

Exercise induced ischemic ST changes in 26 patients and anginal pain alone in 3 (Table I). A positive response to exercise testing was observed in 6 of the 7 D+C+ subjects, in all the D+C− subjects, in 7 D−C+, and in 5 D−C− (Table II).

Control subjects showed negative responses to both exercise and dypyridamole tests.

During infusion hemodynamic changes were studied in symptomatic patients and in the control group. Basal

TABLE II Comparison between the results of dipyridamole testing, (D), exercise testing (E), and coronary angiography (C)

D testing	Subjects with coronary artery stenosis ≥75%	Subjects with coronary artery stenosis <75% or normal coronary arteries
Subjects with ischemic ST depression >0.1 mV or anginal pain without ECG abnormalities	E+6 (7) E−1	E+11 (11) E−0
Subjects with negative dypyridamole test	E+7 (9) E−2	E+5 (7) E−2

E+ = subjects with ischemic ST depression 0.1 mV or anginal pain without ECT abnormalities; E− = negative exercise test
Number in parentheses indicate number of subjects

TABLE III Mean values ± standard deviations of data before (B) and after (A) dipyridamole infusion in normal subjects (N), in patients with positive (D+), and negative (D−) response to the test

		N	D+	D−	D+ vs D−	N vs D+	N vs D−
Heart rate (min^{-1})	B	76.5±6.5	74.5±11.5	73.1±9.9	n.s.	n.s.	n.s.
		p<0.01	p<0.0005	p<0.0005			
	A	94.9±10.4	107.3±13.3	89.4±11.8	p<0.0005	p<0.01	n.s.
Systolic blood pressure (mmHg)	B	120.0±11.1	125.5±13.6	127.4±15.1	n. s.	n.s.	n.s.
		p<0.01	p<0.0025	p<0.0025			
	A	114.5±11.4	117.9±12.1	119.0±15.2	n.s.	n.s.	n.s.
Diastolic blood pressure (mmHg)	B	74.0±8.4	82.9±9.8	80.6±7.7	n.s.	p<0.0125	p<0.025
		p<0.01	p<0.0025	p<0.0025			
	A	69.0±5.7	78.2±9.5	75.3±5.4	n.s.	p<0.005	p<0.005
Heart rate × systolic blood pressure[a]	B	9.20±1.29	8.77±2.47	8.70±1.61	n.s.	n.s.	n.s.
		p<0.0025	p<0.0005	p<0.005			
	A	10.91±1.92	13.41±2.81	11.34±2.9	p<0.02	p<0.05	n.s.

[a] Product of heart rate × systolic blood pressure × 10^{-3} (mmHg/min)
n.s.: not significant.

average values and respective changes of the considered parameters during dipyridamole infusion are shown in Table III. Among the groups heart rate (HR) was not significantly different in basal conditions, while a significant increase at the end of infusion was observed. The increase in heart rate was significantly greater in D+ than in D−, and in normal subjects.

No significant blood pressure differences were found between D+ and D− responses, either before or after infusion. Systolic and diastolic blood pressures at infusion end were significantly lower than basal values in symptomatic patients. In the control group a significant decrease in systolic and diastolic pressures was also observed, but diastolic pressure values were significantly lower than in symptomatic patients both before and after infusion.

Rate-pressure product after dipyridamole infusion has been compared with that reached at the end of exercise test in the same patients. The value of this parameter was greater after exercise than after infusion in all but one patient (Fig. 3).

Discussion

Some authors (Slany *et al.*, 1977; Tauchert *et al.*, 1976) have reported a very high sensitivity of dipyridamole testing in groups consisting only of patients with critical coronary stenoses. In order to assess the diagnostic value (specificity and sensitivity) of this method, and particularly to evaluate the response to infusion in patients with false positive exercise test, a relatively large number of patients with normal coronary arteries and positive response to exercise test were studied.

In our investigation dipyridamole testing has shown poor sensitivity (44%) and specificity (39%) with respect to coronary arteriography. All the patients with false positive response to dipyridamole infusion had a false positive response to exercise test. They exhibited some hemodynamic and morphological patterns suggesting a hyperkinetic condition. They showed at cardiac catheterization ventricular maximal dP/dt higher than that found in the other patients (2198±83 mmHg/s vs. 1707±54; p<0.05), and had a higher fractional shortening at echocardiographic examination (34.2%±4.1 vs. 30.5%±4.5; p<0.05). Moreover, false positive subjects showed some other characteristic patterns at angiographic examination: "corkscrew" coronary vessels (Natarajan *et al.*, 1975) were seen in 6 of 11 D+C− patients while this pattern was seen in only one D−C−, and in no C+ subjects; mild increase of left ventricular

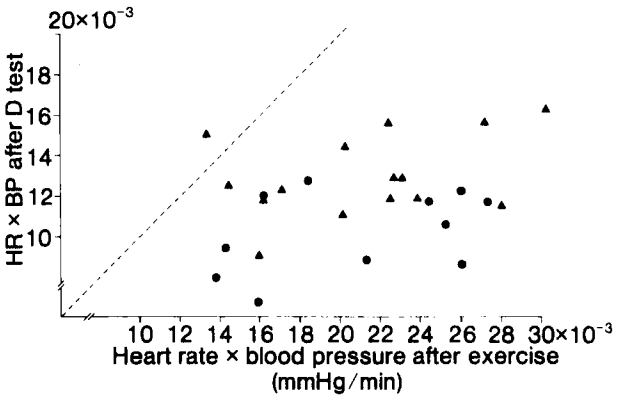

FIG. 3 Relationship between rate-pressure product after infusion of dipyridamole (ordinate) and at peak exercise (abscissa). ▲, patients with positive response to dipyridamole. ●, patients with negative response to dipyridamole. In all except one of the cases the rate-pressure product was higher at ischemic threshold of exercise than at the end of dipyridamole infusion.

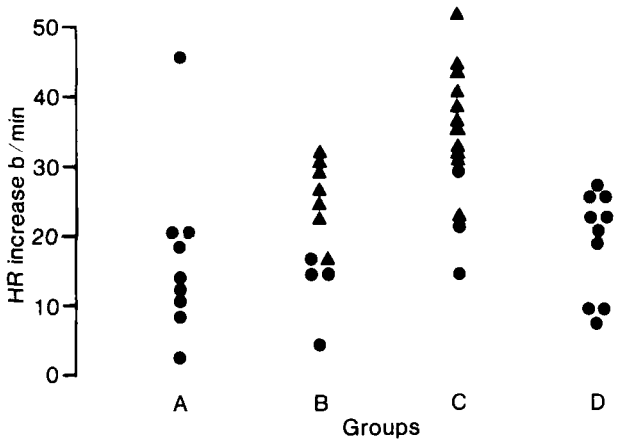

FIG. 4 Heart rate increase (beats/min) after infusion in the following groups: (A) patients with a single critical coronary stenosis (≥75%) or minor abnormalities of the coronary tree; (B) patients with two or more critical coronary stenoses; (C) patients with normal coronary arteries; (D) control subjects. ●, subjects with negative response to dipyridamole; ▲, patients with positive response to dipyridamole.

wall thickness and/or hypertrophy of papillary muscles were found in 6 of 11 D+C−, in only one D−C−, and in no C+ subjects.

Most authors (Albro *et al.*, 1978; De Ambroggi *et al.*, 1978; Gould *et al.*, 1978; Slany *et al.*, 1977; Tauchert *et al.*, 1976; Tavazzi *et al.*, 1977) proposed "coronary steal" as the cause of angina and/or ischemic changes induced by dipyridamole.

However, our results seem to exclude coronary steal as the only cause of the ischemic response because of the relatively high number of positive responses in subjects with normal coronary arteries, and of negative responses in subjects with critical coronary stenoses (Table II).

An increase of myocardial O_2 consumption could also be thought to be the cause of positive responses. In fact, the HR × BP product as an index of myocardial O_2 consumption significantly increased after D infusion in all groups. Moreover, it was slightly but significantly higher in D+ than in D− subjects (Table III). However the rate-pressure product during infusion never reached the value observed at ischemic threshold during exercise test in the same patient (Fig. 3): this suggests that O_2 consumption increase cannot completely explain positive responses. Therefore, an association of the two factors, O_2 consumption increase and the extent of coronary stenosis, is probably involved in determining the ischemic response. The patients with coronary lesions who had positive response to the test had a greater heart rate increase than the other subjects with coronary stenoses, and had at least two vessels involved (Fig. 4). Patients with a single coronary stenosis always exhibited negative response to dipyridamole testing; in these cases an improvement of collateral circulation due to dipyridamole may be supposed on the basis of some experimental data (Becker *et al.*, 1978). The highest heart rate increase was found in D+C− subjects.

In order to explain ischemic ST changes after infusion in subjects without coronary stenoses, it could be suggested that dipyridamole increases myocardial sensitivity to catecholamines (Dai Hyon *et al.*, 1969; Hamilton *et al.*, 1972; Stafford *et al.*, 1966; Weiss *et al.*, 1976), or that the drug induces an "intramural blood steal" from subendocardium to subepicardium in subjects who may have a reduced myocardial compliance.

Conclusions

Dipyridamole testing has been shown to have poor diagnostic value in predicting the presence of critical coronary stenoses. In fact, in this study, we observed not only a high number of false negative responses, but also a high number of false positive responses.

In patients with coronary disease, "coronary flow steal" cannot be the only mechanism to explain chest pain and ST changes. Other factors might play a role in determining a positive response to the drug, namely an increase of O_2 consumption, an enhancement of intracellular effects of catecholamines or a reflex increase of their release.

Finally, the possibility that dipyridamole may induce myocardial ischemia should discourage its intravenous therapeutic use in ischemic heart disease.

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