
Safety of Dipyridamole-Thallium Imaging in High Risk Patients with Known or Suspected Coronary Artery Disease

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The effects of an oral dipyridamole suspension were studied in 400 consecutive patients to determine if certain subsets of patients were at greater risk of suffering major complications. Most patients (69%) experienced at least one side effect. Severe chest pain, severe hypotension, and severe dyspnea occurred in 9%, 2.5%, and 0.3% of patients respectively. Two patients were hospitalized for persistent chest pain but none suffered a myocardial infarction, malignant ventricular arrhythmia, or death. The test was found to be safe for patients over 70 yr old. Severe dyspnea was rare even among patients with lung disease who were withdrawn from theophylline prior to testing. Patients with three-vessel coronary artery disease were more likely to experience severe chest pain and those with significant left ventricular dysfunction were more likely to develop severe hypotension. In 99.5% of patients, side effects were promptly reversed by aminophylline. Dipyridamole-thallium imaging has an acceptable safety profile for a wide variety of patients, including those with severe coronary disease and/or left ventricular dysfunction.

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Dipyridamole-²⁰¹Tl imaging has been successfully utilized to evaluate patients with known or suspected coronary artery disease. Its major advantage is that patients are not required to exercise. Dipyridamole is a potent coronary vasodilator which maximizes regional differences in myocardial perfusion (1). The diagnostic accuracy of dipyridamole-thallium imaging has been shown to be equal to that of exercise-thallium imaging in the detection of coronary artery disease (2,3,16). It is also useful in assessing prognosis in patients prior to vascular surgery (4-6), renal transplantation (7), and general surgery (8), and to stratify risk in patients following myocardial infarction (9) and percutaneous transluminal coronary angioplasty (10).

Dipyridamole is widely available in both oral and intra-

venous forms. Oral dipyridamole doses ranging from 200 to 400 mg can produce perfusion defects comparable to those induced by intravenous dipyridamole (11).

Several studies have examined the safety and diagnostic accuracy of dipyridamole-thallium imaging in patients with suspected coronary artery disease (10-15,19,20,23). However, its potential deleterious effects on certain patients who may be at greater risk has not been examined in a large population. Elderly patients (over 70 yr) might be expected to experience more frequent or severe side effects. Because dipyridamole has the potential for causing bronchospasm, patients with chronic obstructive pulmonary disease, especially those withdrawn from theophylline for the purpose of testing, have been considered unsuitable for the dipyridamole-thallium procedure. Finally, patients with severe coronary disease and/or severe left ventricular dysfunction might be expected to suffer more serious complications than others. The purpose of this study was to determine whether concerns about these particular subsets of patients were justified, i.e., are there patients for whom dipyridamole-thallium scintigraphy is contraindicated?

METHODS

Patient Population

The study population consisted of 400 consecutive patients referred for dipyridamole-thallium imaging at the Palo Alto Veterans Administration Hospital between September 1986 and August 1989. There were 384 men and 16 women with a mean age of 64 yr (range 33 to 83). The clinical characteristics of these patients are shown in Table 1. No patient had a history of unstable angina or myocardial infarction within 1 wk of the time of the study.

Dipyridamole Protocol

All tests were performed in the morning after an overnight fast. Patients were prohibited from consuming caffeinated beverages in the 24 hr prior to testing. Patients taking theophylline refrained from taking it for at least 48 hr prior to testing. None of the latter patients had pulmonary symptoms prior to the administration of dipyridamole.

Tablets of dipyridamole were crushed and suspended in 30 cc of raspberry syrup. The first 165 patients received 300 mg of this oral suspension; the remaining 235 patients received 375 mg.

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TABLE 1
Clinical Characteristics of 400 Consecutive Patients
Referred for Dipyridamole-Thallium Imaging

	Number (%)
Male	384 (96)
Age \geq 70 yr	101 (25)
History of COPD	69 (17)
On theophylline	32 (8)
History of MI	123 (31)
History of hypertension	152 (38)
s/p CABG	74 (19)
s/p PTCA	9 (2)

CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; s/p = status post.

Supine blood pressure, pulse, and electrocardiogram were recorded at baseline and every 15 min following administration of dipyridamole. Three millicuries of ^{201}Tl -chloride were injected intravenously 45 min later, unless severe symptoms or hypotension developed, in which case thallium was injected earlier. All patients were given 100 mg of intravenous aminophylline to reverse the effect of dipyridamole. In the case of severe symptoms or hypotension, aminophylline was infused 5 min after thallium administration; otherwise it was routinely given after the initial images were acquired. Imaging was begun 5 to 15 min after thallium injection. Patients returned 3 to 4 hr later for repeat imaging.

Scintigraphic Data Collection and Analysis

Planar or tomographic images were acquired and processed using commercially available software. Studies were read by one experienced observer who was not always blinded to the clinical history or angiographic report.

Cardiac Catheterization

Selective coronary arteriography and left ventriculography were performed by the Judkins technique. A vessel was considered to have significant obstruction if its diameter was narrowed by 70% or more with respect to the prestenotic segment. Interpretation of angiograms and left ventriculograms were made by a team of independent observers. Results of dipyridamole-thallium were available to the patient's physicians prior to catheterization.

One hundred eleven patients underwent coronary angiography within one yr of dipyridamole-thallium imaging. Twenty-three patients had no significant coronary artery disease. Three patients had left main coronary disease, 25 had single-vessel, 17 had double-vessel, and 18 had triple-vessel disease. Twenty-five patients had prior coronary bypass graft surgery and were excluded from calculations of sensitivity and specificity. Among the 86 patients who had angiography but did not have prior bypass surgery, 45 received 300 mg of dipyridamole and 41 received 375 mg; 57 had planar thallium scintigraphy, and 29 had SPECT-thallium imaging.

Patients who underwent left ventriculography were classified as follows: abnormal left ventricular function if any myocardial segment was contracting abnormally (hypokinetic, akinetic, or dyskinetic); mild dysfunction if only one myocardial segment was contracting abnormally; severe dysfunction if multiple severe

wall motion abnormalities or global hypokinesis of the entire left ventricle were present; moderate dysfunction if left ventricular function was abnormal and did not meet the above criteria for either mild or moderate categories, or, if one large myocardial segment was severely hypokinetic. In 95 patients (with or without prior bypass surgery), the results of left ventricular angiography were reported.

Statistical Methods

Frequency data were compared using chi-square analysis. Student's unpaired t-test was used to compare continuous variables. Results of continuous variables are expressed as mean \pm standard deviation. P values $<$ 0.05 were considered significant.

RESULTS

Hemodynamic Response to Dipyridamole

Systolic blood pressure fell by 13 ± 14 mmHg and heart rate increased by 11 ± 9 bpm. Severe hypotension, defined as a minimum systolic blood pressure less than 90 mmHg, occurred in 10 patients (2.5%). The minimum systolic blood pressure was between 60 and 70 mmHg in two patients, between 70 and 80 mmHg in three patients, and between 80 and 90 mmHg in five patients. Three of the ten patients with severe hypotension had chest pain, six had mild noncardiac symptoms, and three were asymptomatic. None had dizziness or presyncope. Four of these received early administration of aminophylline, two because of severe chest pain and two because of low blood pressure (not associated with symptoms).

There were 108 patients whose systolic blood pressure fell by 20 mmHg or more after dipyridamole. However, their mean minimum systolic blood pressure was 117 mmHg. Forty-seven patients had a fall of systolic blood pressure of 30 mmHg or more after dipyridamole. The mean minimum systolic blood pressure of these patients was 116 mmHg.

Adverse Effects of Dipyridamole

Table 2 presents the untoward effects experienced by patients during testing. The majority of patients (69%) experienced at least 1 side effect. Most patients had multiple side effects. Fifty-three (14%) received early administration of aminophylline because of severe symptoms ($n = 51$) or severe hypotension ($n = 2$). The reasons for early infusion of aminophylline are also shown in Table 2.

Cardiac Side Effects of Dipyridamole

As shown in Table 2, 122 patients (31%) complained of chest pain during the test. Of these, 35 had severe chest pain (9%) requiring early administration of intravenous aminophylline and, in some patients, sublingual nitroglycerine. Chest pain was completely relieved within 15 min in all but one patient who was admitted to the hospital and subsequently showed no evidence of myocardial infarction. Symptoms began to improve 2 to 5 min after the aminophylline infusion began.

The incidence of mild and severe chest pain was examined in three groups of patients with different thallium

TABLE 2
Adverse Effects of Dipyridamole*

	Number (%)	No. requiring early	
		Intravenous aminophylline	
Any side effect	275 (69)	53	
Chest pain	122 (30)	37	
Mild [†]	85 (21)		
Severe [‡]	37 (9)		
Any noncardiac	160 (40)	14	
Headache	79 (20)	4	
Nausea	36 (9)	7	
Dizziness	34 (9)	0	
Pain, not chest	28 (7)	0	
Dyspnea	15 (4)	1	
Vomiting	5 (1)	2	
Wheezing	0 (0)	0	
Syncope	0 (0)	0	
Other	18 (5)	0	
Severe hypotension [§]	10 (3)	2	

* 300 mg or 375 mg.

[†] Not requiring early administration of intravenous aminophylline.

[‡] Requiring early administration of aminophylline.

[§] Minimum systolic blood pressure less than 90 mmHg.

Note: Percentages do not sum to 100% because many patients had more than one side effect.

scanning results (see Table 7): (1) no thallium defects, i.e., a normal scan (n = 105), (2) fixed defects only, i.e., no redistribution of thallium on repeat imaging (n = 73), and (3) reversible defects (with or without coexistent fixed defects). Mild chest pain was fairly common and equally prevalent in all three groups. Severe chest pain was rare among patients with normal thallium scans or with fixed defects (1% and 3% respectively) and significantly more common in patients with reversible thallium defects (16%, p = 0.003).

Significant ST-segment depression (horizontal or down-sloping and greater than 1 mm at J + 80 msec) developed in 47 patients (12%). Patients who experienced severe chest pain were more likely to have ST segment depression following dipyridamole than patients who had mild chest pain (Fig. 1). There was no significant differences in the incidence of ST depression between patients without any chest pain and those with mild chest pain. No patient experienced malignant ventricular arrhythmias (ventricular tachycardia or fibrillation). There were no myocardial infarctions or deaths.

Two patients were admitted to the hospital following the dipyridamole-thallium testing because of severe symptoms. One patient had severe chest pain unrelieved with aminophylline and sublingual nitroglycerine; he did not undergo cardiac catheterization. A second patient had syncope associated with bradycardia and while awaiting repeat thallium imaging approximately 2 hr after routine administration of aminophylline; coronary angiography

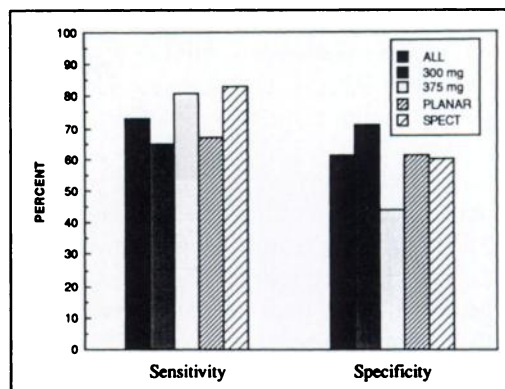


FIGURE 1. Sensitivity and specificity of dipyridamole-thallium scintigraphy for the presence of CAD. Differences between patients given 300 mg or 375 mg of dipyridamole were not significant (p > 0.05). Differences between patients undergoing planar or SPECT thallium scintigraphy were also not significant.

showed no significant coronary artery disease. Neither of these patients showed evidence of myocardial infarction by serial ECGs and cardiac isoenzymes and both were discharged from the hospital in stable condition.

Noncardiac Effects of Dipyridamole

The most common symptoms were headache (20%), dizziness (9%), and nausea (9%). Dyspnea (4%) and vomiting (1%) were less common. Other noncardiac side effects were also unusual (Table 2). Symptoms which occurred in less than 1% of patients were: diaphoresis, diarrhea, fatigue, blurred vision, tinnitus, dysphagia, palpitation, and flushing. It is possible that the latter symptoms were unrelated to the administration of dipyridamole.

Dose of Dipyridamole

The incidence of any side effects was the same in the patients receiving 375 mg as in those receiving 300 mg of dipyridamole (69% versus 68%). There was no difference in the incidence of severe hypotension (3% versus 2%) or severe chest pain (10% versus 8%).

Subset Analysis of Adverse Effects of Dipyridamole

Age (Table 3). The 299 patients who were less than 70 yr compared to the 101 patients who were older than 70

TABLE 3
Correlation Between Patient Age and Incidence of Side Effects of Dipyridamole

	Age (yr)		
	<70	≥70	p value
Number of patients	299	101	
Any side effect	30%	36%	ns
Severe chest pain*	9%	8%	ns
Severe hypotension [†]	2%	3%	ns

* Defined as chest pain requiring early administration of intravenous aminophylline.

[†] Defined as minimum systolic blood pressure less than 90 mmHg.

yr did not differ with respect to the incidence of overall side effects, severe hypotension (minimum systolic blood pressure less than 90 mmHg), or severe chest pain (i.e., requiring early administration of intravenous aminophylline).

Obstructive Pulmonary Disease (Table 4). Sixty-nine patients had a history of chronic obstructive pulmonary disease. Thirty-two were taking theophylline which needed to be withdrawn prior to testing. There was no difference in the incidence of dyspnea in patients without versus those with pulmonary disease (3% versus 7%, respectively; $p = ns$). One patient who was in the theophylline subgroup experienced severe dyspnea requiring early intravenous aminophylline; this represented a significantly higher likelihood of severe dyspnea in this subgroup compared to 331 patients without pulmonary disease none of whom had severe dyspnea ($p = 0.001$).

Coronary Artery Disease. The 63 patients with significant coronary artery disease documented by coronary arteriography had a somewhat higher incidence of overall side effects as those without coronary artery disease but the difference was not statistically significant (73% versus 57%, $p = ns$). Interestingly, among the 20 patients with normal coronary arteries, five had mild chest pain and one had severe chest pain requiring early aminophylline. There was a trend among coronary artery disease patients compared to non-coronary artery disease patients to experience any chest pain (43% versus 26%), severe chest pain (22% versus 4%), and severe hypotension (6% versus 4%) but these differences did not achieve statistical significance.

Among the 63 patients with coronary disease at angiography who did not have bypass graft surgery, the incidence of severe chest pain rose with the number of vessels diseased (Fig. 1). Patients with three-vessel disease were found to be at significantly greater risk than those without coronary artery disease (50% versus 4%, $p = 0.003$). There was no such correlation between the incidence of mild chest pain (i.e., not requiring early administration of aminophylline) and the extent of CAD (Fig. 2).

TABLE 4
Correlation Between Obstructive Pulmonary Disease and Incidence of Side Effects of Dipyridamole

	COPD			All
	No COPD	Not requiring theophylline		
		Requiring theophylline*		
Number of patients	331	37	32	69
Dyspnea	3%	5%	9%	7%
Severe dyspnea†	0%	0%	3%‡	1%§

* Withdrawn from theophylline prior to testing.
 † Defined as requiring early administration of intravenous aminophylline.
 ‡ $p = 0.001$ compared to No COPD group.
 § $p < 0.05$ compared to No COPD group.

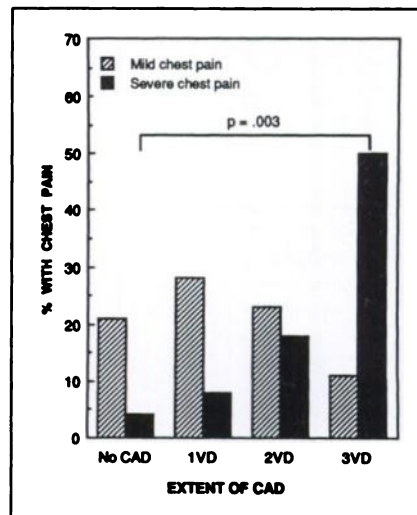


FIGURE 2. Percent of patients with or without CAD who had severe chest pain (black) or mild chest pain (hatched) following dipyridamole. See Methods for definition of mild and severe chest pain. 1VD = single-vessel CAD; 2VD = double-vessel CAD; and 3VD = triple-vessel CAD.

Left Ventricular Dysfunction (Table 5). Sixty-nine patients who had either normal or mildly depressed left ventricular function were compared with 26 patients who had moderate or severe left ventricular dysfunction. There was no difference in the incidence of overall side effects, any chest pain, or severe chest pain between these two subsets of patients. Patients with more severe left ventricular dysfunction developed severe hypotension more often than those with mild dysfunction or normal ventricular function (19% versus 4%, $p = 0.02$).

Recent Myocardial Infarction (Within 3 Weeks). Ten patients had myocardial infarction documented by ECG and/or cardiac isoenzymes within three wk of the time prior to dipyridamole-thallium imaging. Six had no side effects following dipyridamole. Three had noncardiac side effects and only one patient experienced chest pain, which was not severe.

Diagnostic Accuracy

Thallium scintigraphy revealed at least one perfusion defect in 56 of the 63 patients with angiographic coronary artery disease who had no prior bypass surgery (sensitivity

TABLE 5
Correlation Between Left Ventricular Dysfunction and Incidence of Side Effects of Dipyridamole

	Left Ventricular Dysfunction		
	None or mild	Moderate or severe	p value
Number of patients	55	17	
Any side effect	39 (71%)	11 (65%)	ns [§]
Severe chest pain†	8 (15%)	4 (24%)	ns
Severe hypotension‡	0 (0%)	2 (12%)	ns

† Defined as requiring early administration of intravenous aminophylline.
 ‡ Defined as minimum systolic blood pressure less than 90 mmHg.
 § $p > 0.05$.

73%). In the 23 patients with no significant coronary disease, there were no perfusion defects in 14 (specificity 61%). When coronary artery disease was defined as $\geq 50\%$ diameter stenosis of at least one vessel (rather than $\geq 70\%$ stenosis), the sensitivity and specificity did not change (73% and 65%, respectively).

Subset analysis of patients receiving 300 mg (n = 45) or 375 mg (n = 41) of dipyridamole revealed trends toward better sensitivity and worse specificity with the higher dose, but the differences were not significantly different (Fig. 3). Similarly, comparing patients who had planar imaging (n = 57) to those who had SPECT imaging (n = 29), there were no significant differences in sensitivity or specificity (Fig. 3).

DISCUSSION

Dipyridamole-thallium scintigraphy offers important advantages in the evaluation of patients with known or suspected coronary artery disease:

1. Patients who are unable to exercise at all or cannot exercise sufficiently to precipitate myocardial ischemia can be studied.
2. Sensitivity and specificity for coronary artery disease are comparable to that of exercise-thallium imaging (2,16).
3. The diagnostic accuracy of the test is not affected by cardiac drugs such as beta-blockers (17).

Dipyridamole-thallium scintigraphy is diagnostically useful and safe. Although many patients experience minor side effects, several studies have reported that very few experience severe complications (10-15,19,20,23). Most recently, in a study of 3,911 patients receiving intravenous dipyridamole (23), the incidence of major complications (fatal and nonfatal myocardial infarction and acute bronchospasm) was very low (0.3%). However, specific subsets of patients who might be at greater risk of suffering such complications have not been examined to determine if there are patients for whom the test should be contraindicated.

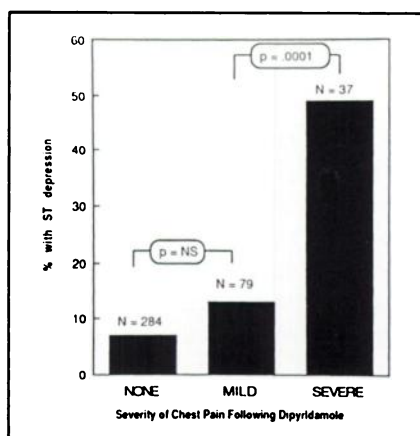


FIGURE 3. Percent of patients with or without chest pain who had ST-segment depression following dipyridamole. NS = not significant.

Hemodynamic Effects

Overall, dipyridamole caused a mild fall in systolic blood pressure (mean 13 mmHg) and rise in heart rate (mean 11 bpm) as would be expected given the peripheral vasodilatory action of the drug. These findings are similar to prior studies. Taillefer et al. (11) found that 400 mg of oral dipyridamole caused the same mild hemodynamic effects as intravenous dipyridamole (0.56 mg/kg).

Only ten patients (2.5%) developed what we defined as a severe hypotensive response (systolic BP less than 90 mmHg). In all ten patients, blood pressure returned to baseline when aminophylline was given and none required volume infusion.

We conclude that *clinically significant hypotension following dipyridamole is rare, is usually not associated with severe symptoms, and is promptly reversed with intravenous aminophylline.*

Adverse Cardiac and Noncardiac Effects

In prior studies using oral dipyridamole (Table 6), 17% to 28% patients experienced chest pain compared to 31% in this series. We made a distinction between mild chest pain (not requiring early administration of intravenous aminophylline) and severe chest pain (requiring early administration of aminophylline); this was a subjective judgement made by the physician supervising the test. *Mild* chest pain, which occurred in 21% of patients, is probably not due to myocardial ischemia. Evidence in favor of this includes the following: (1) Six of 20 patients with normal coronary arteries complained of mild chest pain and (2) Twenty-four of 105 patients with normal thallium scans (23%) complained of mild chest pain. Similarly, Beer et al. (15) found that 6 of 17 patients with no significant coronary artery disease complained of chest pain after oral dipyridamole. Thus, patients without detectable coronary artery disease or thallium-documented ischemia can have mild chest pain induced by oral dipyridamole.

Severe chest pain following dipyridamole occurred in only 9% of patients and probably was caused by myocardial ischemia. This hypothesis is supported by the following:

TABLE 6
Studies of Oral-Dipyridamole Thallium Scintigraphy

Author Reference	No. of Patients	Dose (mg)	Side Effects			
			Chest Any	Chest Pain	ST dep.	VT/VF, MI, or Death
Jain (10)	53	300	42%	28%	26%	0
Taillefer (11)	50	200-400	12%	18%	—	0
Gould (12)	58	200-300	75%	17%	9%	0
Homma (13)	100	300	55%	25%	14%	0
Borges-Neto (14)	100	300	52%	27%	12%	0
Beer (15)	65	300-375	50%	27%	9%	0

MI = myocardial infarction; ST dep. = ST-segment depression; and VT/VF = ventricular tachycardia or ventricular fibrillation.

1. Severe chest pain was associated with reversible thallium perfusion defects ($p < 0.01$), whereas mild chest pain was not (Table 7).
2. ST segment depression during the test was much more likely to occur in patients having severe chest pain than those with mild chest pain ($p = 0.02$, Fig. 2).
3. Patients with three-vessel coronary disease were more likely to have severe chest pain than those without coronary artery disease ($p = 0.02$, Fig. 1).

Our findings may explain why Pearlman and Boucher found that dipyridamole-induced chest pain was not predictive of the severity of coronary artery disease (18). Patients who experienced non-ischemic chest pain may have obscured the correlation between ischemic chest pain and severe coronary disease.

Other cardiac side effects of dipyridamole were infrequent. Only 12% had ST depression and no patient had ventricular pairs or ventricular tachycardia. Previous studies have similarly reported a low incidence of these cardiac side effects (Table 6).

In summary, *the most important cardiac side effect of dipyridamole is severe chest pain which probably represents myocardial ischemia (while mild chest pain does not), occurs uncommonly, and is promptly reversed by intravenous aminophylline.*

Noncardiac side effects were frequent as in prior studies (10–15). No patient experienced presyncope or syncope which is consistent with the fact that severe hypotension was rare (2.5%). Only 14 patients (5%) required intravenous aminophylline to reverse severe noncardiac symptoms. These findings are similar to previous studies which showed that *noncardiac side effects with dipyridamole are common but rarely severe* (Table 6).

Are There Patients for Whom Dipyridamole-Thallium Testing Is Contraindicated?

The Elderly. Two prior studies (19,20) have shown that intravenous dipyridamole in patients 70 yr or older in-

curred the same rate of minor and major complications as in younger patients. More importantly, Lam et al. (19) found that the accuracy of the test was the same in both groups of patients. We found *that elderly patients are no more likely to experience either mild or severe side effects than younger ones* (Table 3).

Patients with Obstructive Pulmonary Disease. The use of dipyridamole in patients with chronic obstructive pulmonary disease could be problematic for two related reasons 1) The potential of dipyridamole to provoke bronchospasm and 2) the necessity of withdrawing theophylline prior to testing because it blocks the coronary vasodilatory action of dipyridamole and substantially reduces its diagnostic utility (21). Some authors have recommended that patients with bronchospastic lung disease should not undergo dipyridamole-thallium imaging (22,23).

The present study included 69 patients with a history of chronic obstructive pulmonary disease, 32 of whom were taking theophylline. Dyspnea was the only pulmonary symptom during dipyridamole testing and was uncommon. Although it occurred slightly more frequently in those with pulmonary disease compared to those without it (7% versus 3%), the difference was not significant. Only one patient experienced such severe dyspnea that aminophylline needed to be administered early in the protocol. This represented an incidence of only 3% (1 of 32) which was significantly higher than the 0% incidence of severe dyspnea among the 331 patients without pulmonary disease ($p < 0.05$). Of note, none of 37 patients with pulmonary disease who were not taking theophylline experienced severe dyspnea. Therefore, *patients with obstructive pulmonary disease, including those withdrawn from theophylline, rarely experience severe pulmonary symptoms following dipyridamole.*

Patients with Coronary Artery Disease. Homma et al. found that patients with coronary artery disease are more likely to experience cardiac symptoms following dipyridamole and equally likely to experience noncardiac side effects (13). In a different study, the same group reported that there was no correlation between the extent of coronary artery disease and the risk of side effects (23). In the 111 patients who underwent coronary angiography in this study, the incidence of overall side effects was the same in those with and without coronary artery disease. However, we found that the incidence of severe chest pain was greater in patients with more extensive coronary disease (Fig. 1). Patients with 3-vessel coronary artery disease were significantly more likely to experience severe chest pain than those with normal coronary arteries ($p = 0.003$). Previous studies may not have detected this difference because of small numbers of patients.

No patient in this study suffered a myocardial infarction, malignant ventricular arrhythmia, or cardiac arrest. There have been two case reports of cardiac arrest following administration of dipyridamole in the literature. Both patients were resuscitated.

TABLE 7
Correlation Between Thallium Findings and Side Effects of Dipyridamole

Defect*	No thallium defect	Fixed defect only	Reversible
Number of patients	105	73	174
Mild chest pain [†]	24 (23%)	17 (23%)	56 (32%)
Severe chest pain [‡]	1 (1%)	2 (3%)	28 (16%) [§]

* With or without fixed defects.

[†] Defined as not requiring early administration of intravenous aminophylline.

[‡] Defined as requiring early administration of intravenous aminophylline.

[§] $p = 0.003$ compared to "no thallium defect" group.

We reviewed 37 clinical studies published between 1978 and 1989 (including the present study) which investigated the effects and/or clinical usefulness of dipyridamole (1-16,18-21,23-41); 8 used oral and 29 used intravenous dipyridamole. The total number of patients who underwent testing was 3,340 (853 received the oral form). There were 1,515 patients with well-documented coronary artery disease (at least one stenosed coronary vessel or a history of myocardial infarction) and 807 had multivessel and/or left main coronary artery disease. Only one death was reported (31) in a 73-yr-old patient with unstable angina and multivessel coronary disease who had received intravenous dipyridamole. Because this patient died 18 hr after the completion of thallium scanning, it is doubtful that dipyridamole contributed to his demise since the half-life of the drug administered intravenously is less than 1 hr (42). Thus, the risk of cardiac arrest or death following dipyridamole is very small, even in patients with coronary artery disease.

In summary, *patients with three-vessel coronary artery disease are more likely to experience severe chest pain after dipyridamole than other patients, but in the vast majority this is reversible with intravenous aminophylline. The risk of cardiac arrest or myocardial infarction with dipyridamole-thallium testing is extremely low in patients with or without coronary artery disease, but as with exercise testing, is not zero. Departments performing this test should have resuscitation equipment readily available in case of a rare emergency.*

Patients with Left Ventricular Dysfunction. Interestingly, we found that a moderate or severe degree of left ventricular dysfunction did not affect the incidence of chest pain (mild or severe) or noncardiac side effects (Table 5). There was, however, a significantly greater incidence of severe hypotension among these patients compared to those with normal or mildly impaired left ventricular function ($p = 0.02$). Such patients are known to be at higher risk of developing postural hypotension as a side effect of any peripheral vasodilator. The mechanism behind this is most likely the blunted inotropic response of the myocardium to reflex sympathetic activity. The relatively severe degree of hypotension in these patients was promptly reversed with intravenous aminophylline and was not associated with symptoms of cerebral hypoperfusion in any patient.

Patients with Recent Myocardial Infarction. Ten patients had a documented infarction within 3 wk of undergoing testing in this study. All tolerated the procedure without difficulty. One patient experienced severe chest pain, which was relieved with aminophylline. Two recent studies (9,41) have examined the prognostic value of intravenous dipyridamole in patients with recent myocardial infarction. There were a total of 95 patients in these studies and no serious complications occurred.

Limitations

One limitation of this study is selection bias, i.e., sicker patients who were at greater risk for suffering serious

complications may have been excluded from testing by their physicians. However, the subset analysis reveals that even among patients with significant obstructive lung disease (even in those requiring theophylline), multivessel coronary artery disease, and severe left ventricular dysfunction, serious complications were uncommon. Nevertheless, our conclusions do not apply to patients with particularly severe or unstable cardiopulmonary disease or to very old individuals (e.g., older than 90 yr).

A second limitation is that myocardial infarction was not definitively ruled out using serial ECGs or cardiac isoenzymes. It is possible that some patients suffered asymptomatic infarctions following dipyridamole due to excessive "coronary steal" phenomenon. However, this is unlikely since the effects of dipyridamole were reversed within 45 min.

A third limitation is that serum dipyridamole levels were not measured. Thus it could be argued that the relatively low incidence of serious side effects was due to low serum levels, either due to an inappropriately low dosage or inadequate absorption of the drug. We do not believe this occurred, based on the following reasons:

1. Segall and Davis have shown that there is no correlation between the serum level of dipyridamole and its hemodynamic or adverse effects (26).
2. Since a majority of patients experienced mild symptoms attributable to the drug, it is difficult to postulate that inadequate gastrointestinal absorption accounts for the low prevalence of serious complications.
3. Dipyridamole-induced consistent, albeit mild, hemodynamic effects.
4. The dosages of dipyridamole employed were diagnostically useful, yielding sensitivity (73%) and specificity (61%) similar to prior studies using comparable dosages in which sensitivity ranged from 48% to 92% and specificity from 65% to 100% (11-15).
5. Oral and intravenous dipyridamole have been shown to be equivalent in terms of serum levels, side-effects and diagnostic accuracy (11,13).

CONCLUSIONS

Dipyridamole-thallium imaging is a relatively safe, non-invasive test for a wide variety of patient subsets referred for evaluation of ischemic heart disease. Certain serious side effects are more common in certain patients:

1. Severe dyspnea occurs rarely but slightly more frequently in patients with obstructive pulmonary disease withdrawn from theophylline.
2. Patients with three-vessel coronary artery disease are more likely to experience chest pain.
3. Patients with significantly depressed left ventricular function are more likely to develop severe hypotension. However, these complications are relatively uncommon and are rapidly reversed with a single dose of intravenous aminophylline. Oral dipyrida-

mole-thallium imaging is well tolerated by the elderly. In reviewing the literature, the risk of myocardial infarction or cardiac arrest appears to be extremely small. None of 400 consecutive patients in this study had such an event. This risk is probably higher in patients with unstable ischemic syndromes for whom both pharmacologic and exercise stress testing is contraindicated.

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