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Review Article

Dipyridamole-echocardiography test: historical background and physiologic basis

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Dipyridamole was first introduced as an antianginal, coronary vasodilator agent. It was soon found that this drug could not prevent effort ischaemia; on the contrary, given intravenously, it could frequently induce ischaemia in the presence of coronary artery stenosis. This property was exploited for the diagnosis of coronary artery disease. The dipyridamole-induced ischaemia was detected by different techniques: ST-segment depression, thallium 201 scintigraphy and echocardiography. This review article describes the mechanisms underlying dipyridamole-induced ischaemia and discusses the value of this pharmacologic stress test for the detection of coronary artery disease.

'Life must be lived going ahead, but it can be understood only coming back' (Soren Kierkegaard).

Introduction

Many authorities of undisputed reputation and expertise believe that dipyridamole infusion causes 'little, if any, myocardial ischaemia'[1]. More recently, claims have been made that dipyridamole stress echocardiography is useful in the diagnosis of ischaemic heart disease[2–3]. The diagnostic end-points are the development of new areas of dyssynergy or of the worsening of preexisting dyssynergy: these transient changes are highly specific to myocardial ischaemia. How can one reconcile such divergent opinions? Review of the history and physiology of dipyridamole will be of help in understanding its present status.

Dipyridamole as an antianginal medication

In 1951 a new, double-ring structure was formed from two pyrimidine rings, and several chemical compounds were synthesized using the new basic structure[4]. One of these compounds, when tested pharmacologically in animals, showed a selective effect on the coronary circulation: vasodilation and increase in myocardial blood flow with no significant influence on peripheral vessels[5,6] (Fig. 1).

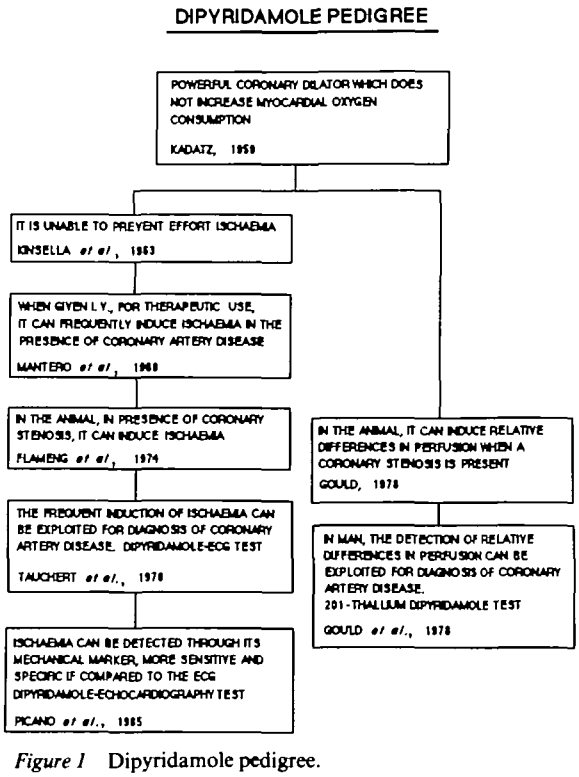

Figure 1 Dipyridamole pedigree.

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This compound was given the name dipyridamole due to the two parental pyrimidine rings[4].

Clinical studies confirmed that a marked increase in coronary blood flow could also be observed in man without significantly affecting myocardial oxygen consumption[7]. Therefore, it appeared reasonable to use dipyridamole as an antianginal drug; myocardial ischaemia is believed to result from imbalance between oxygen supply and demand, dipyridamole markedly increases oxygen supply without significantly augmenting oxygen demand, thus it should reestablish the normal oxygen balance[4]. Initial clinical data were encouraging: anginal patients were treated for 8–10 days with better results than those achieved with papaverine[8]. In another study, without placebo control, significant symptomatic improvement was found in more than two-thirds of 57 patients treated[9]. Anginal patients treated for more than 2 years improved, and the angina disappeared in some cases[10–12].

Unfortunately, initial enthusiasm about the antianginal properties of dipyridamole did not withstand the test of double-blind, placebo-controlled studies[13,14]. Furthermore, in exercise stress tests, dipyridamole failed to prevent changes in the electrocardiogram, whereas nitroglycerine succeeded[14].

Dipyridamole as an inducer of ischaemia

Dipyridamole provoked or aggravated anginal attacks when it was given intravenously to test coronary reserve or to treat unstable angina[15–21]. In 1968, Mantero and Conti reported a 'paradoxical response' to intravenous dipyridamole therapy in unstable angina: 'usually, a 20-minute infusion of 40–60 mg of dipyridamole resulted in an anginal attack'[16].

These clinical observations were experimentally confirmed: in the presence of a coronary obstruction, dipyridamole was found to induce a reduction in subendocardial blood flow, ST segment depression and a fall in left ventricular dP/dt[22]. On the basis of these clinical and experimental observations in 1976, Tauchert *et al.* proposed the dipyridamole-ECG stress test for the diagnosis of coronary artery disease[23]. Thus dipyridamole, born as an antianginal preparation, had become a tool for diagnosing coronary artery disease through provocation of myocardial ischaemia. As in exercise electrocardiography, positivity of the dipyridamole-ECG stress test is based primarily on ST-segment changes and secondarily on the induction of angina.

Having established the potential of dipyridamole to induce myocardial ischaemia, we must next determine the actual incidence of myocardial ischaemia during dipyridamole infusion. Patients with angiographically documented coronary artery disease have shown variable responses (positive tests: 0–62%) in terms of ST-segment depression, regional coronary haemodynamics and thallium-201 myocardial scintigraphy[24–37].

There may be a number of reasons for these discrepancies:

(A) PATIENT SELECTION

The sensitivity of the dipyridamole — ECG stress test is obviously affected by the extent of coronary disease in the study population, i.e. the relative prevalence of single vs. multivessel disease. Another important variable is previous myocardial infarction. The proportion of patients with previous myocardial infarction in the various studies ranges from 0%[37] to 45%[27]. Dipyridamole-induced ST-segment depression has been shown to occur much less frequently in patients with myocardial infarction[34,35]. For instance, Ikeda *et al.*[35] observed an ischaemic ST-segment depression in 84% of the non-myocardial infarction group, 29% of the anterior myocardial infarction group, 63% of the inferior myocardial infarction group and 61% of the total population. Tavazzi *et al.* found the overall sensitivity to be 53%, increasing to 71% in the non-myocardial infarction subset[34].

(B) CURRENT THERAPY

Antianginal therapy was withheld[29] for 12 h[25] to 1 week[30] preceding the test.

This factor can be of paramount significance. To determine the effect of drug therapy on dipyridamole-induced myocardial ischaemia, Kawashima *et al.*[36] repeated the dipyridamole test after premedication in 12 patients who had developed ST-segment depression during the first test. After oral administration of nitrates (four patients) or diltiazem (eight patients), ST-segment depression following dipyridamole infusion was completely suppressed in 11 patients. This result, as well as those of other studies[33], indicates that dipyridamole-induced ischaemia can be easily inhibited by medical treatment. This is not the case for perfusion defect observed at myocardial scintigraphy after dipyridamole administration.

Table 1 Sensitivity of 12 ECG-dipyridamole tests in populations using no antianginal drugs

Author	Journal Year	Number of patients	Dosage (mg kg^{-1})	DIPY-Test Sensitivity ECG	DIPY-Test Sensitivity ECG+ Angina	Exercise test Sensitivity ECG	Exercise test Sensitivity ECG+ Angina
(1) De Ambroggi	Cl Cardiol 1982	34	0·56 in 10 min	44%	44%	81%	88%
(2) Pirelli	G It Cardiol 1985	45	0·56 in 4 min	62%	62%	—	—
(3) Ikeda	J Electrocardiog 1986	41	0·56 in 4 min	56%	—	—	—
(4) Schmolimer	Wien Klin Wschr 1979	79	0·75 in 10 min*	44%	71%	46%	71%
(5) Parsi	Dtsch Ges Wes 1980	82	0·75 in 10 min*	51%	85%	—	83%
(6) Grosse H.	Med Welt 1982	203	0·75 in 10 min*	—	73%	—	72%
(7) Osterspey	Dtsch Med Wschr 1983	500	0·75 in 10 min*	56%	80%	65%	—
(8) Tavazzi	Cardiology 1982	54	0·75 in 10 min	53%	—	—	—

* = 50% of the dosage given within the first 3 min; the remaining 50% over the last 7 min.
— = data not available.

Table 2 Main differences between echo vs. thallium dipyridamole test

	Dipyridamole echocardiography test	Dipyridamole 201-Tl test
End point	transient asynergy	flow heterogeneity
Ischaemia required	+	−
Antianginal therapy lowers sensitivity	+	−
Handgrip increases sensitivity	−	+
Significant hypotension	−	+ (orthostatic)

(C) NUMBER OF ECG LEADS

The number of monitoring leads usually ranged from 3 to 12. Probably, the greater the number of ECG leads, the greater the possibility of detecting dipyridamole-induced ST-segment changes. However, in a body surface electrocardiographic mapping study by Ikeda *et al.*[35] employing 87 leads only 2 out of 25 patients with a positive test had no significant changes in the standard 12 ECG leads. Thus, the best balance of sensitivity and practicality is probably achieved by the 12 lead ECG, which also allows simultaneous echocardiographic monitoring.

(D) DOSAGE

The most common dipyridamole doses were 0·56 mg kg^{-1} in 4 min[27–29, 35–37] and 0·75 mg kg^{-1} in 10 min[31–34] (Range: 0·56 mg kg^{-1} in 10 min to 1 mg kg^{-1} in 10 min[38]). The potential for induction of ischaemia tends to increase with increased dosage and, at a fixed dosage, with increased infusion rates (Table 1, Fig. 2).

To ascertain the actual value of the dipyridamole-ECG stress test, it had to be compared in the same patient population with the most widely used technique for diagnosis of coronary artery disease, the exercise-ECG stress test. Both techniques, in fact, show diagnostic figures heavily dependent upon the criteria for patient selection. When both the exercise- and dipyridamole-ECG stress tests (using the 'high' dose of 0·75 mg kg^{-1} in 10 min, with infusion of 50% within the first 3 min) were performed, their diagnostic accuracy was similar[31–33, 39]. After dipyridamole, ECG ischaemic changes were seen in

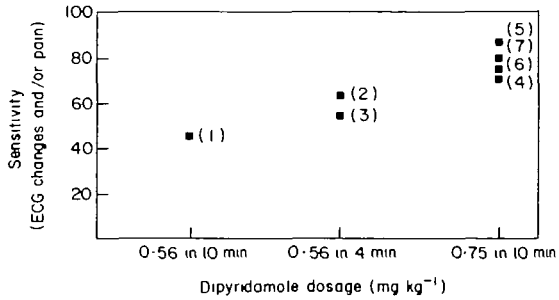


Figure 2 Dose dependence of the sensitivity of dipyridamole test for angiographically assessed coronary artery disease (numbers in parentheses refer to the papers displayed in Table 1).

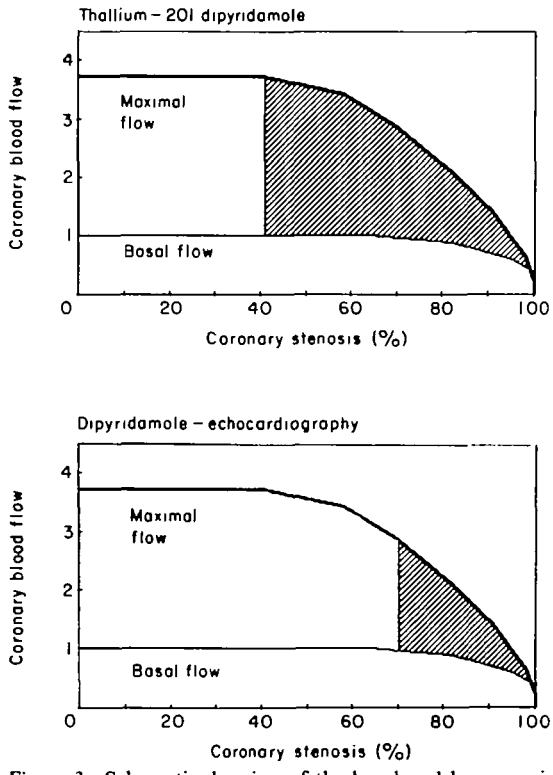


Figure 3 Schematic drawing of the basal and hyperaemic post-occlusive coronary flow curves in the dog, displayed for increasing degrees of stenosis (modified from ref. 58: Gould *et al.* Am J Cardiol, 1974). The cut-off point inducing a hypoperfusion defect at 201-thallium dipyridamole scintigraphy (top) relates to the limitation of reactive hyperaemia; for dipyridamole echocardiography (bottom) it represents the onset of ischaemia.

46%–51% of the population with angiographically proven coronary artery disease[4–6] (Table 1). When both ECG changes and anginal pain were used as criteria for positivity, the sensitivity rose to values ranging from 71% to 85%[4–63] (Table 1).

Since ECG changes and pain do not show ideal sensitivity for detecting myocardial ischaemia, it was logical to add echocardiography. In general, in the presence of stress-induced ischaemia due to epicardial coronary artery narrowing, transient impairment of regional contractility usually occurs earlier and is more sensitive and specific than other markers of ischaemia such as ST-segment depression and pain[40]. The specificity of ST-segment changes (with exercise or dipyridamole) is very low (less than 50%) in certain patients, such as women[41,42] and hypertensives[43,44].

The sensitivity of ST-segment changes is low in other patients, such as those with previous myocardial infarction[34,35], in which subgroup, the sensitivity of echocardiography is particularly high[45].

Furthermore, stress echo provides useful information on the site and extension of the ischaemic area that is inaccessible to non-imaging techniques. This allows accurate determination of the site of the ischaemia-producing coronary artery[46]. The diagnostic end-point of this test is the detection of a new area of asynergy or worsening of pre-existing asynergy; this theoretically indicates ischaemia[2]. With this criterion for positivity, the sensitivity of the dipyridamole-echocardiography test at a standard dosage of 0·56 mg kg^{-1} over 4 min, has been investigated in various patient groups: 56% in 66 consecutive patients with effort angina[2]; 62% in 62 consecutive patients with angina at rest[47]; 53% in 93 consecutive patients with effort angina[3]; 89% in 17 patients under full antianginal therapy, evaluated 8–10 days after myocardial infarction[48]; 78% in 40 patients with rest and/or effort angina[49]; 52%, in 26 non-consecutive patients with rest and/or effort angina[50]. In the latter study, by Margonato *et al.*, the limited sensitivity could be explained by the low dosage employed and also by the use of a single projection — the parasternal short axis. This approach was selected because it allows easier image quantification, nevertheless it does not allow imaging of all ventricular walls, and localized areas of dyssynergy, particularly in the right ventricle, the true apex and the inferior wall, might be missed.

Finally, one must realize that there are some clinical models of myocardial ischaemia where ECG changes and chest pain are usually present in the absence of any detectable regional or global mechanical dysfunction. This peculiar combination

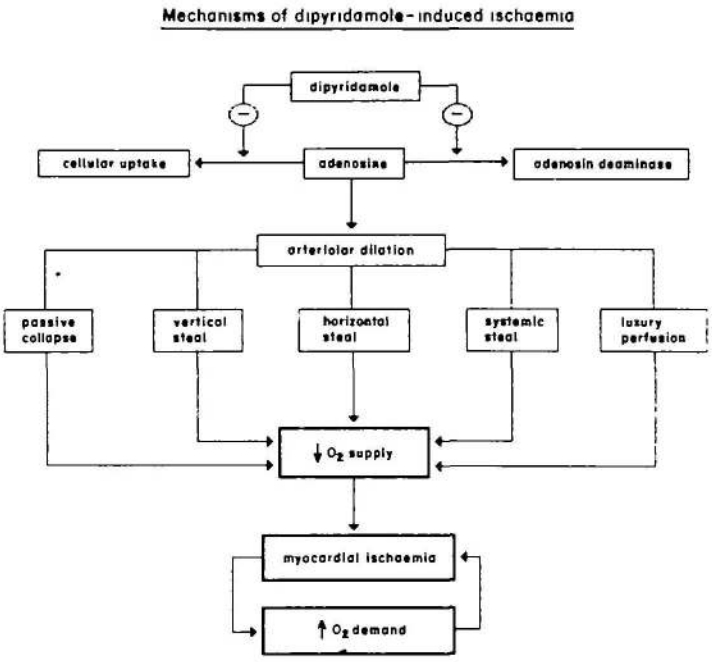


Figure 4 Possible mechanisms of dipyridamole-induced ischaemia.

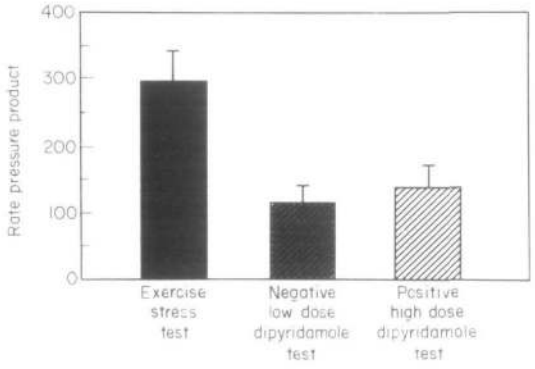


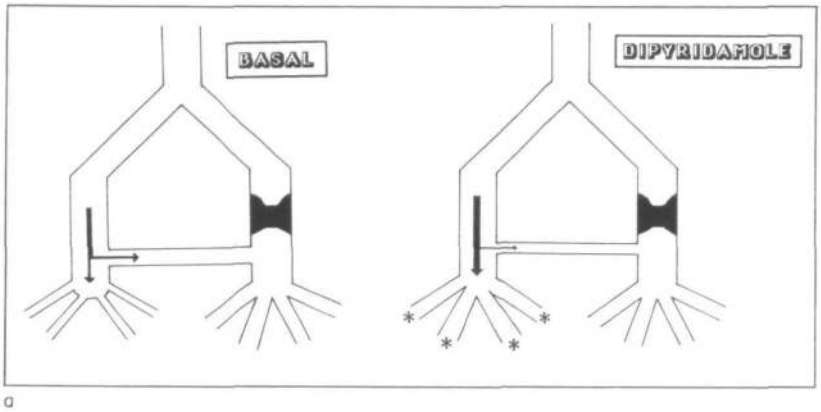
Figure 5 For 15 patients, with negative low dose and positive high dose dipyridamole echocardiography test, three values of rate-pressure product are shown: during exercise stress test (taken at the onset of ischaemia — arbitrarily fixed at 0·1 mV ST segment depression — or at peak exercise in negative tests); at its maximal value during the low dose test; at the onset of ischaemia during the positive high dose test. There is no significant difference between the two latter values, suggesting that the increase in myocardial oxygen consumption takes little or no role in inducing ischaemia during the high dose test.

of 'echocardiographically silent' myocardial ischaemia during dipyridamole stress can be frequently found in Syndrome X[51] or in essential hypertension[44,52]. In both of these conditions, epicardial coronary arteries are angiographically normal and the hypothesis of a 'microvascular' disorder has been put forward[53].

Dosage

We initially performed the dipyridamole-echo test with the same dosage as that used in thallium-201 scintigraphy testing[27–29,54–55]. At that dosage, the test had a sensitivity of 50–60%[2,47]. In order to increase the sensitivity further, based on the clinical experience with the dipyridamole-ECG stress test (summarized in Table 1) we gave, after the standard dose of 0·56 mg kg^{-1} over 4 min, an extra dose of 0·14 mg kg min^{-1} for 2 min, up to a total dose of 0·84 mg kg^{-1} over 10 min[3]. This approach was also based on the suspicion of considerable interpatient variability, thus, a single dipyridamole dosage might not provide maximal vasodilation in all patients. In a study performed on 93 patients, the sensitivity rose from 53% to 74%, when the higher dose of dipyridamole was given to patients with a negative lower dose test. There was no loss in specificity and no apparent increase in risk[3].

Recently, the assumption that the standard dose provides maximal and uniform vasodilation in all patients has been questioned. From the physiologic viewpoint, there is a considerable variation in flow response to dipyridamole, and the higher dose is



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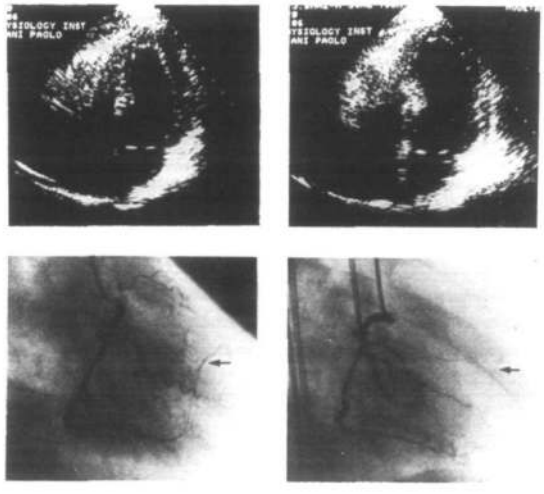

b Basal Dipyridamole

Figure 6 a: Schematic drawing of a possible operating mechanism of horizontal steal. The dilation of the normal vascular bed (asterisks) causes a shunting of blood through these vessels (thick arrow) at the expense of the vascular bed supplied by the stenotic artery (thin arrow). b: An example in which collaterals were supplied by the right coronary artery to the occluded left arterior descending artery. Two-dimensional echocardiographic frames, taken at end-systole (top) and coronary angiographies (bottom), obtained in basal conditions and after dipyridamole administration. After dipyridamole, the apex is dyskinetic; the coronary angiography shows an almost total disappearance of the collateral vessels (arrows).

often required to recruit the coronary reserve fully[56]. This is also consistent with clinical experience with the dipyridamole-ECG test showing how the diagnostic sensitivity rises if one uses progressively higher doses[31–33,39].

In our opinion, such an approach represents a very reasonable trade-off between the need for diagnostic power and the priority of safety.

In our 4-year experience with the high-dose dipyridamole echocardiography test[57], we had no major complications (death, myocardial infarction, malignant arrhythmias) in more than 800 tests performed. Minor side-effects (headache, dyspnoea, nausea, flushing) were frequent (in around 70% of cases) but mild and well tolerated by the patients, so we could complete the test in all cases.

Comparison with thallium-201 dipyridamole scanning

Dipyridamole thallium-201 scintigraphy[54,55] (Fig. 1), exploits the vasodilating properties of

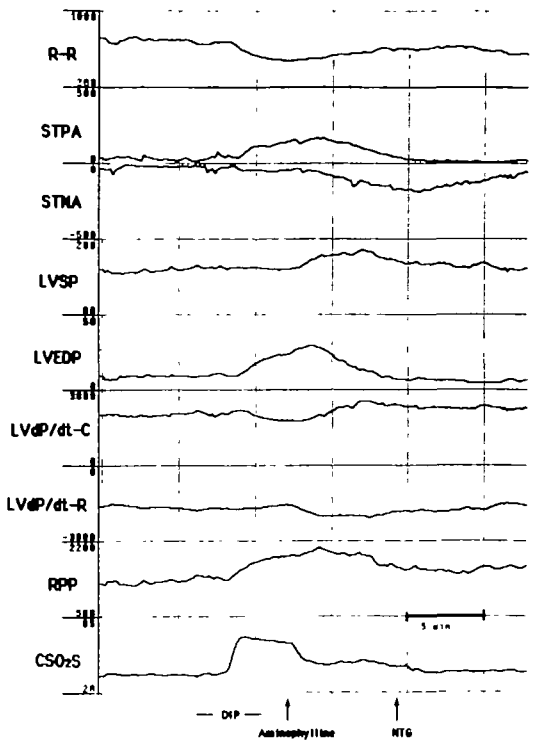

Figure 7 Computer plot of approximately 30 min continuous biventricular haemodynamic monitoring of a dipyridamole-induced ischaemic attack. From top to bottom: R-R = R-R interval; STPA = ST-T positive area; STNA = ST-T negative area; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; LVdP/dt-C = left ventricular dp/dt of contraction; LVdP/dt-R = left ventricular dp/dt of relaxation; RPP = rate pressure product; CSO_2S = great cardiac vein oxygen saturation. With dipyridamole infusion, there is initially a pronounced increase in great cardiac vein oxygen saturation that slowly decreases during overt ischaemia, when RPP, LVEDP, and heart rate rise markedly. At that point (about 3 min after the end of the dipyridamole infusion), the administration of aminophylline (240 mg over 2 min) dramatically reduces CSO_2S promptly aborting the haemodynamic signs of ischaemia. The R-R, LVEDP and RPP revert towards baseline values. About 5 min after aminophylline administration, the ST-segment depression persists in spite of the apparently complete mechanical recovery. There is normal contractility with echocardiography, LVEDP is back to normal, LV dP/dt-C and dP/dt-R show supernormal values. The administration of nitroglycerin (NTG) then quickly normalizes the electrocardiographic markers of ischaemia (STPA and STNA).

dipyridamole and theoretically neglects its potential to induce myocardial ischaemia (Table 2). Since a coronary stenosis may limit coronary reserve without inducing myocardial ischaemia[58], the

Table 3 Interpretation of ST segment elevation during dipyridamole stress test

	Dipyridamole	Dipyridamole +aminophylline
Aminophylline	Resolves ischaemia	Triggers ischaemia
Antidote	Aminophylline	Nitrates
Mechanism	Haemodynamic	Vasospastic
Coronary anatomy	Severe stenosis	Any
Reproducibility	High	Low
Variant angina	Yes/No	Yes

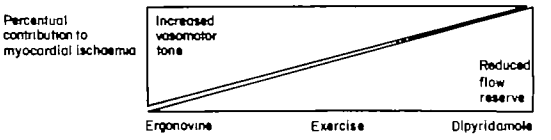

Figure 8 Conceptual allocation of different stress tests in the detection of functional (vasospastic) and organic (physiologic impairment of coronary reserve) pathogenetic mechanisms of myocardial ischaemia.

presence of coronary artery disease can be documented by the different uptake levels of a flow tracer such as thallium-201. Theoretically, myocardial ischaemia is not required for the dipyridamole thallium-201 test to be diagnostically positive[54,55] (Fig. 3) For the dipyridamole-echocardiography test myocardial ischaemia is the diagnostic endpoint, and this requires a degree of stenosis sufficient to induce myocardial ischaemia in the presence of increased metabolic demand (Fig. 3).

Antianginal therapy protects from dipyridamole-induced myocardial ischaemia, without limiting hyperaemic flow[59], in contrast to beta-blockers. As a consequence, antianginal therapy lowers the sensitivity of ECG dipyridamole testing[33,36], but does not appear to affect the sensitivity of thallium-201 testing[28].

The combination of dipyridamole with handgrip increases the flow gradient between myocardial regions supplied by vessels with different degrees of coronary stenosis[60], without increasing the resultant ischaemia[61]. This implies a rise in sensitivity, with respect to dipyridamole alone, for tests based on flow imaging (such as thallium-201 scintigraphy) but only a minimal step up in sensitivity for ECG or echo testing[61]. Conversely, the high dose dipyridamole (vs. the standard dose) increases the sensitivity of ECG and echo testing, without improving thallium-201 testing sensitivity[55]. This

can be explained if thallium-201 myocardial uptake is not strictly related to flow changes in the high flow range[62].

Orthostatic hypotension — which is a limiting problem with thallium-201 scintigraphy, since the latter requires tilting and walking for optimal imaging[27] — is not relevant for ECG or echocardiography, since the patient remains lying on the bed throughout the test. Another important difference relates to the possibility of stratifying the significance of a positive response. The timing of the echocardiographic positivity during the dipyridamole-echocardiography test correlates to the exercise ischaemic threshold: the earlier the positivity, the lower the coronary reserve assessed by the stress test[63]. The positivity of the response can also be usefully stratified, with both thallium and echo tests, on the basis of the associated ECG pattern (ST-segment elevation indicating transmural and ST-segment depression subendocardial ischaemia). Finally, the spatial circumferential extent of the asynergy or the perfusion defect can be semiquantitatively assessed with both techniques.

Apart from theoretical considerations, there is, to date, only one study which compares the diagnostic potential of high dose dipyridamole ($0{\cdot}75\ mg\ kg^{-1}$ over 10 min) echo vs. 201–thallium scintigraphy[64]. In that study of a population of 54 patients under no antianginal therapy referred for angiographic evaluation of chest pain, Ferrara *et al.*[64] found no significant differences in sensitivity (63·3% vs. 70% for echo and thallium testing, respectively) or specificity (91·6% vs. 100%, respectively). Interestingly, the only patient with a false-positive echo test had a dipyridamole-induced transient asynergy of the inferoposterior wall with a 50% stenosis of the left circumflex artery, but without myocardial perfusion defects on thallium scanning.

Recently, Fung *et al.*[65] reported an equivalent experimental study in the dog, using an open chest and a critical stenosis of the left circumflex coronary artery. Myocardial contractility was evaluated by quantitative two-dimensional echocardiography, and regional myocardial blood flow was determined by microspheres. Under these experimental conditions, low-dose dipyridamole ($0{\cdot}14\ mg\ kg^{-1}\ min^{-1}$ over 4 min) induced wall thickening abnormalities in 55% of the dogs studied, a finding that is in close agreement with our clinical experience —sensitivity of 56% using a similar dose of dipyridamole. After the administration of dipyridamole, substantial transmural blood flow heterogeneity was demonstrated in all dogs. However, Gould had previously demonstrated that a flow disturbance ratio of 2:1 is required for detection by thallium scintigraphy[54]. By such criteria, only 66% of the dogs given dipyridamole demonstrated blood flow disturbances of such magnitude (P = ns vs. the 56% of dipyridamole-echo sensitivity).

Mechanisms of dipyridamole-induced ischaemia

The regional transient asynergy occurring after dipyridamole in a region supplied by a critically stenotic coronary artery can be reasonably accounted for by the ischaemia resulting from a local imbalance between myocardial oxygen supply and demand (Fig. 4).

(A) ROLE OF MYOCARDIAL OXYGEN DEMAND

The main determinant of myocardial oxygen consumption, i.e. the rate-pressure product (systolic arterial pressure × heart rate), is moderately increased (usually less than 20%) at the onset of the asynergy after dipyridamole infusion, compared with a mean increase of more than 200% in the same patients during an exercise stress test. Furthermore, in patients with a negative low-dose and positive high-dose test, the rate-pressure product in ischaemia overlaps values reached during a negative low-dose test (Fig. 5). Consequently, the increase in myocardial oxygen consumption cannot, by itself, account for the ischaemia following a high-dose dipyridamole infusion. However, the rate-pressure product tends to increase in the presence of overt ischaemia, possibly inducing more ischaemia independently of the triggering event of flow maldistribution. Aminophylline antagonizes the effects of dipyridamole by blocking adenosine receptors. This may not always be sufficient to break the vicious circle of myocardial ischaemia (ischaemia–increase in oxygen demand–ischaemia), once it has become independent of the initial event of flow maldistribution. In these patients, the administration of nitrates, which decrease demand and increase supply, readily abolishes the symptoms and signs of myocardial ischaemia.

(B) ROLE OF OXYGEN SUPPLY

The mechanism responsible for dipyridamole-induced ischaemia is likely to be flow reduction in the region supplied by the stenotic coronary artery. Five mechanisms that could result in a decrease in myocardial oxygen supply have been suggested:

passive collapse of the stenosis[66]; vertical steal[22,65]; horizontal steal[67]; systemic steal[68]; luxury perfusion[69] (Fig. 4).

Each of these mechanisms results from coronary arteriolar vasodilation induced by dipyridamole due to accumulation of adenosine. Adenosine is a by-product of adenine nucleotide metabolism in myocardial tissue and is likely to play an active role in coronary flow regulation. Dipyridamole acts by inhibiting adenosine-deaminase and by preventing adenosine captation in myocardial tissue[71] (Fig. 4).

Passive coronary collapse. After dipyridamole administration, the arterioles dilate, thereby increasing flow across the stenotic lesion. This increased flow may lead to a larger drop in pressure, the magnitude of which relates to the severity of the stenosis and to the increase in flow. Decreased aortic pressure following dipyridamole administration would also reduce the intraluminal pressure and thereby cause a further decrease in poststenotic intraluminal distending pressure. This may predispose to collapse of the artery, thereby increasing the severity of the stenosis.

Unlike the 'vertical steal', this mechanism of passive coronary collapse postulates that the stenosis is severe but not fixed, i.e. it is able to undergo changes in size. Approximately 75% of all significant coronary stenoses contain a portion of normal wall within their circumference, and therefore have the potential for active or passive vasomotion[72].

In this regard, it is interesting to note that about 50% of patients with dipyridamole-induced ST-segment elevation also had spontaneous or ergonovine-induced ST-segment elevation[73,74]. This might appear paradoxical; however the presence of spontaneous or ergonovine-induced ST-segment elevation implies that the coronary stenosis can undergo active vasoconstriction. This may be indirect evidence that diseased but pliable (not fixed) coronary artery is present, a theoretical prerequisite for a passive collapse of the stenosis. In some patients with tight coronary stenosis, the angiographic findings during dipyridamole-induced ischaemia were consistent with the phenomenon of passive collapse showing almost no poststenotic opacification of the vessel[66].

Vertical steal. One of the interesting aspects of atherosclerotic lesions is that even in the presence of a fixed anatomical stenosis, resistance is not fixed[52]. Because endocardial are greater than epicardial oxygen demands the resistance vessels of the endocardium are more dilated than those of the epicardium. A vasodilator stimulus may then decrease resistance in the subepicardial but not in the subendocardial vessels because the subendocardial vasodilator reserve is already exhausted. Even if total blood flow increases, the net effect is shunting of blood from the subendocardium to the subepicardium, ultimately resulting in myocardial ischaemia.

This explanation has been substantiated by experimental[22,65] and, more recently, clinical[76] evidence. Patients with single vessel disease of the left anterior descending artery exhibited the mechanical manifestation of myocardial ischaemia (regional asynergy after dipyridamole) associated with an increase in anterior coronary flow, but much less than did patients with normal coronary arteries or patients with coronary disease and a negative dipyridamole-echocardiography test.

Horizontal steal. In the presence of a coronary occlusion, it seems conceivable that arteriolar vasodilators might not have any effect: 'Opening the taps wider (i.e. peripheral vasodilation) will not alter the rate at which the bath fills if the water is turned off at the main'[77]. Unfortunately, the hydraulics of the coronary tree are more complex than this, for several reasons, one of which is the presence of collateral circulation. The administration of an arteriolar dilator may be detrimental. When dipyridamole is given, it can fully dilate the resistance vessels of the unoccluded artery, thereby increasing the pressure gradient along the vessel. A partial stenosis exists in vessel feeding the collaterals, the small pressure drop across the stenosis, present under baseline conditions, increases, thereby decreasing the pressure at the point of origin of the collateral vessels. Such a reduction in collateral perfusion pressure decreases collateral blood flow to the myocardium dependent upon the occluded artery (Fig 6a).

In some patients with coronary occlusion, the angiographic findings during dipyridamole-induced ischaemia were consistent with the hypothesized mechanism of horizontal steal, showing less opacification of the collateral circulation in the presence of myocardial ischaemia (Fig. 6b).

Systemic steal. Dipyridamole has a peripheral arteriolar dilatory effect, although less pronounced than other drugs such as nifedipine or nitroprusside. In the presence of severe coronary artery disease and decreased diastolic perfusion pressure, the lowering of arteriolar peripheral resistances can lead to a coronary steal diverting perfusion from an ischaemic coronary vascular bed to a preferentially dilated peripheral vascular bed[68].

Luxury perfusion. After dipyridamole administration, a paradoxical situation takes place. The flow is augmented regionally, but it cannot be used by the metabolism of the myocardial cell, which then suffers oxygen 'hunger amidst affluency'. This can be due to the preferential opening of non-nutritional pathways in the microcirculation[69]. In addition, the increased flow velocity that is induced by dipyridamole reduces the vascular transit time, which limits oxygen cellular uptake[78]. Consistent with this interpretation is the finding that the oxygen saturation in the great cardiac vein is markedly augmented even in the presence of transient anterior myocardial ischaemia induced by dipyridamole (Fig. 7).

The final result of all these mechanisms is a drop in the subendocardial, rarely transmural, 'metabolically useful' flow. This is a prerequisite for regional contractility dysfunction, revealed as a transient asynergy by the dipyridamole-echocardiography test. Interestingly, even when dipyridamole infusion is not sufficient to provoke ischaemia in the presence of coronary artery disease, it sensitizes the myocardium to the ischaemia stress of exercise[79]. Each of the mechanisms determining ischaemia during dipyridamole stress requires an 'organic' limitation of coronary reserve. This indicates that the dipyridamole stress test can be classified as detecting organic, rather than functional, pathogenetic mechanisms of myocardial ischaemia (Fig. 8). However, aminophylline termination of dipyridamole stress (which is also routinely performed in negative tests) can trigger coronary vasospasm, with ST-segment elevation, in almost 30% of patients with variant angina[80]. The mechanism of vasospasm remains elusive. It is possible that aminophylline causes abrupt withdrawal of the dipyridamole vasodilatory stimulus, which might trigger coronary artery spasm. This hypothesized mechanism might be similar in some way (though on a shorter time scale) to coronary vasospasm caused by nitrate withdrawal. It is important to separate this finding from ST-segment elevation that occurs after dipyridamole infusion and is reversed by aminophylline (Table 3).

In summary, the dipyridamole story has taught us some very simple but fundamental lessons. First of all, myocardial ischaemia is a frequent finding after dipyridamole infusion and it is easily detected when looked for appropriately for example, by echocardiography. As with the great majority of pharmacological stresses, a single dosage cannot guarantee an optimal response. With higher doses (still clinically safe and easy to handle) ischaemia is more frequently seen. There is a sound physiologic basis to explain the apparent paradox of a potent coronary dilator, which does not significantly increase myocardial oxygen demand, yet is a strong ischaemic stressor, mainly by inducing complex flow maldistribution phenomena.

'Intelligo, ut credam'
'I understand, therefore I believe'
(Saint Thomas of Aquin).

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