DIPYRIDAMOLE-ECHOCARDIOGRAPHY TEST: A NEW TOOL FOR THE DIAGNOSIS OF CORONARY ARTERY DISEASE

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It is known from experimental and extensive clinical experience that dipyridamole infusion can prove ke myocardial ischemia in the presence of a coronary stenosis[1,2]. On the other side, in the early'80, studies performed on the clinical model of angina at rest had provided the conceptual framework for an echocardiographic approach to the diagnosis of myocardial ischemia in man. Such studies showed that: 1) during ischemia, a regional dyssynergy consistently precedes electrocardiographic changes[3,4]; 2) in the presence of minor or atypical electrocardiographic changes, such as peaking or flattening of T wave, the echocardiographic imaging allows to rule in or out the presence of myocardial ischemia[5]; 3) alterations in the regional thickening and motion are as early as the most sensitive invasive hemodynamic indexes of systolic and diastolic dysfunction, i.e., the decrease of dP/dt of contraction and relaxation[6]; 4) there is frequently a striking dissociation between the site and extent of ischemia, as imaged by 2 D-echo, and its electrocardiographic manifestations[3-6]; 5) the echocardiographic examination during a pharmacological stress (in those studies, ergonovine was used to provoke coronary vasospasm) is feasible and easy to obtain in all patients with an acceptable acoustic window in resting conditions[4].

On the basis of this background, it was reasonable to combine the dipyridamole infusion—widely employed in combination with 12 lead electrocardiogram for the induction of ischemia[1,2] with two dimensional echocardiographic imaging in order to design a new provocative test for the diagnosis of coronary artery disease. This test resulted to have 3 major advantages; 1) the use of a widely employed pharmacological stressor; exercise independent, reasonably safe, as sensitive as exercise when approapriately high doses were employed[2]; e) the adoption of the mechanical marker of ischemia; highly specific, sensitive, allowing a diagnosis of site and extent of ischemia; 3) the advantages of 2 dimensional echocardiography: highly feasible during a pharmacological stress, with excellent spatial and temporal resolution, portable, versatile and relatively unexpensive.

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Mechanisms of action of dipyridamole as an ischemia stress.

We have extensively reviewed these mechanisms elsewhere[2]. Briefly, dipyridamole inhibits cellular uptake of adenosine, thereby determining adenosine accumulation which may provoke complex flow maldistribution phenomena—via arteriolar dilation—and true ischemia in the presence of an epicardial coronary stenosis significantly limiting regional flow reserve[7,8].

Several mechanisms have been hypothesized: ho rizontal steal; vertical steal: systemic steal; luxury perfusion; passive collapse of a tight yet compliant, coronary stenosis (fig. 1). This mechanism of adenosine—mediated "exaggerated" or "inappropriate" vasodilation can mimic a mechanism spontaneously occuring in effort ischemia, when the metabolically mediated vasodilation determines an actual "fall" of flow, in comparison with resting values, in the post-stenotic region (tab. 1). It is consistent with this interpretation that aminophylline (an adenosine receptor blocker) increases effort tolerance in patients with exercise induced ST segment depression reproduced by dipyridamole infusion, both with coronary artery disease[9] or Syndrome X[10]. It is intriguing that aminophylline administration acutely increases the exercise capacity also in patients with intermittent

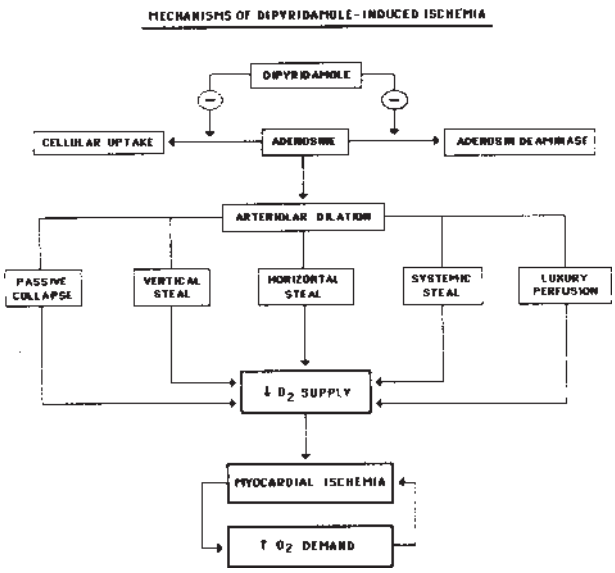

Fig. 1 — Possible mechanisms of dipyridamole-induced ischemia.

TABLE I—Myocardial ischemia during dipyridamole-test: a heterogenous entity.

	"ALTERNATIVE"	"CLASSICAL"	"VASOSPASTIC"
Mechanism: coronary	Adenosine-induced flow maldistribution	Supply-demand mismatch	Epicardial vasospasm
Timing: test (aminophylline-resistant) (aminophylline-induced)	During the test	At the end of the lest	At the end of the test
Antidote:	Aminophylline	Nitrates	Nitrates
Frequency: cases	All cases of dipyridamole-induced ischemia cases	<10% of dipiridamole-positive angina pts) (<30~ % of variant	< 35 of dipyridamole positive
Clinical meaning:	significant epicardial stenosis	severe atherosclerotic disease	variant angina

claudication[11], outlining a possible general role of adenosine—mediated excessive vasodilation as a general—not only myocardial—pathogenetic mechanism of ischemia.

Aside to this "alternative" pathway of myocardial ischemia, dipyridamole can provoke ischemia also through the activation of the classical pathway of "supply-demand" mismatch, with an increase in oxygen consumption exceeding the limited flow supply[13] (tab. I). This mechanism can hardly play any role at the onset of dipyridamole-induce ischemia, when dP/dt of contraction and rate-pressure product are only mildly increased[13]. However, it can become an important mechanism in self-maintaining ischemia, especially in those cases resistant to aminophylline. Here, the marked late rise in rate-pressure product—likely due to sympathetic excitatory reflexes triggered by ischemia—exceeds the ischemic threshold on effort, mantaining ischemia when the flow maldistribution has been reversed by administration of aminophylline. In these cases, the administration of nitrates, either orally or intravenously given, is necessary to abate ischemia[12].

Finally, there is a third vasospastic pathway of ischemia which can become important at the end of the test, especially after the pharmacological termination with aminophylline[14]: tab. I. Vasospasm due to aminophylline termination of dipyridamole stress promptly subsides after nitrates[14].

In conclusion, the 3 pathways of ischemia—the "alternative", adenosine dependent; the "classical", due to supply-demand mismatch; and the "vasospastic" one—can all be met during dipyridamole test, but always "in series" (never "in parallel") according to a well defined and predictable time—sequence. It is important to know and recognize all these heterogeneous mechanisms for a rational treatment of dipyridamole induced ischemia and for a logical interpretation of the test results.

The Dipyridamole-Echocardiography test

Patients are instructed to fast for at least 3 hours before the test and, specifically, to avoid tea, coffee and cola drinks, whose xanthine contents can limit dipyridamole action, in the preceeding 12 hours. Chronic bronchopneumopathic patients needing therapy with xanthines are not suitable candidates for DET.

Dipyridamole is administered intravenously (I.V.) 0.56 mg/kg in 4 minutes followed by 4 minutes of no drug and then by 0.28 mg/kg in 2 minutes. The cumulative dosage is therefore 0.84 mg/kg in 10 minutes (fig. 2).

This higher dose allows to overcome the major limitation of the "standard—dose" (0.56 mg/kg over 4') DET, i.e. a relatively low sensitivity (50 60%)[16] without any loss in specificity and no increase in risk[15]. On the contrary, the combination with handgrip does not add significantly to the sensitivity of DET[17].

During the procedure, the blood pressure is recorded with a cuff sphygmomanometer. A 12-lead ECG is performed before and every minute after starting the intravenous infusion. Some leads (usually V_2 and V_4) are slightly displaced to avoid interfering with the positioning of the transducer.

Two-dimensional echocardiograms are continuously recorded during the dipyridamole infusion and up to 10' minutes after the end of the infusion. In the baseline studies, all standard echocardiogra-

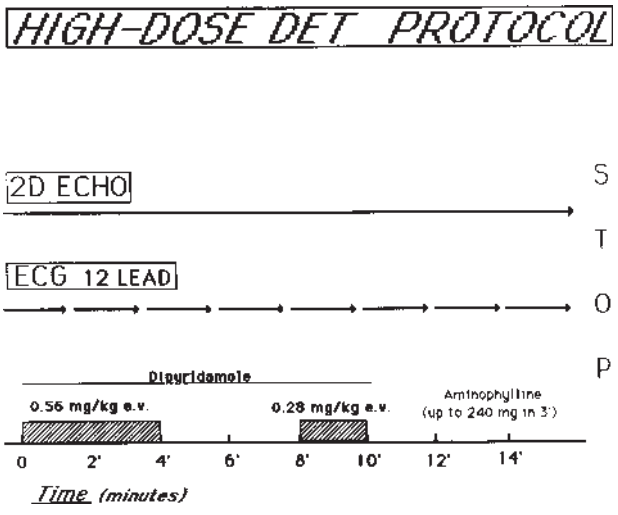

Fig. 2—High-dose dipyridamole-echocardiography test: protocol of execution.

maphic views are obtained if possible[15,16]. During the test, new areas of abnormal wall motion are identified on multiple views by rapidly moving the ultrasound transducer through various positions[15]. After an optimal position for the observation of abnormal wall motion is established, the transducer is held stationary.

Positivity of the lest is linked to detection of transient asynergy that was absent (fig. 3 and 4) or of lesser degree in the baseline examination (e.g., hypokinesis at rest becoming akinesis or dyskinetic after dipyridamole administration) (fig. 4). Any region that is already akinetic or diskinetic in rest conditions is excluded from analysis. The development of the asynergy can be preceded by transient hyperkinesis, which invariably accompanies negative test (Fig. 5). This hyperkinesis results from the decrease in afterload (systolic pressure), the increase in heart rate, and the increased contactility[13].

The test protocol requires ready-to-use availability of: 1) aminophylline (80-240 mg, I.V. infusion in 1-3 minutes, which promptly counteracts dipyridamole effects); 2) nitroglycerin (or sublingual isosorbide dinitrate), to be administered if aminophylline has failed to completely eliminate myocardial ischemia.

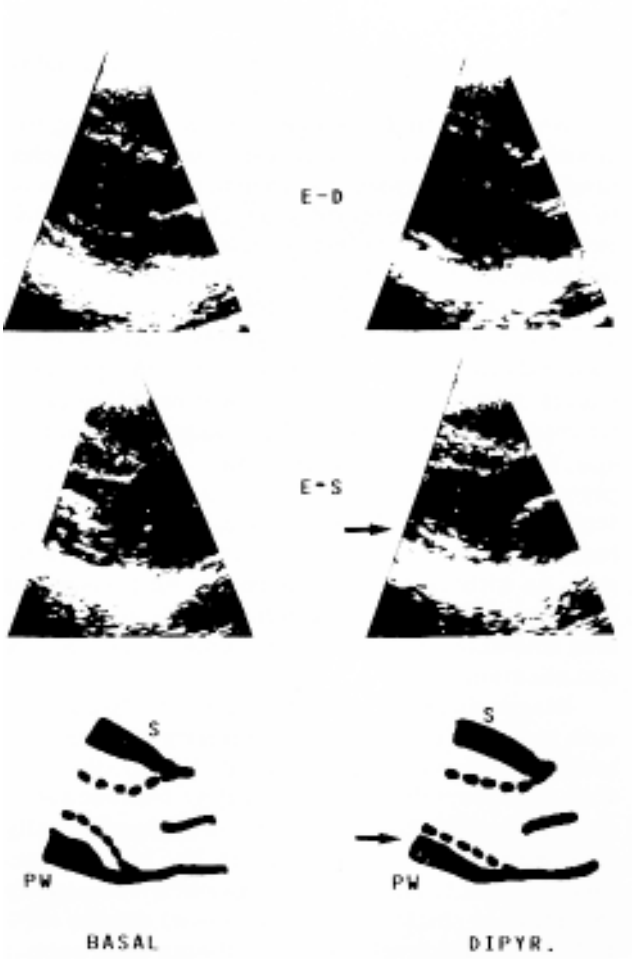

Fig. 3—An example of positive dipyridamole-echocardiography test (parastenal approach, long axis) After dipyridamole administration (DIPYR, on the left) a clear hypokinesia appears on left ventricular posterior wall (PW), that was normally contracting in basal conditions (BASAL, on the right). E-D = end diastole; E-S = end systole.

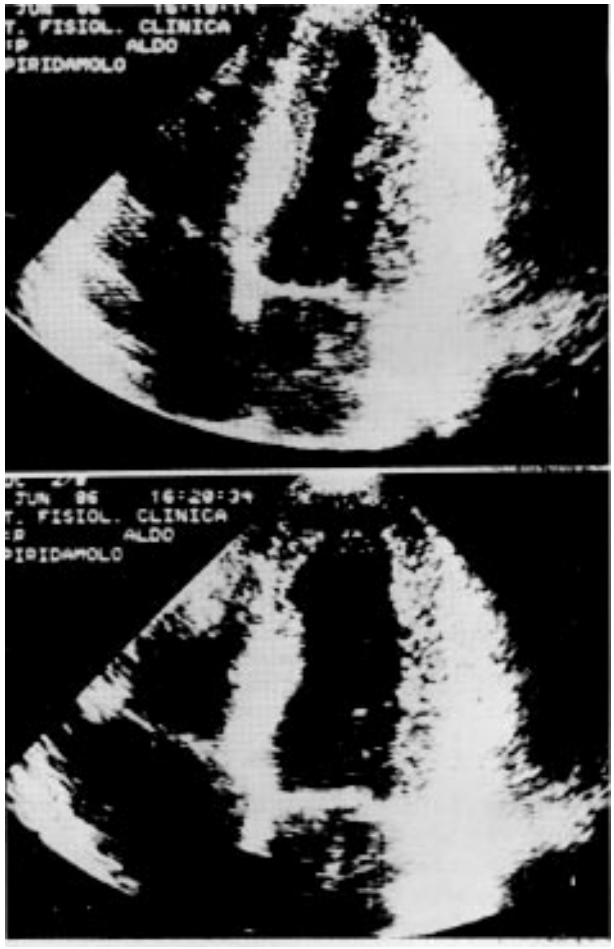

Fig. 4—Another two dimensional example (apical four chambres view, end systolic frames) of dipyridamole test showing the development of apical akinesia (lower panel).

In case of test negativity, aminophylline (40-70 mg over 1') is given at the twentieth minute from the onset for 2 reasons: 1) to abate side effects; 2) to block dipyridamole action, which may last up to several minutes after the infusion, possibly sensitizing the myocardium to spontaneous or exercise induced ischemia[17]. In the early experience with DET, we occasionally observed cases of aminophylline—sensitive spontanous myocardial ischemia, occurring within 2 hours from a negative test during which no aminophylline had been given.

In our experience, with the help of a well trained nurse, the time needed to complete the test is about 30 minutes, not different from that requested for an exercise (cycloergometer) electrocardiographic test.

Feasibility. Over the last 5 years, about 1300 DET's were performed in our Institution, and the test proved to be extremely feasible. With last generation echocardiographic instruments, about 5%, of all candidates for the dipyridamole-echocardiography test are excluded due to poor imaging quality in the basal

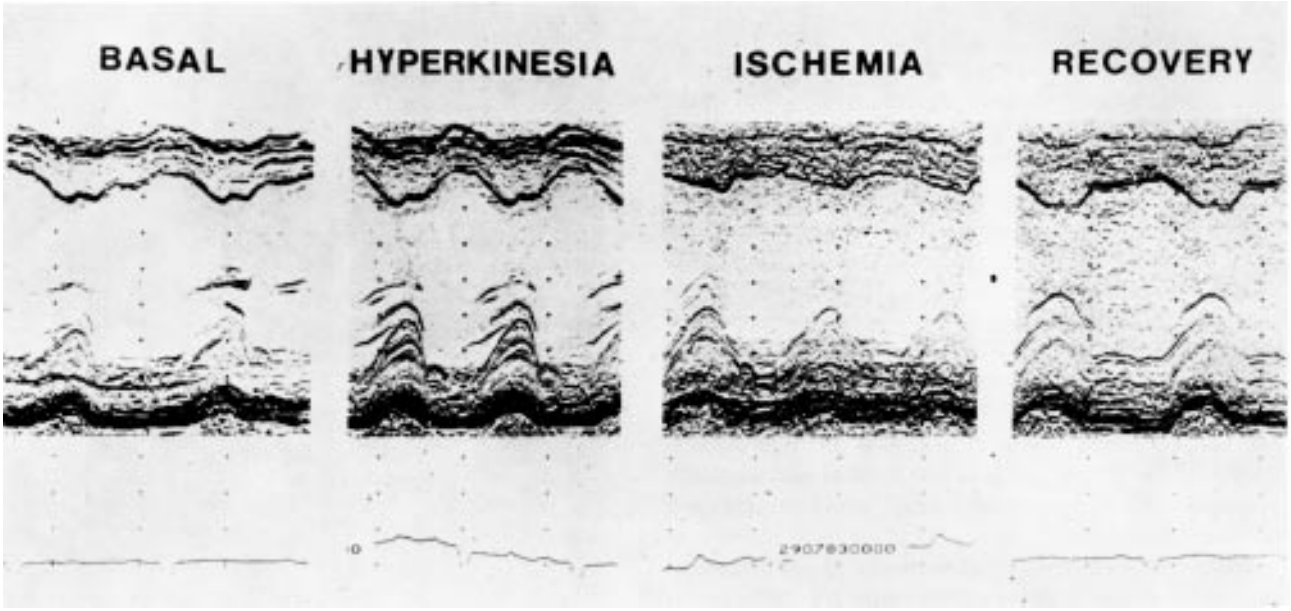

Fig. 5—Monodimensional images (taken below the mitral valve, parasternal approach) showing a positive dipyridamole test involving the interventricular septum. After dipyridamole (1 minute after the end of the infusion), an early hyperkinetic contraction of posterior wall and septum occurs (HYPERKINESIA), 3 minutes after, the posterior wall is still hyperkinetic, while the septum is markedly hypokinetic (ISCHEMIA).

state.

In these patients, dipyridamole infusion can be usefully combined with alternative imaging techniques, such as radionuclide ventriculography[18]. In all studied patients, the quality of echocardiograms during the test was unchanged compared to the basal state and, therefore, the recordings were suitable for analysis.

Safety. About two thirds of patients experienced some minor side effects after dipyridamole infusion: mild transient headache, facial flushing, nausea. No patient had significant arrhtythmias, severe hypotension, or vomiting[19]. No side effects were severe, and we completed the test in all patients. The symptoms quickly resolved after aminophylline administration. A few patients required nitrates as well to completely resolve an induced ischemic attack.

It is generally accepted that dipyridamole infusion is a safe stress test. This statement is based largely on the experience with dipyridamole thallium-201 scanning, which has been proposed as the first line test even in unstable angina patients in whom exercise stress testing is contraindicated[20]. In comparison with thallium-201 or ECG dipyridamole tests, the dipyridamole- echocardiography test has an important advantage that should further increase the safety record: the positivity of the test is based on a mechanical marker of myocardial ischemia, which is usually earlier than other markers such as ECG changes and pain. The beat-by-beat echocardiographic monitoring allows the test to be stopped as soon as obvious myocardial ischemia develops, without the need to inject the radionuclide and to wait several minutes until nuclear imaging is completed. This may permit stopping the test at an earlier stage, therefore avoiding more overt and dangerous manifestations of myocardial ischemia.

We believe that the safety of the test is tightly linked to the ability to continously monitor the mechanical marker of myocardial ischemia and being able to stop the test immediatly when obvious myocardial ischemia develops. It must be underlined that the more dangerous manifestations of dipyridamole induced myocardial ischemia, that is ST-segment elevation[21] or multiple areas of remote asynergy, are more often incurred soon after or even during the infusion of the standard case (0.56 mg/kg in 4') Bearing this in mind, we conclude that although dipyridamole infusion cannot be considered harmless, if one takes the obvious precautions that the administration of a powerful potentially ischemic stress requires, it is safe particularly when combined with echocardiographic monitoring. As with all testing procedures for myocardial ischemia, a physician with advanced life support training should be immediately available to manage any complications.

Diagnostic accuracy. In a subset of 710 patients with history of chest pain and coronary angiography, studied in absence of antianginal therapy, the high dose dipyridamole-echocardiography test showed a sensitivity of 74% for the detection of angiographically assessed coronary artery disease (> 70% lumen reduction of at least 1 major coronary vessel). The sensitivity was lower in single than in multivessel disease (52% and 89%, respectively) and in patients with normal resting function in comparison with those showing a resting regional dyssynergy. DET positivity allowed an objective documentation of myocardial ischemia in over 50% of patients with history of chest pain,

angiographically assessed CAD and negative or non-diagnostic exercise-electrocardiography test[22]. The overall specificity was 96%. No gender gap was found between females and males[23] and there was no difference between hypertensives and normotensives[24]. The short-term reproductibility of the test was excellent[25].

Doppler-dipyridamole echocardiography

In our experience, the usefulness of Doppler-derived information does not add significantly to the diagnostic value of DET, for 2 main reasons: 1) global systolic indexes, such as dP/dt of contraction, are less sensitive markers of dipyridamole induced ischemia than regional dyssynergy, as it happens in other clinical models of myocardial ischemia[6]: it is therefore not surprising that transaortic Doppler has a low sensitivity for CAD and only detects more extensive forms of ischemia[26,27]; 2) diastolic indexes, such as dP/dt of relaxation, provide a more sensitive marker of dipyridamole induced ischemia than global systolic indexes[10]. Unfortunately, the transmittal flow velocity curve is affected by hemodynamic changes induced by dipyridamole which may mask or mimic effects of myocardial ischemia on atrioventricular inflow pattern, therefore dramatically lowering the sensitivity of the test[27,28].

Stratification of a positive response

We have previously used conventional sensitivity-specificity analysis to describe the relation between dipyridamole-induced transient dyssynergy and arteriographic disease. This method requires binary (positive vs negative) classification of both imaging and arteriographic results. However, as pointed out by Demer et al.[29], there are three main limitations to this use of sensitivity- specificity analysis for assessing accuracy of noninvasive tests for coronary disease: 1) coronary disease is not an all-or-none condition: binary classification requires arbitrary threshold criteria and creates artificial distinctions in coronary artery disease that, in actuality, has a continuous spectrum of severity; 2) sensitivity and specificity values are determined by the disease distribution of the study population: a sample distribution with a high frequency of mild disease will be distributed centrally near the threshold values where scatter is more likely to lower sensitivity and specificity; 3) percent diameter narrowing is not an adequate standard for quantifying stenosis in clinical studies.

DET, however, does not give a dichotomous, "all or none", response. Rather, a positive response can be stratified along temporal and spatial coordinates which greatly strengthen the diagnostic and prognostic information derived from a positive test (fig. 6).

Time coordinate: the dipyridamole time (i.e., the time from onset of dipyridamole infusion to development of a regional asynergy) is conceptually similar to exercise time, i.e., the time from onset of exercise to development of 0.1 mVolt of ST segment depression. This similarity is substantiated by several lines of evidence, obtained comparing the results of DET versus anatomic (extent of angiographically assessed coronary disease; lesion geometry in single vessel disease), physiologic (exercise tolerance in CAD patients) as well as prognostic standards:

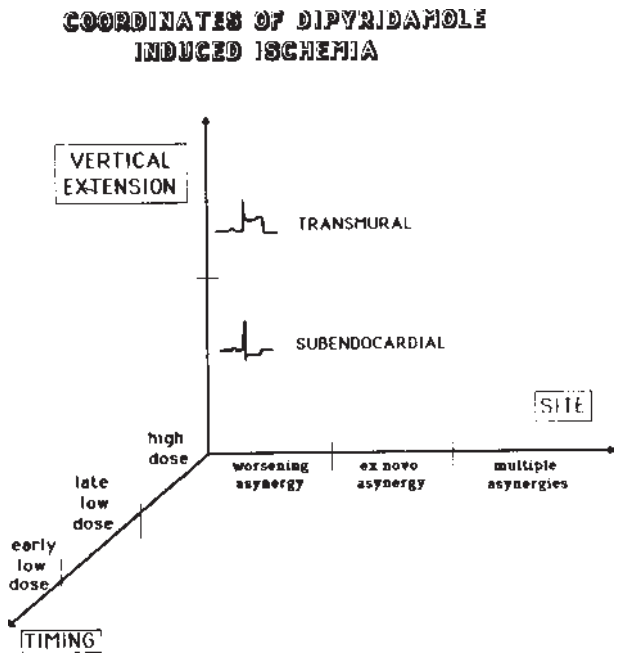

Fig. 6—Spatiotemporal coordinates of dipyridamole-induced ischemia. The x-axis represents the horizontal circumferential extent of ischemia. The y axis represent the vertical transmural extent, as grossly indicated by the electrocardiography pattern associated with the dyssynergy. The z-axis represents the temporal allocation of dyssynergy during the test, which is related to the functional impairment in coronary reserve.

1) The dipyridamole time is inversely related to the extent of coronary disease, being the standard dose positivity more often found in multivessel disease[15,16]. In patients with single vessel disease, more severe degrees of coronary stenosis—estimated by quantitative coronary angiography—are found in patients with shorter dipyridamole time[30].

2) The ischemic threshold on effort (assessed through the Rate-Pressure Product at 0.1 mVolt of ST segment depression) is higher in patiens with longer dipyridamole time[31].

3) The prognostic impact of DET positivity is clearly worse with low dose (i. e., dipyridamole time < 8 minutes) versus high dose (i.e., dipyridamole time > 8 minutes) positivity[32].

Space coordinate: As all diagnostic tests exploiting imaging techniques, DET can offer information on the geographic localization and spatial extent of ischemia. This has obvious clinical relevance, since it allows to identify the area at risk

in the individual patient, and also possibly the ischemia producing vessel in patients with multivessel disease who candidates to coronary angioplasty[33]. In term of correlation with coronary anatomy, there are 2 mechanical patterns which pathognomonically identify multivessel disease:

1) multiple dyssynergies in territories fed by different coronary arteries in patients with normal resting function: this pattern is quite rare, probably due to our policy to interrupt the test whenever an obvious asynergy has been clearly documented. We found this pattern only in the few patients in whom the multiple asynergies developed almost simultaneously, and always with very early low dose positivity.

2) Remote (heterozonal) positivity in patients with a resting dyssynergy: this pattern is relatively frequent in patients with a previous myocardial infarction, and it must be clearly separated from homozonal positivity, where the asynergy develops in the infarcted—although still viable—region[34].

Time and space coordinates of dipyridamol induced ischemia should always be considered in the evaluation of the test response. The temporal and spatial allocation of the dipyridamole-induced dyssynergy are even more important than its presence.

Comparison with the literature and with other stress tests

For a critical evaluation of any new test, it is essential to examine the possible conflicting evidence emerging from the literature and to compare the test directly, i.e., in the same patient population, to other commonly used methods.

DET vs DET. In our original report with the standard dose (0.56 mg/kg over 4') version of the test on 66 patients with effort angina, we reported a sensitivity of 56% in comparison with angiographically assessed coronary artery disease[16]. In another series of 93 patients with effort angina, we reported a sensitivity of 53% (74% with the high dosed, and in a third series of 62 patients with angina at rest, the sensitivity was 62%[35].

At that dosage, 2 papers on DET have appeared up to now in the literature. They are important to underscore some simple, but crucial, methodological aspects of the technique which are frequently neglected. Margonato et al, reported a 52% sensitivity on 22 patients with previous myocardial inferior infarction, positive exercise stress test and multivessel disease[36]: however, only short axis views of the left ventricle at the mitral valve level were obtained in that study. According to the Taijik's segmentation[37], only 5 of 14 segments of the left ventricle can be visualized in this way. Therefore, the majority of segments of the left ventricle is missed, and since the asynergy can be transient and localized, many studies can be judged as "false negatives". All views and projections should be obtained at baseline and during stress to fully exploit the potentialities of 2-dimensional echocardiography for imaging transient ischemia.

The second paper by Labovitz et al, evaluated a much larger population of 100 patients, studied with the standard stress-echo technique of exploring all views and projections[38]. The reported sensitivity was 66% markedly better than the 52% we reported, at that dose, on a similar patient population. Furthermore, the population of the study by Labovitz et al. was kept under antianginal therapy at the moment of testing.

A few data are also available with higher dipyridamole dosages.

Ferrara et al., with the dosage of 0.75 mg/kg over 10' reported a 63% sensitivity in a population of 57 patients with effort angina, studied off therapy[39] Bolognese et al, studied 74 patients early after acute un complicated myocardial infarction, at the dose of 0.84 mg/kg over 10', with our same infusion protocol[40]. They reported a sensitivity of 68% for multivessel disease, in a population obviously kept under full antianginal therapy. As a further indirect confirmatory evidence, there are the data of Cates et al., on 31 patients studied with dipyridamole-radionuclide ventriculography at the dosage of 0.725 mg/kg over 6'[18]. The reported sensitivity was 58% taking the transient dyssynergy as a criterion of positivity, and it rose to 67% adopting the criterion of a blunted increase in ejection fraction; the specificity was 92%. It is difficult to conceive a lower sensitivity with echocardiography instead of ventriculographic imaging, in view of the unquestionably higher spatial and temporal resolution of the echocardiographic technique, of the higher dose employed in DET, and of the fact that patients studied by Cates et al. were kept under antianginal therapy. With 400 mg of oral dipyridamole, Cohen et al. reported a sensitivity of 81% using digital echocardiography, which allowed a continuous cine-loop, quad screen format display[41].

On the basis of the available evidence, we conclude that dipyridamole, at appropriately high doses, frequently induces ischemia, which is easily found when it is appropriately looked for, for instance with 2-dimensional echocardiography or—when an adequate echocardiogram is difficult to obtain—with radionuclide ventriculography.

DET vs nuclear medicine perfusion imaging.

DET shows a similar sensitivity versus nuclear medicine perfusion imaging by Thallium[38,39,42] or MIBI[43] (with either exercise[38,42] or with high dose dipyridamole[39,43]). It is essential to note that patients enrolled in these 3 studies were off antianginal therapy. Antianginal therapy lowers the sensitivity of echo-testing, as it does with dipyridamole-ECG

testing, but it should not affect to a similar extent the sensitivity of Thallium-201 testing, which at least theoretically does not require myocardial ischemia as a diagnostic end-point[2]. Preliminary data are also available on the comparison between Dipyridamole-Radionuclide Ventriculography (which requires, similarly to DET, a mechanical marker of ischemia as the diagnostic end point) versus Thallium dipyridamole test. Dipyrimole-Radionuclide

Venticulography showed a similar sensitivity, with a greater specificity, for the diagnosis of coronary artery disease[14].

DET vs other stress echo procedures. Other provocative stresses associated with echocardiography for the diagnosis of coronary artery disease have been proposed. Exercise causes hyperventilation, tachycardia, and excessive chest wall movement that severely limit the acoustic approach during the exam[45]. Post exercise echo has been proposed to overcome such limitations[46], but this approach suffers on its turn of several problems: wall motion abnormalities due to transient ischemia may resolve rapidly and be normal at the time of delayed imaging: single loop format (necessary to have an acceptable feasibility) requires additional apparatus and expense: the diagnosis is often made on a single cardiac cycle and on a single echo projection, which cannot allow a complete visualization of all ventricular regions; post-exercise imaging does not allow the accurate identification of the level of exercise required to induce ischemia, which is essential for accurate stratification of disease severity.

Echocardiography monitoring during atrial pacing—from the transvenous[47] and transesophageal[48] approaches—is more feasible. However, atrial pacing is invasive and not always well tolerated by the patient, and the test cannot be completed in a significant number of patients due to the inability to achieve atrial capture or because of the development of second degree (Wenckebach) heart block. The handgrip test is technically feasible with echocardiography and is noninvasive[45], but its sensitivity is poor[43]. The dobutamine test is feasible, noninvasive, and adequately sensitive[8,50,51] but it may be unsafe at effective doses due to the high arrythmogenicity of the drug[52,53]. For equal, or similar, values of diagnostic accuracy there is no question that stress echo techniques have potential for much more widespread use, are less costly, do not need ionizing energy and require a much lower imaging time. In front of these advantages, there is the important limitation of stress-echo techniques that cannot be performed in the small proportion of patients with a poor acoustic window in resting conditions. More importantly, they are much more operator-dependent than nuclear medicine imaging. It is certain that a stress-echo procedure performed and intepreted by an echocardiographer lacking a specific training in this field is likely to create more diagnostic problems than it can solve. Also an experienced echocardiographist, but with no background on stress echo, needs a period of training in the stress echo-lab (about 6 months) to reach a satisfactory diagnostic accuracy in interpreting the tests[54].

There are many studies which are unquestionably negative or positive; still, there is a "gray zone" of interpretable tests where the visualization of some regions can be suboptimal and the level of experience of the cardiologist interpreting the test is critical for a correct reading. There are some precautions to minimize this "echocardiographic disease": 1) to agree in advance not to call minor degrees of hypokinesia; 2) to performs in selected cases, even for routine diagnostic reasons, joint reading between 2 independent observers; 3) to read the test "blindly" to other provocative tests and to angiographic data; 4) to try to document a dyssynergy from more than 1 projection, when possible. It is also wise to "weigh" the results of stress echo in the individual patient decision making according to the experience of the laboratory making the stress and also to the quality of images obtained in the individual patient.

Dipyridamole—Electrocardiography test: an echocardiographic view

For the detection of an angiographically assessed significant coronary stenosis, electrocardiographic markers suffer obvious limitations: 1) limited sensitivity (52% in our population); 2) very low specificity (41% in our population); 3) inability to detect the site and extent of ischemia, with the only exception of ST segment elevation in the absence of a resting q wave[55].

However, the information provided by the electrocardiogram can be very useful for at least 2 reasons: 1) the electrocardiographic pattern should be always compared with the findings during exercise eletrocardiography test. When the same electrocardiographic pattern is reproduced during both tests, it is an educated guess that also the prevaling pathogenetic mechanism of exercise induced ischemia recognizes an organic, rather than vasospastic, basis[52,56]. This might have important pathophysiological and therapeutic implications; 2) the presence of electrocardiographic positivity (i.e., ST segment depression) in the absence of a mechanical impairment is highly predictive of angiographically normal coronary arteries[57]. We frequently found this pattern in several conditions, where a diffuse involvement of coronary microcirculation has been described: arterial hypertension[21], syndrome X[57], acute heart rejection[58]. We named this entity as "echocardiographically silent myocardial ischemia", since the typical diagnostic pattern consists of obvious

electrocardiographic changes, often accompanied by chest pain, which can be consistently elicited by dipyridamole infusion in the absence of any detectable, regional or global, mechanical change. This sequence of events appears to mirror the well known "ischemic cascade" occurring in the presence of epicardial coronary stenosis and stress-induced ischemia, where the transient regional dyssynergy consistently precedes electrocardiographic changes and chest pain.

Whether these changes represent true "ischemia" is still debated. However, the absence of a mechanical marker of ischemia cannot be considered an evidence against the true ischemic nature of ST segment depression and/or chest pain in Syndrome X. In fact, myocardial ischemia must be transmurally extended to at least 30-40% of the myocardium to give a regional dyssynergy[50]. Therefore, the absence of mechanical impairment in no way rules out the ischemic nature of electrocardiographic changes. In the presence of a diffuse involvement of coronary microcirculation determining a reduction in coronary flow reserve, myocardial ischemia should be enough extended in a transmural sense to give eletrocardiographic changes, but at the same time enough limited in a transmural direction to remain mechanically occult.

As an alternative explanation, dipyridamole infusion might simply elicit a "false positive" electrocardiographic response, as exercise does, reflecting the inherent instability of the electrocardiographic marker of ischemia. This is certainly true if we accept the angiographic stenosis as the only possible gold standard. However, provocative tests are aimed to unmask myocardial ischemia, which can be certainly evoked even in the absence of coronary stenosis. If we look for more appropriate standards, dipyridamole induced ST segment depression does not necessarily yield a truly "false positive" response, since: 1) in patients with normal coronary arteries, it correctly identifies the subset with depressed flow reserve[1]; 2) in hypertensives, it recognizes patients with greater incidence of significant left ventricular arrhythmias[60]; 3) in patients with recent orthotopic heart transplantation, it correctly identifies patients with acute rejection, which has been linked to a transient depression of flow reserve[58].

We believe that the integration of the electrocardiographic and echocardiographic information is the only way to avoid the "stunning" of the cardiologist[61] in front of the flourishing of diagnostic markers and techniques, and to get the most of the pathophysiological and clinical information that the dipyridamole test—and, most likely, any provocative test for myocardial ischemia—can offer. The systematic integration of echocardiographic and eletrocardiographic information is the only way to better understand the different aspects of myocardial ischemia.

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