Review Article

ST Changes in Dipyridamole Pharmacological Stress Testing: Do They Have Diagnostic or Prognostic Significance?

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Dipyridamole (DIP) is a vasodilatory substance which is widely used to perform pharmacological stress tests, almost always in combination with other imaging techniques, such as myocardial perfusion imaging (MPI) and, less commonly, echocardiography. Pharmacological stressing is necessary when investigating patients who have a reduced capability to perform exercise. This may be either due to physical limitations, such as musculoskeletal or neurological problems or poor general physical condition, or the result of drug therapy that prevents the attainment of an adequate double product with treadmill exercise, such as the use of β-adrenoceptor antagonists.

The mechanism of action of DIP is via the blockade of cell membrane transport of adenosine, thus raising the extracellular levels of adenosine, which in turn raises cAMP levels and calcium uptake in coronary smooth muscle cells, leading to coronary vasodilation.[1,2] This dilation leads to a three- to five-fold increase in coronary blood flow in healthy coronary arteries with no stenoses or damaged endothelium. In abnormal arteries, the failure to dilate leads to increased vascular resistance of those vessels and preferential blood flow through the normally dilated arteries. This heterogeneity of blood flow reserve causes relative ischaemia of the myocardium supplied by the stenosed or abnormal coronary arteries and is referred to as coronary steal.[2-5] One of the advantages of DIP is that it does not cause tachycardia and has no positive inotropic effects; thus it has no significant effect on myocardial oxygen demand and consumption.[2,3]

The relative ischaemia induced by DIP is usually clinically silent. However, on occasion, it may be expressed clinically as angina pectoris or as ST segment depression on the patient's electrocardiogram, as has been noted in 6-34% of patients undergoing DIP pharmacological stressing.[6]

The aim of this review is to examine the significance of DIP-induced ST segment depression and to explore its possible diagnostic and prognostic implications.

What is the significance of ST depression after DIP infusion in the investigation of patients with suspected or known coronary artery disease?

The relative ischaemia caused by DIP, as mentioned previously, is due to the development of myocardial flow heterogeneity and coronary steal. The phenomenon of coronary steal occurs when coronary flow to a stenosed artery is preferentially diverted upon vasodilator administration, via collateral vessels that supply that particular territory, to a territory supplied by the artery from which the collaterals have originated. This is due to the fall in resistance in the non-ste-

nosed, collateral-supplying artery, which does not occur in the stenosed artery.[6,7] The phenomenon of coronary steal was originally described by Becker et al in experimental models as an absolute decrease in perfusion from resting blood flow in a segment following vasodilation, due to diminished driving pressure at the proximal end of a stenosed artery supplied by collateral vessels. This is due to decreased resistance in the supplying, conductance artery, as well as a nominal or blunted fall in resistance in the collateral circuit.[8]

In this article we describe the significance of the appearance of the relatively rare finding of ST segment depression after DIP infusion and its relationship to coronary steal and relative myocardial ischaemia. We also discuss its possible implications regarding the diagnosis of coronary artery disease or of microvascular dysfunction and its ability to determine their severity and extent.

The studies conducted to date on the significance of DIP-induced ST segment depression are small, non-randomised, and usually view DIP pharmacological testing in combination with MPI or stress echocardiography. However, they provide an indication of the possible significance of this finding, when it is present. They also provide an impetus for further investigation of this unusual phenomenon and its implications regarding the diagnosis and prognosis of coronary artery disease.

Accordingly, Tavazzi et al studied 54 patients with angina pectoris, using high dose (0.75 mg/kg) DIP stress testing and subsequent coronary angiography, and found that only patients with >50% stenoses had ST segment depression (74% of patients with effort related angina). Furthermore, a positive response was more common in patients with more extensive coronary artery disease, particularly those with two-vessel disease (36% in 1VD, 79% in 2VD and 60% in 3VD).[9] Vilanueva et al later found that ST segment depression after DIP infusion was associated with a larger number of myocardial segments demonstrating Tl-201 redistribution.[10] Similarly, Chambers et al noted that DIP-induced ST segment depression was a highly specific indicator of the presence of coronary artery disease, although it was not highly sensitive on its own. They also found that the presence of collateral vessels was one of the most important predictors of the development of ST depression.[11]

Furthermore, the finding of ST depression may be able to predict coronary artery restenosis after coronary angioplasty.[12] Pirelli et al found in one study that DIP-induced ST segment depression correlated well with the presence of restenosis in asymptomatic patients who had undergone coronary angioplasty. This was confirmed by thallium scintigraphy and stress echocardiography.

Although DIP may occasionally cause both angina and ST depression in the presence of relative ischaemia, previous studies have shown that the presence of angina without electrocardiographic changes was neither predictive of coronary artery disease nor able to identify high risk individuals. The predictive value of angina was significant only when ST depression was present.[13,14] Ortega et al investigated 593 consecutive patients with chest pain, using DIP stress testing in combination with Tc-99m tetrofosmin scintigraphy. They demonstrated that when patients developed angina upon DIP infusion without ST changes, there was no statistically significant increase in the extent or the severity of coronary artery disease, when compared to patients with no anginal symptoms. Conversely, in the presence of concurrent ST changes after DIP administration, there was a higher frequency of perfusion defects (93% in patients with ST depression versus 76% in patients without ST depression) and of scintigraphically observed ischaemia (89% versus 49%).[13] Similarly, a study of 72 consecutive patients with angina pectoris revealed that chest pain alone was not a sensitive marker of coronary artery disease. Only patients with angiographically confirmed stenoses had DIP-induced ST depression.[14] DIP itself can cause non-ischaemic chest pain due to stimulation of local nerve endings via adenosine, which have a similar somatic distribution to the pain caused by true myocardial ischaemia. This is not true angina; it is not accompanied by electrocardiographic changes and it is readily relieved by the administration of aminophylline, which directly blocks the action of DIP and adenosine on nerve endings.[2] This manifestation is one reason why pain alone after DIP infusion is not a good diagnostic or prognostic indicator, which was confirmed in a study by Dabizzi et al on 227 consecutive patients undergoing coronary angiography and DIP-thallium scintigraphy. DIP-induced angina was indicative of the presence of coronary artery disease, but was not a sensitive or specific marker on its own. When DIP-induced ST depression was present, though, it was a more sound indicator for the presence of three-vessel disease or of extensive collaterals.[15] When DIP angina and ST depression were combined with scintigraphic findings, as in a study performed on 57 patients with coronary artery disease, 21 patients with near normal coronary arteries and 20 healthy subjects, their sensitivity in diagnosing triple vessel disease was

significantly increased. When they were considered alone, angina and ST depression had positive predictive values of 93% and 88%, but negative predictive values of 40% and 42%, respectively.[16] This indicated that, although the occasional presence of DIP-induced ST segment depression alone is not highly specific, when viewed in combination with scintigraphic findings, it can be a useful additional indicator of coronary artery disease severity.

The presence of a previous myocardial infarction was also a contributing factor to the sensitivity of DIP angina as a determinant of severe coronary artery disease. A group of 74 patients with suspected coronary artery disease was investigated with DIP-thallium scintigraphy and coronary angiography. In patients who had previously suffered a myocardial infarction, DIP-induced chest pain did not predict the presence of more severe coronary stenoses. In the group with no previous myocardial infarction, the subjects who developed chest pain after the infusion of DIP had more severe ischaemia than the patients with no pain.[17] A possible explanation for this finding is that in the presence of collaterals there is a greater degree of coronary steal, due to the active vasodilation that is already taking place in these vessels. Therefore, they cannot produce any further response to the increased levels of local adenosine after DIP administration. There is thus a more pronounced alteration in the local coronary blood flow of those areas, and this is translated into a higher incidence of pain and ST depression. In patients who have had a previous myocardial infarction, after myocardial necrosis ensues the collateral vessels supplying the infarcted area slowly close, as there is no longer an ischaemic drive in this area stimulating their development. Consequently, there is less coronary steal and chest pain after DIP administration.

The issue of coronary steal and its effects on the diagnostic sensitivity of DIP pharmacological stress testing with regard to coronary artery disease was examined as early as 1982 by De Ambroggi et al.[18] They compared 34 patients with chest pain to 10 normal subjects, using DIP pharmacological stressing and coronary angiography. This was a small-scale study, performed on a limited number of patients, that resulted in a poor sensitivity (44%) and specificity (39%) and investigated DIP stress testing alone, without MPI or echocardiography. The investigators inferred that coronary steal was not the sole cause of an "ischaemic" response to DIP, which was translated as angina or ST segment depression.

A later study by Ikeda et al on 167 patients undergoing coronary angiography demonstrated that patients with a previous myocardial infarction who had DIP-induced ST depression appeared to be at increased risk of an adverse cardiac event and had more severe stenoses.[19] Ninety-one of the patients studied had a previous myocardial infarction and the rest had no previous myocardial infarction. In both of the aforementioned groups, ST depression correlated well with a finding of coronary artery stenoses greater than 90% (83% of non-infarct patients and 71% of infarct patients). Patients with coronary artery stenoses less than 90% had a lower incidence of ST depression after DIP infusion (16% in non-infarct patients and 19% in infarct patients). The sensitivity of DIP-induced ST depression as an indicator of severe (i.e. >90%) coronary artery stenoses was 82% in non-infarct patients and 71% in infarct patients and the specificity was 84% in non-infarct patients and 81% in infarct patients. The specificity and sensitivity of DIP-induced ST segment depression was lower for stenoses <90%, which nevertheless also require intervention. This study indicated that the occasional finding of ST depression may be a good marker of severe stenoses, but not necessarily of the presence of critical stenoses in general.

Moreover, two later studies indicated that DIP-induced ST segment depression may potentially be a good marker of greater extension of coronary artery disease, a higher frequency of multivessel disease and a worse overall prognosis with respect to cardiac morbidity and mortality.[20,21]

One peculiarity of DIP infusion was that ST depression in patients with severe coronary artery stenoses occurred more commonly in those who had highly developed collaterals. This was postulated to be due to a greater degree of coronary steal from the small collateral vessels, which are already chronically dilated under the influence of pre-existing local adenosine released as a response to the upstream stenosis.[11,22-3] In fact, highly developed collaterals and a greater increase in double product attained after DIP infusion were both strong predictors of ST depression.[11]

DIP-induced ST depression has also been found to be an independent predictor of adverse perioperative cardiac events after major vascular surgery. In a study of 509 patients about to undergo vascular surgery, high dose (0.84 mg/kg) DIP stress testing and DIP stress echocardiography were performed pre-operatively, with 17.3% of the subjects having wall motion abnormalities following DIP infusion. DIP-induced ST segment depression was shown, via multivariate analysis, to be a predictor of adverse cardiac events perioperatively, independently of stress echo test positivity.[24]

Finally, in a study by Ho et al of 1174 patients undergoing vasodilator stress perfusion imaging, where 653 patients underwent coronary angiography and 521 patients were followed up without angiography (prognostic population), vasodilator-induced ST segment depression was an independent variable, which along with summed reversibility score and increased thallium lung uptake greatly increased the ability of thallium scintigraphy to identify low, intermediate and high risk patients. Also, it was an independent prognostic indicator for myocardial infarction and death at 7 years follow up (91% of high risk patients vs. 51% of low risk and 73% of intermediate risk patients).[25]

Special patient subgroups

Hypertensive patients

Hypertensive patients are a special subgroup in which DIP-induced ST depression has been more closely examined, using high dose DIP infusion (up to 0.84 mg/kg) in combination with echocardiography. These were patients in whom the raised arterial blood pressure placed them at an increased risk of coronary artery disease, left ventricular hypertrophy and microvascular disease. All of these factors affect the coronary microcirculation by reducing the capillary density within the hypertrophied myocardium, which also causes myocardial capillary compression and has increased oxygen demands. None of the patients studied had pre-existing coronary artery disease, and the studies were an initial assessment of the prognostic value of the occasional presence of DIP-induced ST segment depression in hypertensive patients.[26-29]

Three of the above studies focused on asymptomatic hypertensive patients who, upon DIP infusion, showed no echocardiographic evidence of left ventricular dyssynergy. Up to 30% of patients[26] had DIP-induced ST segment depression and these patients tended to have a higher left ventricular mass index and longer duration of hypertension, both of these factors indicating increased coronary resistance and reduced coronary flow reserve.[26,29] Picano et al, who studied 28 hypertensive patients and 20 controls using high dose DIP stress echocardiography, also showed that ST segment depression (in 36% of the hypertensive patients) appeared before the development of dyssynergy of left ventricular wall motion.[27]

Lucarini et al examined 28 hypertensive patients who had a history of angina pectoris, with normal coronary angiograms. The patients who developed DIP-induced ST segment depression (57% at high dose DIP, 0.84 mg/kg) had a greater incidence of left ventricular hypertrophy, but no patients had evidence of left ventricular dyssynergy.[28]

Studies involving follow up and risk stratification of these patients are still lacking, and will be needed in order to understand the full implication of the appearance of DIP-induced ST segment depression in hypertensive patients. The current data, though, indicate that there are many changes at the level of the microcirculation and the endothelium, which are possible causes of diminished coronary reserve and potential ischaemia, but they are not readily detectable in their early phase by other modalities, such as angiography, myocardial scintigraphy or stress echocardiography. Nevertheless, DIP-induced ST segment depression, when present, may indicate their existence.

Patients with syndrome X

Microvascular and endothelial dysfunction are also very important factors in patients categorised as having syndrome X, where they display clinical and electrocardiographic ischaemia without any evident coronary artery stenoses. A study of 19 patients with syndrome X showed that, as in the case of hypertensive patients, high dose DIP-induced ST segment depression occurred in the absence of left ventricular wall motion dyssynergy on stress echocardiography, indicating "echocardiographically silent myocardial ischaemia."[30]

When comparing 6 normal subjects to 20 patients with known coronary artery disease and 10 patients with syndrome X, Nadazdin et al found that the patients with coronary artery disease or syndrome X displayed high dose DIP-induced ST segment depression (50% of coronary patients and 60% of syndrome X patients), but only patients with coronary artery disease developed dyssynergy on stress echocardiography.[31] Both patients with coronary artery disease and those with syndrome X had an abnormal left ventricular filling pattern, which was similar in the two groups. This was an indication that the echocardiographically silent ischaemia in patients with syndrome X is more diffuse.

Once more, prospective follow up studies with larger cohorts are necessary to determine the significance of DIP-induced ST segment depression, when present, which seems to be a more common occurrence amongst patients with syndrome X.

Studies are lacking at present in other disorders which primarily affect the coronary microcirculation,

particularly in their early stages, such as in diabetes mellitus.

Other subgroups

DIP stress testing has also proved to be useful, particularly since it is non-invasive, in diagnosing coronary artery disease in children who suffer from Kawasaki disease. In fact, the degree and the extent of ST depression were correlated with the severity of the coronary artery disease.[32] In a study by Tomita et al in 17 Japanese children with Kawasaki disease, all of the children with DIP-induced pain and ST depression had coronary artery disease.

Another subgroup which was studied was patients with hypertrophic cardiomyopathy, where the presence of ST depression after high dose DIP infusion was a predictor of worse survival and a greater number of adverse cardiac events.[33] Lazzeroni et al studied 79 patients with hypertrophic cardiomyopathy, 37% of whom had a positive DIP stress test with ST depression (Group A) and 63% of whom had no electrocardiographic changes (Group B). Neither group of patients developed any transient left ventricular wall motion abnormalities on stress echocardiography. They were all followed up for a mean of 72 months and adverse cardiac events were noted. These included left ventricular or left atrial enlargement, unstable angina, syncope, atrial fibrillation and the development of bundle branch block. The patients in Group A had a much lower event-free survival rate (36.2%) when compared to the patients in Group B (84.2%). The authors therefore inferred that clinically induced myocardial ischaemia may play an important role in identifying patients with hypertrophic cardiomyopathy who are more likely to suffer from adverse cardiac events.

In heart transplant patients, acute rejection may be diagnosed by DIP-induced ST depression, even in patients with normal left ventricular systolic function. Picano et al[34] studied 47 heart transplant patients within their first 5 post operative weeks, by DIP stress testing and myocardial biopsy. Eleven of the patients studied had ST depression. The sensitivity and specificity of DIP stress testing in diagnosing acute rejection (using biopsy as a gold standard) were 72% and 94% respectively. Many of these patients continued to have normal left ventricular systolic function on echocardiography. Nevertheless, the ST depression induced by DIP was indicative of early small vessel damage, which was brought on by early, acute rejection and this test was sensitive, yet non-invasive.

Study considerations

Many of the studies concerning DIP-induced ST changes have been performed on Japanese patients, who could be considered as a different group when compared to European and American populations. This may be a potential limitation in the evaluation of the above studies. Nevertheless, all groups of researchers concluded that the presence of ST depression after DIP administration may be a good marker of the presence of multiple vessel disease, of more severe stenoses and of the extensive development of collaterals. As the number of vessels affected increased, so did the sensitivity of DIP pharmacological stress testing.[11,15,16,19,25]

Another potential limitation is that nearly all of the studies of DIP-induced ST segment depression in patients with hypertension, syndrome X and hypertrophic cardiomyopathy were performed using high dose DIP stress echocardiography (up to 0.84 mg/kg) rather than the conventional dose of 0.56 mg/kg used in myocardial perfusion imaging.

Dipyridamole-induced ST elevation

Only two cases have been described where the infusion of DIP led to ST elevation.[35,36] This was explained as severe transmural ischaemia caused by extensive coronary steal and was a marker of very severe coronary artery disease.

In a study by Fujita et al, although 16 patients with vasospastic angina displayed ST elevation during an attack, upon DIP infusion they had ST depression, which did not always correspond to territories affected by coronary artery spasm or to any evident coronary artery stenoses. This indicates that patients with variant angina may also have an underlying dysfunction of their microcirculation.[37]

Conclusion

ST depression induced by DIP infusion may be a good predictor of macro- and microvascular coronary artery disease, with moderately high sensitivity and specificity. Stressing with DIP has the advantage of being a safe and non-invasive approach and its predictive values are greatly improved when it is used in conjunction with other non-invasive modalities, such as MPI and stress echocardiography, as is generally done in current daily medical practice. In fact, DIP-induced ST depression predicts more defects on thallium scintigraphy.[11] The presence of this electrocardiographic

phenomenon could be an indicator of poor prognosis, particularly in patients after myocardial infarction and hypertensives, and it may indicate the presence of microvascular dysfunction in patients with hypertension and syndrome X. Moreover, it is a potentially good marker of the severity of coronary artery disease and the presence of collaterals.[38,39]

Current studies are still lacking in adequate patient cohort sizes and follow up, which will be needed in order to give a truly accurate picture of the value of this finding. They do indicate, however, that it may be a significant finding. There is a need for further investigation of the phenomenon which, when present, may enable us to better understand the pathophysiological basis of microvascular and endothelial dysfunction and reduced coronary reserve in patients who may not yet have developed epicardial coronary artery stenoses or regional wall motion abnormalities, as evidenced by stress echocardiography.

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