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Temporal Sequence and Spatial Distribution of Ischaemic Changes During Dipyridamole Stress Test – the Key Role of Microvascular Dysfunction

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Background: It is accepted that, in patients with epicardial coronary atherosclerosis, ischaemia produces a time sequence of events in myocardial regions supplied by stenotic branches characterised by regional wall motion abnormalities (WMA) followed by electrocardiographic changes and angina. Yet, the evidence indicates that patients with coronary atherosclerosis present a diffuse impairment of distal coronary vessels even in remote myocardial regions supplied by non-stenotic branches. Thus, temporal sequence of ischaemic events and the distribution of WMA may be influenced by microcirculatory dysfunction.

Method and Results: The study population consisted of 21 patients with stable angina and isolated stenosis of left anterior descending coronary artery (LAD). Patients underwent electrocardiographic and echocardiographic monitoring during dipyridamole infusion (DIP). During DIP, 14 patients exhibited both echocardiographic abnormalities and electrocardiographic changes and/or angina. In 8 patients (57 %) echocardiographic abnormalities represented the first ischaemic event; in the remaining 6 patients (43 %) the first ischaemic event was represented by electrocardiographic changes and/or angina. WMA appeared in LAD-dependent territories in 4 of 15 patients (27 %), in non-LAD-dependent territories in 5 patients (33 %), in both LAD and non-LAD-dependent territories in the 6 remaining patients (40 %). The mean percentage of abnormal segments and the mean WMA score were similar among the 3 groups (p = 0.8 and p = 0.47).

Conclusions: In patients with stable angina, the mechanisms of myocardial ischaemia are determined by a complex interplay between epicardial obstructions and microvascular dysfunction. This evidence underscores the need in individual patients of a tailored treatment based on the main mechanisms of myocardial ischaemia. J Clin Basic Cardiol 2005; 8: 47–53.

Key words: coronary stenosis, dipyridamole, myocardial ischaemia, stable angina

The current pathophysiological view, largely derived from experimental models, postulates that in patients with epicardial obstructive coronary atherosclerosis, ischaemia produces a well defined time sequence of events in myocardial regions supplied by stenotic coronary artery branches characterised by a decline in left ventricular regional wall motion followed by electrocardiographic (ECG) changes and, in a minority of patients, by angina pectoris [1]. This sequence of events has been named ischaemic cascade [1]. A growing body of evidence, however, indicates that patients with obstructive coronary atherosclerosis, differently from experimental models, present a diffuse impairment of distal coronary vessels even in remote myocardial regions supplied by non-stenotic coronary branches [2]. Thus, spatial extent of perfusion abnormalities and hence of mechanical dysfunction may be influenced by coronary microcirculatory dysfunction [2, 3].

We hypothesised that, in patients with chronic stable angina, stress-induced myocardial dysfunction might occur not only in myocardial regions supplied by the stenotic coronary branches but also in remote regions supplied by non-stenotic coronary branches. To test this hypothesis we assessed the temporal sequence of ischaemic events and the regional distribution of wall motion abnormalities (WMA) in a well selected group of patients with chronic stable angina, no history of myocardial infarction and a single critical stenosis in the proximal segment of the left anterior descending coronary artery (LAD) who underwent ECG and echocardiographic continuous monitoring during dipyridamole infusion.

Furthermore, we reassessed the spatial and temporal sequence of ischaemic events 12 months after coronary revascularisation by using the same study protocol.

Methods

Study Population

The study was carried out in a consecutive series of patients consisting of 17 men and 4 women (mean age 58 ± 9 years; range 43–76 years) who were selected on the basis of the following inclusion criteria:

1) a history of chronic stable angina (Class II–III of the Canadian Cardiovascular Society; symptom duration ranging from 6 to 24 months) without clinical history and instrumental evidence of previous myocardial infarction;
2) reproducible positive exercise tests for ECG myocardial ischaemia (horizontal or downsloping ST segment depression ≥ 2.0 mm of the baseline value 0.08 seconds after the J-point) and angina;
3) angiographically normal left ventricular function (mean left ventricular ejection fraction 61 ± 6 %, range 50–67 %);
4) isolated stenosis of LAD > 70 % measured by quantitative computerised angiography (mean reduction of the luminal diameter: 85 ± 10 %, range 70–98 %);
5) right dominant coronary circulation, and
6) good echocardiographic windows.

Resting ECG, echocardiogram and Doppler mitral flow pattern (a measure of left ventricular diastolic performance) were normal in all patients. The presence of collateral circulation to LAD was scored according to Rentrop’s classification [4]: grade 0: no filling of collateral vessels; grade 1: filling of non-epicardial collateral vessels; grade 2: partial filling of epicardial vessels and grade 3: complete filling of epicardial vessels. Collateral circulation ≥ grade 2 was observed in 12 patients. No patient had evidence of left ventricular hypertrophy, mitral valve prolapse or conduction defects that could...
interfere with the interpretation of ST segment changes and no patient was taking digitalis. Blood potassium levels were within normal range in all patients. Family history of ischaemic artery disease in first-degree relatives before the age of 60 years was present in 13 patients (62 %), hypertension (blood pressure > 140/90 mmHg) was present in 3 patients (14 %), and hypercholesterolaemia (plasma cholesterol levels > 200 mg/dl in two separate occasions) was present in 12 patients (57 %). Six patients (28 %) were current smokers (> 5 cigarettes per day). No patient had history nor family history of diabetes or glucose intolerance. A period of pharmacological washout of at least 72 hours was allowed before the study with the exception of sublingual nitrates if needed and all patients abstained from caffeine-containing drinks for 48 hours before the study. Study protocol was approved by the Institutional Ethics Committee and written informed consent was obtained by all patients.

Study Protocol

After the patients were placed in the left lateral decubitus position, two-dimensional echocardiograms were obtained using a commercially available phased-array imaging system with 2.5 MHz transducer (Hewlett Packard, Sonos 5500). All studies were recorded on super VHS videotape. Four views (parasternal long-axis, parasternal short-axis at the mitral, papillary muscle and apical level, apical four chamber view, and apical two-chamber) were obtained as previously described [5]. Two-dimensional echocardiographic monitoring was performed at baseline, during dipyridamole infusion (0.56 mg/kg for 4 min segments, were divided by 0.28 mg/kg in 2 minutes) and up to 20 minutes after the end of dipyridamole administration [6]. The cumulative dose of dipyridamole infused was 0.84 mg/kg over 6 minutes. Left ventricular wall motion was assessed in a qualitative manner as the appearance of systolic abnormalities (hypokinesis, akinesis and dyskinesia) during dipyridamole infusion. To this end the left ventricle was divided into 16 segments [5] and echocardiographic motion was arbitrarily divided in LAD-dependent and/or non-LAD-dependent segments (Fig. 1). Regional wall motion was graded as normal (0), hypokinetic (1), akinetic (2), and dyskinetic (3), and evaluated independently by two expert echocardiographers not involved in the study. A third investigator reviewed the echocardiograms in blinded manner if the first two investigators were not in agreement. The time to onset of regional WMA (in seconds from the beginning of dipyridamole infusion) was recorded. For the purposes of this study the number of segments showing WMA was measured and expressed as percentage of the total LAD-dependent and/or non-LAD-dependent segments; furthermore, the mean severity score of segments showing WMA was also calculated. Doppler mitral flow was also recorded and the E/A ratio (the ratio between early diastolic and late diastolic velocities) was calculated in all patients. A reduction of the E/A ratio > 30 % or its inversion during dipyridamole infusion was arbitrarily considered abnormal and indicative of left ventricular diastolic dysfunction. The time to onset of an abnormal E/A ratio (in seconds from the beginning of dipyridamole infusion) was recorded.

Twelve-lead ECG was continuously monitored during the procedure and recorded every minute throughout the procedure. The level of ST segment, 80 ms after the J-point was calculated after signal averaging by means of a computer assisted system in all 12 leads. The time to onset of ST segment depression 0.5 mm below the baseline value (measured in seconds from the beginning of dipyridamole infusion) and the ECG lead was immediately recorded.

At the beginning of dipyridamole infusion, patients were informed that they could develop the usual angina pain or other unpleasant symptoms. This request was not repeated during the infusion of dipyridamole in order to avoid any potential bias. Patients were instructed to promptly report pain onset. The time to onset of typical angina (in seconds from the beginning of dipyridamole infusion) was immediately recorded. Immediately after the infusions, patients were asked to report the maximal severity of pain using a visual analogue scale as previously described [7]. To this end the 100 mm scale was marked from no symptoms to severe symptoms. The scale was measured from 0 to the subject’s mark in millimetres.

During the procedure, blood pressure (by Riva-Rocci cuff sphygmomanometer) was recorded every minute. All patients received intravenous aminophylline (240 mg) at the end of the test.

Coronary Revascularisation and Follow-Up

In all patients coronary revascularisation was carried out by coronary artery stent implantation at the site of the culprit lesion. The in-hospital course was uneventful in all patients. After a mean follow up time of 11 ± 2 months from revascularisation all patients were asymptomatic. Repeated coronary angiography documented patency of the revascularised coronary vessel with residual stenosis < 10 %. Two days after coronary angiography, patients underwent dipyridamole test according to the same modalities described above.

Statistical Analysis

Continuous normally distributed data are expressed as mean ± 1 standard deviation and were analysed by two-tailed unpaired Student’s t-test. Factorial analysis of variance was used to compare multiple groups; for a p-value < 0.05 pairwise comparisons were performed by using Scheffe’s F-test. Chi-square test with continuity correction was applied to compare proportions. Differences between groups were considered to be statistically significant at a p-value < 0.05.

Results

Pre-Revascularisation Study

Dipyridamole infusion was well tolerated by all patients so that the test could always be completed. The detailed haemodynamic findings recorded during the procedure are reported in Table 1.
Response to Dipyridamole Stress Test

During dipyridamole infusion, 2 patients (9%) did not develop ST segment changes, regional WMA nor angina. A total of 16 patients (76%) developed echocardiographic abnormalities. Nine patients (56%) developed regional WMA only. Seven patients (44%) showed an abnormal transmural flow during dipyridamole infusion; in 6 patients (37%) the abnormal transmural flow was followed by regional WMA while in 1 patient the abnormal transmural flow was not associated with regional WMA. No relation was found between mitral flow abnormalities and spatial distribution of regional WMA. A total of 13 patients (62%) presented ST segment depression ≥0.5 mm; in 12 patients ST segment depression was localised in leads V4–V6 and in 1 patient in leads II, III, aVF. Maximal ST segment depression was 1.1 ± 0.4 mm. A total of 16 patients (76%) lamented angina during dipyridamole infusion; the character of the pain was similar to the habitual angina experienced during daily life; maximal pain severity was 57 ± 19 mm. Four patients had transient facial flushing and 1 had transient headache.

Temporal Sequence of Ischaemic Events (Figs. 2a, 3)

During dipyridamole infusion, 14 patients exhibited echocardiographic abnormalities and ECG changes and/or angina. In 8 patients (57%) echocardiographic abnormalities represented the first ischaemic event; in the remaining 6 patients (43%) the first ischaemic event was represented by ECG changes in 5 patients or by pain in 1 patient. The time interval between the first and the second ischaemic event was similar in the 2 groups (191 ± 118 vs. 205 ± 147 s, p = 0.85). The prevalence of cardiovascular risk factors and of collateral circulation at angiography was similar in patients in whom the first ischaemic event was represented by echocardiographic abnormalities or ECG changes and/or angina (Tab. 2). In patients with ECG changes and/or angina as first manifestation of myocardial ischaemia, LAD stenosis was more severe than that observed in patients in whom echocardiographic abnormalities represented the first ischaemic event (95 ± 5% vs. 80 ± 10%, p = 0.007).

Table 1. Haemodynamic data*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Dipyridamole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>80 ± 12</td>
<td>91 ± 14†</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129 ± 19</td>
<td>115 ± 16†</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75 ± 9</td>
<td>68 ± 9†</td>
</tr>
<tr>
<td>Double product (mmHg x beats/min)</td>
<td>103 ± 15</td>
<td>105 ± 18</td>
</tr>
</tbody>
</table>

* Plus-minus values are means ± 1 standard deviations; † p < 0.05

Table 2. Prevalence of cardiovascular risk factors and collateral circulation in patients with regional wall motion abnormalities (WMA) or electrocardiographic changes and/or angina (ECG) as first manifestation of myocardial ischaemia

<table>
<thead>
<tr>
<th>Variables</th>
<th>WMA (n = 8)</th>
<th>ECG (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of IHD</td>
<td>5/8 (62)</td>
<td>6/13 (46)</td>
</tr>
<tr>
<td>Systemic Hypertension</td>
<td>3/8 (37)</td>
<td>2/13 (16)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>3/8 (37)</td>
<td>10/13 (76)</td>
</tr>
<tr>
<td>Tabagism</td>
<td>3/8 (37)</td>
<td>3/13 (23)</td>
</tr>
<tr>
<td>Collateral circulation ≥ grade 2</td>
<td>4/8 (50)</td>
<td>4/13 (31)</td>
</tr>
</tbody>
</table>

Numbers in brackets are percentages. Differences between groups are not statistically significant. IHD: ischaemic heart disease.
Spatial Distribution of Regional WMA (Figs. 2a, 3)
Regional WMA appeared in LAD-dependent territories only in 4 of the 15 patients (27 %) (mean percentage of abnormal segments: 32.5 ± 9.5 %; mean WMA score: 1.33 ± 0.31), in non-LAD-dependent territories only in 5 patients (33 %) (mean percentage of abnormal segments: 36.4 ± 7.6 %; mean WMA score: 1.5 ± 0.1), in both LAD- and non-LAD-dependent territories in 6 patients (40 %) (mean percentage of abnormal segments in both LAD- and non-LAD-dependent territories: 34.0 ± 8.7 %; mean WMA score: 1.34 ± 0.1; mean percentage of abnormal segments and WMA score in LAD-dependent territories: 32.5 ± 9.0 % and 1.31 ± 0.12, respectively; mean percentage of abnormal segments and WMA score in non-LAD-dependent territories: 35.8 ± 7.2 % and 1.4 ± 0.1, respectively; mean percentage of abnormal segments and the mean WMA score were similar among the 3 groups (p = 0.8 and p = 0.47, respectively). The prevalence of cardiovascular risk factors and the presence of collateral circulation were similar in these 3 groups of patients such as LAD stenosis severity (95 ± 4 % vs. 85 ± 11 % vs. 83 ± 11 %, p = 0.08).

Post-Revascularisation Dipyridamole Stress Test
Response to Dipyridamole Stress Test (Figs. 2b, 4)
During dipyridamole infusion, 13 patients (62 %) did not develop ST segment changes, echocardiographic abnormalities nor angina compared to 9 % in the pre-revascularisation study (p < 0.03). Six patients (28 %) developed echocardiographic abnormalities compared to 76 % in the pre-revascularisation study (p < 0.01). Five patients showed an abnormal transmitral flow during dipyridamole infusion and 4 WMA. One patient presented regional WMA only. In the 3 patients with systolic and diastolic abnormalities these latter always preceded regional WMA. No patient showed ECG ischaemic changes compared to 62 % in the pre-revascularisation study (p < 0.001). Two patients (9 %) lamented angina during dipyridamole infusion compared to 76 % in the pre-revascularisation study (p < 0.001). The character of pain was similar to the habitual angina experienced during daily life; maximal pain severity was 25 mm and 35 mm, respectively.

Spatial Distribution of Regional WMA (Figs. 2b, 4)
Regional WMA were in LAD-dependent territories only in 2 of the 4 patients (50 %) (mean percentage of abnormal segments: 31.0 ± 8.7 %; mean WMA score: 1.4 ± 0.35), in both LAD- and non-LAD-dependent territories in 2 patients (50 %) (mean percentage of abnormal segments: 32.5 ± 9.5 %; mean WMA score: 1.33 ± 0.31).

Discussion
This study carried out in a well selected group of consecutive patients with chronic stable angina, normal left ventricular function and isolated proximal LAD stenosis undergoing pharmacological stress echocardiography with dipyridamole demonstrates that:
1) in about two-thirds of patients who developed dipyridamole-induced regional WMA the latter occurred in non-LAD-dependent regions;
2) among patients who exhibited both echocardiographic changes and ECG changes and/or angina, the sequence of events was remarkably different; indeed, about half of these patients exhibited mechanical changes first, while
the remaining half exhibited ECG changes and/or angina first;
3) coronary revascularisation significantly reduced the incidence of dipyridamole-induced regional WMA and totally abolished ischaemic ECG changes.

Taken together these findings indicate that in patients with chronic stable angina the mechanisms of ischaemia can not be predicted by clinical and angiographic findings.

Mechanisms of Dipyridamole-Induced Myocardial Ischaemia

Dipyridamole causes an extracellular accumulation of adenosine, the main physiological modulator of coronary arteriolar vasodilation, by inhibiting cellular adenosine uptake. In the presence of an epicardial coronary stenosis an inappropriate arteriolar dilation of subepicardial layers may exert a detrimental effect on transmural myocardial perfusion. Indeed, the fall in post-stenotic pressure secondary to the increase in flow across the epicardial stenosis can decrease perfusion in subendocardial vessels where extravascular resistance is higher and residual vasodilator reserve more easily exhaustible (“vertical steal”) [8]. The rationale of dipyridamole stress echocardiography is based on the experimental observation that a decline of regional subendocardial blood flow is paralleled by a decline of regional myocardial function detectable by echocardiography. Indeed, a number of studies have shown that dipyridamole stress echocardiography is a reliable test for the detection of epicardial coronary stenoses [8]. The significance of ECG changes during dipyridamole stress echocardiography is less defined. Cortigiani et al. have shown that ECG changes in addition to wall motion abnormalities during dipyridamole stress echocardiography are associated with more extensive coronary artery disease than observed in the presence of WMA only [9]. Yet, in several clinical conditions associated with angiographically normal epicardial coronary arteries and distal coronary vessel dysfunction such as cardiac syndrome X [10], hypertrophic cardiomyopathy [11], systemic hypertension [12], and acute rejection of transplanted heart [13], dipyridamole-induced ischaemic-like ECG changes and angina typically occur in the absence of WMA. In this setting, ECG changes and angina may represent a marker of “true” myocardial ischaemia possibly related to distal coronary vessel dysfunction [14].

Temporal Sequence of Ischaemic Changes During Dipyridamole Stress Test

It is generally accepted that the ischaemic cascade is characterised by a well defined time sequence of events in which alterations in left ventricular diastolic and systolic function are considered to represent the first manifestation of myocardial ischaemia followed by ECG changes and, in a subset of patients, by angina pectoris [1]. In the clinical setting, this sequence of events translates into a higher sensitivity, on the average, of imaging techniques, such as echocardiography and radionuclide angiography, over ECG signs of ischaemia [8, 15]. Yet, this classic temporal sequence of events has been generally described in unselected groups of patients under different clinical conditions and with different angiographic patterns by using ischaemic stimuli which increase myocardial oxygen demand, such as exercise test [16] or atrial pacing [17] or abrupt reduction or interruption of oxygen supply, such as coronary angioplasty [18] or spontaneous coronary spasm [19].

In the present study, we evaluated the ischaemic cascade in a well selected group of patients with stable angina and isolated LAD stenosis by using a well accepted pharmacological stressor, i.e. the intravenous infusion of dipyridamole, a potent vasodilator of distal coronary vessels. Our findings indicate

**Figure 4.** Flow chart showing the different ischaemic events in the study group during dipyridamole infusion after coronary artery revascularisation. Numbers indicate the number of patients. ECG: electrocardiographic changes; ECHO: echocardiographic changes; LAD-dep: systolic changes in left anterior descending coronary artery-dependent territories; non-LAD-dep: systolic changes in left anterior descending coronary artery-independent territories; LAD-dep and non-LAD-dep: systolic changes in left anterior descending coronary artery-dependent and -independent territories.
Temporal and Spatial Manifestations of Myocardial Ischaemia

Spatial Distribution of Ischaemic Changes During Dipyridamole Stress Test

In our study we observed a high incidence of segmental WMA during dipyridamole infusion in myocardial regions not supplied by the culprit vessel. Indeed, in about two-thirds of our patients segmental WMA could be detected in myocardial regions perfused by angiographically normal coronary vessels. These findings are in agreement with previous studies in the setting of acute myocardial infarction [3, 21–22], in which impaired perfusion and myocardial dysfunction were observed in non-infarct-related artery-dependent myocardium. Furthermore, a reduced coronary flow reserve served as an indicator of microvascular dysfunction [23]. A reduced coronary flow reserve in the myocardium supplied by angiographically normal coronary arteries has been constantly observed also in patients with obstructive coronary atherosclerosis and stable angina [2, 24–26]. However, these studies failed to establish whether coronary microvascular dysfunction could be as severe as to cause transient regional WMA. Our study adds further information and shows that, in a substantial proportion of patients with severe 1-vascular disease and stable angina, transient WMA may occur in myocardial regions supplied by non-stenotic epicardial coronary arteries.

The causes responsible for regional WMA in myocardial segments perfused by angiographically normal coronary vessels cannot be deducted from the results of this study. Theoretically, they might be caused by spasm of large epicardial vessels; however, this mechanism is unlikely because our patients did not have a clinical history suggestive of vasospastic angina, they showed ST segment depression rather than elevation and, finally, dipyridamole is a weak stimulus for coronary vasodilator function in infarcted and normal myocardium after myocardial infarction. N Engl J Med 1994; 331: 222–6. So, it cannot be implied that the vasomotor capacity of resistance vessels could impair the vasomotor capacity of resistance vessels.

Clinical Implications

In conclusion, our study demonstrates that the mechanisms of stress-induced myocardial ischaemia in patients with obstructive atherosclerosis are multiple and determined by a complex interplay between epicardial coronary artery obstructions and microvascular dysfunction. The important role of microvascular dysfunction is highlighted by evidence of stress-induced WMA in myocardial regions perfused by angiographically normal coronary vessels in about two-thirds of a consecutive series of patients with stable angina and single- vessel disease. Our results suggest that the treatment of myocardial ischaemia in chronic stable angina should be guided by the prevailing mechanisms of ischaemia which varies in individual patients. The results of recent studies show that adenosine antagonists, statins and endothelin antagonists can improve myocardial ischaemia in patients with chronic stable angina independently of their effect on epicardial coronary stenosis [31–34]. Thus, already existing drugs can be effective in treating microvascular dysfunction-dependent myocardial ischaemia.

References:

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