Impact of culprit lesion morphology on prevalence of provoked myocardial ischaemia in patients with old myocardial infarction

A dipyridamole stress echocardiography, exercise electrocardiography and angiographic study

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We have recently shown that in patients with single vessel disease and no myocardial infarction, a complex plaque morphology makes myocardium more vulnerable to ischaemia during dipyridamole echocardiography testing. Whether coronary lesion morphology in the infarct-related artery in a chronic phase may also modulate prevalence of ischaemia in the same territory remains unknown. In order to determine the possible relationship between culprit lesion morphology in the infarct-related artery and the prevalence of homotopic ischaemia during stress tests, data from high dose dipyridamole echocardiography tests (up to 0.84 mg · kg⁻¹ over 10 min), exercise electrocardiography and coronary angiography from 73 in-hospital patients with a previous myocardial infarction and patent infarct-related single-vessel disease (≥50% diameter reduction) were analysed.

An angiographic culprit lesion was considered complex (Amброс classification) when irregular borders, ulcers, thrombus and/or intraluminal lucencies were present. According to angiographic lesion morphology, two groups were identified: Group I, with simple-type culprit lesions; Group II, with complex type culprit lesions. Number of patients (I = 36; II = 37), age (I = 57 ± 11 vs II = 55 ± 9 years), ejection fraction (I = 58.8 ± 11.3 vs II = 56.5 ± 10.2%), number of Q or non-Q wave myocardial infarctions, prevalence of rest angina (I = 9; II = 11) or effort angina (I = 10; II = 10), culprit lesion stenosis severity (I = 57.9 ± 7.2% vs II = 57.7 ± 6.2% by computer analysis) and degree of infarct artery anterograde flow (I = 2.64 ± 0.48 vs II = 2.56 ± 0.50 by Thrombolysis in Myocardial Infarction definition) did not differ between the two groups (P=ns for all intergroup differences). Dipyridamole echocardiography test-induced ischaemia (considered as new or worsening abnormal wall motion) in the infarct-related artery territory was 25% in Group I and 59% in Group II (P<0.01). Among positive dipyridamole echocardiography tests, low dose (0.56 mg · kg⁻¹ over the 4 min) positivity occurred in two out of nine Group I patients and in 16 out of 22 Group II patients (22 vs 73%, P<0.05). Exercise electrocardiography was positive in seven out of 32 Group I patients, and in 16 out of 35 Group II patients (22 vs 46%, P<0.05). The peak rate pressure product tended to be higher in Group I than in Group II patients (282 ± 65 vs 257 ± 65 mmHg x beats · min x 10², P=0.07). Thus, in patients with previous myocardial infarction and a patent infarct-related artery, complex culprit lesion morphology is associated with a higher prevalence of ischaemia and a lower ischaemic threshold during both exercise and dipyridamole stress testing. The morphology of culprit stenosis is important in modulating different stress responses in the chronic phase of myocardial infarction.

Key Words: Myocardial infarction, ischaemia, stress echocardiography, exercise, lesion.
modulates the prevalence of ischaemia remains unknown.

We hypothesized that the morphology of culprit lesions in post-infarction patients may influence stress test results, as happens in non-infarction patients. Therefore, the aim of the present study was to assess the possible relationship between culprit lesion morphology in the infarct-related artery and the prevalence of residual ischaemia during stress tests, such as the dipyridamole echocardiography test and upright bicycle exercise electrocardiography. Accordingly, data from dipyridamole echocardiography tests and exercise electrocardiography were analysed in two groups of post-infarction patients with patent infarct-related single-vessel disease, with comparable quantitatively assessed stenosis severity, and with either 'simple' or 'complex' culprit lesions.

**Materials and methods**

**Study patients**

Data from dipyridamole echocardiography tests, exercise electrocardiography and angiography data were reviewed in consecutive in-hospital patients with a previous myocardial infarction, referred to our Institute for cardiac catheterization. Dipyridamole echocardiography testing, exercise electrocardiography and coronary angiography were performed within 5 days. Patients eligible for the study were those who had: survived an acute myocardial infarction >1 month, a patent but stenotic (≥50% diameter stenosis by quantitative analysis) infarct-related artery, no angiographically evident lesions in the remaining coronary arteries. Of the initial population of 105 patients with previous myocardial infarction and single-vessel disease, 32 were ruled out because of: (1) previous angioplasty procedures (n=8); (2) angiographic cinefilms of insufficient quality for assessment of morphology (n=13); (3) non-infarct-related diseased artery (n ± 6); (4) segmental wall motion abnormality during dipyridamole echocardiography testing occurring in a territory different from the infarcted one and interpreted as possible false-positive (n = 2); (5) severe stenosis or regurgitation of the mitral or aortic valve assessed by either echo-Doppler or angiography (n=3).

From the remaining 73 patients, two groups with either 'simple' (Group I) or 'complex' (Group II) lesion morphology were serially identified on the basis of the filling defects, other than a concentric or eccentric narrowing with irregular borders and/or multiple irregularities and/or overhanging edges, or with an 'abrupt proximal face' or a 'rough' or 'sawtooth' profile suggestive of ulceration.[12,10]

**Exercise electrocardiography test**

Patients performed a multistage upright cycle ergometer test, with an initial load of 25 W and subsequent increments of 25 W every 2 min. Electrocardiographic tracings were considered diagnostic for myocardial ischaemia when an ST segment shift of at least 0·10 mV, 0·08 s after the J point, could be detected. Electrocardiographic tracings were analysed visually by an experienced cardiologist, blind to angiographic and dipyridamole echocardiography test findings. The rate pressure product (heart rate × systolic blood pressure) and exercise time (in min), assessed either at peak exercise (in negative tests) or at the onset of ischaemia (≥0·10 mV ST segment depression in positive tests), were also evaluated.

**Dipyridamole echocardiography test**

Dipyridamole was infused at a dose of 0·56 mg. kg⁻¹ over 4 min followed by 4 min of no dose and then 0·28 mg. kg⁻¹ in 2 min[12]. The cumulative dose was therefore 0·84 mg. kg⁻¹ over 10 min. Aminophylline (up to 240 mg over 3 min) was administered at the end of all tests. In baseline studies as well as during stress, all standard echocardiographic views were obtained when possible. During the test, new areas of abnormal wall motion were identified in multiple views whenever possible. The echocardiographic images were evaluated from the on-line digitized quad-screen display and also from the off-line videotape playback by two experienced observers who were unaware of the result of coronary angiography. The low level of intra-observer and inter-observer variability obtained in our laboratory between experienced readers has been previously documented[11].

The left ventricle was divided into 11 segments[13]. Segment wall motion was graded as: normal — normal motion at rest, with normal/increased wall motion (hyperkinesis) after dipyridamole (score = 1); hypokinetic (score = 2); akinetic (score = 3); dyskinetic (score = 4). The wall motion score index (WMSI) was derived by summation of individual segment scores divided by the number of interpreted segments. Inadequately visualized segments were not scored. A test result was considered positive for myocardial ischaemia when the wall motion score increased by one grade or more at peak stress. However, an akinesis becoming dyskinesis was not considered a criterion for positivity, since this can be due to passive stretching phenomena rather than to 'active' ischaemia unless the akinetic segment initially improved (viability response) during or after low dose dipyridamole infusion (0·56 mg. kg⁻¹ over 4 min) and worsened thereafter at high dose (bi-phasic response). In positive tests, the dipyridamole time
Table 1. Angiographic characteristics of patients with simple or complex plaque. The differences between the groups were not statistically significant

<table>
<thead>
<tr>
<th></th>
<th>Group I (simple lesion)</th>
<th>Group II (complex lesion)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 36)</td>
<td>(n = 37)</td>
</tr>
<tr>
<td>Distribution of offending coronary artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>21 (58%)</td>
<td>16 (43%)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>5 (14%)</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>Right</td>
<td>10 (28%)</td>
<td>15 (40%)</td>
</tr>
<tr>
<td>Location of lesion at branch point</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Location of lesion at acute bend</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Mean % diameter stenosis</td>
<td>57.9 ± 7.2</td>
<td>57.7 ± 6.2</td>
</tr>
<tr>
<td>TIMI grade</td>
<td>2.64 ± 0.48</td>
<td>2.56 ± 0.50</td>
</tr>
<tr>
<td>Collaterals</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>58.8 ± 11.3</td>
<td>56.5 ± 10.2</td>
</tr>
</tbody>
</table>

(min) was also determined as the interval from the beginning of the drug infusion to the occurrence of stress-induced asynergy. In negative tests, the dipyridamole time was arbitrarily assumed to be 17 min (when aminophylline was administered).

Analysis of coronary lesions

Routine coronary angiography was performed according to the standard Judkins technique with a minimum of five views of the coronary system, a minimum of three view of the right coronary system and a left ventricular angiogram in the right anterior oblique projection. Additional appropriate projections were obtained in case of superimposition of side-branches or foreshortening of the single stenotic segment. Infarct-related lesions were visually evaluated by two independent investigators. In case of disagreement, a third more experienced observer (M.M.) reviewed the angiogram and his judgement was binding. The interobserver variability in plaque assignment to either simple or complex morphology was 5%; the intraobserver variability assessed by the same observer on 20 angiograms was also 3%. Quantitative coronary angiography by automatic contour detection was performed using the image analysis system (Mipron, Kontron, Germany). The % diameter stenosis (in the projection in which the stenosis appeared most severe) was measured for each culprit artery stenosis. The degree of infarct-related artery antegrade flow was also assessed according to the Thrombolyis in Myocardial Infarction (TIMI) definition[^14]. Patients with TIMI grade 0 and TIMI 1 flow were considered to have total occlusion and were excluded from the study.

Statistical analysis

All data are shown as mean values ± 1 SD. Differences between the result of exercise electrocardiography and the dipyridamole echocardiography test in the different angiographic subsets were compared by using the chi-square test and unpaired t-test; a Fisher’s exact test was used when appropriate. A P value below 0.05 was considered statistically significant.

Results

Clinical features

Of the 73 enrolled patients 40 had a Q wave and 33 a non-Q wave myocardial infarction. Thrombolytic therapy during the acute phase was carried out in 18 (25%) patients. Resting angina, effort angina and atypical chest pain were present in 20 (27%), 20 (27%) and three (4%) patients, respectively. Thirty (41%) patients were asymptomatic. The mean age was 55.6 ± 10.0 years, 66 patients were male and seven female. The mean ejection fraction was 57.8 ± 10.8%.

Angiographic data (Table 1)

There were no significant differences between the groups as regards the distribution of the offending coronary arteries, the location of the culprit lesion at an acute bend or at a branch point, or TIMI grading of antegrade flow. The quantitative angiographic data in the two groups were similar, with comparable % diameter reduction.

Exercise electrocardiography results

No major complications occurred during exercise electrocardiography. In six patients exercise electrocardiography could not be performed and/or completed up to diagnostic end-points. In the remaining 67 patients, exercise electrocardiography was positive in 23 and negative in 44. The peak rate pressure product was
Table 2 Characteristics of 73 patients with simple or complex plaques. The differences between the groups were not statistically significant

<table>
<thead>
<tr>
<th></th>
<th>Group I (simple lesion)</th>
<th>Group II (complex lesion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD years)</td>
<td>57 ± 11</td>
<td>55 ± 9</td>
</tr>
<tr>
<td>Gender</td>
<td>33 M. 3 F</td>
<td>33 M. 4 F</td>
</tr>
<tr>
<td>Time from MI (month)</td>
<td>4-1 ± 2.9</td>
<td>5.0 ± 3.5</td>
</tr>
<tr>
<td>Q wave</td>
<td>17 (47%)</td>
<td>23 (62%)</td>
</tr>
<tr>
<td>Non-Q wave</td>
<td>19 (53%)</td>
<td>14 (38%)</td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td>8 (22%)</td>
<td>10 (27%)</td>
</tr>
<tr>
<td>Symptom after MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>15 (42%)</td>
<td>15 (41%)</td>
</tr>
<tr>
<td>Rest angina</td>
<td>9 (25%)</td>
<td>11 (30%)</td>
</tr>
<tr>
<td>Effort angina</td>
<td>10 (28%)</td>
<td>10 (27%)</td>
</tr>
<tr>
<td>Atypical chest pain</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

25 800 ± 5680 in patients with a positive test and 27 500 ± 6990 mmHg x beats . min⁻¹ in patients with a negative test (P=ns).

Dipyridamole echocardiography test results

No major complications or limiting side effects occurred during dipyridamole echocardiography test.

In the overall population of 73 patients, residual ischaemia was detected in 31 patients with a 42% positivity rate. Abnormal resting wall motion was present in 57 (78%) patients; the resting WMSI was 1.27 ± 0.26 and rose to 1.36 ± 0.29 at peak stress. The dipyridamole time was 12.6 ± 5.0 min.

Correlation of clinical features with lesion morphology data (Table 2)

The groups (I, simple; II, complex) were comparable as regards number, age and gender proportion. The groups were similar as regards the number with a Q wave or non-Q wave infarction, the time from acute myocardial infarction, the number with thrombolysis, the presence of rest angina or effort angina, the number of asymptomatic patients, and left ventricular function.

Correlation of exercise electrocardiography results and lesion morphology data (Table 3)

Of the 67 patients with exercise electrocardiography, 32 had a 'simple-type' and 35 a 'complex-type' culprit lesion stenosis. Ischaemia was detected in patients with complex (Group II) plaques but rarely in patients with simple plaques (Group I) (46 vs 22%, P<0.05). Group I patients had a trend towards a higher rate pressure product than Group II patients.

Correlation of dipyridamole echocardiography test results and lesion morphology data (Table 3)

The occurrence of ischaemia was significantly lower in Group I than in Group II (25 vs 59%, P<0.01). Group I exhibited a lower peak wall motion score index than Group II (1.29 ± 0.32 vs 1.44 ± 0.27, P<0.05), but a similar resting wall motion score index. By restricting the analysis to patients with an ischaemic response, 'complex-type' relative to 'simple-type' morphology was associated with a significantly shorter dipyridamole time (Group II=6.7 ± 2.8 vs Group I=9.8 ± 2.3 min, P<0.01) and with more frequent low dose positivity (73 vs 22%, P<0.05); peak and resting WMSI were similar.

Of the 23 patients with at least one akinetic segment at rest, in nine (I=5 vs II=4 patients, P=ns) their akinetic segments showed improvement during low dose testing (viability responder); however, in six (I=3 vs II=3 patients) the segment worsened after high dose dipyridamole (biphasic response).

Discussion

We have recently reported that in non-infarcted patients, dipyridamole echocardiography testing is able to provoke ischaemia more frequently in patients with 'complex-type' coronary stenosis than in those with 'simple-type' stenosis of similar severity [9]. The findings of the present study confirm and extend our previous observation to post-infarction patients, showing that the complex morphology of the residual stenosis of the culprit vessel in the chronic phase has a stronger ischaemic potential during stress than the simple plaque for any given severity of lumen reduction. In patients with previous myocardial infarction and patent infarct-related single-vessel disease, complex morphology of the culprit lesion is associated not only with a higher prevalence of stress-induced ischaemia (in the infarcted territory), but also with a higher vulnerability to ischaemia, as shown by the greater prevalence of low dose dipyridamole echocardiography test positive responses as well as by the trend to a lower ischaemic threshold during exercise electrocardiography. Although both transmural and circumferential ischaemia enter the domain of WMSI, in positive dipyridamole echocardiography tests, the dipyridamole time 'ischaemia free stress time' showed greater discriminatory power than peak WMSI. Since the development of a new wall motion abnormality was an absolute end point of the test in this study, in order to prevent potential complications from severe or prolonged ischaemia, it is not surprising that in positive patients peak WMSI was not able to discriminate between these two groups, whereas the dipyridamole time was significantly shorter in positive patients with a complex type morphology (Table 3). From the results it appears that the presence or absence of irregular residual stenosis in a patent culprit coronary artery is...
Table 3  Response to stress tests depending on plaque morphology

<table>
<thead>
<tr>
<th></th>
<th>Group I (simple lesion)</th>
<th>Group II (complex lesion)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>32</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>7 (22%)</td>
<td>16 (46%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Rate pressure</td>
<td>28 200 ± 6530</td>
<td>25 700 ± 6440</td>
<td>P=0.07</td>
</tr>
<tr>
<td>DET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>36</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>9 (25%)</td>
<td>22 (59%)</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Rest WMSI</td>
<td>1.25 ± 0.29</td>
<td>1.28 ± 0.23</td>
<td>ns</td>
</tr>
<tr>
<td>Peak WMSI</td>
<td>1.29 ± 0.32</td>
<td>1.44 ± 0.27</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>*Low dose positive</td>
<td>2/9 (22%)</td>
<td>16/22 (73%)</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>*Dipyridamole time</td>
<td>9.8 ± 2.3</td>
<td>6.7 ± 2.8</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>*Rest WMSI</td>
<td>1.34 ± 0.30</td>
<td>1.25 ± 0.21</td>
<td>ns</td>
</tr>
<tr>
<td>*Peak WMSI</td>
<td>1.53 ± 0.32</td>
<td>1.52 ± 0.24</td>
<td>ns</td>
</tr>
</tbody>
</table>

*only in patients with a positive DET.

EET = exercise electrocardiography test; DET = dipyridamole echocardiography test; WMSI = wall motion score index.

important in modulating stress-induced ischaemia in post-infarction patients.

Proposed mechanism

The explanation for this phenomenon could be related to fluid dynamics at the level of the culprit lesion, possibly mediated by impaired endothelial modulation of coronary tone [9]. Anterograde flow via a patent infarct culprit lesion may be sufficient to prevent a homotopic ischaemia in resting conditions. During stress testing, different culprit lesion morphology may be associated with different degrees of vasomotion alteration, leading to inadequate blood flow to the 'zone of marginal perfusion'. In a normal epicardial coronary artery, endothelium-mediated vasodilation in response to intravenous administration of dipyridamole as well as to physical exercise contributes to the increase in coronary flow [15-18]. It has been demonstrated that endothelium-dependent vasodilation is lost in atherosclerosis. In this regard, it has been shown that atherosclerotic coronary arteries constrict both during exercise [19-21] and during intracoronary administration of acetylcholine endothelium-dependent vasodilator [22-24]. The angiographic pattern of complex coronary stenosis is associated with extensive and severe endothelial involvement causing impairment in endothelium-mediated vasodilation due to reduced production of endothelium-derived relaxing factor(s) and to increased sensitivity to constriction [25-27]. During dipyridamole or exercise, loss of endothelial integrity — probably more marked on or around the 'complex' atherosclerotic plaque than at the level of 'simple' smooth border plaque — may reduce flow, endothelium-mediated vasodilation of large epicardial arteries, without affecting downstream endothelium-independent dilation of small resistance coronary vessel [27]. Since epicardial vessel diameter is related to the fourth power of vessel resistance to flow, even a minimally reduced increase in epicardial artery luminal diameter markedly increases the transmural pressure gradient and therefore the functional severity of stenosis [28].

Comparison with previous studies

To our knowledge, no data are available regarding the relationship between culprit lesion morphology and provoked ischaemia in post-infarction patients as assessed by pharmacological stress echocardiography — dipyridamole echocardiography test, compared with physiological stress testing, exercise electrocardiography. Complex culprit lesion morphology was found in about one half of post-infarction patients in the present study. This prevalence is a lower than those reported in previous investigations [1,2,29] and could be explained by time-dependent changes in culprit lesion morphology. Angiography in the present study was performed after the acute phase of myocardial infarction. Davies et al. have shown that remodelling of coronary lesions occurs early after thrombolytic recanalization of the infarct-related coronary artery, with a tendency to smoother lesions and a lower ulceration index, as the interval between acute infarction and arteriographic examination increases [29].

Complex coronary lesion morphology has been found in about 70% of non-infarction patients with unstable angina and in about 20 to 30% of patients with chronic stable angina [1,2,30]. In our study population, there was no higher prevalence of angina at rest in the group of post-infarction patients with complex-type lesions as might have been expected. However, the selection criteria of our study should be taken into account: all patients had to withstand stress testing, and therefore unstable angina syndromes referred directly to angiography were not included; in the majority of patients studied, clinical conditions allowed therapy withdrawal before testing, indicating that none had
refractory angina or preinfarction angina. In addition, after myocardial infarction patients often have evidence of silent residual ischaemia[31].

Study limitations

The plaque morphology was assessed visually. Although analysis of arterial borders with complex computer algorithms has been proposed[32] which may allow a more objective assessment of lesion irregularity or roughness, many characteristics of complex plaque morphology, such as translucency or filling defects within the borders of the lesion[10] are not readily amenable to quantitative angiography and those techniques have not been extensively applied to date[19,33,34]. Assessment of plaque morphology as any qualitative or quantitative analysis of coronary angiograms is plagued by inherent radiographic distortions[35]. These limitations lead to the implicit belief that minor border irregularities in a lesion would be overlooked at cineangiography, even if poor quality angiograms are discarded, as in the present study. Furthermore, angiography in comparison with angioscopy is very insensitive in thrombus and complex plaque detection[50], and intravascular ultrasound[57].

Clinical implications

Different plaque morphologies not only imply different susceptibilities to reocclusion, but probably reflect different degrees of endothelial dysfunction and different reactions to ischaemia stimuli in post-infarction patients. Results of provocative tests probably depend both on stenosis hydraulics and stenosis biology. The link between coronary lesion morphology and stress test induced ischaemia may explain, at least in part, their role in prognosis of patients with or without myocardial infarction[13,38-40]. The results of this study further challenge the hydraulic dogma (i.e. disease severity depends upon stenosis severity) and emphasize the need for a more integrated assessment of angiographic data in order to understand the results of provocative tests. Whether time-dependent morphology changes are consistent with changes in the ischaemic response to provocative stress tests in the same patient needs to be verified by further studies. Finally, whether the results obtained in this study can be extrapolated to other pharmacological stresses, such as dobutamine echo stress, or to other imaging techniques, such as perfusion scintigraphy, whose positivity is related to flow distribution rather than to ischaemic mechanical and regional dysfunction, as an issue to be addressed in future studies.

References