Why is recurrent myocardial ischaemia a predictor of adverse outcome in unstable angina?

An observational study of myocardial ischaemia and its relation to coronary anatomy

D. J. Patel, A. H. Gomma, C. J. Knight, D. A. Mulcahy, C. A. Wright, H. J. Purcell and K. M. Fox

Royal Brompton Hospital, London, U.K.

Objective To establish why recurrent myocardial ischaemia predicts adverse outcome in patients with refractory unstable angina on maximal medical treatment.

Design Prospective observational study in 101 patients with refractory unstable angina who underwent continuous ST-segment monitoring and kept detailed pain charts prior to cardiac catheterization.

Setting Tertiary referral centre.

Results Significant coronary disease was identified in 90 subjects with 74 (82%) having multivessel disease, 41 (46%) complex lesion morphology, and 10 (11%) subjects with definite features of intra-coronary thrombus. The frequency of complex lesions or intra-coronary thrombus did not differ in relation to the extent of coronary disease. Recurrent chest pain was present in 72 of the 90 (80%) subjects, while transient ischaemia was detected in 26 (29%). The presence of transient ischaemia was a powerful predictor of complex lesions or thrombus (odds ratio 7.1; P<0.001). Subjects with severe recurrent chest pain had a greater frequency of intracoronary thrombus (odds ratio 9.5; P<0.05).

Conclusions In unstable angina once the normal mechanisms causing myocardial ischaemia (i.e. increased myocardial demand and coronary vasoconstriction) have been treated using maximal antianginal treatment, the continued development of transient myocardial ischaemia is strongly associated with complex coronary lesion morphology and intracoronary thrombus. It is already known that patients with complex lesion morphology and intracoronary thrombus have an adverse outcome in unstable angina and therefore it is this association that explains why transient ischaemia is a predictor of poor outcome in unstable angina.


© 2001 The European Society of Cardiology

Key Words: Myocardial ischaemia, unstable angina, complex lesion morphology.

See page 1972, doi:10.1053/euhj.2001.2827 for the Editorial comment on this article
do identify such a subset[2–7]. Clearly, the release of troponins is associated with myocardial damage and by implication this is likely to be caused by plaque rupture and thrombosis. However, it is not clear why recurrent chest pain with ECG changes and the persistence of myocardial ischaemia predict adverse outcome in patients with unstable angina whilst they do not in chronic stable angina[4–7]. Since the majority of myocardial ischaemic episodes are silent the use of continuous ST-segment monitoring, in patients with acute coronary syndrome, has been shown to be particularly useful in detecting recurrent ischaemia, and the detection of transient ischaemia in this way has been shown to be of more prognostic value than recurrence of chest pain[8], or the presence of ST-segment changes on a resting electrocardiogram[9].

Coronary angiographic studies in unstable angina have shown that multivessel disease is common[8–11] and detailed analysis of lesion morphology has shown that the morphology of these lesions is distinct from that of lesions in stable coronary disease, with a high prevalence of complex lesions demonstrating acute angulation with irregularity or features of intraluminal thrombus formation[9–13]. It is this anatomy that is particularly associated with adverse outcome in unstable angina[9]. Although transient ischaemia in selected high risk patients has been shown to be associated with complex lesion morphology[6,14,16] and also to the presence of multivessel disease[6], it is not known whether persistent ischaemia despite maximal medical therapy independently reflects the presence of underlying complex lesion morphology which suggests plaque disruption, or simply the presence of multivessel disease. In addition the predictive value of recurrent chest pain or baseline ECG changes for the presence of complex lesion morphology in this setting has not been fully evaluated.

We have prospectively evaluated patients with refractory unstable angina, assessing the predictive value of baseline ECG characteristics, recurrent chest pain and transient ischaemia despite maximal medical therapy, for the extent of coronary disease and the complexity of lesion morphology at angiography.

We postulated that the presence of ongoing recurrent myocardial ischaemia in patients with unstable angina, on optimal medical therapy that reduces myocardial oxygen consumption and improves coronary blood flow, relates more to complex lesion morphology than simply to the extent of coronary artery disease.

Patients and methods

One hundred and five consecutive patients with unstable angina, who fulfilled the entry criteria, were recruited over a 22 month period at our hospital. Patients were considered for inclusion if they had presented with typical acute chest pain necessitating admission to their local hospital. Patients were only included at the time of transfer if chest pain had continued despite medical therapy, and at least one episode of chest pain had occurred in the 48 h prior to transfer. Patients were excluded if acute myocardial infarction had occurred during the initial admission, if coronary angioplasty or bypass surgery had been performed in the previous 6 months, or if there were resting electrocardiographic changes that made further interpretation of ST-segment changes difficult — namely the presence of left ventricular hypertrophy and strain, left bundle branch block morphology, or if they were on medications that might have influenced the interpretation of ST-segment changes. Resting electrocardiographic evidence of ischaemia was not a prerequisite for inclusion. Three subjects with evidence of myocardial infarction were excluded during the index admission and one subject did not undergo angiography, thus 101 subjects constituted the study population.

Treatment was standardized to include oral aspirin and intravenous heparin 25 000 i.u./24 h, titrated to maintain a target APTT (activated partial thromboplastin time) between 1·5–2·5 of control value. Antianginal therapy was also standardized unless there were specific contraindications including an oral beta-blocker, diltiazem and intravenous glyceryl trinitrate. Both intravenous heparin and nitrates were maintained up to the time of catheterization.

The study protocol had been approved by the hospital ethics committee, and all patients were required to give informed consent prior to recruitment.

Resting ECG

A 12-lead resting ECG was recorded at admission for all patients and was analysed by two observers blinded to the other clinical data. The presence of ST-segment depression of ≥0.2 mV was noted, as was the presence of inverted or biphasic T waves, the presence of Q waves or any other abnormalities.

ST-segment monitoring

After enrolment and treatment optimization, continuous ST-segment monitoring was performed for at least 24 h prior to cardiac catheterization unless the patient’s condition necessitated urgent angiography. Monitoring was performed with pre-gelled electrodes to record two bipolar leads, the anterior lead CM5, and a modified inferior lead. Sites and methods of application have been previously described[15]. Two-channel recordings were then obtained on magnetic tape using frequency-modulated Oxford Medilog MR35 dual channel recorders, with a frequency response 0·05–40 Hz, and tapes were analysed on the Oxford MA20 analyser independently. All potential episodes of ST-segment depression were identified by visual review at 60–120 times normal speed and were then printed and measured. The automatic ST trend was also examined for any further possible episodes.
significant ST-segment depression was defined as ≥0.1 mV planar or downsloping ST-segment depression from baseline at 80 ms after the J point lasting for more than 60 s. ST elevation was defined as the development of ≥0.2 mV ST elevation at the J point. Each episode had to be separated by a return of the ST segment to baseline at 80 ms after the J point lasting for more than 60 s. ST elevation was defined as any pain of grade 3 or more.

**Chest pain**

Detailed chest pain charts were kept by all patients prior to cardiac catheterization. The time and severity of pain, on a scale of 1 (mild)–5 was recorded for each episode. Severe pain was defined as any pain of grade 3 or more.

**Angiographic analysis**

Coronary angiography was performed within 1 week of admission (mean 2–4 days). All angiograms were performed via the femoral route using biplane imaging. Intracoronary GTN 0.2 mg was administered prior to the acquisition of the first image for all vessels, and multiple views were taken of each coronary vessel with magnified views of all potential lesions. Stenosis severity was graded independently by two observers experienced in angiographic interpretation. Both observers were blinded to clinical and electrocardiographic data. Differences between observers were mediated by consensus or by a third observer if consensus could not be reached. A significant lesion was defined as any stenosis with a greater than 50% luminal narrowing. The number of vessels with a significant stenosis was noted and the morphology of all significant lesions was graded as: (a) a simple stenosis — any smooth symmetrical or eccentric narrowing with a shallow leading or trailing edge; (b) a complex lesion — a lesion with either an acute or convex angle of the leading edge to the normal segment vessel, or with distinct scalloping, or with marked irregularity of the intraluminal surface. Intracoronary thrombus was considered to be present if there was a radiolucent filling defect surrounded by contrast, and for total occlusions if there was an abrupt occlusion with an irregular and convex border.

**Statistical analysis**

All data analysis was performed using the Statistical Package for Social Sciences (SPSS Release 6.0) software. Continuous variables are expressed as the mean ± standard deviation or as the median value with the range. Percentages are not presented for frequency counts for the overall population in view of the population size (n=101). Two sided P values are quoted throughout with P<0.05 considered to represent significance. Comparisons of categorical variables were evaluated by chi-square analysis using Yates’ continuity correction and Fisher’s exact test was used when the event rate or characteristic for any group was 5 or less in number. Multiple stepwise logistic regression analysis was used for the prediction of multivessel disease, complex coronary morphology, thrombus or the presence of either complex lesion morphology or thrombus using the variables of interest and variables identified of potential significance (P<0.02) in the preliminary analysis.

**Results**

The study population consisted of 105 consecutive patients, mean age 62 years (range 36–79), 74 of whom were men. A history of smoking was present in 76 subjects, hypertension in 30, diabetes in seven, hyperlipidaemia in 62, and a family history of premature coronary disease in 44 subjects. Of the 101 patients studied, 11 had no significant coronary lesions at angiography. These patients were more likely to have a normal admission ECG, 9/11 82% (P<0.05), and none demonstrated ischaemic activity during ST-segment monitoring, although recurrence of chest pain was as common in the subjects without significant coronary lesions 9/11 (82%) as in those with significant stenoses 72/90 (80%). In order to allow for meaningful comparisons, only the data for these 90 subjects with significant coronary disease is presented in the results that follow.

The baseline clinical characteristics including admission ECG findings are presented in Table 1 for all 90 patients with coronary artery disease and also according to the presence of recurrent chest pain or the development of transient ischaemia. Subjects with a normal admission ECG were younger (P<0.01); however, there were no other significant baseline clinical predictors of the admission ECG findings. No baseline characteristic predicted the likelihood of recurrent chest pain. Transient ischaemia was less frequent in subjects with previous myocardial infarction; however, no other baseline variable predicted its presence.

A total of 293 episodes of chest pain, median 3, range 1–19, occurred in 72 (80%) subjects despite maximum medical therapy, and in only 15 (17%) subjects were these associated with significant ECG changes. Severe pain was reported on at least one occasion by 45 (72%) subjects. During 4122 h of ECG recording, 26 (28%) subjects developed a total of 123 episodes of transient ischaemia, median 3, range 1–27 episodes, most of which were silent (76%). The median total duration of ischaemia was 119.5 min (9–723), with 13 (50%) having greater than 60 min of TMI/24 h. There was no significant association between ischaemic activity and the presence, frequency or severity of recurrent chest pain.

**Coronary angiographic findings**

The angiographic findings in the subjects with significant coronary disease is demonstrated in Table 2. Multivessel
disease was common, with over 50% of subjects having significant disease in all three vessels. Patients with multivessel disease were older, 63 ± 9 (9 ± 0) years vs 59 ± 2 (7 ± 2) years (P < 0.05), and were more likely to be hypertensive (P < 0.001), but no other baseline clinical or electrocardiographic variables were significantly predictive of multivessel disease. Severe luminal narrowing was also common, with 47% of patients having at least one totally occluded vessel. Total occlusions were more common in older and male subjects and in those with a history of hypertension or myocardial infarction (P < 0.05). Complex lesion morphology was common, being present in 41 (46%) subjects and appearances of thrombus were present in 10 (11%) subjects. None of the baseline clinical characteristics or the resting ECG findings were predictive of the presence of complex lesion morphology and/or intra-coronary thrombus. Stepwise multiple regression analysis of significant baseline variables, all admission ECG variables, the presence of recurrent severe chest pain, and transient ischaemia, showed transient ischaemia to be the most powerful independent predictor for a complex lesion and/or intracoronary thrombus. Severe recurrent chest pain was associated with a greater frequency of intracoronary thrombus. Multivessel disease was predicted by age > 65 years and a history of hypertension and both were significant independent predictors Table 3.

**Discussion**

The results of this prospective study of patients with refractory unstable angina demonstrates that complex coronary lesions, or appearances suggestive of intracoronary thrombus are common, being present in more than half of the subjects studied. Transient myocardial ischaemia, present in 29% of subjects despite maximal medical therapy, was mainly silent, and was the most important predictor of complex morphology or intracoronary thrombus. Multivessel disease although present in over 80% of subjects was more common in those over 65 years and was not associated with the presence of any baseline ECG changes. The diagnosis of unstable angina represents a spectrum of clinical conditions with varying underlying pathology and prognosis. Detailed pathological studies of subjects dying from unstable angina have demonstrated acute plaque rupture and thrombus formation to be common findings[17].

---

**Table 1 Clinical characteristics at admission**

<table>
<thead>
<tr>
<th></th>
<th>Patients with significant CAD n=90 (%)</th>
<th>Patients with recurrent pain n=72 (%)</th>
<th>Patients with transient ischaemia n=26 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 years</td>
<td>38 (42)</td>
<td>30 (42)</td>
<td>12 (46)</td>
</tr>
<tr>
<td>Males</td>
<td>66 (73)</td>
<td>54 (75)</td>
<td>19 (73)</td>
</tr>
<tr>
<td>Smokers</td>
<td>68 (68)</td>
<td>56 (78)</td>
<td>18 (69)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (30)</td>
<td>21 (29)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (8)</td>
<td>6 (8)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>41 (46)</td>
<td>37 (51)</td>
<td>12 (46)</td>
</tr>
<tr>
<td>Family history</td>
<td>39 (44)</td>
<td>31 (44)</td>
<td>11 (42)</td>
</tr>
<tr>
<td>Previous angina</td>
<td>69 (77)</td>
<td>57 (79)</td>
<td>21 (81)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>48 (53)</td>
<td>39 (54)</td>
<td>9 (35)*</td>
</tr>
</tbody>
</table>

**Table 2 Coronary angiographic findings: lesion morphology, intra-coronary thrombus and extent of coronary disease**

<table>
<thead>
<tr>
<th></th>
<th>1-vessel disease n=16 (18%)</th>
<th>2-vessel disease n=28 (31%)</th>
<th>3-vessel disease n=46 (51%)</th>
<th>Total n=90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple lesions only</td>
<td>9 (56%)</td>
<td>15 (54%)</td>
<td>23 (50%)</td>
<td>47 (52%)</td>
</tr>
<tr>
<td>Complex lesions</td>
<td>6 (38%)</td>
<td>13 (46%)</td>
<td>22 (48%)</td>
<td>41 (46%)</td>
</tr>
<tr>
<td>IC thrombus</td>
<td>1 (6%)</td>
<td>2 (7%)</td>
<td>7 (15%)</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>Complex lesions or IC thrombus</td>
<td>7 (44%)</td>
<td>13 (46%)</td>
<td>23 (50%)</td>
<td>43 (48%)</td>
</tr>
</tbody>
</table>

*P<0.05 when comparing to patients without significant coronary disease.
which is also common in unstable angina[9]. Thus clinical come independent of the presence of multivessel disease, bus, have been shown to be predictive of adverse out-

Although these predictors of adverse outcome include the presence of multivessel disease, which is also common in unstable angina[9]. Thus clinical factors that predict complex coronary lesion morphology are likely to be more important in determining outcome than those which predict multivessel disease.

Previous reports have shown that in unstable angina predictors of adverse outcome include the presence of ST-segment changes on a resting ECG[7], the development of recurrent chest pain[7], and the presence of transient myocardial ischaemia detected by continuous ST-segment monitoring[4], the latter having been shown to be one of the most powerful predictors of prognosis in this setting.

Despite maximal medical therapy the majority of patients in this study continued to experience chest pain, and transient ischaemia was detected in 29%. The proportion of subjects with no significant coronary disease (11%) is an indicator of the difficulties in establishing a precise diagnosis of unstable angina. Although most of the subjects without significant coronary disease had a normal resting ECG (9/11), this represented only a third of all subjects with a normal ECG. Furthermore, transient ischaemia was detected in 4/26 (15%) of subjects with a normal ECG, and complex coronary morphology was present in 10 (38%) subjects with a normal ECG. Thus, although a normal admission ECG is associated with a lower prevalence of coronary disease, it does not preclude the presence of complex lesions or the development of transient ischaemia.

**Clinical and pathophysiological implications**

Recurrence of chest pain is common but does not appear to accurately reflect recurrent myocardial ischaemia since the vast majority of such episodes are mild without associated ST-segment change. The mechanism of recurrent chest pain without ST-segment changes is unclear. Changes in T wave vector alone could have accounted for these episodes which are more difficult to interpret with continuous ECG monitoring. Conversely, patients with unstable angina in view of their clinical condition could have over-reported episodes of chest pain which are of a non-specific nature and not cardiac in origin. This assumption is supported to some extent by the high frequency of chest pain reported by subjects despite maximal medical therapy and also by a similar prevalence of chest pain in those without any significant coronary disease. However, when only severe chest pain is considered as reflecting myocardial ischaemia, there is a strong association with the presence of intracoronary thrombus. Transient and predominantly silent ST-segment changes, despite medical therapy, are present in over a quarter of the patients and have a strong relationship to complex coronary lesion morphology and intracoronary thrombus.

In view of this association of transient ST-segment changes to complex coronary morphology, it is conceivable that the recurrence of transient myocardial ischaemia, despite maximal medical therapy, may be caused primarily by transient fluctuations in the size of intracoronary thrombus and/or the change in the local coronary vasomotor tone in complex lesions. Thrombus formation is a dynamic process and the size of thrombus changes with time[18,19]. This may determine the degree of coronary blood flow and hence myocardial ischaemia.

Supportive evidence for fluctuations in coronary thrombosis has been provided by the confirmation of cyclic variation in coronary flow in unstable angina, which is abolished by the selective antifibrinogen binding agent, C7E3[20]. Vasomotor reactivity has also been shown to be impaired in unstable angina especially so at sites of complex lesions[21,22].

Thus in patients with unstable angina refractory to medical treatment, ST-segment monitoring appears to offer dual advantages. Firstly, it objectively identifies myocardial ischaemia even when it is not associated with symptoms, and it is also of use in assessing the significance of frequent recurrent chest pain. The presence of transient ischaemia, despite maximal medical therapy even if silent, implies a high likelihood of adverse coronary morphology and in view of its known prognostic importance should indicate the need for early angiography and revascularization.

---

**Table 3  Independent predictors of multivessel disease, complex lesion morphology, intracoronary thrombus or either of the latter two**

<table>
<thead>
<tr>
<th></th>
<th>Multivessel disease</th>
<th>Complex lesion morphology</th>
<th>IC thrombus</th>
<th>Complex lesion or IC thrombus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>P value</td>
<td>Odds ratio</td>
<td>P value</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>4·66</td>
<td>0·03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11·87</td>
<td>0·02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient ischaemia</td>
<td>6·82</td>
<td>0·0003</td>
<td>3·33</td>
<td>0·09</td>
</tr>
<tr>
<td>Severe recurrent pain</td>
<td>9·47</td>
<td>0·04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Eur Heart J, Vol. 22, issue 21, November 2001
This study would not have been possible without the considerable help of the nursing and radiography staff at the Royal Brompton Hospital.

Dr Patel has been supported by Augustus Newman Foundation grant, and both Dr Gomma and Dr Knight have been supported by British Heart Foundation grants.

References