Clinical Characteristics Determining the Mode of Presentation in Patients With Acute Coronary Syndromes

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Objectives. The purpose of this study was to examine clinical characteristics of patients with acute coronary syndromes to identify factors that influence the mode of presentation.

Background. In acute coronary syndromes, presentation with myocardial infarction or unstable angina has major prognostic implications, yet clinical factors affecting the mode of presentation are not well defined.

Methods. A prospective cohort study was made of 1,111 patients with acute coronary syndromes. Baseline demographic, clinical and biochemical data were compared in groups with myocardial infarction or unstable angina. The importance of plaque rupture and thrombosis in the pathogenesis of acute coronary syndromes is well established, with a significant likelihood of presentation with myocardial infarction or unstable angina depending largely on whether the thrombus is occlusive or subocclusive (1–3). This in turn is related to the degree of plaque disruption and the magnitude of the thrombotic response as determined by the balance between local prothrombotic and antithrombotic activity (4). Major physiologic contributors to this equilibrium are the vascular endothelium and the coagulation cascade, which interact to regulate platelet function, lytic activity, thrombin production and vascular tone (5).

Modification of the thrombotic response to plaque rupture plays a major role in management of acute coronary syndromes. Thrombolytic therapy and aspirin help restore coronary patency in acute myocardial infarction, permitting reperfusion of the ischemic zone (6), while heparin and aspirin protect against thrombotic occlusion in unstable angina (2,3). Treatments of this type, applied after the plaque event, have significantly improved the prognosis of these acute coronary syndromes by reducing or protecting against irreversible myocardial injury (7,8).

If therapeutic modification of thrombotic responses to plaque rupture can favorably influence the natural history of acute coronary syndromes, it is possible to speculate that the mode of presentation might itself be influenced by the balance between prothrombotic and antithrombotic activity that obtains at the time of the plaque event. Thus, Garcia-Dorado et al. have reported that patients with acute coronary syndromes who are taking aspirin are more likely to present with unstable angina than myocardial infarction, suggesting that aspirin taken before the plaque event might attenuate the severity of the thrombotic response (9). In the present study we have prospectively logged the demographic and clinical characteristics of a consecutive series of patients with acute coronary syndromes to identify factors influencing the mode of presentation.

Methods

Patient population. Between January 1995 and December 1997, 1,200 patients were admitted to the coronary care unit of...
Newham General Hospital with acute coronary syndromes. Repeat admissions during this period (n = 66) were excluded, as were an additional 23 unstable angina patients who did not fulfill criteria for Braunwald class 3B: cardiac chest pain at rest within the preceding 48 h that was not attributable to noncardiac causes (10). This left 1,111 patients with a discharge diagnosis of myocardial infarction (n = 633) and Braunwald class 3B unstable angina (n = 478). Myocardial infarction was diagnosed if any two of the following three criteria were fulfilled: a) cardiac chest pain lasting at least 30 min; b) $\geq$0.1 mV ST elevation in at least one standard lead or $\geq$0.2 mV ST elevation in two or more contiguous chest leads, and c) creatine kinase $\geq$400 IU/liter (upper limit of reference range: 200 IU/liter).

**Data collection.** Baseline clinical characteristics including demographic, clinical and biochemical data were collected prospectively by a dedicated cardiologist and stored on a purpose built electronic database. Aspirin and beta-adrenergic blocking agent therapy at the time of admission was recorded, as were previous hospital admissions with acute coronary syndromes and revascularization procedures (percutaneous transluminal coronary angioplasty and coronary artery bypass grafting [CABG]). Diabetes was recorded in patients on insulin, oral hypoglycemic drugs or dietary restriction. Hypertension was recorded in patients taking antihypertensive drugs. Current smokers were classified as smokers, while ex-smokers and nonsmokers were grouped as nonsmokers for the purpose of this study. If racial group (African, Asian, white) was not obvious, it was determined by direct inquiry. Blood samples were taken in the Emergency Department for measurement of cholesterol, glucose, potassium and creatinine concentrations. The upper limit of the reference range for creatinine in our laboratory is 106 μmol/liter.

**Statistical analysis.** Comparison of discrete variables was by chi-square analysis and continuous variables by the Mann–Whitney U test. To evaluate their independent influence, variables showing significant differences or marked trends in univariate analyses or believed to be of clinical or biological relevance were entered into a logistic regression analysis for which there were 1,008 complete data sets, representing 90.7% of all patients included in the study. Improvements in model fit were based on comparison of likelihood ratios. Odds ratios are quoted together with 95% confidence intervals.

**Results**

**Clinical characteristics.** Table 1 shows baseline clinical characteristics of patients with acute myocardial infarction and unstable angina. There were small differences in the age and gender distributions between the groups, patients with myocardial infarction being older and more commonly male, but the groups were similar as regards racial groups. Significantly fewer patients with myocardial infarction than unstable angina were on treatment with aspirin and beta-blockers at the time of admission, but more were smokers. Hypertension, previous coronary syndromes and previous myocardial revascularization procedures were all less common in patients with myocardial infarction.

**Admission biochemistry.** Although diabetes was somewhat less common in patients with myocardial infarction, their admission blood glucose concentration tended to be higher and potassium tended to be lower compared with patients with unstable angina. Blood creatinine concentration tended to be higher in patients with myocardial infarction. Cholesterol concentrations showed no difference between the groups (Table 2).

**Multivariate predictors of discharge diagnosis.** Stratification by age showed that in patients $\geq$70 years the odds of myocardial infarction were more than double those of unstable angina. Smoking increased the odds of infarction by almost half. In patients admitted on aspirin, the odds of infarction were about one third, and in patients with a history of hypertension about two thirds those of unstable angina. Previous acute coronary syndromes and revascularization procedures each reduced the odds of infarction by about two thirds. Among biochemical variables, an increase in creatinine from the 10th (80 μmol/liter) to the 90th (140 mmol/liter) centile of
Predictors of Non–Q wave myocardial infarction. Non–Q wave myocardial infarction was recorded in 217 of the patients with a discharge diagnosis of myocardial infarction. Analysis of those variables applied in Table 3 showed that the only significant multivariate predictor of non–Q wave infarction was hypertension (odds ratio 1.64; 95% confidence interval 1.10 to 2.45).

Discussion

This prospective cohort study of patients with acute coronary syndromes has shown that the mode of presentation may be influenced by a range of clinical, therapeutic and biochemical factors. Many of these factors have the capacity to interact with the hemostatic system and modify thrombotic responses to plaque rupture, prothrombotic effects favoring coronary occlusion and myocardial infarction, anti-thrombotic effects favoring coronary patency and unstable angina. Other factors may modify the ischemic consequences of plaque events by affecting myocardial mass and the collateralization of the coronary circulation.

The effect of aspirin. Our finding that patients with acute coronary syndromes who were taking aspirin were more likely to be discharged with a diagnosis of unstable angina than myocardial infarction confirms the observations of Garcia-Dorado et al. (9) and is presumably attributable to the effects of aspirin on the thrombotic process. Aspirin inhibits thromboxane synthesis, which in turn inhibits platelet aggregation and thrombus formation. It is possible to speculate, therefore, that reduction of the thrombotic response to plaque rupture in those patients taking aspirin helped preserve coronary patency and resulted in proportionately more of them developing unstable angina. If the clinical expression of plaque events can be modified in this way, it is also possible to speculate that an indeterminate number of patients treated with aspirin who would otherwise have an ischemic event may experience no symptoms at all if thrombus formation is diminished to the point that it remains confined within the plaque without affecting coronary flow. Subclinical plaque rupture of this type is found at autopsy in up to 5% of individuals who have coronary atheroma but die of noncardiac causes (11). The potential for aspirin to influence the pathogenesis of plaque events in this way may contribute importantly to its prognostic benefits in patients with coronary artery disease.

The effect of smoking. If the anti-thrombotic effects of aspirin help preserve coronary patency following plaque rupture, favoring presentation with unstable angina, then pro-thrombotic factors would be expected to exaggerate the thrombotic response and heighten the probability of coronary occlusion and myocardial infarction. This may explain why current smokers were more likely to be discharged with a diagnosis of myocardial infarction than unstable angina. The prothrombotic effects of smoking are well documented and include increased circulating levels of fibrinogen and adverse effects on coronary endothelial function with platelet activation and alterations in the secretion of tissue plasminogen activator and its inhibitor (PAI-1), which combine to reduce fibrinolytic activity (12–14). Moreover, endothelium-dependent vasodilatation is compromised in smokers, reducing coronary luminal diameter and heightening still further the probability of coronary occlusion for a given thrombotic response (15). Thus the adverse prognostic effects of smoking may relate not only to the increased risk of developing atherosclerosis but also to the increased risk of occlusive thrombosis and myocardial infarction. Indeed, in young patients, cigarette smoking has been associated with thrombotic coronary occlusion even in the absence of angiographic atherosclerotic disease (16).

Other prothrombotic factors: age and renal impairment. The effect of advanced age on the mode of presentation was similar to that of smoking, patients >70 years being over twice as likely to have a discharge diagnosis of myocardial infarction

### Table 2. Admission Biochemistry

<table>
<thead>
<tr>
<th></th>
<th>Acute Infarction (n = 633)</th>
<th>Unstable Angina (n = 478)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (mmol/liter)</td>
<td>Median (mmol/liter)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>513</td>
<td>373</td>
</tr>
<tr>
<td>Glucose</td>
<td>591</td>
<td>446</td>
</tr>
<tr>
<td>Hypertension</td>
<td>627</td>
<td>473</td>
</tr>
<tr>
<td>Diabetes</td>
<td>627</td>
<td>473</td>
</tr>
<tr>
<td>Creatinine</td>
<td>627</td>
<td>473</td>
</tr>
<tr>
<td>Potassium</td>
<td>627</td>
<td>473</td>
</tr>
</tbody>
</table>

Data are median (interquartile range).

### Table 3. Multivariate Predictors of Discharge Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) &lt;50</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>0.98</td>
<td>0.59 to 1.62</td>
<td>0.013</td>
</tr>
<tr>
<td>60–69</td>
<td>1.18</td>
<td>0.73 to 1.92</td>
<td>0.004</td>
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<tr>
<td>≥70</td>
<td>2.21</td>
<td>1.33 to 3.66</td>
<td>0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.49</td>
<td>1.09 to 2.03</td>
<td>0.016</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.64</td>
<td>0.47 to 0.86</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.97</td>
<td>0.70 to 1.36</td>
<td>0.87</td>
</tr>
<tr>
<td>Drugs on admission</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.37</td>
<td>0.27 to 0.52</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>0.79</td>
<td>0.53 to 1.18</td>
<td>0.25</td>
</tr>
<tr>
<td>Previous acute coronary syndromes</td>
<td>0.36</td>
<td>0.26 to 0.51</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Previous revascularization</td>
<td>0.36</td>
<td>0.21 to 0.62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Admission biochemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>0.78</td>
<td>0.56 to 1.10</td>
<td>0.20</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.30</td>
<td>1.05 to 1.94</td>
<td>0.02</td>
</tr>
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</table>

*Potassium and creatinine were both fitted as continuous variables with odds ratios representing change in risk for an increment from the 10th to the 90th centile of the relevant distribution. Odds ratios represent odds of myocardial infarction relative to unstable angina. Note that admission glucose correlated closely with diabetic status and was not included in the analysis. CI = confidence interval.
than unstable angina. Again, a plausible explanation for this finding is age-related changes in vascular endothelial function (17,18) and thrombogenicity, the elderly showing marked increases in circulating fibrinogen and factor VII levels compared with younger individuals (19). Age-related deterioration in renal function may also contribute to enhanced thrombogenicity in the elderly through deleterious effects on endothelial function with adverse consequences for fibrinolytic activity and coronary vasodilator responses (20–23). Indeed our data suggest an independent effect of renal function, an increase in creatinine from the 10th (80 μmol/liter) to the 90th (140 mmol/liter) centile of the distribution increasing the odds of myocardial infarction by nearly one third. Other differences in biochemical variables included a tendency for blood glucose to be higher and potassium lower in the infarct groups, probably reflecting greater sympathoadrenal activation in myocardial infarction, which stimulates glycogenolysis and drives potassium intracellularly (24,25).

Left ventricular hypertrophy and coronary collaterals. Other factors apart from enhanced thrombogenicity may play a contributory role in determining the clinical expression of plaque events. In hypertension, for example, endothelial dysfunction is common (26,27), but our data suggest that any associated tendency toward increased thrombogenicity and myocardial infarction is outweighed by the increased oxygen demand of the hypertrophied ventricle, which ensures that some plaque events that would normally be silent provoke presentation with unstable angina. Endothelial function may also be impaired in diabetes (28–30), yet this did not appear to affect the mode of presentation. This was surprising but may reflect other differences between diabetic and non-diabetic coronary artery disease combining to obscure those attributable to enhanced thrombogenicity. One possibility is that the diffuse and chronic nature of diabetic coronary disease (31) encourages collateralization of the myocardium, which protects against ischemic injury in the event of thrombotic coronary occlusion (32,33). This may also account for the independent effect of previous coronary syndromes and revascularization procedures, which each favored presentation with unstable angina, reducing the odds of infarction by about two thirds.

Non–Q wave myocardial infarction. Previous investigators have reported that aspirin consumption may also modify the presentation of acute myocardial infarction by protecting against Q wave development (9,34,35). We were unable to confirm this in our patient population, possibly because the inner-city location of our hospital ensure that patients with myocardial infarction present early, and the majority (>70%) are eligible for thrombolytic therapy, obscuring the potential influence of prior aspirin therapy on Q wave development (36). Indeed the only multivariate predictor of non–Q wave infarction was hypertension, presumably reflecting the vulnerability of the hypertrophied ventricle to subendocardial ischemic damage.

Conclusions. A range of factors with the capacity to influence thrombogenicity, myocardial mass and collateralization of the coronary circulation may also influence the clinical presentation of patients with acute coronary syndromes. Our data show that presentation with myocardial infarction is favored by cigarette smoking, advanced age and renal impairment, all of which increase thrombogenicity. Presentation with unstable angina is favored by treatment with aspirin, which reduces thrombogenicity, hypertension, which increases myocardial mass and a history of previous coronary syndromes and revascularization procedures, which may be associated with increased collateralization of the coronary circulation.

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