Sudden coronary death in Glasgow: nature and frequency of acute coronary lesions

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SUMMARY A detailed pathological study of the coronary arteries was carried out on 130 random white subjects (91 male and 39 female) who died suddenly in the Glasgow area. In 30 there was a clearly defined cause of death that was not due to ischaemic heart disease. In eight subjects the cause of death was in doubt. Ninety two of the 130 showed coronary stenosis resulting in a loss of more than 75% of coronary artery cross sectional area and/or acute coronary events with no other cause of death. Of these 92 subjects considered to have died suddenly of ischaemic heart disease, 64% showed plaque rupture and thrombosis which occurred at sites of previous high grades of stenosis. Twenty two subjects had intraluminal thrombosis unrelated to plaque fissuring. Thirty eight (41%) showed histological evidence of recent myocardial necrosis; acute coronary events occurred in 34 of these. There was no correlation between the duration of symptoms before death and the occurrence of acute coronary events.

Acute coronary events, mainly in the form of plaque rupture, are a common finding in sudden coronary death when a careful study is made of the whole coronary arterial tree.

In view of the fact that atherosclerosis has been recognised for many years and the fact that ischaemic heart disease is so prevalent it may seem surprising that controversy still surrounds the mechanism of sudden death from coronary disease. Severely diseased and narrowed coronary arteries may be compatible with many years of symptom free life but when sudden death occurs in individuals with ischaemic heart disease the mechanism and triggering event are still in dispute. Sudden death in the majority of subjects with ischaemic heart disease is attributed to cardiac arrhythmia, and previous pathological studies have suggested that the frequency of coronary thrombi and acute lesions is low. Others have claimed that coronary thrombi are consequences rather than causes of myocardial infarction. More recently, attention has been drawn to the importance of acute plaque events and the role of coronary thrombosis in sudden cardiac death. In cases of sudden unexpected death pathological examination usually takes place as a medicolegal necropsy aimed primarily at excluding unnatural death. It is thus understandable that appropriate detailed pathological data from this source have been scanty. A study was therefore undertaken of 130 random cases of sudden death submitted to medicolegal necropsy in Glasgow with the aim of further clarifying the mechanism of death and of assessing the status of the coronary tree and myocardium.

Patients and methods

We studied 130 white subjects under the age of 70 (91 male and 39 female) who died suddenly in the Glasgow area and who were submitted to medicolegal examination at the Department of Forensic Medicine and Science of the University of Glasgow. Thirty subjects were identified who had a clear cause of death other than ischaemic heart disease. Ninety two had more than a 75% loss of coronary artery cross sectional area and/or an acute coro-
nary lesion and no other cause of death. They therefore were considered to have died from ischaemic heart disease. The remaining eight had less severe coronary artery atherosclerosis (degrees of stenosis less than 75% of cross sectional area) and had no other clear cause of death.

Sudden death was defined as death occurring within 24 hours of the onset of symptoms in a subject who had not consulted a doctor at any time during the previous three weeks. Case notes were reviewed to determine the subject's activity at the time of onset of symptoms or death. A detailed necropsy was undertaken in each case, including histological study where necessary. When appropriate, toxicological examinations were undertaken to identify alcohol, carbon monoxide, or drug poisoning.

The heart was removed unopened for initial angiographic study. The right and left coronary arteries were selectively injected with a barium-gelatin mixture and radiographic delineation of the coronary vessels was obtained. The warm mixture was injected through a hand-held syringe until satisfactory filling of epicardial vessels was noted. The major epicardial coronary arteries were dissected from the fixed heart; then they were decalcified for five days and the radiographic study was repeated. The coronary arteries examined included the entire right coronary artery with its posterior descending and posterolateral branches; the left main coronary artery; the anterior descending coronary artery and its major diagonal branches; and the circumflex coronary artery and its marginal branches.

After postmortem angiography a low midventricular 2 cm transverse slice was cut. The level of the cut was sometimes changed according to the site of the infarct if any had been detected macroscopically. Nitroblue tetrazolium staining was used to complement routine histological examination.12

Histological blocks were then made at approximately 3 mm intervals in the major arteries and labelled for identification according to a standard code13 (fig 1). Each histological section, stained with haematoxylin and eosin, was examined microscopically and coded for the presence of plaque fissuring and dissecting haemorrhage from the lumen, intraluminal thrombosis, intramural thrombosis, or old occlusion. Plaque fissuring or rupture was diagnosed when the intimal cap was disrupted and resulted in a free continuity between the atheromatous material and the lumen. Intraluminal thrombosis when present was recorded. An accumulation of red blood cells within the intima without fissuring or thrombotic material was designated as an intimal haemorrhage.

Each coronary section was measured by a quantitative microscope. The degree of stenosis was esti-
thrombosis. There were 80 instances of plaque rupture in these 59 subjects—35 in the right coronary artery, 30 in the anterior descending coronary artery, and 15 in the circumflex artery. Figure 3 shows a typical example of plaque rupture. Plaque rupture and accompanying acute lesions were more common at sites with higher grades of pre-existing stenosis (table 1). Intraluminal thrombus was often found where there was stenosis of more than 75%.

**Intraluminal thrombus**

Intraluminal thrombi were found in 61 subjects. In 22 of these, no associated underlying fissuring could be identified. Seventy five separate thrombi were found: 48 were occluding more than 50% of the lumen and 27 occupied less than 50%. Figure 4 shows the appearance of a typical intraluminal thrombus associated with plaque fissuring. Table 2 shows the distribution and degree of thrombotic occlusion of the largest thrombus in each of the 61 subjects.

**Distribution of the acute events**

Figure 5 shows the distribution of plaque rupture in the different segments of the coronary tree. Certain segments, such as the second segment of the right coronary, the first three segments of the anterior descending branch, and the first two segments of the circumflex branch were the sites most affected by acute lesions.

**Table 1**  Degree of pre-existing stenosis at sites of plaque rupture and the accompanying acute lesions (total 80 plaque ruptures)

<table>
<thead>
<tr>
<th>Acute lesion</th>
<th>Pre-existing stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 50%</td>
</tr>
<tr>
<td>Intimal haemorrhage and intramural thrombus</td>
<td>1</td>
</tr>
<tr>
<td>Intraluminal thrombosis</td>
<td>0</td>
</tr>
</tbody>
</table>

**Fig 3**  Photomicrograph showing fissuring of an atheromatous plaque with resealing by a small mural thrombus (arrows).
Table 2  Degree of thrombotic occlusion caused by intraluminal thrombi in 61 victims of sudden cardiac ischaemic death

<table>
<thead>
<tr>
<th>Size of largest thrombus per case (% of lumen)</th>
<th>Number of subjects</th>
<th>Coronary artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-24</td>
<td>12</td>
<td>RCA 3 LAD 6 Cx 3</td>
</tr>
<tr>
<td>25-50</td>
<td>14</td>
<td>7 5 2</td>
</tr>
<tr>
<td>51-75</td>
<td>12</td>
<td>5 6 1</td>
</tr>
<tr>
<td>76-100</td>
<td>23</td>
<td>9 7 7</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>24 (39%) LAD 24 (39%) Cx 13 (22%)</td>
</tr>
</tbody>
</table>

RCA, right coronary artery; LAD, left anterior descending artery; Cx, circumflex artery.

ACTIVITY AND DURATION OF SYMPTOMS
There was no correlation between the duration of symptoms before death and the occurrence of plaque rupture or intraluminal thrombus (tables 3 and 4). The occurrence of acute coronary lesions was not related to activity at the time of death (table 5).

STATUS OF THE MYOCARDIUM
The nitroblue tetrazolium method used in combination with routine histology showed that 38 (41%) of the 92 subjects in whom there was unequivocal evidence of coronary death had recent myocardial necrosis. Thirty four of these 38 showed evidence of acute coronary events. Table 6 summarises the findings in the subjects with myocardial necrosis.

Forty six (50%) subjects had old (or healed) myocardial infarctions. Twenty four of these had old lesions in one or more of the coronary arteries (recanalisation).
Table 3 Relation of the interval between onset of symptoms and death to occurrence of plaque rupture (total number 92 subjects)

<table>
<thead>
<tr>
<th>Interval</th>
<th>15 min</th>
<th>15–60 min</th>
<th>1–6 h</th>
<th>6–24 h</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>31 (65%)</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>Number with plaque rupture</td>
<td>20 (65%)</td>
<td>9 (32%)</td>
<td>6 (55%)</td>
<td>6 (55%)</td>
<td>18 (64%)</td>
</tr>
</tbody>
</table>

Table 4 Relation of the interval between onset of symptoms or death to the presence of a thrombus (total number 92 subjects)

<table>
<thead>
<tr>
<th>Interval</th>
<th>15 min</th>
<th>15–60 min</th>
<th>1–6 h</th>
<th>6–24 h</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>31 (65%)</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>Number with thrombus</td>
<td>20 (65%)</td>
<td>7 (64%)</td>
<td>8 (73%)</td>
<td>8 (73%)</td>
<td>18 (64%)</td>
</tr>
</tbody>
</table>

Table 5 Relation of activity at time of death to presence of acute lesion (total number 92 subjects)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Luminal thrombosis</th>
<th>Plaque rupture with mural thrombosis or haemorrhage</th>
<th>No acute lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleeping or sedentary (61 subjects)</td>
<td>42 (69%)</td>
<td>13 (21%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Moderate activity (15 subjects)</td>
<td>9 (60%)</td>
<td>3 (20%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Strenuous activity (16 subjects)</td>
<td>10 (63%)</td>
<td>4 (25%)</td>
<td>2 (12%)</td>
</tr>
</tbody>
</table>

Table 6 Findings in 38 cases with recent myocardial necrosis

<table>
<thead>
<tr>
<th>Location of necrosis</th>
<th>Number of infarcts</th>
<th>Right coronary event</th>
<th>Left anterior descending event</th>
<th>Left circumflex event</th>
<th>Recent event in more than one artery</th>
<th>Recent event in unexpected artery</th>
<th>No recent event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>9</td>
<td>5</td>
<td>8</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lateral</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Posterior</td>
<td>10</td>
<td>3</td>
<td>7</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Circumferential</td>
<td>8</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Septal</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Subjects in whom the cause of death was in doubt

Eight of the 100 subjects showed varying degrees of stenosis, between 20% and 73% (mean maximum stenosis 53%), without demonstrable acute coronary lesions and the cause of death must be considered to be in doubt. In common with a similar London study14 these subjects were excluded from further analysis.

Non-ischaemic deaths

Table 7 shows the identified cause of death in the group of 30 subjects in whom a non-ischaemic cause of death was found. No intraluminal thrombosis was found in any of these 30 subjects. Plaque fissuring accompanied by intimal haemorrhage was, however, present in one (a victim of drug overdose).

Discussion

The controversy about the frequency of coronary thrombi and plaque rupture in sudden ischaemic death is unresolved, with various groups reporting markedly different findings.8 14 15 The data reported in the present study indicate that in 88% of subjects where death occurred suddenly from ischaemic heart disease there was a recent lesion in one or more of the coronary arteries. The findings in this study resemble those of a recent similar study by Davies and Thomas.10 Both studies confirm that when a careful and detailed examination of the whole epicardial coronary tree is made acute lesions are often found. This study has demonstrated the nature and frequency of acute coronary events in sudden death from ischaemic heart disease. Pathological exami-
inflammation, however, cannot determine the precise pathophysiological mechanisms involved—low cardiac output (pump failure) or arrhythmia (ventricular fibrillation).

Plaque rupture or fissuring has been recognised by pathologists for many years, yet it is still not widely appreciated that rupture of the soft lipid rich plaque is a major and common life-threatening event. The degree of pre-existing stenosis appears to play a decisive role in the sequelae of plaque fissuring. When there is rupture of a plaque that occupies <75% of the cross sectional area of the artery intimal haemorrhage without thrombosis is frequently found. When the plaque causes stenosis >75% of the cross sectional area its rupture is often associated with thrombosis. This accords with the findings of Falk.

This study of sudden death shows that plaque fissuring is more common in certain segments of the coronary tree than in others. These segments, however, were also the sites of higher grades of stenosis and highest frequency of thrombosis, and therefore anatomical site by itself probably does not determine the likelihood of plaque rupture. Plaque rupture seems to be an important part of the atherosclerotic process which may result in acute vessel occlusion and its outcome is determined to a great extent by the degree of pre-existing stenosis. If the pre-existing stenosis is severe, acute vessel occlusion will occur; less severe stenosis may only result in an increase in plaque size. The size of the cracked intimal cap and the platelet response at the site of rupture also play an important role in determining the nature of the lesion accompanying the rupture. This study confirms that intraluminal thrombosis is a common finding in segments of coronary artery in which there is plaque rupture.

Our study has identified a subgroup in the 92 subjects who died suddenly from ischaemic heart disease in whom no acute coronary lesion could be identified. This group of 11 subjects with definite ischaemic heart disease but no acute coronary lesion showed stenosis producing more than 75% loss of luminal cross sectional area in at least one major coronary artery. Although we cannot rule out the possibility of missing a small area of plaque fissuring or a tiny thrombus there are other possible mechanisms for sudden cardiac death. These include platelet microthrombi, coronary artery spasm, myocardial oxygen supply/demand imbalance, or disturbances of rhythm.

Acute lesions in the proximal coronary arteries may produce larger areas of ischaemic myocardium and are more likely to cause death. This seems to accord with the clinical and angiographic findings when severely stenosed proximal arteries are bypassed by grafts and long term survival is improved.

Local vascular spasm precipitated by plaque rupture is another possible explanation for the mechanism of death, as is a large mural thrombus bulging into the lumen and obstructing the vessel in the absence of associated intraluminal thrombosis. Another possibility is that there may have been spontaneous lysis of intraluminal thrombus ante-mortem.

The relatively low frequency of demonstrable myocardial infarction in the present study (41%) must in part reflect the sudden nature of death, as the nitroblue tetrazolium test and conventional histology do not detect infarction where the survival period is short.

Acute coronary lesions were a common finding in cases with recent myocardial necrosis and in all cases except two they occurred in the artery supplying the area of infarction. In cases with diffuse sub-endocardial infarction significant stenoses were noted in all three major coronary vessels. The study also showed that in about half the cases with healed infarcts the ischaemic damage was probably due to an old coronary event. This was suggested by the presence of recanalisation in the supplying artery in 24 of the 46 cases with old infarcts.

This study provides no evidence of an association between the occurrence of acute coronary lesions and the interval between the onset of symptoms and time of death. Others have claimed that acute coronary lesions are not found in subjects dying instantaneously from ischaemic heart disease. It was also claimed that the longer the duration of survival after the onset of symptoms, the more frequently are acute lesions present. Our study does not confirm claims that plaque rupture is more commonly the underlying fatal event in older rather than younger patients; however, we found a higher frequency of intimal haemorrhage accompanying the rupture in the older group. Furthermore, our study has shown no association between the activity at the time of death and the presence of acute coronary events. This finding does not contradict the possibility that sudden unaccustomed activity may precipitate sudden coronary death. It is possible, however, that the sudden rupture of the thin fragile cap may require no more than normal haemodynamic stresses.

The importance of acute coronary lesions as the mechanism of sudden ischaemic death is emphasised by their absence in the majority of subjects who died of causes other than ischaemic heart disease (plaque fissuring was noted in only one of 30 such subjects). Circumferential myocardial infarction was present in two of these subjects and may be explained by pre-terminal hypotension, as one died of intracere-
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Sudden coronary haemorrhage and the other of a drug overdose. The results of this study emphasise the importance of acute plaque events in atherosclerotic coronary arteries as the major cause of sudden cardiac death in Glasgow. The events take the form of plaque rupture and are commonly associated with thrombosis. The findings in this study and in a similar recent London study suggest little difference between the two cities in the nature and frequency of acute coronary events occurring in those who die suddenly.

This work was supported by a grant from the Scottish Hospital Endowments Research Trust.

References

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doi: 10.1136/hrt.57.4.329

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