Pathology of acute myocardial infarction with particular reference to occlusive coronary thrombi

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Analysis of the pathological findings in 500 cases of fatal acute myocardial infarction showed that in 469 this was localized to one transmural area of the left ventricle; in 31 there was diffuse subendocardial necrosis. In the former occlusive coronary thrombus was found in the related artery in 95 per cent of cases. Variation in the percentage of occlusions found was noted between different prosectors and when coronary artery calcification was present. Only 4 of the 31 patients with subendocardial necrosis had recent occlusion; triple vessel disease was common in this group suggesting general failure of coronary perfusion. It is essential in necropsy studies of the relation of coronary thrombosis to myocardial infarction to be sure that muscle necrosis is present, to distinguish the two forms of myocardial necrosis, and to employ a meticulous dissection technique with decalcification of the arteries when necessary.

It is hardly credible that there should be continuing debate about what is ostensibly so simple a morphological problem, the relation of coronary thrombosis to acute myocardial infarction. For well over half a century opinion has swung from one extreme to the other and once again it is being suggested, particularly in the United States of America (Roberts, 1974), that the two are not constantly or causally related and even that coronary thrombosis may be a complication of myocardial infarction. The reported proportions of fatal acute myocardial infarcts in which occlusive thrombi are found have varied from less than 50 per cent (Baroldi, 1965; Kagan et al., 1968; Roberts and Buja, 1972) to approaching 100 per cent (Chapman, 1974; Harland and Holburn, 1966). A recent workshop of 10 pathologists (Chandler et al., 1974) in the United States trying to resolve the question succeeded only in once again highlighting the controversy (Burchell, 1974). As pathologists interested in this subject in the United Kingdom, we have reviewed our own necropsy experience of acute infarction in an attempt to identify factors that might explain this wide variation.

Methods

For this study myocardial infarction was rigidly defined as a localized and discrete area of muscle

necrosis in the myocardium visible to the naked eye at necropsy and larger than 3 cm in diameter in one axis. The left ventricular circumference was divided into anterior, posterior, lateral, and septal segments for anatomical definition of the site of localized infarction. No attempt was made to measure accurately the percentage of left ventricular muscle involved in the infarction, though where two or more segments were involved the infarcts were large. Diffuse subendocardial necrosis was rigidly defined to mean circumferential myocardial necrosis involving the inner zone of the whole left ventricle and often the central zone of the papillary muscles. This form of necrosis often associated with additional scattered foci of necrosis up to half a centimetre in diameter is regarded by us as an entity pathologically distinguishable from the localized areas of infarction over 3 cm in diameter.

Over a 10-year period all necropsies were performed by consultant pathologists A, B, C, and D, and a changing population of trainee pathologists under supervision of the consultants and designated as group E. From January 1964 to February 1974 inclusive 6400 routine hospital necropsies were carried out at St. George's Hospital; of these, 500 were performed on patients with myocardial infarction. No forensic necropsies carried out for the coroner are included, all patients having been inpatients of the hospital for a minimum of 24 hours.

There was no selection of cases by individual pathologists, who are responsible for necropsies on a monthly roster; the different number of necropsies carried out by each merely reflects greater or lesser number of months on the roster. The number of necropsies carried out per year on patients with myocardial infarcts ranged from 43 to 67. Age, sex, and history of hypertension or diabetes were recorded for each patient. Hypertension was defined as blood pressure high enough to have received treatment. The time interval between onset of pain and death was recorded in days.

In this department the standard method of examining the coronary artery tree is by transverse section at 5 mm intervals. Two prosectors (A and B), when there is extensive calcification, routinely decalcify the coronary arteries before transection. In 80 cases post-mortem coronary angiography had been performed before dissection of the heart.

Thrombus was defined as a mass of fibrin and platelets without large numbers of red cells and was regarded as occlusive when completely blocking the lumen of the artery by naked eye examination. Histological examination often reveals some minimal retraction of the thrombus away from the arterial wall; when this led to reappearance of not more than 10 per cent of the lumen, the lesion was still regarded as occlusive. This retraction is at least in part likely to occur in tissue embedding for histological examination.

Occlusive thrombi were recorded as being in the main left coronary artery (L), left circumflex (LC), left anterior descending (LAD), left marginal (LM), right (R), or posterior descending (PD) coronary artery. Our standard necropsy protocol allows a crude pictorial representation of the severity and extent of coronary atherosclerosis and the degree of arterial stenosis; significant stenosis is taken as more than 75 per cent reduction of the lumen.

In common with clinical practice the cases were divided into those with disease affecting one, two, or three major vessels. The left anterior descending, right, and left circumflex are the three vessels considered in this method of assessment. Cases of single vessel disease were divided further into those with a single area of stenosis and those with multiple stenotic areas.

Results

There were 336 male and 164 female patients. The mean age of male patients was 60, and of female patients 69, at death. Of the total, 25 men (7·4%) and 23 women (14·0%) were diabetic; 80 men

(23·8%) and 46 women (28%) had hypertension as previously defined.

Site of infarction

Of the myocardial lesions, 31 were designated as diffuse, subendocardial necrosis. The site of the remaining 469 localized infarcts, as defined by segment involved, is shown in Table 1. Three infarcts were confined to the right ventricle; all three hearts showed right ventricular hypertrophy. Previous old infarction with fibrous scarring in the left ventricle visible to the naked eye was recorded in 204 of 500 patients (40·8%).

Frequency and site of occlusive thrombi

In the whole series, 52 (10·4%) had no occlusive thrombi at necropsy. Of 469 patients with localized infarcts, only 25 (5·3%) had no occlusive thrombi. When these results were analysed in relation to which pathologist carried out the necropsy considerable variation emerges (Table 2). The incidence of occlusion in each artery is shown in Table 3.

Extent of coronary atherosclerosis

Sufficient information for accurate grading of coronary atherosclerosis was available in 448 of these cases; 82 (18·3%) had single vessel disease, 157 (35%) double vessel disease, and 209 (46·7%)

TABLE 1 *Site of infarction: 469 localized transmural infarcts*

Anterior	Anterior alone	127 ⎫	
	Anteroseptal	74	⎬ 242
	Anterolateral	19	
	Anterolateral-septal	22 ⎭	
Posterior	Posterior alone	102 ⎫	
	Posterolateral	33	⎬ 167
	Posteroseptal	24	
	Posterolateral-septal	8 ⎭	
Lateral alone		31	
Septal alone		3	
Right ventricle alone		3	
Large infarcts involving over 75 per cent of left ventricle		23	

TABLE 2 *Analysis of occurrence of thrombi with different prosectors: 469 localized myocardial infarcts*

		Total no. of cases	No thrombi found
Pathologist	A	131	2 (1·5%)
	B	52	1 (1·9%)
	C	30	0 (0)
	D	81	16 (19·8%)
Pathologists	E	175	6 (3·4%)

TABLE 3 *Site of recent coronary occlusion: 469 localized myocardial infarcts*

Main left	15
Left anterior descending or major branch	219
Left circumflex	63
Left marginal	10
Right	160
Posterior descending	9
More than one recent occlusion	31

triple vessel disease. Of the 82 patients with single vessel disease, only 18 had occlusions in association with single isolated areas of stenosis.

Severe coronary arterial calcification was noted as a positive finding in 115 cases (23%) of the whole series. Coronary calcification was noted in 17 of the 25 (64%) cases of localized infarction without occlusion.

Diffuse subendocardial necrosis

Only 4 of the 31 cases of subendocardial necrosis had a recent occlusion. Twenty-eight of the 31 (90%) had triple vessel disease; 23 of the cases had fibrotic areas of healed localized infarction.

Mural thrombus

Thrombus in the left ventricle was recorded in 139 of the 500 cases (27·8%). Systemic emboli occurred in 48 of the 139, and 24 of these were cerebral.

External cardiac rupture

A total of 42 patients died as the result of pericardial tamponade; of these 22 (52%) were women and 20 were men (48%). Rupture of the left ventricle was present in 39, of the anterior wall of the right ventricle in 1, and in 2 cases blood appeared to have oozed from the surface of the infarct without frank rupture. The mean age of women dying with tamponade was 74 and of men 68. Cardiac rupture became more common with increasing age in both men and women. Under the age of 70, 10 of 241 men (4·1%) and 7 of 77 women (9·1%) died of cardiac rupture. Over the age of 70, 7 of 87 men (7·9%) and 15 of 95 women (15·7%) died of cardiac rupture. In 33 of these 42 cases, sufficient information was available to assess the degree of atheroma; of these 16 had single, 15 had double, and 2 had triple vessel disease.

Internal cardiac rupture

Eleven examples of acquired ventricular septal defects were recorded (2·2%) and six of ruptured papillary muscle (1·2%).

Pulmonary emboli

Major pulmonary emboli were recorded in 56 of the 500 cases (11·2%).

Discussion

This retrospective study has produced a wealth of data, much of it not controversial. Myocardial infarction is more common in men than women and, on average, occurs a decade earlier in the former than in the latter. It is interesting, but as yet unexplained, that acute myocardial infarction with rupture in the elderly tends to occur with less coronary atherosclerosis than in younger people and in the absence of old infarcts (*British Medical Journal*, 1972). The present study suggests that the risk of external rupture is greater in women than in men at all ages, a fact previously recorded (Mitchell and Parish, 1960). Detailed population rather than hospital study has suggested, however, that in old age, while more cases of cardiac rupture in myocardial infarction are seen in women, the sex and age-corrected incidences are identical (Crawford and Morris, 1960). Haemopericardium may occur occasionally in patients who have no demonstrable cardiac rupture and who may or may not have been treated with anticoagulants (Aarseth and Lange, 1958).

Involvement of the right ventricle in infarcts of the left ventricle is not uncommon, when looked for, particularly in posterior infarcts. On the other hand, isolated right ventricular infarction is decidedly uncommon and is associated in our experience, as in that of others, with right ventricular hypertrophy resulting from severe pulmonary hypertension (Wade, 1959).

The distribution of infarcts and related recent coronary occlusions in our series is much the same as that reported in other published series, but is biased in favour of posterior infarcts because of the number of patients with complete heart block referred to the pacing unit in our hospital. No discordance between infarct site and coronary occlusion was noted and we have found no evidence to support the concept of paradoxical infarction.

The major point at issue is the incidence of recent occlusive coronary thromboses and their relation to myocardial infarcts. This study suggests a constant and probably causal link between occlusive coronary thrombosis and acute infarction. Other workers have not found this relation; explanations must be sought to account for these conflicting observations. First, it seems essential that a rigid definition of acute myocardial infarction be adopted, as in this study, where we used the term in its exact pathological meaning as an easily demonstrable localized

area of muscle death. For this to be easily visible the patient must have survived the onset of the acute episode for at least 12 and preferably 24 hours. It is to be regretted that diffuse, circumferential, subendocardial necrosis is still classed by many observers (Baroldi *et al.*, 1974; Ehrlich and Shinohara, 1964) as myocardial infarction when its pathogenesis is different, though the two conditions, localized infarction and diffuse subendocardial or laminar necrosis, may coexist. In our series, the incidence of occlusive thrombi in diffuse subendocardial necrosis (13%) is very low, whereas the incidence of occlusive thrombi in localized infarction is high (95%), a fact emphasized by Miller, Burchell, and Edwards (1951) and Mitchell and Schwartz (1963). The severity of atherosclerosis as judged by the incidence of triple vessel disease is greater in subendocardial laminar necrosis, as is the incidence of healed infarction, indicating that severe diffuse coronary artery disease is the important predisposing factor. These findings suggest that this form of myocardial necrosis is the result of inadequate perfusion of the inner quarter of the myocardium of the left ventricle as a result of advanced, stenosing coronary atherosclerosis. In these cases there is a strong tendency to progressive dilatation of the left ventricle, the development of mitral regurgitation, and cardiac failure. An identical form of diffuse subendocardial necrosis is often seen in the hearts of patients who fail to survive cardiac bypass, when the coronary artery tree is anatomically normal but inadequately perfused at operation (Pomerance and Davies, 1975).

A second cause of confusion is the inclusion in other necropsy series of cases of sudden death attributable to coronary artery disease and thought to be the result of acute myocardial infarction (Spain and Bradess, 1960). The pathology of sudden cardiac death, at least in the United Kingdom, is still unknown largely because of the limits imposed on scientific investigation by the requirements of the coroner system. We believe, as do others (Friedman *et al.*, 1973; Liberthson *et al.*, 1974), that cases of sudden death from coronary artery disease can be subdivided into at least two groups, one consisting of patients with acute coronary occlusion in whom myocardial infarction could be anticipated had they survived long enough, and the other consisting of those with coronary artery disease who, for one reason or another, develop ventricular fibrillation but who would not necessarily have developed myocardial infarction had they survived. The relative size of the two groups is unknown and may be different in different places. It follows that when large numbers of cases of sudden death are in-

cluded in series with the intention of investigating the pathology of myocardial infarction there will be a sharp drop in the incidence of coronary thromboses found at necropsy.

In our opinion localized myocardial infarction is the direct result of thrombotic occlusion of a major coronary artery, and in our series there was always a direct relation between the site of occlusion and the area of the infarct. Analysis of the small number of localized infarctions where no occlusion was found showed that in most of them there was severe calcification of the coronary arteries which had not been decalcified before dissection, making demonstration of thrombi difficult. Furthermore, even within our own department, there are significant differences between different prosectors in the proportion of patients with acute infarcts in which occlusive thrombi were found in the coronary arteries. We interpret this to indicate that the opinions of the prosector and the techniques employed in searching for thrombi must play a major role in producing the variability of reported results. In our series there is nothing to suggest that selection factors operate to influence results as necropsies were performed on a monthly roster system. We are not the first to suggest that the number of occlusive coronary thrombi found at necropsy is directly related to the care and energy expended in the search (Mitchell and Schwartz, 1963; Crawford, 1964; Chapman, 1974), and the interest and experience of the prosector.

Finally, the explanations invoked for infarction without occlusion leave much to be desired and pose more questions than they solve. If infarction does indeed cause coronary thrombosis, what is the explanation for those cases of sudden death, a not inconsiderable number, probably between 30 and 50 per cent, with coronary thrombosis but no infarct? Much of the argument in favour of the coronary thrombosis being a secondary result of stasis in the related artery following infarction is based on attempts to 'age' thrombi related to infarcts (Branwood and Montogomery, 1956; Baroldi, 1965). Ageing thrombi can be very difficult unless step serial sectioning is undertaken through the whole of the occlusion. A random section through a zone of propagated thrombus will be quite misleading when the original, older zone of occlusion has escaped observation. The further inability of pathologists to date accurately the duration of infarction makes any comparison of thrombus age to infarct duration 'doubly hazardous' (Burchell, 1974).

Incorporation of ^{125}I into coronary thrombi after the onset of chest pain and electrocardiographic signs of infarction in living patients has been taken

to prove that thrombosis follows infarction (Erhardt, Lundman, and Mellstedt, 1973). Two alternative explanations, however, exist: thrombi may propagate and thereby incorporate new fibrin; and labelled fibrinogen can diffuse into old thrombi. The confirmation of the latter finding in animal models (Kravis *et al.*, 1974) seriously questions the work of Erhardt and his colleagues (1973).

Careful histological examination of acute occlusions in coronary arteries indicates that plaque rupture commonly initiates thrombosis. This fact is clearly strong evidence against the suggestion that the thrombus is secondary to the infarct (Chapman, 1965; Bouch and Montgomery, 1970). It is of some interest that this finding has caused a change of view on the part of Montgomery, whose earlier paper (Branwood and Montgomery, 1956) is so often quoted by supporters of the view that thrombosis follows infarction. Finally, old canalized thrombi are a not infrequent finding in human coronary arteries without evidence of old myocardial infarction. It seems strange that Duguid's (Duguid, 1946) repeated assertion that mural thrombi are the major factor in plaque growth and the production of stenosis is now gaining general acceptance (Roberts, 1973), yet the same authors deny that thrombi are the final cause of occlusion. The occurrence of multiple old coronary occlusions in patients with recent infarction strongly suggests a generalized thrombotic tendency preceding the acute episode, and there is good evidence of long-standing episodic mural thrombi in the aortae of such patients (Woolf, Sacks, and Davies, 1969).

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