Coronary artery narrowing without irreversible myocardial damage or development of collaterals

Assessment of "critical" stenosis in a human model

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SUMMARY Postinfarction cardiac rupture is the result of thrombotic occlusion of a functional end artery with no previous myocardial damage in the perfusion area of the occluded artery. The pre-existing atherosclerotic stenosis at the site of thrombosis is thus "non-critical" in relation to the development of collateral vessels and/or irreversible myocardial damage.

Eleven cases of postinfarction cardiac rupture were studied by microscopy of cross-sections of the thrombosed segments. At the site of the thrombosis, pre-existing atherosclerosis had narrowed the lumen to 11% or less of its normal cross-sectional area. Maximal pre-existing narrowing of the proximal left anterior descending artery was found in a case with 97% stenosis (histologically measured cross-sectional area reduction) and an estimated residual lumen of 0.71 mm². The pre-stenotic luminal area which is usually considered angiographically as "normal" was in all cases shown histologically to be severely narrowed by a diffuse intimal thickening.

It is concluded that organic coronary stenosis must be far greater than 75% to be responsible for the development of collateral vessels and/or irreversible myocardial damage.

Coronary artery stenosis that limits blood flow below basal demands is usually considered critical. In human disease, however, the term "critical stenosis" is poorly defined, especially as no consistent relation has been documented between symptoms of ischaemic heart disease and the extent and severity of coronary narrowing.¹⁻³ In addition, a severe stenotic lesion may be bypassed and adequately compensated by collateral vessels, which make evaluation of the ischaemic significance of the stenosis, *per se*, impossible. In animal studies, however, a critical level of stenosis has been identified. Isolated proximal coronary stenosis has to reduce the luminal cross-sectional area by about 95% before resting myocardial flow fails to meet the demand.^{4,5} At that degree of acute obstruction, the peripheral vascular bed is maximally dilated and further narrowing will cause myocardial ischaemia at rest.

At necropsy we are occasionally provided with a human model which is comparable with the experimental, isolated coronary stenosis. Thus it has previ-

ously been shown that a uniform patho-anatomical substrate exists in postinfarction cardiac rupture, consisting of an acute coronary occlusion with a recent myocardial infarct which is transmural and totally unprotected by scar or collateral vessels.⁶ Consequently, in these hearts we find acute occlusions of functional end arteries, and the pre-existing organic stenosis at the site of thrombosis can thus be considered "non-critical" in relation to the development of collateral vessels and/or irreversible myocardial damage.

This paper presents a quantitative assessment of the pre-existing luminal narrowing in acutely thrombosed coronary arteries from 11 patients with postinfarction cardiac rupture.

Subjects and methods

Nine consecutive necropsy patients with heart rupture from Randers Hospital and two cases referred from another hospital in the same period (1 February 1980 to 30 June 1981) form the basis for this study.

After the heart was weighed the coronary arteries were gently flushed via the aorta with 100 ml 4% formaldehyde solution and then a barium gelatine

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medium at 40°C was injected under a pressure of 150 mmHg maintained for 15 minutes. The medium was hardened by cooling and angiograms were taken in different projections. The heart was fixed for two weeks in a 4% formaldehyde solution, decalcified for three weeks in EDTA (ethylenediaminetetraacetic acid), and then stored for at least one week in formalin. The main coronary arteries and those of their branches thicker than 1 mm were cross-sectioned at 3 mm intervals. Each segment, angiographically shown to be stenosed or occluded, was processed for microscopy. All thrombosed segments were cross-sectioned at 200 μ m intervals and the point of maximal luminal reduction resulting from old atherosclerotic plaques was identified. The ventricular portion of the heart was cut into 1 cm thick slices parallel to the atrioventricular groove, photographed, and x-rayed, with each slice placed directly on the film. Several histological sections were prepared from the perfusion area of each coronary artery and from the myocardium adja-

cent to the rupture.

TISSUE SHRINKAGE

To calculate the shrinkage that occurs when an artery is processed for microscopy the following experiment was performed. Unfixed segments of injected arteries were dissected free from the hearts, placed directly on radiographic film, and x-rayed. X-rays were repeated after fixation, dehydration, clearing, and embedding in paraffin. During this procedure and at the final microscopical examination of the histological sections it was observed that the shrinkage of the radio-opaque medium was equal to or a little more pronounced than the shrinkage of the artery lumen. The segments where the shrinkage of the x-ray medium equalled the luminal shrinkage were selected for measurements. The luminal diameters were measured on the radiographs and the luminal area shrinkage resulting from tissue processing was calculated. One-hundred and fifty measurements were done on 15 different vascular segments.

Table 1 Clinical data in 11 patients with postinfarction cardiac rupture

Case No.	Age (y)	Sex	Survival* (d)	Preinfarction cardiac symptoms†
1	82	F	1	None
2	69	M	<1	Unstable angina
3	69	M	3	None
4	80	M	<1	None
5	71	F	<1	Unstable angina?
6	77	M	5	None
7	79	M	<1	Unstable angina
8	67	M	4 weeks	None
9	74	F	10 weeks	Unstable angina
10	86	M	<1	None
11	68	M	<1	None

*Histological dating of the infarcts according to the criteria of Mallory *et al.*°

†No patient had stable angina pectoris.

Table 2 Histological and angiographic data in 11 patients with postinfarction cardiac rupture

Case No	Heart weight (g)	Thrombosed artery	Size of perfusion area	Measured histological areas			Calculated stenoses		True residual** lumen (mm ²)
				Residual* lumen (mm ²)	Original† lumen (mm ²)	Prestenotic‡ lumen (mm ²)	Angiographic§	Histological¶	
1	430	LAD (prox.)	39%	0.47	17.28	7.56	94%	97%	0.71
2	450	LAD (prox.)	42%	1.30	15.08	7.29	82%	91%	1.95
3	370	LM	15%	0.94	11.20	2.54	63%	92%	1.41
4	490	LAD	20%	1.07	13.66	4.01	73%	92%	1.61
5	500	LAD	21%	0.26	11.33	5.51	95%	98%	0.39
6	450	R	37%	0.47	12.53	6.36	93%	96%	0.71
7	350	LAD	22%	1.47	13.78	4.32	66%	89%	2.21
8	600	LAD (prox.)	43%	0.51	24.62	5.18	90%	98%	0.77
9	440	R	37%	1.13	19.60	7.29	84%	94%	1.70
10	385	LAD	22%	0.55	13.17	4.12	87%	96%	0.83
11	430	LAD	22%	1.63	15.87	11.92	86%	90%	2.45

Abbreviations: LAD, left anterior descending artery; (prox.) indicates that the occlusion is located proximal to the first diagonal branch; LM; left marginal branch; R, right coronary artery.

* Cross-sectional luminal area at maximal stenosis resulting from old atherosclerotic plaques.

† Cross-sectional area encircled by the internal elastic membrane.

‡ Cross-sectional luminal area of adjacent prestenotic segment which, angiographically, would be judged as "normal".

§ Residual lumen/prestenotic lumen.

¶ Residual lumen/original lumen.

** Residual lumen corrected for shrinkage caused by processing for microscopy (residual lumen $\times$ 3/2).

Fig. 1 Case 2 illustrating how severe a stenosis can be without collateral development or evidence of irreversible myocardial damage in the form of scar. (A) Postmortem angiogram in the anteroposterior view showing total occlusion of the proximal left anterior descending artery (thick arrow) without collateral distal filling of the vessel (original natural size). (B) Radiograph of a transverse myocardial slice showing no collateral vascular filling in the perfusion area of the left anterior descending artery (original natural size). (C) Photograph of the same myocardial slice showing rupture of the anterior left ventricular wall. Microscopy showed antero-septal infarction less than 1 day old; no myocardial fibrosis was present (original natural size). (D) Histological section from angiographic "normal" segment (thin arrow in A) showing diffuse intimal thickening with the lumen 64% obliterated (original magnification $\times 8$). (E) Histological section showing occluding thrombus at the site of maximal atherosclerotic narrowing (thick arrow in A). This degree of old stenosis (91% cross-sectional area reduction) has not caused collateral development or produced irreversible myocardial damage in the form of fibrosis. In this case a histological area stenosis of 91% corresponds to an angiographic area stenosis of 82% (original magnification $\times 8$).

Fig. 2 Correlation of angiographic and pathological findings (case 5). (A) Angiogram showing total occlusion of left anterior descending artery (thick arrow) with poor collateral distal filling of the vessel (original natural size). (B) Histological section of the left anterior descending artery just after the bifurcation of the left main artery (thin arrow) where the vessel angiographically appears "normal" with a wide lumen. Nevertheless, the luminal narrowing resulting from diffuse atherosclerotic intimal thickening is 71% at that point. That is the reason why the real stenosis is consistently underestimated angiographically (original magnification $\times 14$). (C) Histological section from the left anterior descending artery at the site of maximal stenosis resulting from old atherosclerotic plaques (thick arrow); the residual lumen is occluded by a recent thrombus. The histological area stenosis of 98% corresponds in this case to an angiographic area stenosis of 95% (original magnification $\times 14$).

Fig. 3 Shrinkage of tissue and contrast medium caused by processing for microscopy. (A) Radiograph of an unfixed vascular segment placed directly on the x-ray film. (B) The same segment after fixation and decalcification. (C) The same segment after dehydration, clearing, and paraffin infiltration. That the shrinkage of the contrast medium equals the luminal shrinkage is shown by radiographs of corresponding cross-sections and by microscopy of the final histological sections (D). The total shrinkage (A to C) results in a reduction of the luminal area to approximate two thirds of the original area of the unprocessed vessel. ((A), (B), and (C) original magnification $\times 2.5$; (D) original magnification $\times 11$)).

PERFUSION AREA

The relative amount of ventricular myocardium supplied by the three large coronary arteries varies according to the anatomy of the coronary artery tree. The perfusion areas of the coronary arteries were identified from the angiograms, and the percentage of ventricular myocardium supplied by each artery was determined according to the results of Kalbfleisch and Hort.⁷ The perfusion area of the first diagonal branch was considered as large as that of the left anterior descending artery distal to the first diagonal branch.⁸

DEFINITIONS

Histological stenosis: the ratio between the cross-sectional area of the residual lumen and the assumed original cross-sectional luminal area of the vessel at the point under consideration (the area encircled by the internal elastic membrane). All cross-sectional areas are calculated from measurements of maximal and minimal diameters assuming an elliptical cross-section (measured by projection microscopy using a Reichert Lanometer).

Angiographic stenosis: the ratio between the stenotic luminal area and the greatest prestenotic luminal area (which angiographically would be judged as "normal"). As the vessels in question are thrombosed and thus not visualised on the angiograms, the two areas had to be determined by microscopy of the histological sections.

Results

Clinical and pathological findings are summarised in Table 1 and 2.

Recent thrombi superimposed on atherosclerotic plaques were found in all patients, and the site of myocardial rupture corresponded with the point of arterial occlusion. At the site of the thrombus, all patients had histological stenosis of more than 89% caused by old atherosclerotic plaques. Apart from cases 8 and 9, the angiograms disclosed no collateral vessels bypassing the thrombotic occlusions (Fig. 1 and 2) and careful microscopical examination of the myocardium showed no fibrosis in the perfusion area of the thrombosed artery. Cases 8 and 9 had ruptured ventricular aneurysms. The prestenotic segments which, on angiograms, are usually considered as "normal" were in all cases severely narrowed because of diffuse intimal thickening (confluent atherosclerotic lesions) (Fig. 1 and 2). Formalin fixation did not cause any significant tissue shrinkage (no difference between vessels dissected free and vessels in situ) but the subsequent tissue processing resulted in a reduction of the luminal area to approximate two-thirds of the original area of the unfixed vessel (median: 65%, range: 50% to 74%) (Fig. 3).

Discussion

Necropsy studies have shown that the infarction size is usually smaller than the perfusion area of the obstructed vessel¹⁰⁻¹² and even cases of total coronary occlusion with no myocardial damage have been reported.^{11,13} The ability of collateral vessels to protect jeopardised myocardium is thus obvious. Therefore, to evaluate the ischaemic significance of organic stenoses, one has to identify stenotic lesions not bypassed by collateral vessels. But as many functional

collateral vessels are below the resolution of modern cineangiographic equipment,¹⁴ in vivo determination of the human "critical stenosis" may be unreliable. The degree of coronary artery narrowing causing irreversible myocardial damage is thus poorly defined clinically. In fatal heart disease, however, the necropsy occasionally discloses postinfarction cardiac rupture, and in these cases the existence of significant collateral vessels can be excluded in the light of functional considerations, not merely because of inability to detect such vessels angiographically.

Thus, using a refined injection and dissection technique, Wessler *et al.*⁶ have shown that postinfarction cardiac rupture is the result of thrombotic occlusion of a functional end artery with no evidence of previous myocardial damage (fibrosis) in the perfusion area of the thrombosed artery. The reliability of their technique in showing collateral vessels in human hearts without coronary artery disease has been questioned^{15 16} but their method has been reliable in hearts with coronary occlusions.¹⁵ The present study was not undertaken to clear up the pathogenesis of postinfarction cardiac rupture, but our results are in agreement with the results of Wessler *et al.* Cases 8 and 9 are unusual cases of late myocardial rupture (ruptured aneurysms four and 10 weeks after the acute infarction) and the angiographically visible collateral vessels have probably developed secondarily to the thrombotic occlusions.

The aim of our study was to determine the maximal degree of old organic obstruction in the thrombosed coronary artery in cases of postinfarction cardiac rupture. These stenoses have not yet reached a degree that causes collateral development and/or irreversible myocardial damage.

Many pathologists consider an histological area stenosis of 75% as significant.^{1 17 18} This study, however, shows that a pure organic stenosis far greater than 75% may be well tolerated. Thus, stenoses greater than 95% were observed without evidence of irreversible myocardial damage in the corresponding perfusion area.

Minor degrees of organic obstruction may of course be clinically significant in causing myocardial ischaemia and angina during exercise and, if vasoconstriction (spasm) is superimposed, even at rest.^{19 20}

Histological stenosis is not comparable with angiographic stenosis. The pathologist compares the residual lumen with the presumed original lumen (area encircled by the internal elastic membrane) while the clinician compares the most narrowed segment with the adjacent "normal" arterial segment as depicted on the angiogram. The adjacent "normal" segment, however, is never normal, as the coronary arteries in ischaemic heart disease in addition to focal stenotic lesions have diffuse intimal thickening¹⁸

which often corresponds to a histological area reduction of 75%.^{1 18} The result is that the angiographer compares stenotic segment with adjacent "normal looking" but, nevertheless, narrowed segment, and the real degree of stenosis is thus consistently underestimated. To overcome this problem in angiographic-histological correlative studies, it is necessary to measure the stenotic residual lumen precisely and then to calculate the true size of the lumen. The clinician has to compensate for dimensional errors caused by angiographic magnification while the pathologist has to correct for postmortem alterations and tissue shrinkage secondary to processing for microscopy. Our histological procedures resulted in an area reduction to two-thirds of the area of the unprocessed vessel. This figure is in general agreement with the results obtained by measurements of volume changes of whole organs and tissue specimens fixed in formalin and processed for embedding in paraffin.^{21 22}

McMahon *et al.*²³ have measured angiographically the minimum cross-sectional lumen area in patients with unstable angina and proximal single vessel disease without collateral vessels and found it 0.6 mm² (92% cross-sectional area reduction). Our cases 1, 6, and 8 show proximal stenoses with a residual lumen of the same magnitude (0.71, 0.71, and 0.77 mm²). As all stenoses in our cases are "non-critical", the present study fully confirms the observation of McMahon *et al.* that a very severe coronary stenosis can be tolerated in a functional end artery without irreversible myocardial damage in the perfusion area of the obstructed vessel. Stenotic coronary lesions with less than 90% angiographic diameter reduction can undoubtedly produce myocardial ischaemia and anginal pain during exercise, but from a haemodynamic point of view they are of moderate degree only, since they are practically never accompanied by angiographically visible collateral circulation.^{14 24} The present pathological study confirms clinical observations that an organic stenosis has to be very severe to be held responsible for development of collateral vessels.

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