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MORPHOLOGIC STUDIES

Failure of Angiography to Accurately Depict the Extent of Coronary Artery Narrowing in Three Fatal Cases of Percutaneous Transluminal Coronary Angioplasty

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The angiographic and pathologic findings are described in three patients who died <24 h after failed percutaneous transluminal coronary angioplasty. In two of the three patients, coronary angiography performed before angioplasty disclosed apparently focal lesions in the left anterior descending and right coronary arteries. In these two patients quantitative angiographic analysis disclosed a minimal lumen cross-sectional area of 1.82 and 0.47 mm², respectively, at the sites of apparently focal stenoses before angioplasty; corresponding percent lumen area narrowing measured 84% and 91%, respectively, by quantitative angiography at these two sites.

In the third patient, coronary angioplasty was undertaken when the patient developed spontaneous occlusion of the right coronary artery several hours after diagnostic angiography. Retrospective quantitative angiographic analysis of the right coronary artery revealed a minimal lumen cross-sectional area of 1.14 mm², with 85% lumen area narrowing at the site of subsequent total occlusion and angioplasty.

In each of these three patients, necropsy examination disclosed that the distribution of coronary narrowing in the artery treated by angioplasty was in fact not focal; rather, in each of these three patients, the artery treated by angioplasty, as well as the extra-mural coronary arteries not treated by angioplasty, were severely narrowed by diffusely distributed atherosclerotic plaque. The angiographic and necropsy findings in these three patients document that coronary narrowing that remains occult by virtue of diffuse distribution may complicate evaluation of patients being considered for coronary angioplasty.

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Although certain limitations of coronary angiography have been repeatedly documented by pathologic (1-9) and physiologic (10-13) studies, modifications involving instrumentation and analysis have been considered to obviate many of these previously established liabilities. Certain liabilities, however, remain unsolved. Chief among these is the pathoanatomic finding of diffuse, severe coronary artery narrowing. Diffusely diseased arteries have been demonstrated at necropsy (14-17) and are recognized to constitute a pitfall of diagnostic angiography (18); such diffuse, severe narrowing has less frequently been documented or even considered in patients undergoing percutaneous transluminal coronary angioplasty in whom angiographic evidence of focal narrowing represents the essential criterion for nonsurgical therapy.

The three patients described in this report document the extent to which diffuse coronary narrowing continues to pose a liability for angiographic analysis, including quantitative analysis of images recorded in multiple orthogonal obliquities. In particular, these three cases illustrate the extent to which this liability may compromise attempts to perform percutaneous coronary artery revascularization.

Methods

Clinical data. Coronary angiography and coronary angioplasty were performed on three patients at two institutions with standard diagnostic and interventional techniques. The clinical history was obtained retrospectively from medical records, catheterization records and reports of pathologic examination.

Angiographic analysis. Selective representative end-diastolic frames of coronary arteriograms were analyzed in at least two orthogonal views. Cine frames were digitally acquired onto computer memory by using a cine video camera mounted on a standard cine projector (Tagarno). Digitally acquired images were then quantitatively analyzed with use of a previously validated commercially available edge-detection computer-assisted software program (Image-Comm). Calibration was performed by using the known dimensions of the angiographic catheter. Standard gray scales were employed. Absolute artery dimensions (lumen diameter and cross-sectional area) were determined for sites.
of both maximal stenosis and reference segments (segments with angiographically normal appearance adjacent to sites of maximal stenosis). Percent stenosis was calculated as the difference between the lumen cross-sectional area of the reference segment and the stenotic segment, divided by the lumen cross-sectional area of the reference segment.

Pathologic examination. At necropsy, the epicardial coronary arteries were excised intact and serially cross-sectioned at 5-mm intervals. In Patient 3, the procedure was performed after the coronary arteries had been selectively cannulated and perfused with 10% buffered formalin at a mean pressure of 80 mm Hg. In the remaining two cases the coronary arteries were examined without pressure perfusion fixation. Each 5-mm section was inspected grossly for percent cross-sectional area narrowing and the presence of intracoronary thrombus, and these findings were recorded. The 5-mm sections were then prepared for light microscopic examination as described previously (19). Briefly, each coronary artery was decalcified in a solution of 10% formic acid and formalin if necessary, and fixed overnight in 10% buffered formalin. Segments were then dehydrated in graded alcohol, cleared with xylene, impregnated with and embedded in paraffin, and sectioned into 4-µm thick sections.

Sections stained with Verhoeff’s elastic tissue stain as well as sections stained with hematoxylin-eosin were prepared from each 5-mm segment. The elastic-tissue-stained sections prepared from the coronary arteries of each patient were then inspected by light microscopy. Lumen cross-sectional area narrowing was calculated by using the measured and available computer software and hardware (Summasketch-MacMeasure, Apple Computer). Percent cross-sectional area narrowing was calculated by using the measured and original lumen areas.

**Case Reports**

**Patient 1**

A 54-year old man had a history of stable exertional angina for 8 years. One month before admission, he developed a crescendo anginal pattern, with angina occurring up to 3 times/day with minimal exertion. Elective coronary angiography performed 2 weeks before admission revealed a left dominant coronary circulation, focal stenosis of the proximal left anterior descending coronary artery (Fig. 1a and b), and no focal narrowing of the remaining vessels.

Coronary angioplasty and emergency coronary bypass surgery. The patient was readmitted for elective coronary angioplasty of the left anterior descending coronary artery. A 0.014-in. (0.036-cm) guide wire was advanced easily beyond the proximal stenosis into the distal left anterior descending artery. However, the angioplasty catheter could not be advanced across the high grade stenosis, and ventricular tachycardia developed. The arrhythmia was treated successfully with a precordial thump and intravenous lidocaine, but hypotension required insertion of an intracor-}

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he presented with severe substernal chest pain that was relieved with 3 tablets of sublingual nitroglycerin.

Coronary angiography. He was initially treated with intravenous nitroglycerin and heparin. Coronary angiography was performed and demonstrated a tubular stenosis in the mid-right coronary artery (Fig. 1c). focal narrowing of the left circumflex artery and apparently nonobstructive narrowing in the left anterior descending artery. After completion of the diagnostic study, as the balloon catheter was being prepared for angioplasty, he developed severe chest pain. Repeat angiography of the right coronary artery showed no obvious change. The ST segment elevation then developed in leads II, III and aVF and failed to respond to intracoronary nitroglycerin and sublingual nifedipine. A repeat angiogram of the right coronary artery now showed complete occlusion at the level of the previous stenosis.

Coronary angioplasty. Emergency angioplasty, performed with a 2-mm balloon, at first appeared to successfully open the right coronary artery. However, shortly thereafter, the patient’s blood pressure decreased. and repeat angiography disclosed that the artery was now occluded by apparent thrombus at the angioplasty site. Intracoronary streptokinase was then administered. and repeat balloon dilatation performed. Despite these maneuvers, the patient remained hypotensive and ventricular fibrillation developed. Attempts to resuscitate the patient were unsuccessful and he died.

Necropsy. Examination of the heart revealed extensive subendocardial scarring of the posterior left ventricular free wall. No other evidence of an acute or remote myocardial infarction was found. Histologic examination of the coronary arteries disclosed severe diffuse three-vessel coronary artery narrowing that contrasted with the angiographic findings suggesting focal obstruction. Histologic examination of the right coronary artery in particular revealed lumen cross-sectional area narrowing that varied from 86.5% to 97.7% (Fig. 2, middle right; Fig. 4).

Quantitative angiography. Post-hoc quantitative angiographic analysis of the right coronary artery before angioplasty disclosed that the apparently nonstenotic reference segment measured 2.6 mm in diameter and 5.3 mm² in cross-sectional area. The site of most severe stenosis before coronary angioplasty measured 0.78 mm in diameter and 0.47 mm² in cross-sectional area; calculated percent stenosis for the site of most severe stenosis before angioplasty was 91% (Fig. 2, middle left).

Patient 3

A 37-year old man presented to another hospital after the sudden onset of substernal chest pain that had begun 6 days earlier while he was driving a truck. An electrocardiogram recorded on admission to the emergency room revealed only
PATIENT No. 1

LEFT ANTERIOR DESCENDING CORONARY ARTERY
(proximal to distal)

PATIENT No. 2

RIGHT CORONARY ARTERY (proximal to distal)

PATIENT No. 3

RIGHT CORONARY ARTERY (proximal to distal)
peaked T waves anteriorly. The patient's chest pain resolved after treatment with sublingual nitroglycerin and intravenous morphine. He was admitted to the coronary care unit and developed a non-Q wave myocardial infarction associated with a peak creatine kinase value of 268 (positive MB fraction). His postinfarction recovery was unremarkable and he was placed on therapy with atenolol, isosorbide dinitrate, and diltiazem. He was then transferred on hospital day 6 for coronary angiography.

Coronary angiography and angioplasty. The results of coronary angiography performed 1 day later are illustrated.
Figure 4. Patient 2. Serial 5-μm histologic sections of the right coronary artery. The sections are arranged in sequence from proximal (R₁) to distal (R₆) orientation.
for the right coronary artery in Figure 1d; no focal lesions were recognized in the left coronary circulation. Several hours after catheterization, the patient developed substernal chest pain and ST segment elevation in leads II, III and aVF. Emergency repeat angiography was performed and disclosed a total occlusion of the proximal right coronary artery. Administration of intracoronary nitroglycerin and recombinant tissue-type plasminogen activator successfully reopened the artery. Several minutes later, however, the patient reported recurrent chest pain, and repeat angiography showed that the right coronary artery was again occluded. The artery was then again successfully reopened with use of a 0.014-in. (0.036-cm) guide wire and a 3-mm balloon angioplasty catheter.

After angioplasty, however, the patient had a cardiac arrest with complete heart block. Cardiopulmonary resuscitation was successfully applied and a temporary transvenous pacemaker was inserted. Repeat coronary angiography revealed that the right coronary artery was patent. Sixteen hours later, however (18 h after initial coronary angioplasty), the patient developed ventricular tachycardia, became asystolic after cardioversion and could not be resuscitated.

Necropsy. Examination revealed an acute transmural myocardial infarction involving the posterior left ventricular free wall, posterior ventricular septum and posterior right ventricular free wall. Gross examination of the external coronary arteries showed diffuse severe atherosclerosis involving all three major coronary arteries. Histologic examination of the right coronary artery in particular revealed lumen cross-sectional area narrowing that varied from 55.6% to 92.7% (Fig. 2, bottom right; Fig. 5).

Quantitative coronary angiography. Post-hoc quantitative angiographic analysis of the right coronary artery (before angioplasty) disclosed that the angiographically apparent nonstenotic reference segment measured 2.48 mm in diameter and 4.53 mm² in cross-sectional area. Retrospective examination of the initial diagnostic angiogram disclosed focal narrowing at the site of subsequent total occlusion where the most severe stenosis measured 1.2 mm in diameter and 1.14 mm² in cross-sectional area; calculated percent stenosis for the site of most severe stenosis before angioplasty was 85% (Fig. 2, bottom left).

Discussion

Liabilities of coronary angiography. In the 3 decades that have passed since coronary arteriography was introduced into clinical practice (20), certain liabilities associated with this technique have been identified, studied and, in some cases, solved. In patients with coronary heart disease studied at necropsy, for example, it was observed that the residual nonoccluded lumen was often eccentric in location and slilike in shape (21): because such a lumen may allow contrast opacification of most or all of the lumen diameter in a given plane, the severity of lumen narrowing could be underestimated. Attempts to solve this issue led to the routine recording of multiple, including, orthogonal views (22).

It was subsequently recognized, however, that variations in coronary anatomy, body habitus and lesion location often precluded accurate angiographic depiction of a putative lesion in its narrowest dimensions because of overlap with other vessels and foreshortening of the vessel of interest. This issue was answered in large measure by the development of more versatile angiographic gantries allowing a greater range of nonaxymmetric views.

Even when a lesion could be successfully isolated and depicted in its most severely narrowed orientation, visual estimates of the resulting degree of lumen narrowing varied significantly among different observers (23–26), leading to both occasional inaccuracies and limited reproducibility. Quantitative coronary arteriography, proposed initially by Brown et al. (27), validated by Gould et al. (28) and subsequently modified to include computer-assisted automated edge detection (29–32), resulted in more objective angiographic analyses and thereby aided the precision of lesion assessment.

Previously reported necropsy findings. Histopathologic studies of human coronary arteries, however, disclosed yet another feature potentially limiting the accuracy of angiographic analyses, namely, the fact that coronary atherosclerosis is characteristically diffuse (14–17). Diffuse narrowing forces the angiographer to compare sizes of maximal narrowing to adjacent sites that may be less, but still severely, narrowed, seldom leaving the angiographer with a truly normal lumen diameter from which estimates of relative lumen narrowing can be accurately derived.

The impact of this anatomic fact on the angiographic analysis of lumen narrowing has been documented by previous investigators in several ways. Diffuse narrowing has been indicted, for example, as the principal basis for pathologically documented angiographic underestimation of coronary narrowing. In one such study (7), among 465 5-mm segments of coronary artery examined histologically from 10 patients, 209 (44%) were narrowed by 76% to 100% and 139 (29%) were narrowed by 51% to 75%; only 45 (<10%) of the total 465 segments were narrowed by <26% in cross-sectional area.

Glagov et al. (33) and others (34) have demonstrated that even when the degree of narrowing resulting from diffusely distributed plaque is less severe, the accuracy of coronary angiography may be compromised. This is because mild to moderate atherosclerosis is associated with compensatory arterial dilation: consequently, in arteries narrowed by up to 40% in cross-sectional area, absolute lumen dimensions may remain relatively well preserved.

White et al. (12) used intraoperative assessment of reactive coronary hyperemia to determine the physiologic importance of coronary stenoses identified by quantitative angiography. In 39 lesions with apparently discrete coronary narrowing, measurement of percent stenosis by coronary angiography was not significantly correlated (r = −0.25)
with the reactive hyperemic response. These investigators (12) concluded that the most important factor responsible for this documented discrepancy was "the usually diffuse nature of coronary atherosclerosis."

Even when the coronary segment of interest is relatively short, elimination of a truly normal baseline by submaximal narrowing constitutes a serious liability. The left main coronary artery, for example, is the shortest of the major extramural coronary arteries; however, when it is narrowed to an equivalent degree over its entire length, identification of left main coronary artery disease may be missed (9,35). Beatt et al. (36) demonstrated that the development of mild to moderate narrowing in the segments directly adjacent to sites of stenosis treated by coronary angioplasty may lead one to underestimate the degree of restenosis apparent upon repeat angiography.

Identification of diffuse narrowing. The angiographic and necropsy findings in the present three patients document that previous concerns regarding coronary narrowing that remains occult by virtue of diffuse distribution extend to the evaluation of patients being considered for coronary angio-
plasty. The angiographic finding of focal narrowing has long been regarded as the essential criterion for coronary angioplasty (37,38). Because of the limited number of patients studied at necropsy shortly after angioplasty, the prevalence of diffuse disease masquerading as a nearly normal baseline remains undetermined. However, the present three cases suggest that such anatomy may be more common than has been previously recognized.

Algorithms developed for quantitative angiography diminish to some extent the liabilities posed by diffusely diseased vessels. Harrison et al. (11), for example, found that measurement of minimal lumen diameter improved the correlation between lesion assessment by coronary angiography and reactive hyperemic response \( r = 0.731 \). Beatt et al. (36) showed that use of the interpolated reference diameter permitted more accurate assessment of restenosis after angioplasty. As our three cases illustrate, however, unless the absolute lumen dimensions can be interpreted to distinguish nonobstructed, diminutive arteries from arteries that are diffusely and severely narrowed, the extent of coronary disease in patients undergoing coronary angioplasty may nevertheless be underestimated.

In the present three cases, the extent to which diagnostic angiography failed to reflect severe, diffuse coronary artery disease may have contributed to each patient’s death. Not only was coronary narrowing more diffuse and more severe than anticipated in the artery selected for angioplasty, but also, the other extramural arteries were similarly affected. As a result, the ischemic burden at the time of balloon inflation was underestimated in these three patients. Had each been recognized to have diffuse three-vascular coronary artery narrowing, it is questionable—at least in the elective cases of Patients 1 and 2—that angioplasty would have been recommended.

How may the assessment of patients such as those described in this report be improved? Previous investigations (39), including those of Harrison et al. (11) and White et al. (12) cited earlier, have indicated that complementary use of physiologic tests, such as assessment of coronary flow reserve, may serve to distinguish diffusely diseased arteries from nonobstructed vessels of lesser caliber. In certain patients being considered for coronary angioplasty, however, such as Patients 1 and 2 in the present report, the issue is not whether the lesions recognized by angiography are capable of causing myocardial ischemia, but rather to what extent the vessels are in fact compromised. Gould (39) previously suggested that the ideal instrument for assessment of stenosis severity should allow composite analysis of both relative and absolute percent narrowing, as well as lesion length, absolute diameter of the normal artery and blood viscosity. Certain new imaging techniques, such as intravascular ultrasound (40–43), which permit most of these measurements, may ultimately provide more accurate definition of the diffusely diseased artery.

Potential limitations. Because pathologic examination was employed as the reference standard in this report, certain limitations of this methodology must be acknowledged. First, the coronary arteries from Patients 1 and 2 were examined at necropsy without pressure distension. Winiwarter and Glatzer (44) previously demonstrated a corresponding increase in the radius of rabbit aortas examined at necropsy as intraluminal distending pressure is increased from 5 to 80 mm Hg. Second, Siegel et al. (45) previously demonstrated that in nondistended vessels with moderate to severe atherosclerosis, histologic processing leads to a reduction in total arterial area without a corresponding reduction in the area of the residual arterial lumen. Thus the former may lead to overestimation of lumen narrowing, whereas the latter may lead to its underestimation. It is difficult to determine with certainty the extent to which each of these factors affected pathologic analyses in the present three cases. However, because the issue in the present report concerned the distribution rather than the absolute dimensions of coronary artery narrowing, the validity of the observations reported here appears to be preserved.

References