Coronary artery spasm may cause angina at rest, but its pathogenesis is unclear. Spasm is usually associated with atherosclerotic encroachment of the lumen, but this may be minimal.1, 2 Whereas small doses of ergonovine given to patients with angina due to spontaneous coronary spasm usually produce spasm,3,7 larger doses given to normal controls or to patients with noncardiac chest pain produce only a mild, generalized vasoconstriction.4, 6 This difference suggests that the arteries of patients with spontaneous spasm are hypersensitive to ergonovine at the sites of atherosclerotic lesions. MacAlpin8 recently proposed that this hypersensitivity was due to the amplification of normal vasoconstriction at sites of atheromatous luminal encroachment, the degree of vasoconstriction being related to the severity of encroachment (geometric theory). We undertook the present study to determine whether this geometric theory could explain the hypersensitivity of arteries in patients with vasospastic angina.

Methods

Patient Selection

Eleven patients (seven men and four women, mean age 51 ± 8 years) with documented9 or clinically suspected8 variant angina formed the study population (group A). All patients had a positive ergonovine test in the cardiac catheterization laboratory. Coronary angiograms demonstrated normal findings in two patients and minor lesions in nine (2–52% luminal diameter reduction; mean 25%). Twenty-one patients (eight men and 13 women, mean age 49 ± 8 years) with chest pain atypical for myocardial ischemia and a negative ergonovine test were used as controls for com-
parison of ergonovine-induced vasoconstriction in normal proximal coronary artery segments (group B). Coronary angiograms demonstrated normal findings in 11 and minor atherosclerotic lesions below the normal proximal segment in 10. All patients in group B had normal left ventricular function. The 10 patients with minor lesions from group B and four other patients with minor lesions, atypical chest pain and a negative ergonovine test made up a second control group (group C) for comparison of ergonovine-induced vasoconstriction at the site of a stenotic lesion. The severity of atheromatous lesions in the 14 group C patients ranged from 7% to 44% (mean 26%), similar to the severity of lesions in group A patients.

Ergonovine Testing

Ergonovine was given in divided doses (0.05, 0.1, 0.2 and 0.3 mg) at 3–5-minute intervals until chest pain or coronary spasm occurred or until the maximal dose of 0.65 mg was reached. The mean ergonovine dose was 0.38 ± 0.19 mg for group A, 0.57 ± 0.17 mg for group B and 0.54 ± 0.20 mg for group C. Nitrates were not given before angiography. A positive test was arbitrarily defined as >55% luminal diameter narrowing in a normal arterial segment or an additional reduction of luminal diameter >55% at the site of an atheromatous lesion. All patients with variant angina had positive responses (fig. 1).

Arterial Measurement

Arterial dimensions were measured in the same projection at specific distances from identifiable branch points in diastolic frames before and after ergonovine administration. Selected cine frames were projected onto a screen (magnification × 3) with a Tagarno projector; arterial outlines and the tip of the catheter in the coronary ostium were traced on paper and measured with vernier calipers. The luminal diameter was estimated by relating the arterial size to the known dimensions of the catheter tip. The error of duplicate measurements of arterial diameter using this technique was 0.4 mm (twice standard deviation of the unsigned residuals, n = 42 duplicate measurements). Lesions were measured at the site of maximal narrowing, and the adjacent normal segments were measured to calculate the vasoconstriction adjacent to the lesion.

In group A patients, the lesions undergoing spasm, the adjacent normal segments, and the proximal segments of uninvolved arteries (if injected) were measured. There were 12 arteries with spasm in 11 patients (one patient had spasm in two arteries). In three of the 12 arteries, spasm was proximal, so the adjacent normal segments were measured distal to the site of spasm. In the remaining nine arteries, the adjacent normal segments were measured proximally. Fifteen segments of uninvolved arteries were also suitable for measurement. In group B patients, 19 right coronary, 20 left anterior descending and 20 left circumflex artery segments were measured. All measurements were made in the proximal segment. In group C patients, 22 lesions (four patients had two lesions and two patients had three lesions) and 22 adjacent normal segments were measured.

Geometric Theory

In MacAlpin’s report, the derivation of an equation adapted from previous work by Folkow et al. and Conway was not published, although curves derived from the equation were shown. The derivation of an equation to predict the narrowing expected at a lesion site, given the severity of the lesion and the degree of vasoconstriction of the adjacent normal segment, is shown in figure 2.

Statistical Analysis

The t test was used to compare differences between groups means for arterial narrowing after ergonovine.

Results

The severity of arterial vasoconstriction produced by ergonovine in the three groups is shown in table 1. In group B, there was no difference between the degree of vasoconstriction in the three major coronary arteries. The data were therefore pooled (B1 + B2 + B3), resulting in a mean vasoconstriction of 17 ± 12% in
GEOMETRIC THEORY

Adjacent normal segment  Stenotic segment

ABBREVIATIONS: Ro, Ri, ro, ri = outside and inside radii of adjacent normal segment and stenotic segment respectively; Ro*, Ri*, ro*, ri* = radii after ergonovine-induced vasoconstriction; \( y \% \) = \% reduction in adjacent normal luminal diameter or \( R_i \) after ergonovine; \( P \% \) = \% stenosis of lesion; \( x \% \) = \% reduction of luminal diameter or \( R_i \) at lesion after ergonovine.

ASSUMPTIONS:

A. \( Ro = ro \). \% change in Ro and ro is the same after vasoconstriction.
B. The lesion is represented as a circumferential stenosis.
C. Vasoconstriction in the normal segment is fully translated to the lesion.
D. Area of vessel wall remains constant after vasoconstriction.

DERIVATION

by definition of \( P \) \( ri = R_i(1-P/100) \) (1)

rearranging (1) \( R_i = ri/(1-P/100) \) (1a)

after \( y \% \) constriction \( R_i = R_i(1-y/100) \) (2)

since area stays constant \( \pi(Ro^2 - Ri^2) = \pi(Ro^2 - Ri^2) \) (3)

rearranging (3) \( Ro^2 - Ro*2 = Ri^2 - Ri*2 \) (4)

substituting (2) for \( Ri* \) \( Ro^2 - Ro*2 = Ri^2[1-(1-y/100)^2] \) (5)

since area stays constant \( Ro^2 - Ri^2 = Ro^2 - Ri^2 \) (6)

rearranging (5) \( Ro^2 - Ro^2 = Ri^2 - Ri^2 \) (7)

because of assumption A. \( Ro^2 - Ro^2 = Ro^2 - Ro^2 \) (8)

substituting (6) in (7) \( Ro^2 - Ro^2 = Ri^2 - Ri^2 \) (9)

substituting (1a) in (10) \( R_i^2 = R_i^2[(1-P/100)^2 + (1-y/100)^2 - 1] \) (10)

rearranging (11) \& squ.root \( ri/ri = \sqrt{[(1-P/100)^2 + (1-y/100)^2 - 1]} \) (11)

by definition \( ri = ri(1-x/100) \) (12)

rearranging (11) \( ri/ri = x/100 \) (13)

substituting (14) in (12) \( x = 100 \) (1 - \( \sqrt{[(1-P/100)^2 + (1-y/100)^2 - 1]} \) (14)

and rearranging \( x = 100 \) (1 - \( \sqrt{[(1-P/100)^2 + (1-y/100)^2 - 1]} \) (15)

this group with negative ergonovine tests. Five of 59 arterial segments increased in diameter by 1–9% (mean 4%) after ergonovine, but three of these five segments were from one patient.

The mean vasoconstriction of the segments undergoing spasm in group A patients (83 ± 17%) was much greater than the combined group B control value. The degree of vasoconstriction of the adjacent normal segments of arteries undergoing spasm (A2 = 15 ± 12%) was not different from the control value (B1 + B2 + B3 = 17 ± 12%). The mean vasoconstriction of the other arteries uninvolved by spasm (A3 = 24 ± 13%) was slightly greater than the control value (p = 0.05). When the adjacent normal segments were combined with the other arteries uninvolved by spasm (A2 + A3), the mean vasoconstriction (20 ± 13%) was slightly greater than the control value (NS).

The vasoconstriction at the sites of lesions in group C patients (mean 20 ± 16%) was plotted against the severity of stenosis (fig. 1). For comparison, the mean vasoconstriction of the normal proximal arterial segments from patients in group B (B1 + B2 + B3) and the spasm segments (A1) from group A patients were plotted on the same axes. There was no overlap between groups B and C and group A.

Geometric Theory

From equation 15 in figure 2, the expected degree of ergonovine-induced constriction at a stenotic lesion was predicted from the percent narrowing of the adjacent normal segment after ergonovine and the severity of the stenosis. The severity of stenosis was calculated by dividing the diameter of the lesion by the diameter of the adjacent normal segment (percent stenosis). The ergonovine-induced narrowings at the lesion site and in the adjacent normal segment were calculated for each lesion in groups A and C. The predicted percent constriction at the lesion derived from the geometric theory was plotted against the observed percent constriction from the arterial measurements (fig. 3). The line represents identity between predicted and observed values. For group C patients, at the lower levels of predicted narrowing the observed values lay close to the line of identity. As predicted values increased, the
observed values fell below the line. In contrast, all values from group A patients were above the line, which indicates that contrary to the predictions of the geometric theory, the observed spasm could not be explained by amplification of normal vasoconstriction at a lesion site.

Discussion

The present study supports the hypothesis that coronary artery spasm results from increased sensitivity of coronary arteries to vasoconstrictors, localized at the sites of atheromatous lesions. The segments of arteries adjacent to the site of spasm and the other arteries uninvolved by spasm were slightly, but not significant-

ly, more sensitive to ergonovine than the normal proximal segments of arteries from control patients. These findings agree with those of Curry et al., who showed a similar small increase in sensitivity of the uninvolved segments to ergonovine. In the present study, the dose of ergonovine given to group A patients was lower than that given to group B patients because spasm occurred. If a similar dose had been given to group A patients, the small increase in sensitivity of the uninvolved segments might have been significant.

MacAlpin proposed that the increased sensitivity of arteries at the sites of lesions was a direct consequence of the luminal encroachment by atheroma and the resulting increase in wall area at that point. The present study does not support this hypothesis. If the geometric theory fully explained the increase in sensitivity at the lesion site, then all the points in figure 3 would have fallen on the line of identity between observed and predicted constriction. All points from group A patients were above the line. Thus, hypersensitivity at the lesion site cannot be explained by geometric considerations alone. A similar conclusion could be drawn from the work of Brown et al., in which lesions from patients with variant angina were more sensitive to propranolol or propranolol plus adrenaline than lesions of similar severity in control patients, despite equal sensitivity of normal arterial segments in both groups.

MacAlpin used arterial measurements from three cases to support the geometric theory. In one case, spasm after ergonovine was not explained by geometric considerations, and in another the provoked spasm was less than the 55% cutoff point we used to distinguish between normal and abnormal vasoconstriction. The geometric theory was supported only by the findings in a patient with a 69% stenotic lesion, which was more severe than those of group A patients in the present study. The selection of severe lesions to illustrate the geometric theory could bias the results, because even small amounts of vasoconstriction are greatly magnified in severe lesions.

The geometric theory does not describe the vasoconstriction at lesion sites in patients without coronary artery spasm (group C). In these patients, the theory would predict significant vasoconstriction, but the measured vasoconstriction was small and the points in figure 3 frequently fell below the line of identity. This effect was predicted by MacAlpin and explained by a decreased pliability of arteries at sites of atherosclerotic plaques. Thus, a given degree of vasoconstriction in the adjacent normal segment would be incompletely expressed at the lesion site because of increased rigidity of the artery. An alternative explanation is that the destruction of smooth muscle by the atherosclerotic process may reduce the degree of vasoconstriction possible at a lesion site.

The present findings do not exclude a contribution from geometric factors to the observed hypersensitivity, but suggest that others are important. It is not known why a mild atheromatous lesion causes arterial hypersensitivity. This finding indicates a shift to the left of the dose-response curve for ergonovine in
smooth muscle. Recent work by Henry and Yokoyama supports this concept. Atherosclerotic rabbit aortas were hypersensitive to ergonovine. This hypersensitivity was mediated by a serotonergic mechanism, which they postulated was due to accumulation of cholesterol in the vessel wall. If this is the reason for arterial hypersensitivity at lesion sites in patients with vasospastic angina, it is not clear why plaques from other patients behave differently. Also, this mechanism may not explain the relatively infrequent occurrence of spasm in angiographically normal coronary arteries or at different sites in the same artery.

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