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Original Studies

Does Intracoronary Papaverine Dilate Epicardial Coronary Arteries?
Implications for the Assessment of Coronary Flow Reserve

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Intracoronary papaverine is used as a means to induce a strong and short-lasting hyperemia in several recently developed methods to measure coronary flow reserve. Changes in stenosis geometry from papaverine would influence the measured coronary flow reserve. Therefore, we investigated the influence of intracoronary papaverine on stenosis geometry with quantitative analysis of the coronary angiogram and assessed the influence of papaverine on pressure-flow characteristics of the stenosis and coronary flow reserve. The cross-sectional areas (mean ± SD) of the stenosis increased 18% ± 7% after papaverine. The normal proximal and distal parts of the coronary artery dilated 5% ± 2% after papaverine. This results in a decrease of the calculated pressure drop over the stenosis varying from 20% to 30%. Coronary flow reserve of a flow-limiting epicardial stenosis is overestimated by 16% when papaverine is used to induce hyperemia. These papaverine-induced changes can nevertheless be circumvented by maximal vasodilation of the major epicardial coronary artery with 3 mg intracoronary isosorbidedinitrate prior to the investigation of the coronary flow reserve with papaverine.

Key words: isosorbidedinitrate, coronary stenosis

INTRODUCTION

Recently several methods have been developed to measure coronary flow reserve [1,2] and to calculate pressure-flow characteristics of a coronary stenosis [3]. Induction of a maximal coronary hyperemia is an essential part of these methods. Intracoronary papaverine induces a short-lasting, reproducible, and maximal hyperemic response in the coronary circulation, so this agent has been proposed as an ideal vasodilator for these investigations [4,5]. Changes in geometry of epicardial stenoses from intracoronary administration of papaverine would influence the viscous (Poiseuille) and turbulent resistance and consequently alter the pressure-flow characteristics of the coronary stenoses and the measured coronary flow reserve [6]. The goal of the present investigation was to assess the influence of intracoronary papaverine on coronary arterial dimensions and pressure-flow characteristics and to establish whether prior intracoronary administration of a vasodilator of the epicardial coronary artery (isosorbidedinitrate) could prevent these papaverine-induced alterations.

PATIENTS AND METHODS

Coronary angiography was performed in 11 patients as part of an ongoing study of restenosis after percutaneous transluminal coronary angioplasty. Selection of these patients was based on the occurrence of restenosis to some extent. Informed consent was obtained for the additional investigation. All patients were studied without premedication, but their standard postangioplasty medical treatment, consisting of aspirin 500 mg/day and nifedipine 60 mg/day, was continued. No patient received oral or IV nitrates. No patient had clinical evidence for vasospastic angina.

Angiographic Procedure

Coronary angiography was performed with the Judkins technique. The angiographic projection was selected such that the stenosis and the proximal and distal parts of the coronary artery were clearly visible and were parallel to the image intensifier. Hand injections were made at a rate and volume sufficient to cause back-flow of the contrast agent into the aorta. Therefore, essentially all blood in the epicardial coronary arteries was replaced by

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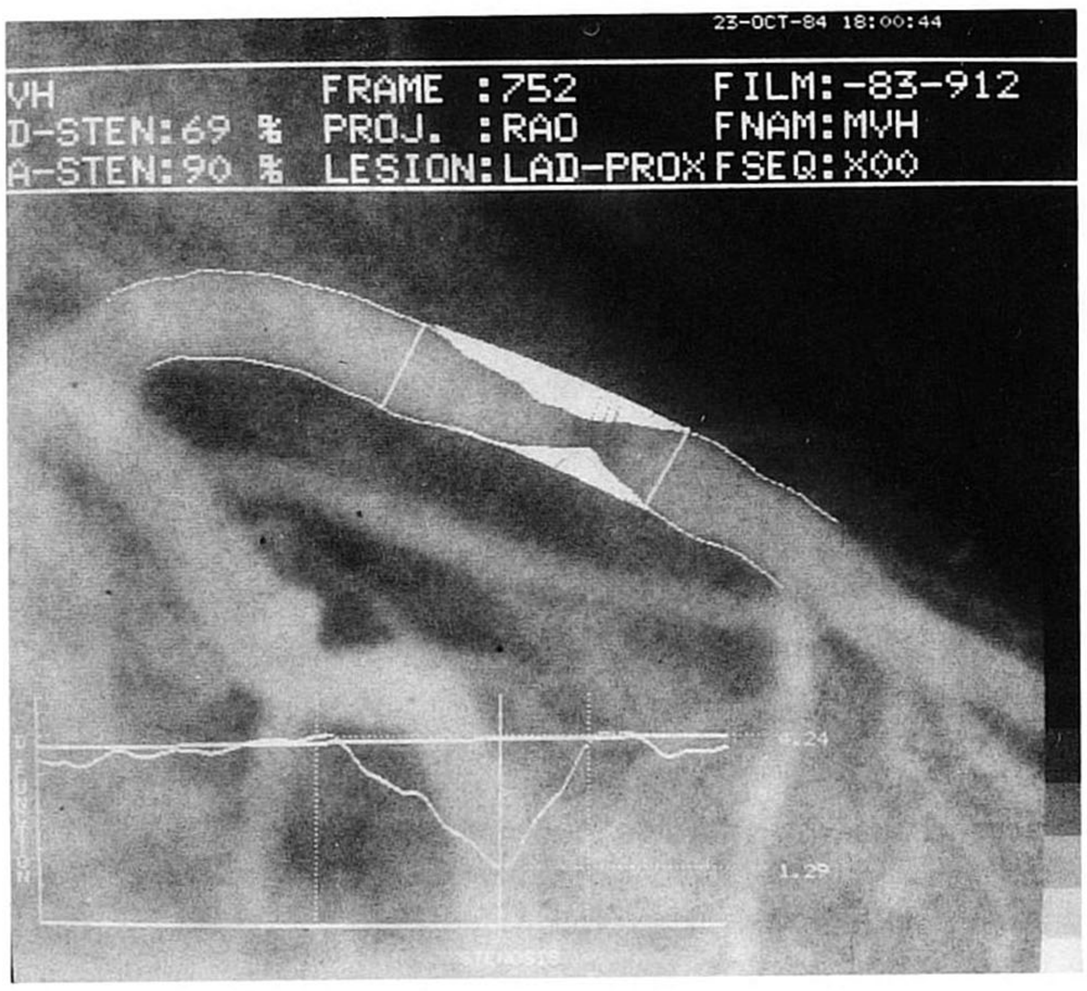

Fig. 1. Detected contours for a representative stenosis of the left anterior descending coronary artery. The normal size of the artery over the obstruction has been estimated by the interpolated method. The diameter function is shown on the bottom.

contrast agent. Iopamidol, a nonionic agent, was injected at 37°C. At this temperature, it has a viscosity of 9.4 cP, the osmolality is 0.796 osm · kg^{-1}, and the iodine content is 370 mg/ml. For this investigation, 30–40 ml of this agent was used per patient. Consequently, the maximal change in blood viscosity induced by this procedure is only 2%. Therefore, blood viscosity was assumed to be constant. A total of four angiograms were obtained in the selected angiographic view. First, a baseline angiogram was made. A second angiogram was performed 30 sec after a bolus injection of 12.5 mg papaverine into the coronary artery. After a pause of 5 min, 3 mg intracoronary isosorbidedinitrate was administered, and 30 sec later a third angiogram was performed. Finally, immediately following this third angiogram, 12.5 mg intracoronary papaverine was given, and the last angiogram of the study was made 30 sec later.

Quantitative Coronary Cineangiography

The procedures for the quantitative assessment of coronary arterial dimensions from 35-mm cinefilm have been implemented on the computer-based Cardiovascular Angiography Analysis System (CAAS) and have been described extensively [7,8]. For the assessment of the absolute and relative dimensions of selected coronary segments with the CAAS, the boundaries of a selected coronary segment are detected automatically from optically magnified and video-digitized regions of interest of an end-diastolic cineframe. Calibration of the diameter data in absolute values (mm) is achieved by detecting the boundaries of a section of the contrast catheter and comparing the computed mean diameter in pixels with the known size in millimeters. Each catheter is measured individually with a micrometer to determine its true size [9]. To correct the contour positions of the arterial and catheter segments for the pincushion distortion of the image intensifier, a correction vector is computed for each pixel based on a computer-processed cineframe of a centimeter grid placed against the input screen of the image intensifier [8].

The procedure for contour detection requires the user to indicate a number of center positions with the writing tablet from the proximal to the distal end of the selected arterial segment such that the straight lines connecting these points are within the artery. The contours of the vessel are detected on the basis of the weighted sum of first and second derivative functions applied to the digitized brightness information along scanlines perpendicular to the local centerline directions. From the detected contours, the diameter function is determined in absolute millimeters. Since the functional significance of a stenosis is also related to the expected normal cross-sectional area of the vessel at the point of the obstruction, we use a computer estimation of the original arterial dimensions at the site of the obstruction to define the reference region (interpolated reference). A representative example with the detected contours and the reconstructed reference contours is shown in Figure 1. The computed reference diameter function allows for tapering of the vessel. The interpolated percentage area stenosis (AS) is then computed by comparing the squared minimal diameter value at the obstruction with the squared value of the reference diameter function at this position, thereby assuming circular cross section:

$$\text{AS} = [1 - (\text{minimal diameter}/\text{reference diameter})^2] \times 100\%.$$

The estimation of the length of the obstruction is made on the basis of a curvature analysis of the diameter function.

The pressure-drop ($\triangle$P) over the stenosis for coronary flows of 1, 2, 3, 4, and 5 ml/sec is calculated using the following hemodynamic equation:

$$\Delta P = \frac{8\eta u L}{MLCA}\left[\frac{1}{MLCA}\right]Q + \frac{d}{0{,}266}\left[\frac{1}{MLCA} - \frac{1}{NA}\right]_2 Q^2,$$

or $\Delta P = fQ + sQ^2$, where u = blood viscosity, L = stenosis length, NA = normal cross-sectional area,

TABLE I. Clinical Characteristics (n = 11)

Mean age in years (range)	57 (41 – 71)
Sex	9 male, 2 female
0[a]	1
1	8
2	2
LVEF[b] > 50%	11

[a]0, 1, 2, Number of vessels per patient with an area stenosis in excess of 50%.
[b]LVEF, left ventricular ejection fraction.

MLCA = minimal luminal cross-sectional area, Q = volume flow, d = blood density, f = coefficient of viscous resistance (Poiseuille), and s = coefficient of turbulent resistance or exit separation [3,10,11].

Statistical Methods

Comparisons between data were carried out with the Student's t test for paired observations.

RESULTS

The clinical characteristics of the patients are shown in Table I. The mean age of the 11 patients was 57 years (range 41–71 years). Nine patients were male. Eight patients had single-vessel disease, two had two-vessel disease, and one had no significant coronary artery disease (area stenosis in excess of 50%). All patients had a normal left ventricular ejection fraction. Eleven discrete proximal stenoses were analyzed quantitatively (Table II). When compared to the baseline measurements, 12.5 mg intracoronary papaverine induced a 5% ± 2% increase in cross-sectional area of the normal proximal and distal part of the coronary artery, and this resulted in a 5% ± 2% increase in interpolated reference area. The cross-sectional area of the stenoses increased from 2.0 ± 1.1 mm^2 to 2.3 ± 0.9 mm^2 after intracoronary papaverine (18% ± 7% increase). After the first papaverine injection, percentage area stenoses decreased from 72% ± 11% to 69% ± 10% because of the increase in absolute terms in stenosis area. After isosorbidedinitrate, the proximal and distal parts of the coronary artery dilated, respectively, by 10% ± 4% and 10% ± 3%. The increase of the stenosis area after isosorbidedinitrate was of the same magnitude as after papaverine. Since isosorbidedinitrate changed the stenosis area and the interpolated reference area to the same extent, the relative percentage area stenosis was comparable to baseline (72% ± 11% vs. 71% ± 10%). Given after isosorbidedinitrate, intracoronary papaverine induced no changes in proximal and distal cross-sectional area, cross-sectional stenosis area, or relative percentage area stenosis.

The hemodynamic consequences of these vasodilator-induced changes in coronary arterial dimensions are

TABLE II. Changes in Stenosis Geometry After Coronary Vasodilatation (n = 11)[†]

	Cross-sectional area (mm^2)			Stenosis area		Diameter (mm)			Stenosis diameter	
Angiogram	Proximal	interp. ref.	Distal	mm^2	Percent	Proximal	interp. ref.	Distal	mm	Percent
1. Baseline	8.3 ± 3.1	7.2 ± 2.8	6.0 ± 2.9	2.0 ± 1.1	72 ± 11	3.24 ± 0.62	3.02 ± 0.58	2.75 ± 0.64	1.57 ± 0.51	47 ± 10
	*	*	*	*	*	*	*	*	*	*
2. Pap ic	8.7 ± 3.1	7.6 ± 3.0	6.3 ± 2.9	2.3 ± 0.9	69 ± 10	3.34 ± 0.65	3.12 ± 0.60	2.83 ± 0.63	1.72 ± 0.42	44 ± 10
Percent change compared to 1	5 ± 2 *	5 ± 2 *	5 ± 2 *	18 ± 7 *	4 ± 3 *	3 ± 2 *	3 ± 2 *	3 ± 2 *	10 ± 6 *	6 ± 3 ns
	*	*	*	ns	*	*	*	*	ns	*
3. ISDN ic	9.6 ± 3.5	8.4 ± 3.3	7.0 ± 3.2	2.4 ± 1.0	71 ± 10	3.50 ± 0.70	3.28 ± 0.73	2.99 ± 0.68	1.75 ± 0.47	46 ± 10
Percent change compared to 1	16 ± 7	17 ± 7	17 ± 6	20 ± 8	2 ± 2	8 ± 3	9 ± 4	9 ± 4	11 ± 6	2 ± 1
	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Percent change compared to 2	10 ± 4*	11 ± 4*	10 ± 3*	3 ± 2 ns	3 ± 2*	5 ± 2	5 ± 2	6 ± 3	2 ± 1	4 ± 2
4. ISDN + pap ic	9.6 ± 3.2	8.3 ± 3.1	6.9 ± 3.0	2.3 ± 1.0	72 ± 11	3.49 ± 0.69	3.25 ± 0.63	2.97 ± 0.62	1.72 ± 0.49	47 ± 11
Percent change compared to 3	0 ± 1	0 ± 2	0 ± 2	−3 ± 2	1 ± 2	0 ± 1	0 ± 2	0 ± 1	−2 ± 1	2 ± 2

[†]Results are expressed as mean ± SD. *$P < 0.05$; interp. ref., interpolated reference; pap, papaverine; ISDN, isosorbidedinitrate; ic, intracoronary; ns, not significant.

TABLE III. Hemodynamic Effects of Altered Stenosis Geometry After Vasodilation*

	Baseline	Pap	ISDN	ISDN + pap
f	1.88	1.38	1.31	1.38
s	0.42	0.29	0.28	0.30
ΔP				
1	2	2	2	2
2	5	4	4	4
3	9	7	7	7
4	14	10	10	11
5	20	14	14	15

*Pap, intracoronary papaverine; ISDN, intracoronary isosorbidedinitrate; ΔP, $fQ + sQ^2$; ΔP, pressure drop (mm Hg) over the stenosis for coronary flows of 1, 2, 3, 4, and 5 ml/sec; Q, flow (ml/sec); f, viscous coefficient (mm Hg/ml/sec); s, separation coefficient (mm $Hg/ml^2/sec^2$). Results are mean values from 11 patients.

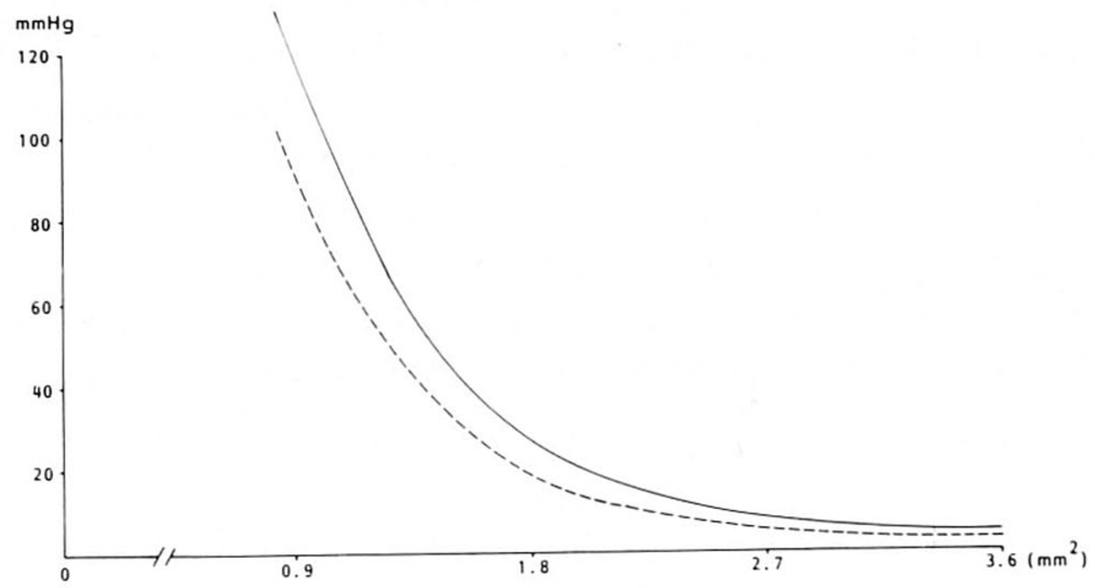

Fig. 2. Relation between the pressure drop over the stenosis at a coronary flow of 5 ml/sec at baseline (———) and after papaverine (– – – – –) as a function of baseline stenosis severity.

TABLE IV. Hemodynamic Effects of Altered Stenosis Geometry After Vasodilation*

	Baseline	Pap	ISDN	ISDN + pap
A[a]				
f	0.58	0.45	0.44	0.45
s	0.05	0.04	0.04	0.04
ΔP5	4	3	3	3
B[b]				
f	9.3	7.1	7.0	7.1
s	3.4	2.7	2.7	2.7
ΔP5	130	102	104	103

*Abbreviations as in Table III.
[a]A, patient with a 48% area stenosis.
[b]B, patient with an 86% area stenosis.

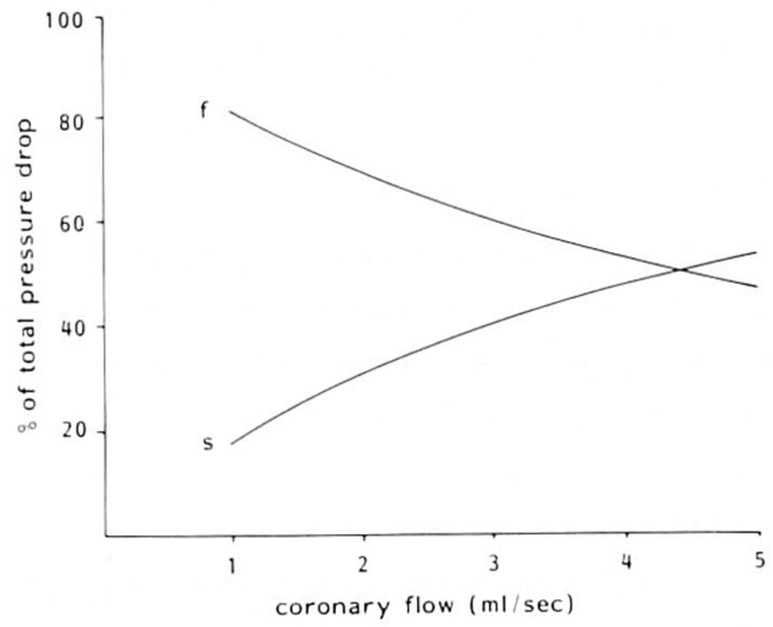

Fig. 3. Contribution to the stenosis resistance of viscous (f) and separation (s) resistances as a function of coronary blood flow.

characterized by the alterations in viscous (Poiseuille) resistance and separation resistance as well as the consequent change in pressure drop over the stenosis. Therefore, we calculated the viscous and separation coefficient and the resulting pressure drop over the stenosis for a physiological range of coronary blood flows (Table III). The magnitude of the resulting change in pressure drop over the stenosis was critically dependant on the baseline severity of the coronary stenosis. The patient with the most severe (86%) percentage area stenosis and the patient with the mildest (48%) percentage area stenosis are shown in Table IV as examples of this phenomenon. The relation between the pressure drop over the stenosis at a coronary flow of 5 ml/sec at baseline and after papaverine as a function of baseline stenosis severity is shown in Figure 2. The reduction in pressure drop from papaverine ranged from 20% to 30%. The relative contribution of the viscous and separation resistance to the pressure drop over the stenosis is a function of the coronary blood flow. With coronary blood flows of 1–2 ml/sec, the viscous resistance is the dominant factor, whereas, with higher coronary blood flows (4–5 ml/sec), viscous and separation resistances are quantitatively comparable (see Fig. 3). After both papaverine and isosorbidedinitrate, this relation remained essentially unchanged.

The total resistance over a coronary stenosis depends mainly on three geometric factors: cross-sectional area of the stenosis, normal area of the coronary artery, and length of the stenotic lesion. The length of the stenotic lesions (mean ± SD 7.1 ± 1.9 mm) did not change significantly after papaverine and/or isosorbidedinitrate. The vasodilator-induced reduction of the viscous resistance is due to the increase in cross-sectional area of the stenosis. The vasodilator-induced changes in separation resistance are related to both the increase in normal distal area of the coronary artery and the increase in cross-sectional area of the stenosis (Table V). The increase in normal distal area of the coronary artery results in an augmention of the separation resistance. The increase in cross-sectional area of the stenosis results in a decrease

TABLE V. Hemodynamic Effects of Altered Stenosis Geometry After Vasodilation*

	Baseline (mm Hg/ml^2/sec^2)	Pap (%)	ISDN (%)	ISDN + pap (%)
StA	0.42	−40	−45	−40
NDA	0.42	+5	+14	+12
StA + NDA	0.42	−31	−33	−29

*Relative contributions to the change in separation coefficient of the vasodilator-induced increases in stenosis cross-sectional area (StA) and normal distal area (NDA).

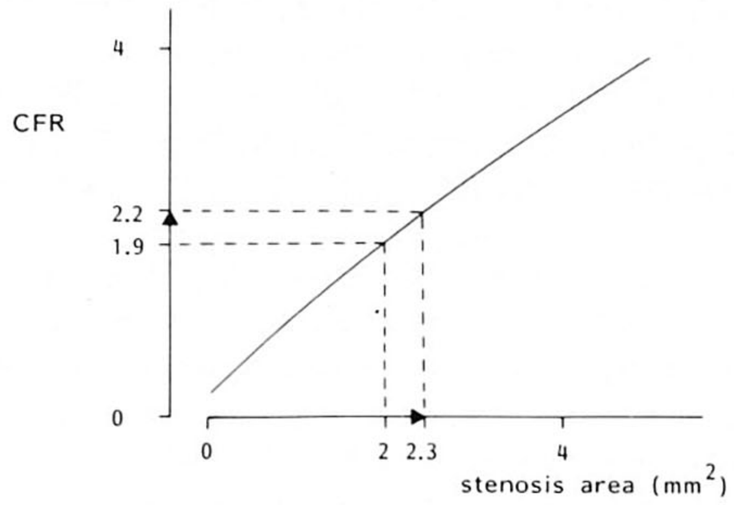

Fig. 4. Influence of intracoronary papaverine on coronary flow reserve (CFR) as a result of the change in stenosis area. The relation between CFR and stenosis area was established in a previous study in our laboratory. Papaverine induced an increase (mean value of 11 patients) in stenosis area from 2.0 to 2.3 mm^2, which corresponds to an increase in CFR from 1.9 to 2.2.

of the separation resistance. This latter change is of greater magnitude, so the alteration in separation resistance stems predominantly from the increase in absolute stenosis area.

DISCUSSION

The variability in quantitative measurements of various parameters of coronary arterial segments is reported in a previous paper from our laboratory [7]. The mean difference between obstruction diameters of the stenoses from repeated angiographic studies is 0.0, with a standard deviation of the difference of 0.22 (mm). Therefore, this system of quantitative analysis allows for a reliable assessment of even very small changes in coronary artery dimensions resulting from interventions such as administration of vasodilating agents. Papaverine is an attractive vasodilator for studies of the coronary circulation in human beings, since it induces a maximal fall in coronary vascular resistance, has few side effects, and has a duration of action less than 2 min [4]. The exact dose of intracoronary papaverine needed to induce a maximal coronary vasodilation has recently been established. Wilson and White [5] compared the coronary hyperemic response after 4, 8, 12, and 16 mg intracoronary papaverine and reported a maximal hyperemic response after 8 or 12 mg.

However, using papaverine, Gould and Kelley [6] described important changes in dogs in stenosis geometry and consequently important alterations in pressure-flow characteristics of the stenosis. Wilson and White [5] studied in human beings the impact of papaverine on coronary arterial dimensions and concluded that papaverine induced no significant alterations. In a previous study from our laboratory, we reported that papaverine had a small but significant effect on stenosis geometry [1]. However, the patients of Wilson and White and the patients in our previous study were all treated with nitrates during the investigational procedure. The ideal vasodilator should dilate exclusively the resistance vessels without affecting the geometry of the flow-limiting stenosis in the epicardial coronary artery. Unfortunately, as is indicated by our results, intracoronary papaverine influences both resistance vessel and epicardial coronary artery. The hyperemia induced by intracoronary papaverine cannot be solely attributed to a fall in arteriolar resistance but is partially due to changes in epicardial stenoses geometry. In other words, the methodological approaches using this drug affect the investigated phenomenon, namely, the pressure-flow relationship of the flow limiting stenoses. In a previous study from our laboratory [1], we established the relation between coronary flow reserve and the stenosis area in patients with single-vessel coronary artery disease. An increase in stenosis area from 2.0 to 2.3 mm^2 would correspond to an increase in coronary flow reserve from 1.9 to 2.2, that is, a 16% increase, and therefore overestimation of the real coronary flow reserve (see Fig. 4).

In accordance with our findings, Gould and Kelley [6] found important changes in stenoses geometry from papaverine in dogs. However, there are some qualitative differences between their results and ours, probably because of the different nature of the human coronary atherosclerotic lesion and stenoses produced by external constriction of normal coronary arteries in dogs. In our material, the most significant change in stenosis geometry was the increase in cross-sectional stenosis area; in their material, the change in cross-sectional area of the "normal" parts of the coronary artery was the predominant factor in the papaverine-induced changes in pressure-flow relationship. The predominance of viscous

resistance over separation resistance at "resting" coronary flows was similar in our patients and in their material. However, at high coronary flows, the separation resistance contributed about four times more to the pressure drop over the stenosis than the viscous resistance in the study of Gould and Kelley, whereas, in our material, viscous and separation resistances were equally important at higher coronary flows. In these dogs, an isolated increase in "normal" areas without change in the externally constricted vessel lumen further augments the separation loss of pressure, whereas the viscous resistance remains unchanged. In human atherosclerotic coronary artery lesions, both separation and viscous resistance are significantly changed, because the human atherosclerotic coronary artery lesion still has a capability of dilating. This is in accordance with the findings of Brown et al. [12], who documented a significant increase in stenosis area and decrease in stenosis resistance after nitroglycerin in human atherosclerotic coronary arteries.

There are two potential mechanisms for this papaverine-induced response. As reported by Holtz et al. [13], drugs that cause coronary dilatation can be classified according to their mode of action. Some drugs have a direct effect on the arterial vasculature, for instance, nitroglycerine and isosorbidedinitrate. On the other hand, adenosine and dipyridamol induce a flow-dependent, endothelium-mediated, indirect effect, by which even small variations in coronary blood flow may induce substantial alterations in coronary artery dimensions. The relative importance of these two mechanisms in the papaverine-induced changes in stenosis geometry remains to be established.

CONCLUSIONS

In human beings with atherosclerotic coronary artery lesions, intracoronary papaverine induces significant increases in cross-sectional stenosis area and in normal proximal and distal areas of the coronary artery. As a consequence of these geometric changes, the viscous and separation resistance as well as the resulting pressure drop over the stenosis decrease considerably. The papaverine-induced alterations in stenosis geometry and pressure-flow relationship are a serious methodological problem, since the magnitude of the changes is sufficient to influence measurements of coronary blood flow velocity or regional coronary flow reserve significantly. These papaverine-induced changes can nevertheless be circumvented by maximal vasodilation of the major epicardial coronary arteries with 3 mg intracoronary isosorbidedinitrate prior to the investigation of the coronary flow reserve with papaverine.

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