Dilatation of coronary artery stenoses after isosorbide dinitrate in man^{*}

WOLF RAFFLENBEUL, FERDINAND URTHALER, RICHARD O RUSSELL, P LICHTLEN, THOMAS N JAMES

From University of Alabama Medical Center, Birmingham, Alabama, USA; and Medical University, Hanover, Germany

SUMMARY The effect of isosorbide dinitrate (ISDN), 5 mg sublingually, on the diameters of coronary artery stenoses ($n=27$) was examined in 20 patients. Another 18 patients with angiographically normal coronary arteries received the same amount of ISDN and were used as controls. Prestenotic and stenotic diameters were measured with a vernier calliper having an accuracy of 0.05 mm. The degree of stenosis was expressed as percentage of cross-sectional area reduction. ISDN caused uniform dilatation of every normal epicardial artery; mean increase in diameter was 21 per cent (range: 17 to 26%). In 18 stenoses (28 to 95% obstruction) there was very little change after ISDN. The mean prestenotic diameter increased from 2.82 ± 0.48 mm to 3.05 ± 0.43 mm and the mean stenotic diameter from 1.45 ± 0.49 mm to 1.59 ± 0.51 mm. However, in the nine other stenoses (35 to 89% obstruction) the mean degree of obstruction decreased significantly from 68 ± 15.6 per cent to 47 ± 15.6 per cent after ISDN. This improvement was a result of a significant increase of the mean stenotic diameter from 1.71 ± 0.47 mm to 2.41 ± 0.55 mm, whereas the prestenotic diameter showed only an insignificant increase from 3.17 ± 0.63 mm to 3.31 ± 0.58 mm after ISDN. In four patients with two obstructions in different coronary branches ISDN dilated one without significantly affecting the other lesion. From these data we conclude that ISDN can dilate some coronary artery stenoses but that this response may vary from one site to another even in the same patient.

Administration of nitrates constitutes one of the more important treatments for the relief of angina. The beneficial effect is dually attributed to the reduction of left ventricular preload by venous pooling and afterload by reducing systemic blood pressure.^{1 2} The combination of these effects results in a decrease in left ventricular volume and wall tension, hence lower myocardial oxygen demand. However, from numerous studies³⁻⁶ we have also learned that in man, nitrates dilate epicardial coronary arteries. Since any increase of luminal area in an obstructed coronary artery segment should improve blood flow substantially,^{7 8} some of the therapeutic effects of nitrates may be attributable to dilatation of coronary artery stenoses.

Using a recently developed morphometric method for the exact measurements of coronary artery diameters,^{9 10} this study examines the influence of

sublingually administered isosorbide dinitrate (Isordil†) on the diameter of coronary arteries, with particular emphasis directed towards its effect on coronary artery stenoses.

Method

Two different groups of patients were entered in the study. The first group is composed of 18 patients evaluated for chest pain and in whom normal coronary arteries were found at angiography. The second group included 20 consecutive patients in whom clearly defined stenoses in one or more of the three major coronary branches were readily recognised in at least two different projections on angiography. In both groups the coronary angiogram was repeated five minutes after administration of 5 mg isosorbide dinitrate sublingually. In both the initial and the repeat coronary angiogram, coronary artery diameters were measured at the same sites from the screen of a Tagarno projector using a

^{*} This work was supported by the National Heart, Lung and Blood Institute (Program Project grant and SCOR on Ischemic Heart Disease). Dr Rafflenbeul is the recipient of a research grant of the Deutsche Forschungsgemeinschaft, Federal Republic of Germany.
Received for publication 18 August 1979

†Isordil was supplied by Ives Laboratories, New York

vernier calliper as described previously.¹⁰ The enlargement factor caused by the image magnifier and the projection was approximately threefold and was determined exactly by comparison with the measurement of the catheter tip placed in the coronary ostium.

In angiographically normal coronary arteries only the arteries running nearly parallel to the image plane were measured in the different projections. Thus, we assessed the left anterior descending artery in the right anterior oblique projection, whereas the left circumflex and the main trunk of the right coronary artery were measured in the left anterior oblique projection. To minimise errors from pincushion distortion which can average as much as 7 per cent, the measurements were consistently performed near the central x-ray beam. Though we were unable to find any change in lumen diameter during the cardiac cycle, we always measured at end-diastole in order to eliminate blurring effect from rapid heart movements as well as errors caused by axial or spatial rotations.

In coronary arteries with obstructions, measurements were obtained from the prestenotic segment (5 to 10 mm before the stenosis) and from the narrowest portion of the obstruction. Taking into account the eccentric lumen of many obstructions, coronary lesions were measured in at least two different projections before and after isosorbide dinitrate. The degree of each stenosis was calculated by the formula:

$$\text{Per cent area stenosis} = 1 - \frac{D_{\text{sten}}^2}{D_{\text{norm}}^2} \times 100$$

In this formula D_{norm} is the diameter of the angiographically normal prestenotic vessel segment and D_{sten} the average stenotic diameter calculated as arithmetic mean of the measured stenotic diameters in different projections. This calculation uses the formula of the surface area of a circle ($A = \pi r^2$) to determine the respective cross-sectional area. Validation of this method has been established previously.¹⁰

To minimise observer bias and variability all angiograms were assessed by the same observer in a random sequence. Results are expressed as mean ± 1 standard deviation (SD). The significance of a difference was assessed by the two-tailed paired Student's *t* test and a *p* value of < 0.05 was regarded as statistically significant.¹¹

Results

Table 1 illustrates the diameter changes of normal coronary arteries after administration of 5 mg

isosorbide dinitrate. The portion of the left anterior descending artery from its origin to the apex of the heart and the portion of the right coronary artery from its aortic orifice to the crux cordis were arbitrarily subdivided into a proximal, middle, and distal third. The left circumflex artery between its origin and the most distal obtuse marginal branch was divided into a proximal and a distal half. We compared measurements before and after administration of the nitrates, and in all these segments of normal coronary arteries there was a uniform and significant increase of vessel diameter. After isosorbide dinitrate the calibre of enlargements ranged from 17 to 26 per cent.

Table 2 summarises the results obtained before and after administration of isosorbide dinitrate to patients with coronary artery stenoses. A total of 27 obstructions, 10 in the left anterior descending artery, four in the left circumflex artery, and 13 in the right coronary artery were examined. In 16 patients with 18 stenoses, ranging from 28 to 95 per

Table 1 Effect of isosorbide dinitrate 5 mg sublingually on the diameters (mm) of normal coronary arteries

Coronary artery segment	Before	Isosorbide dinitrate	After
LAD			
Proximal	3.0 $\pm$ 0.11		3.5 $\pm$ 0.13*
Middle	2.5 $\pm$ 0.08		3.0 $\pm$ 0.10*
Distal	1.6 $\pm$ 0.12		2.0 $\pm$ 0.12*
LCX			
Proximal	2.7 $\pm$ 0.10		3.4 $\pm$ 0.10*
Distal	2.4 $\pm$ 0.09		2.9 $\pm$ 0.11*
RCA			
Proximal	3.2 $\pm$ 0.12		3.8 $\pm$ 0.13*
Middle	2.9 $\pm$ 0.11		3.5 $\pm$ 0.12*
Distal	2.6 $\pm$ 0.11		3.1 $\pm$ 0.13*

**p* < 0.05. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 2 Effect of isosorbide dinitrate 5 mg sublingually on coronary artery stenoses

	Before	Isosorbide dinitrate	After
Group A (n=18)			
Degree of stenosis (% area)	70 $\pm$ 17.3%		69 $\pm$ 17.5%†
Prestenotic diameter (mm)	2.82 $\pm$ 0.48		3.05 $\pm$ 0.43†
Stenotic diameter (mm)	1.45 $\pm$ 0.49		1.59 $\pm$ 0.51†
Group B (n=9)			
Degree of stenosis (% area)	68 $\pm$ 15.6%		47 $\pm$ 15.6%*
Prestenotic diameter	3.17 $\pm$ 0.63		3.31 $\pm$ 0.58†
Stenotic diameter (mm)	1.71 $\pm$ 0.47		2.41 $\pm$ 0.55‡

Group A = 16 patients; Group B = 8 patients; n = number of stenoses. **p* < 0.025; † NS; ‡*p* < 0.05.

cent area, isosorbide dinitrate had virtually no effect (group A of Table 2). The degree of obstruction before and after isosorbide dinitrate averaged 70 ± 17.3 per cent and 69 ± 17.5 per cent, respectively. The prestenotic diameters showed variable changes after nitrate, ranging between -6 and $+27$ per cent of the original diameter, but the average increase in prestenotic diameter did not exceed 8 per cent (from 2.82 ± 0.48 mm to 3.05 ± 0.43 mm). The average stenotic diameter increased only by 10 per cent (from 1.45 ± 0.49 mm to 1.59 ± 0.51 mm). None of these differences was significant.

In contrast, in eight other patients with nine stenoses (group B of Table 2) isosorbide dinitrate significantly enlarged the stenotic diameter. In this group the degree of stenosis before the nitrates ranged from 35 to 89 per cent area stenoses and the mean decrease in the degree of stenoses after isosorbide dinitrate was 32 ± 10 per cent. The stenotic diameters increased in all these stenoses and the range varied between $+8$ and $+83$ per cent (mean $44 \pm 22\%$). The prestenotic segments, however, showed a non-uniform response since the changes in the measured diameters varied between -11 and $+50$ per cent, but the average increase in prestenotic diameter was only 4 per cent (from 3.17 ± 0.63 mm to 3.31 ± 0.58 mm) and not significant. The significant ($p < 0.025$) decrease in the average degree of stenosis from 68 ± 15.6 to 47 ± 15.6 per cent can therefore unequivocally be attributed to a significant increase of the mean stenotic diameter that enlarged from 1.71 ± 0.47 mm to 2.41 ± 0.55 mm.

Discussion

Nitrates cause generalised relaxation of vascular smooth muscle. Dilatation of large coronary arteries after administration of nitrates has repeatedly been shown angiographically. In the intact coronary arterial system the resistance to flow is mainly regulated at the precapillary level and is greatly influenced if not completely determined by the metabolic demands of the myocardium. Therefore, dilatation of the "conduit" vessels should not be a major determinant of coronary blood flow. Our own results examining the effect of nitrates on normal coronary arteries are in complete accordance with those studies previously reported.⁵⁻⁸

In contrast to the uniform dilatation observed in normal coronary arteries after administration of isosorbide dinitrate, a distinctively different response to the same dose of nitrates was observed in patients with coronary artery disease. Though in the majority of coronary artery stenoses the degree of obstruction was not significantly diminished by the

nitrates, *no less* than one-third of the obstructions showed evidence for a significant decrease in the degree of stenosis. In the group without response the absence of a substantial decrease in the degree of stenosis is probably the result of fibrosis and/or calcification of the diseased vessel. Numerous anatomical studies have shown that foci of calcification can occur in almost every arteriosclerotic lesion. Calcium deposits develop independently of the severity of coronary stenosis and have sometimes been shown to invade the whole vascular circumference.¹²⁻¹³ Even in the prestenotic segment, which always appeared normal in our angiographic study, undetectable intramural calcium deposits could resist pharmacological dilatation in spite of adequate relaxation of the vascular smooth muscle.

Most importantly, this study shows that stenoses of any degree and at any site can dilate in response to nitrates. In other words, the chance for a beneficial response to nitrates is as good in a stenosis with high degree of obstruction as in a stenosis with a low degree of obstruction. In four patients with two stenoses each, isosorbide dinitrate dilated one stenosis without affecting the other, showing that there can be a different response by different stenoses even in the same patient.

Since stenoses can dilate as shown in the present study and constrict¹⁴ after pharmacological manoeuvres, it seems reasonable to assume that tonic dynamic changes will often and perhaps continuously influence the stenotic cross-section area. Optimal evaluation of coronary artery lesions will thus need to include a more detailed assessment of the functional anatomy of coronary artery stenoses.

Non-uniform responses of different segments of the coronary tree have already been observed by several authors.¹⁵⁻²⁰ Most of them focused on the difference between large and small coronary arteries and attributed the variable response to different neural receptors,¹⁵⁻¹⁶ different smooth muscle cell membrane properties,¹⁷⁻¹⁹ or even to a different pharmacological behaviour of smooth muscle.²⁰ Sympathetic stimuli normally dilate epicardial coronary arteries but constriction usually occurs after beta-receptor blockade.²¹ A comparable observation was made when serotonin, a potent dilator of coronary arteries, was shown to cause vasoconstriction when there was decreased neurogenic tone.²² From these and similar observations it is apparent that the pharmacological response of coronary arteries can change and that it is greatly affected by variations of autonomic nervous influences. A similar mechanism involving abnormal autonomic discharge in the atherosclerotic segment could interfere with the usually expected vasodilatation produced by nitrates.

References

- ¹Mason DT, Braunwald E. The effects of nitroglycerin and amyl nitrate on arteriolar and venous tone in the human forearm. *Circulation* 1965; **32**: 755–66.
- ²DeMaria AN, Vismara LA, Auditore K, Amsterdam EA, Zelis R, Mason DT. Effects of nitroglycerin on left ventricular cavity size and cardiac performance determined by ultrasound in man. *Am J Med* 1974; **57**: 754–60.
- ³West JW, Guzman SV. Coronary dilatation and constriction visualized by selective arteriography. *Circ Res* 1959; **7**: 527–36.
- ⁴Likoff W, Kasparian H, Lehman JS, Segal BL. Evaluation of 'coronary vasodilators' by coronary arteriography. *Am J Cardiol* 1964; **13**: 7–9.
- ⁵Gensini GG, Kelly AE, Da Costa BCB, Huntington PP. Quantitative angiography: the measurement of coronary vasomobility in the intact animal and man. *Chest* 1971; **60**: 522–30.
- ⁶Feldman RL, Pepine CJ, Curry C, Conti CR. Case against routine use of glyceryl trinitrate before coronary angiography. *Br Heart J* 1978; **40**: 992–7.
- ⁷Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. *Am J Cardiol* 1974; **33**: 87–94.
- ⁸Logan SE. On the fluid mechanics of human coronary artery stenosis. *IEEE Trans Biomed Eng BME*—1975; **22**: 327–37.
- ⁹Rafflenbeul W, Heim R, Dzuiba M. Morphometric analysis of coronary arteries. In: Lichtlen PR, ed. *Coronary angiography and angina pectoris*. Stuttgart: Thieme, 1976: 255.
- ¹⁰Rafflenbeul W, Smith LR, Rogers WJ, Mantle JA, Rackley CE, Russell RD Jr. Quantitative coronary arteriography. Coronary anatomy of unstable angina pectoris reexamined one year after optimal medical therapy. *Am J Cardiol* 1979; **43**: 699–707.
- ¹¹Snedecor GW, Cochran WG. *Statistical methods*, 6th ed. Iowa: The Iowa State University, 1973: 447–67.
- ¹²Eggen DA, Strong JP, McGill HC Jr. Coronary calcification. Relationship to clinically significant coronary lesions and race, sex, and topographic distribution. *Circulation* 1965; **32**: 948–55.
- ¹³Vlodaver Z, Edwards JE. Pathology of coronary atherosclerosis. *Prog Cardiovasc Dis* 1971; **14**: 256–74.
- ¹⁴Heupler FA Jr, Proudfit WL, Razavi M, Shirey EK, Greenstreet R, Sheldon WC. Ergonovine maleate provocative test for coronary arterial spasm. *Am J Cardiol* 1978; **41**: 631–40.
- ¹⁵Zuberbühler RC, Bohr DF. Responses of coronary smooth muscle to catecholamines. *Circ Res* 1965; **16**: 431–40.
- ¹⁶Needleman P, Jakschik B, Johnson EM Jr. Sulfhydryl requirement for relaxation of vascular smooth muscle. *J Pharmacol Exp Ther* 1973; **187**: 324–31.
- ¹⁷Winbury MM, Howe BB, Hefner MA. Effect of nitrates and other coronary dilators on large and small coronary vessels: an hypothesis for the mechanism of action of nitrates. *J Pharmacol Exp Ther* 1969; **168**: 70–95.
- ¹⁸Schnaar RL, Sparks HV. Response of large and small coronary arteries to nitroglycerin, NaNO₂, and adenosine. *Am J Physiol* 1972; **223**: 223–8.
- ¹⁹Harder DR, Belardinelli L, Sperelakis N, Rubio R, Berne RM. Differential effects of adenosine and nitroglycerin on the action potentials of large and small coronary arteries. *Circ Res* 1979; **44**: 176–82.
- ²⁰Norton JM, Detar R. Adenosine and isolated coronary vascular smooth muscle (abstract). *Physiologist* 1970; **13**: 273.
- ²¹Nayler WG, Carson V. Effect of stellate ganglion stimulation on myocardial blood flow, oxygen consumption and cardiac efficiency during beta-adreno-receptor blockade. *Cardiovasc Res* 1973; **7**: 22–9.
- ²²Page IH, McCubbin JW. The variable arterial pressure response to serotonin in laboratory animals and man. *Circ Res* 1953; **1**: 354–62.

Requests for reprints to Professor Thomas N James, Department of Medicine, University of Alabama Medical Center, Birmingham, Alabama 35294, USA.