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Long-acting coronary vasodilatory action of the molsidomine metabolite Sin I: a quantitative angiographic study

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The vasodilatory action of molsidomine was studied by intracoronary injection of its active metabolite, Sin 1. In 10 patients repeat coronary angiography in multiple projections was performed before and 2 minutes after administration of 1 mg of Sin 1, and before and after a second injection 60 minutes later. Contours of obstructed and non-obstructed segments of the left coronary artery were quantitatively analysed with a computer-based angiography analysis system. Immediately after its administration, Sin 1 increased the mean diameters of 44 normal coronary segments by 12% ($P<0{\cdot}001$). Significant vasodilation (8%) was still observed after 60 minutes. At that time, repeated administration of Sin 1 increased the vasodilation by an additional 14% with respect to the control situation. An increase in obstruction diameter was observed in 6 out of 8 obstructed segments. Mean increase in the minimal obstruction diameter was still 10% after 60 minutes.

Introduction

Molsidomine (M-ethylcarbonyl-3-morpholino-sydnonimine, Sin 10) belongs to a class of drugs called sydnonimines, which have haemodynamic effects similar to those of nitrates[1,2]. In the liver, molsidomine is enzymatically transformed to its active metabolite Sin 1, which has, like nitro compounds, a nitric oxide moiety in its molecule[3]. Previous experimental and clinical data have demonstrated that the duration of haemodynamic effects of molsidomine is considerably longer than that of nitrates[3–8], and after oral administration molsidomine has been shown to have an anti-anginal effect lasting six hours or more[9].

Acute coronary vasodilatory properties of Sin 1 after intracoronary injection have recently been demonstrated[10]. The purpose of the present study was to further assess the vasodilatory effect of intracoronary Sin 1, and to determine the persistence of this effect on normal and obstructed epicardial vessels over a period of 60 minutes. A computer-assisted coronary angiography analysis system was utilised to quantify changes in the coronary diameters of specific segments repeatedly visualized.

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Methods

STUDY POPULATION AND PROTOCOL

The study group consisted of 10 male patients undergoing cardiac catheterization for the investigation of suspected coronary artery disease. Mean age was 53 years (range 37 to 63 years) and mean ejection fraction 58%. One patient had normal coronary arteries, 3 patients had single-vessel disease, 3 double-vessel disease, and 3 patients triple-vessel disease. Anti-anginal treatment was withheld 24 hours prior to catheterization, which was performed without pre-medication after an overnight fast.

The patients were studied according to the following protocol, after each patient had given informed consent before entering the study. Angiography of the left coronary artery was performed in the control state in standard views, including cranial and caudal angulations. The geometry of the X-ray gantry, and the kV and mA

Table 1 Variability in X-ray gantry and X-ray generator settings with repeated cine angiographies

	Mean value	Mean difference	SD diff
Rotation U arm, degrees	31·2	0·3	4·2
Rotation patient/C arm, degrees	26·4	0·3	2·2
Isocenter-image intensifier distance, cm	22·6	1·1	3·0
Focus-Isocenter distance, cm	72·8	−0·3	0·8
Object-Isocenter distance, cm	5·3	0·2	1·4

SD = standard deviation, diff = difference

of the X-ray generator were acquired and recorded on-line for each angiogram. Immediately after the control angiogram (angio 1), 1 mg of intracoronary Sin 1 was administered and the angiography repeated (angio 2) to study the immediate effect of the drug on the dimensions of the coronary arteries. One hour later the angiogram was repeated (angio 3) and again a fourth time following a second intracoronary administration of 1 mg of Sin 1 (angio 4). For each series of angiograms the X-ray system was positioned in projections corresponding as closely as possible to those used during the control angiograms. The overall mean values and the variabilities in the X-ray gantry and X-ray generator settings are presented in Table 1. To determine the angular variations, the absolute differences in angular settings were calculated. The angular variability was less than 4·0 degrees, and the variability in the various gantry settings was less than 1·6 cm. There were no significant differences between the corresponding X-ray system settings for the 4 consecutive angiograms.

All angiograms were obtained using the Judkins technique and recorded on Kodak 35 mm cinefilm at a rate of 25 frames per second. A non-ionic contrast medium, Omnipaque®, was injected manually.

QUANTITATIVE CORONARY ANGIOGRAPHY

The quantitative analysis of selected coronary segments was carried out with the computer-assisted Cardiovascular Angiography Analysis System (CAAS), which has been described in detail elsewhere[11,12]. To analyse a coronary arterial segment in a selected frame of 35 mm cinefilm, an optically magnified portion of the image encompassing that segment is converted into video format by means of a cine-video converter. The contours of the vessel are detected automatically on the basis of the weighted sum of first and second derivative functions applied to the digitized brightness information. Calibration of the diameter data of the vessels in absolute values (mm) is achieved by using the contrast catheter as a scaling device. To this end, the contours of a user-defined portion of the optimally magnified catheter (optimal magnification factor $2\sqrt{2}$) are detected automatically and corrected for pincushion distortion caused by the image intensifiers. From the contours, the vessel diameter functions, in absolute mm, are determined by computing the shortest distances between the left and right contour positions.

A representative analysis, with the detected contours and the diameter functions superimposed on the original video image, is shown in Fig. 1. For non-obstructed coronary segments, the mean arterial diameter of the analysed segment was computed. For obstructed segments, the minimal

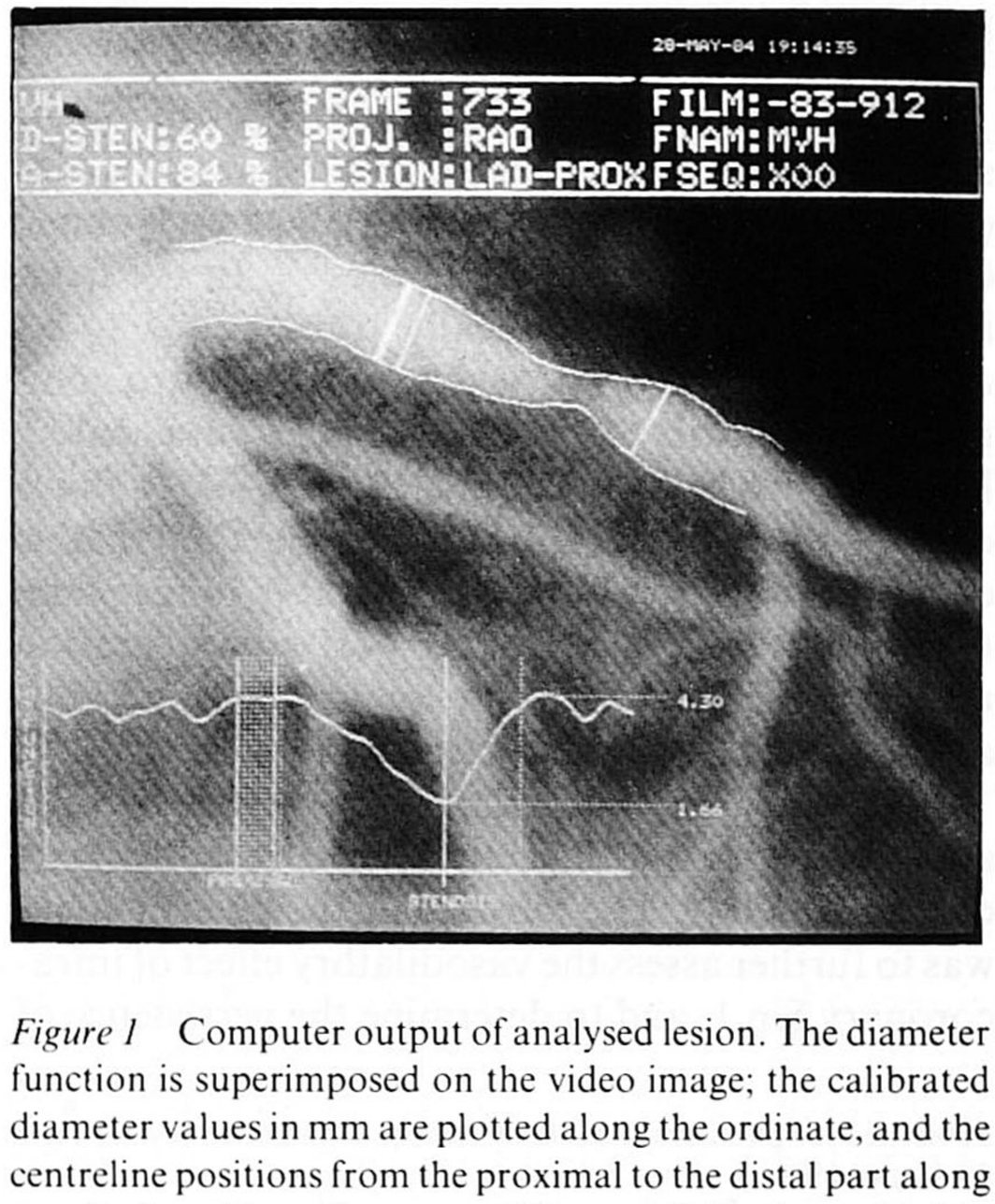

Figure 1 Computer output of analysed lesion. The diameter function is superimposed on the video image; the calibrated diameter values in mm are plotted along the ordinate, and the centreline positions from the proximal to the distal part along the abscissa. The reference position was defined proximal to the obstructive lesion, as indicated in the diameter function by the shaded vertical bar. The central reference position is marked in the artery by a straight line connecting the opposing contour sides. A percentage diameter reduction of 60%, with respect to the user-defined reference region, was found.

obstruction diameter was assessed. When more than 1 view of a particular segment was analysed, averaged diameters were calculated.

Fifty-two coronary segments, 8 stenotic and 44 non-stenotic, were selected from the study group angiograms for analysis. The fact that a limited number of stenotic lesions ($N=8$) were analysed in this study, is due to the following: (1) selection was based on the technical quality of the angiograms, with clear views of the pre- and post-stenotic segments; (2) orthogonal projections of the stenotic lesions were required; (3) only repeat angiography of the left main coronary artery was performed.

The localization and quantitative coronary angiography characteristics of the 8 stenotic lesions in 7 male patients, of which 1 had a tandem lesion in the proximal desending artery, are summarized in Table 2. An inventory of the 44 non-stenotic coronary segments, with the average number of angiographic views used for the analysis of each segment, is given in Table 3. The segments were named according to the proposals of the American Heart Association[13].

To insure exact reproducibility of all 4 angiographic studies, the following four measures were undertaken:

First, as mentioned above, the X-ray system was repositioned in the settings corresponding as closely as possible to the projections used during the previous angiographies. For this purpose, the angular settings of the X-ray gantry and the various height levels were readjusted according to the values previously documented with the on-line registration system.

Second, for all studies, cineframes to be analysed were selected at end-diastole, to minimize any possible foreshortening effect.

Third, the user-determined beginning and end-points of the major coronary segments between side branches were standardized according to the definitions of the American Heart Association[13].

Last, Polaroid pictures were taken of the video image with the detected contours superimposed, to ensure that the analyses were performed on the same coronary segment in the 4 consecutive angiograms. Consequently, between angiograms 2 and 4 the mean difference in length of the non-stenosed segments proved to be non-significant ($-0{\cdot}03$ mm, SD $\pm 1{\cdot}02$ mm). The mean length of these non-stenosed segments was 14·03 mm.

For the 8 obstructed coronary segments the theoretical pressure gradients across the stenotic lesion, at selected theoretical coronary flow rates of

Table 2 Localization and characteristics of the 8 stenosed segments in the basal state in 7 male patients

Patient		Length of stenosis (mm)	Area stenosis (%)	Minimal cross-sectional area (mm^2)
1	Left main	4·5	56	4·50
2a	LCX proximal	4·38	84	0·68
2b	LCX proximal	2·19	61	1·68
3	Left main	6·84	36	5·93
4	LCX proximal	5·0	65	4·13
5	LAD proximal	6·0	77	2·42
6	LAD proximal	12·5	81	3·12
7	LAD proximal	6·27	52	1·77

Abbreviations: LAD = left anterior descending artery
LCX = left circumflex artery

Table 3 Inventory of the 44 non-stenosed segments

	Number of patients	Average number of views per segment
Left main	7	2
LAD proximal	8	2·1
LAD mid-portion	8	1·8
LAD distal	6	1·7
LCX proximal	9	2·4
LCX distal	6	2·2

Abbreviations: As in Table 2

1, 2, 3, and 4 ml s^{-1}, were calculated by using the data obtained at quantitative analysis of the angiogram, according to the well-established formulas described in the literature[14,15].

$$P_{grad} = Q\,(R_p + QR_t),$$

where P_{grad} is the theoretical pressure drop (mmHg) over the stenosis, Q the mean coronary blood flow (ml s^{-1}), R_p the Poiseuille resistance and R_t the turbulent resistance. These resistances have been defined as follows:

$$R_p = C_1\,\frac{(\text{length obstruction})}{(\text{obstruction area})^2},$$

where $C_1 = 8\pi$(blood viscosity), and blood viscosity $= 0{\cdot}03$ g cm^{-1} s^{-1},

$$R_t = C_2\left(\frac{1}{\text{obstruction area}} - \frac{1}{\text{normal distal area}}\right),$$

Table 4 Absolute diameters (mm) in 8 stenotic and 44 non-obstructed segments following intracoronary administration of Sin 1

	Angio 1	Angio 2	Angio 3	Angio 4	*P*-value*
Stenotic segments ($n=8$)	1·96	2·27	2·16	2·26	0·07
Non-obstructed segments ($n=44$)					
Main ($n=7$)	4·29	4·80	4·60	4·85	0·004
LAD prox ($n=8$)	2·68	2·97	2·93	3·02	0·04
LAD mid ($n=8$)	2·26	2·50	2·35	2·53	0·02
LAD distal ($n=6$)	1·85	2·01	1·93	2·06	0·04
LCX prox ($n=9$)	2·62	2·99	2·83	3·04	0·0003
LCX distal ($n=6$)	1·99	2·32	2·24	2·43	0·0002

Abbreviations: as in Table 2.
*P-value from analysis of variance.

where C_2 = blood density/0·266, with blood density = 1·0 g cm^{-3}[16].

STATISTICAL ANALYSIS

To evaluate statistically the vasodilation in the 4 angiograms the following procedure was adopted. If an analysis of variance between the 4 angiograms was statistically significant, pair-wise differences between the angiograms were statistically assessed with Student's t-test. A P-value of $\leqslant 0{\cdot}05$ was considered significant.

Results

Analysis was made of 44 non-obstructed and 8 obstructed segments of the left coronary artery. The absolute diameters (mm) of the coronary segments, as measured during the 4 angiographies, are presented in Table 4.

In the 44 non-obstructed segments, the mean diameter increased by 12% immediately after the administration of Sin 1 [Figure 2(a)]. Although the initial increase in arterial dimension had diminished

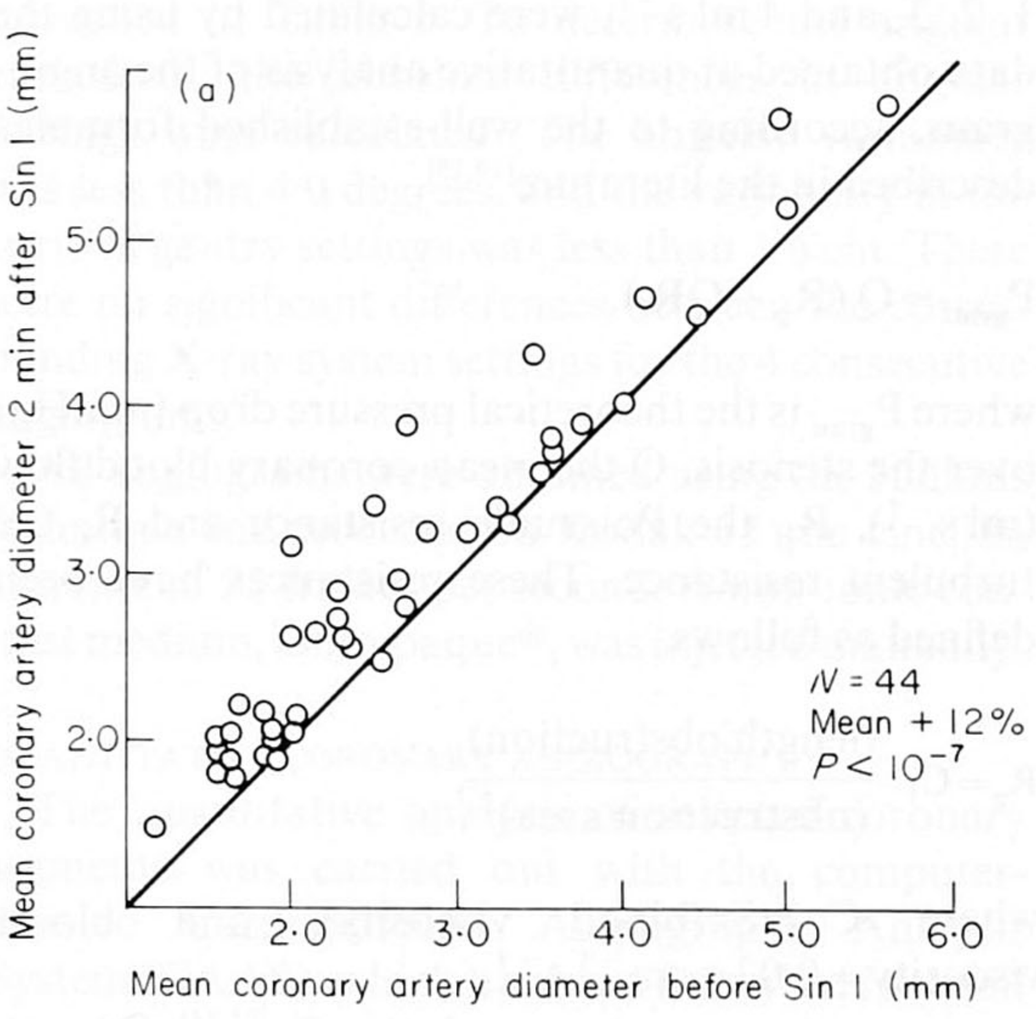

Figure 2(a) Immediate effect of intracoronary administration of 1 mg of Sin 1 on mean coronary artery diameters of non-obstructed segments.

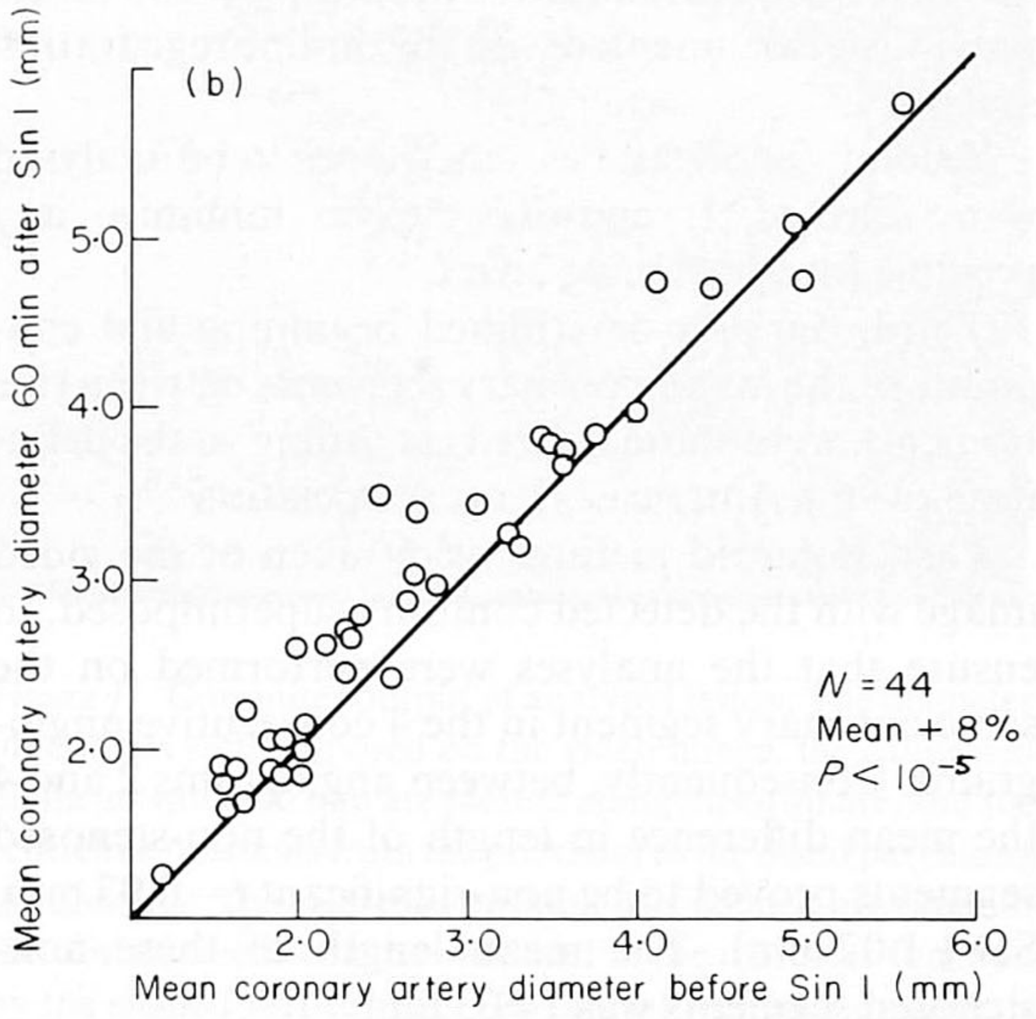

Figure 2(b) Effect of intracoronary administration of 1 mg of Sin 1 on mean coronary artery diameters of non-obstructed segments after 60 minutes.

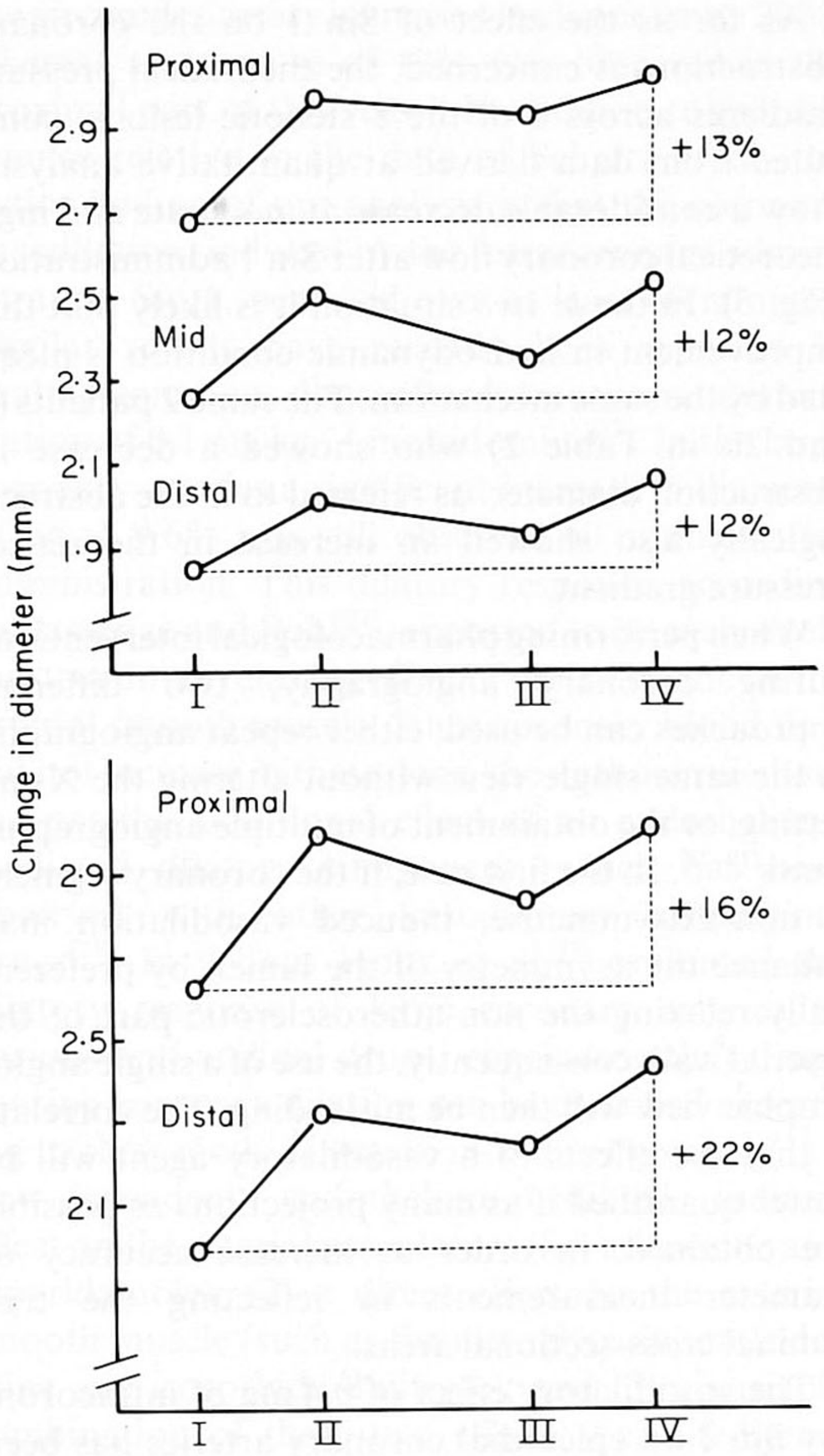

Figure 3 Changes in normal coronary artery diameter in proximal, mid and distal parts of the left anterior descending (LAD) (a), and proximal and distal circumflex (CX) (b). Percentage value given is the change in final appearance from control (I = control angiogram, II = angiogram 2 minutes after administration of Sin 1, III = 60 minutes after administration of Sin 1, IV = angiogram 2 minutes after second administration of Sin 1).

after 60 minutes, vasodilation was still observed [8%, Figure 2(b)] at this time. The second injection of Sin 1 resulted in an additional dilation of the non-obstructed segments, causing a diameter increase of 14% with regard to the control situation.

Analysis of variance revealed significant changes in the coronary diameters of all anatomical divisions. Two minutes after intracoronary Sin 1 (angio 2) the diameter of the left main coronary artery increased from 4·29 to 4·80 mm (+12%), while percentage diameter changes in the left anterior descending artery of 11%, 11% and 9% were observed in the proximal, medial and distal parts, respectively. Corresponding values from the proximal and distal segments of the circumflex artery were 14% and 17% (all $P<0{\cdot}05$). After one hour (angio 3), significant vasodilation was still present in the proximal left anterior descending artery (9%, $P<0{\cdot}04$), and proximal (8%, $P<0{\cdot}02$) and distal (13%, $P<0{\cdot}02$) segments of the circumflex artery. Increases in diameter of the left main and mid and distal segments of the left anterior descending arteries, did not reach statistical significance. After the second injection of Sin 1 further vasodilation was found in all segments; however, only the increase in the distal circumflex artery reached statistical significance. The changes in diameter with each angiogram are shown in Fig. 3(A) for the left anterior descending artery, and in Fig. 3(B) for the left circumflex, with the final percentage change in relation to the initial diameter indicated numerically.

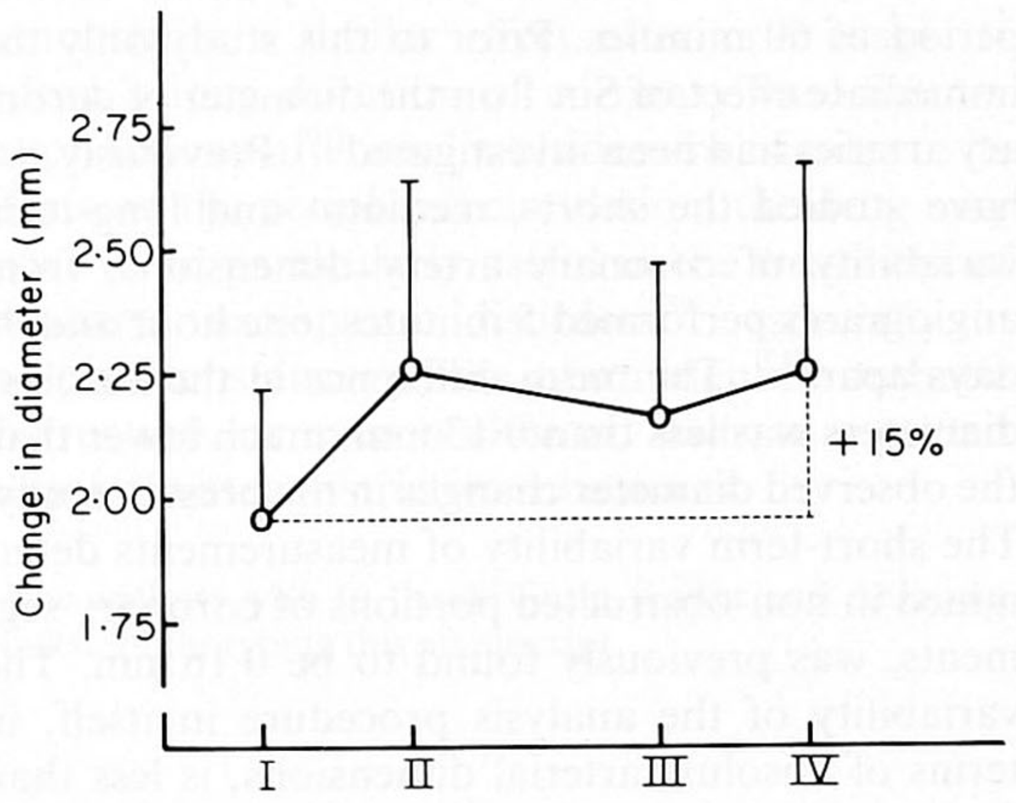

Figure 4 Changes in obstruction diameters. For abbreviations see Fig. 3. Percentage value given is the change from control to final appearance.

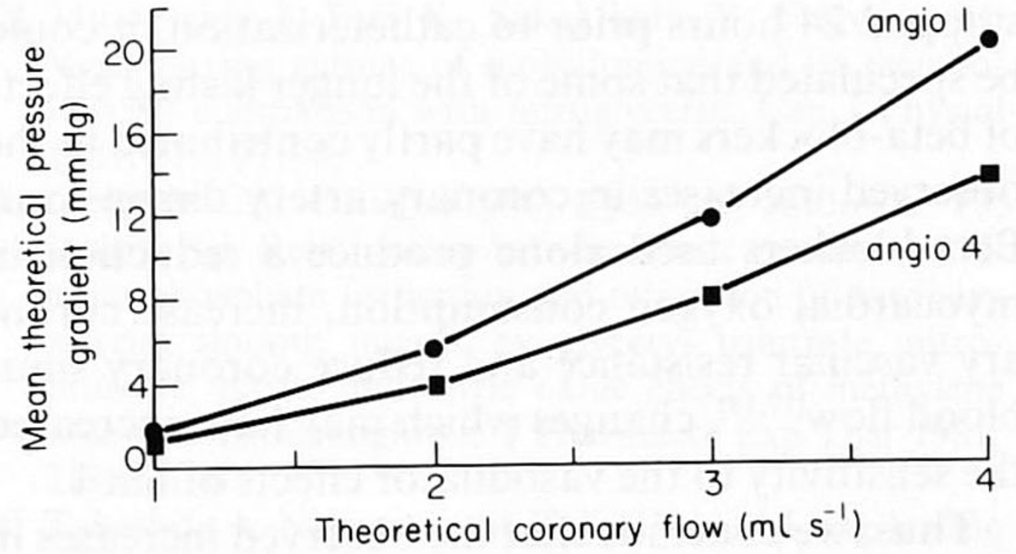

Figure 5 Change in mean theoretical pressure gradient across 6 of the 8 stenotic lesions, at a theoretical coronary flow of 1, 2, 3 and 4 ml s^{-1}, when comparing angio 1 with angio 4.

Among the 52 segments analysed, 8 stenotic segments were measured. After injection of Sin 1, an increase in the obstruction diameter was observed in all but 2 of the stenotic lesions. In comparison with the control angiogram, the mean increase in minimal diameter was 16% immediately after Sin 1, and 10% after 60 minutes (Figure 4). The overall decrease in the theoretical pressure gradients across 6 of the 8 stenotic lesions, comparing the control state (angio 1) with the situation 2 minutes after the second administration of Sin 1 (angio 4), is depicted in Fig. 5.

Discussion

The results of the present study demonstrate that left main coronary artery injection of Sin 1, the active metabolite of molsidomine, causes a significant vasodilation of the major epicardial vessels. In addition, this vasodilatory effect persists over a period of 60 minutes. Prior to this study only the immediate effect of Sin 1 on the diameter of coronary arteries had been investigated[10]. Previously, we have studied the short-, medium- and long-term variability of coronary artery dimensions, from angiograms performed 5 minutes, one hour and 90 days apart[12]. The mean difference in the absolute diameters was less than 0·13 mm, much lower than the observed diameter changes in the present study. The short-term variability of measurements determined in non-obstructed portions of coronary segments, was previously found to be 0·16 mm. The variability of the analysis procedure in itself, in terms of absolute arterial dimensions, is less than 0·12 mm. The accuracy and precision of the edge-detection procedure, as assessed from cine-films of contrast-filled perspex models, are $-30\,\mu$ and $+90\,\mu$, respectively[12].

Since in this study anti-anginal treatment was stopped 24 hours prior to catheterization, it could be speculated that some of the longer lasting effects of beta-blockers may have partly contributed to the observed increases in coronary artery dimensions. Beta-blockers used alone produce a reduction in myocardial oxygen consumption, increase coronary vascular resistance and reduce coronary sinus blood flow[17,18], changes which may have increased the sensitivity to the vasodilator effects of Sin 1.

Thus, we conclude that the observed increases in coronary dimensions are indeed the result of Sin 1 administration, although the magnitude of the observed increases may have been accentuated by persisting beta-blockade effect.

As far as the effect of Sin 1 on the coronary obstructions is concerned, the theoretical pressure gradients across 6 of the 8 stenotic lesions, computed from data derived at quantitative analysis, show a considerable decrease at moderate and high theoretical coronary flow after Sin 1 administration (Fig. 5). In the *in vivo* situation it is likely that this improvement in hydrodynamic condition is mediated by the same mechanism. The same 2 patients (1 and 2b in Table 2) who showed a decrease in obstruction diameter, as referred to in the abstract, logically also showed an increase in theoretical pressure gradient.

When performing pharmacological interventions during coronary angiography, two different approaches can be used: either repeat angiography in the same single view without altering the X-ray setting, or the obtainment of multiple angiographic views[19–21]. In the first case, if the coronary segment is non-axisymmetric, induced vasodilation may enhance the asymmetry of the lumen by preferentially relaxing the non-atherosclerotic part of the arterial wall; consequently, the use of a single angiographic view will then be misleading. The correlate is that the effects of a vasodilatory agent will be better quantified if as many projections as possible are obtained, in order to increase accuracy of diameter measurements in reflecting the true luminal cross-sectional areas.

The vasodilatory effect of 0·4 mg of intracoronary Sin 1 on epicardial coronary arteries has been evaluated by Schultz and co-workers in 23 patients with coronary artery disease[10]. Diameter changes of non-stenotic coronary arteries in proximal, medial and distal segments as well as changes in the residual luminal diameters of coronary stenoses, were determined before, immediately after and 10 minutes following intracoronary Sin 1 injection. These authors found an immediate increase in the diameters of non-stenotic coronary segments of 9%, 18% and 26% in the proximal, medial and distal segments, respectively. Whether this more pronounced distal vasodilation was observed in the anterior descending or in the circumflex artery was not specified. Using a dosage of 1 mg of Sin 1, we found a similar degree of epicardial vasodilation. However, our results differ from those of Schultz *et al.* in one respect: in the left anterior descending coronary artery, Sin 1 did not dilate the distal segments to a greater degree than the proximal segments. In fact, the percentual increase in the diameters of the segments was similar over the entire course of the descending artery. The distal part of

the circumflex artery increased its diameter by 20%, whereas an increase of 12% was observed in the proximal part of this vessel. In addition to this difference relative to the data of Schultz *et al.*, the major finding of our analysis is that the coronary vasodilation, induced by the intracoronary administration Sin 1, persisted over at least 60 minutes. Similar results have recently been reported in healthy conscious dogs, after intravenous administration of 0·1 mg kg^{-1} molsidomine[22]. In the large coronary arteries a significant increase in diameter of up to 9·6% was still observed 60 minutes after administration. This dilatory response, according to Bassenge and Pohl[22], appeared to be exclusively due to a direct relaxing effect of molsidomine on the arterial smooth muscle. Since coronary blood flow did not increase in these dogs, the authors ruled out the possible additional effect of an endothelium-mediated dilatory component, which has been observed with other vasodilatory antianginal drugs[23]. In 9 dogs Holtz *et al.*[23] evaluated the dilatory response of large coronary arteries to various anti-anginal drugs, concluding that drugs causing coronary dilation can be classified according to their mode of action into three groups: (1) a flow-dependent, endothelium-mediated, indirect effect on the arterial vasculature (f.e. adenosine and dipyridamole); (2) a direct effect on the arterial smooth muscle (such as for nitroglycerin, molsidomine and isosorbide dinitrate); and (3) a variable combination of these two effects (f.e. nifedipine, diltiazem and verapamil)[23]. As far as the aforementioned indirect effect is concerned, it has been inferred that the increase in coronary flow is the direct stimulus for and the cause of the dilation. To explain this effect Holtz and co-workers have proposed the following mechanism: Increases in flow through an artery induce elevations in shear stress upon the luminal surface of the endothelium, and this is the trigger causing the release of an unidentified dilating factor which then acts on the adjacent smooth muscle cells of the arterial wall. Thus, this phenomenon observed *in vivo* has been called a 'flow-dependent, endothelium-mediated dilation'[23].

As mentioned above, Sin 1 and nitrates seem to act directly on vascular smooth muscle; nitric oxide is considered to be the common active intermediate of these drugs[3]. Their vascular smooth muscle relaxing effects are probably mediated by increased cyclic GMP levels, brought about by an effect on intracellular guanylate cyclase[24]. However, Sin 1 can stimulate the activity of this enzyme without a previous reaction with a thiol[25], whereas nitrates are dependent on the prior activation of thiols[26,27]. With time, there is a consumption of these thiols, which can lead to tolerance to the action of the nitrates. The relatively long duration of action of Sin 1 may be explained by this lack of reliance on such intermediary compounds. In fact, prolonged treatment with molsidomine has thus far been reported not to cause major tolerance[28–30]. Ostrowski *et al.* have recently reported on the mean half life of molsidomine, the results being consistent with its duration of action[31]. Clinical studies assessing the anti-anginal effect of oral molsidomine, have established a duration of clinical action of at least 6 hours. It is unclear whether this long acting anti-anginal effect of molsidomine is related more to its peripheral vasodilatory effect than to direct coronary vasodilation. Although dilation of epicardial coronary arteries has been recorded after 2 mg of intravenous molsidomine[32], studies are awaited to demonstrate a similar effect after oral usage. If indeed a long duration of coronary vasodilatory action follows after oral molsidomine, similar to its effects on the peripheral circulation, the drug may prove to be particularly useful in the treatment of coronary vaso-spastic disorders[33], especially in those circumstances where intermittent thrombotic obstruction, or even occlusion, leads to repeated release of vasoconstrictive substances.

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