Coronary Vasodilatory Action After a Single Dose of Nicorandil

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Coronary hemodynamics and vasodilatory effects on major epicardial arteries were investigated after a single dose of nicorandil in 22 patients undergoing cardiac catheterization for suspected coronary artery disease. Nicorandil, 20 mg, was administered sublingually to 11 consecutive patients and 40 mg to 11 others. Systemic blood pressure decreased significantly without affecting the heart rate. Coronary sinus blood flow did not change significantly. As the mean aortic pressure decreased significantly by 13% after 20 mg and 21% after 40 mg of nicorandil, the calculated coronary vascular resistance decreased but did not reach statistical significance. There was a decrease in myocardial oxygen consumption (−14% and −22%, respectively), and this was consistent with a significant decrease in the calculated pressure-rate product of 19% and 24%, respectively. A total of 103 selected coronary segments, including 17 stenotic segments, were analyzed quantitatively using a computer-assisted coronary angiography analysis system. After 20 or 40 mg of nicorandil, a significant increase of the mean diameter was observed in the proximal (+9% and +7%), midportion (+10% and +11%) and distal (+15% and +13%) parts of the left anterior descending coronary artery. Corresponding values for the proximal (+13% and +10%) and distal (+10% and +15%) segments of the circumflex artery were observed. An increase in the obstruction diameter was also observed in all but 3 of the analyzed stenotic segments. The results demonstrate that nicorandil, in the route and doses used, causes a significant vasodilatation in the major epicardial coronary segments, including most stenotic segments, and decreases the myocardial oxygen demand with little effect on the resistance vessels.

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Nicorandil (N-(2-hydroxyethyl) nicotinamide nitrate (ester)) is a potent coronary vasodilator and when administered orally, is rapidly absorbed from the mucosa of oral cavity and gastrointestinal tract.[1,2] The pharmacologic profile is partly similar to that of nitroglycerin.[3] Both induced similar dose-related changes in the hemodynamics and coronary circulation,[4] but unlike nitroglycerin, nicorandil developed only slight tolerance in vivo, and no tolerance in vitro.[5] Previous experimental and clinical data have shown that nicorandil, in dose-dependent increments, decreased peripheral resistance, decreased end-diastolic and end-systolic volumes and increased the coronary blood flow with little effects on myocardial oxygen consumption and atrioventricular conduction.[1,3,4,6–12] The effects of nicorandil indicate a preload reduction equal to nitroglycerin and an afterload reduction approaching that of dihydralazine.[13] In the nonischemic heart, nicorandil dose-dependently increases transmural left ventricular blood flow with the greatest increases occurring in the sub- and midepicardium.[7–9,14,15] It appears to act primarily by dilatation of the large coronary arteries with little effect on the myocardium.[3,9,11,16]

We investigated the coronary hemodynamic effects and assessed, quantitatively, the vasodilatory effect on the epicardial vessels after a single dose of nicorandil. A computer-assisted coronary angiography analysis system was used to quantify changes in the coronary diameters.

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Methods

Patients: The study population consisted of 22 patients (19 men and 3 women), undergoing cardiac catheterization for the investigation of suspected coronary artery disease. The mean age was 54 years (range 39 to 68). All were in sinus rhythm, none had signs of cardiac failure and all gave informed consent to participate in the study. The effects of 2 different dosages of nicorandil were investigated; nicorandil 20 mg (group 1) was given sublingually to 11 consecutive patients and 40 mg (group 2) to 11 others. Clinical and angiographic data are summarized in Table I. The groups were comparable with respect to age, degree of coronary artery disease, resting ejection fraction and coronary sinus blood flow (unpaired Student *t* test).

Protocol: All medications were discontinued at least 24 hours before the study. Cardiac catheterization was performed with patients in the fasting state without premedication. After a Webster thermodilution flow catheter was inserted into the coronary sinus, angiography of the right and left coronary artery was performed in standard views, including cranial and caudal angulations. The geometry of the x-ray gantry, and the kilovolts and milliamperes of the x-ray generator were acquired and recorded on-line for each angiogram. Heart rate, aortic pressures, thermodilution coronary sinus blood flow and oxygen saturation obtained simultaneously from the aorta and coronary sinus were measured in the resting state 15 minutes after coronary angiography. Nicorandil, 20 or 40 mg, was then administered sublingually and all measurements were repeated at 5, 10, 20 and 30 minutes. Left coronary angiography was repeated 30 minutes after the drug administration in all projections, corresponding to those used during control angiograms, in order to study the effect on the dimensions of the epicardial coronary arteries. All angiograms were obtained using the Judkins technique and recorded on Kodak 35-mm cinefilm at a rate of 25 frames/s. A nonionic contrast medium (iopamidol) was injected manually.

Coronary sinus blood flow measurements and calculations: The on-line computer system assessed the coronary sinus blood flow using a constant infusion thermodilution technique. Arterial and coronary sinus blood oxygen saturation were measured spectrophotometrically (Lex-O_2-CON, Lexington Instruments Corp.) and oxygen content calculated. Myocardial oxygen consumption was calculated as a product of coronary sinus blood flow and arterial-coronary sinus oxygen content difference. Coronary vascular resistance was derived from the ratio of the mean aortic pressure to coronary sinus blood flow.

Quantitative coronary angiography: The quantitative analysis of selected coronary segments was carried out with the computer-assisted Coronary Angiography Analysis System (CAAS), which has been described in detail previously.[17,18] To analyze 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 vessels 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 intensifier. 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 Figure 1. For nonobstructed coronary segments, the mean arterial diameter of the analyzed segment was computed. For obstructed segments, the minimal obstruction diameter was assessed. A total of 103 coronary segments, including 17 stenotic segments, were selected from the study group angiograms for analysis. The fact that a limited number of stenotic lesions were analyzed in this study is due to: (1) selection was based on the technical quality of the angiograms, with clear views of the pre- and poststenotic segments; (2) orthogonal projections of the stenotic lesions were required; and (3) only repeat angiography of the left coronary artery was performed. To ensure exact reproducibility of the sequential angiographic studies, the following measures were taken. First, as mentioned, the x-ray system was repositioned in the settings corresponding to the projections used during

TABLE I Baseline Data of Patients Receiving 20 mg of Nicorandil (Patients 1 to 11) and 40 mg (Patients 12 to 22)

Pt	Age (yr), Sex	NYHA	PMI	Coronary Artery Disease				EF (%)
				LM	LAD	LC	Right	
1	45, M	II	–	–	–	–	–	66
2	47, M	III	–	–	+	–	+	77
3	68, M	II	–	–	–	–	–	69
4	54, F	II	–	–	+	–	+	79
5	57, M	II	–	–	+	–	–	64
6	57, M	II	–	–	–	+	–	65
7	47, M	II	+	–	+	–	+	63
8	44, M	II	–	–	–	–	+	61
9	49, M	II	+	–	+	–	+	63
10	68, M	II	–	–	+	+	+	67
11	68, M	III	+	+	+	+	+	58
12	60, M	II	–	–	–	+	–	
13	58, M	II	–	–	–	–	–	70
14	54, M	II	–	–	+	+	–	66
15	51, M	III	–	–	+	+	+	64
16	39, M	II	–	–	+	–	–	65
17	49, F	II	+	–	+	+	+	60
18	67, F	II	–	–	–	+	+	63
19	60, M	II	–	–	+	+	+	72
20	54, M	II	–	–	+	–	–	66
21	48, M	II	+	–	–	+	–	
22	48, M	II	–	–	+	+	–	75

EF = global ejection fraction; LAD = left anterior descending coronary artery; LC = left circumflexus; LM = left main coronary artery; NYHA = New York Heart Association functional class; PMI = previous myocardial infarction.

TABLE II Coronary Hemodynamics After 20 mg of Nicorandil (n = 11)

	Control	5 minutes	10 minutes	20 minutes	30 minutes
CSBF (ml/min)	115 ± 12	122 ± 12	123 ± 14	113 ± 12	109 ± 12
CVR (mm Hg/ml/min)	1.0 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
AO O_2 content (ml %)	18.6 ± 0.4	18.6 ± 0.4	18.5 ± 0.4	18.5 ± 0.4	18.5 ± 0.4
CS O_2 content (ml %)	9.6 ± 0.3	9.7 ± 0.3	10.2 ± 0.4*	10.3 ± 0.4†	10.2 ± 0.4*
(AO-CS) O_2 diff (ml %)	9.0 ± 0.4	8.9 ± 0.4	8.4 ± 0.5*	8.2 ± 0.4†	8.3 ± 0.5†
MVO_2 (ml/min)	10.2 ± 0.9	10.5 ± 0.9	9.8 ± 0.7	9.0 ± 0.8	8.8 ± 0.9
Pressure-rate product (mm Hg × beats/min)	9,976 ± 705	9,937 ± 835	9,281 ± 592*	8,901 ± 653†	8,097 ± 622‡

AO = aorta; CSBF = coronary sinus blood flow; CVR = coronary vascular resistance; O_2 = oxygen; diff = difference; MVO_2 = myocardial oxygen consumption.

Values are expressed as mean ± standard error of the mean. Only p values <0.05 (vs control) are reported: * p <0.05; † p <0.01; ‡ p <0.0005.

the baseline angiography. Second, all study cineframes to be analyzed were selected at end-diastole, to minimize any possible foreshortening effect. Third, the user-determined beginning and endpoints of the major coronary segments between side branches were standardized according to the definitions of the American Heart Association.[19] Finally, 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 2 consecutive angiograms.

Statistical analysis: Results are expressed as the mean ± standard error of the mean. Analysis of variance for repeated measurements was used and when overall significance was observed, multiple comparisons were statistically assessed with Student *t* test. A p value of <0.05 was considered significant.

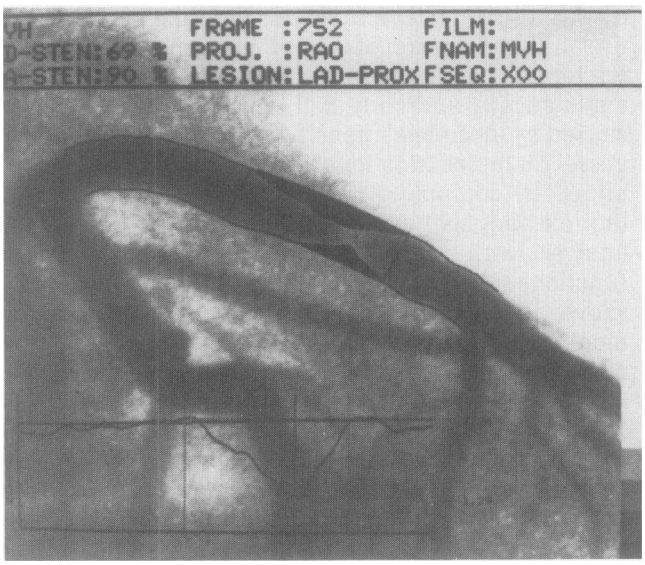

FIGURE 1. Computer output of an analyzed coronary segment. The diameter function is superimposed on the video image; the calibrated diameter values in mm are plotted along the ordinate, and the centerline positions from the proximal to the distal part along the abscissa. The reference position was defined proximal of the stenotic 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 side.

Results

The systemic responses after 20 mg (group 1) and 40 mg (group 2) of nicorandil are summarized in Figure 2. During spontaneous heart rate, nicorandil produced a significant decrease in aortic pressures, while heart rate remained unchanged. After 30 minutes, the mean changes were 25 mm Hg in group 1 (−17%, p <0.005) and 42 mm Hg (−28%, p <0.00005) in group 2 for the systolic aortic pressure, 7 mm Hg (−9%, p <0.005) and 12 mm Hg (−15%, p <0.005) for the diastolic aortic pressure and 14 mm Hg (−13%, p <0.005) and 23 mm Hg (−21%, p <0.0005) for the mean aortic pressure, respectively.

Coronary hemodynamics: Coronary sinus blood flow did not change significantly in both groups. As the mean aortic pressure decreased significantly by 13%

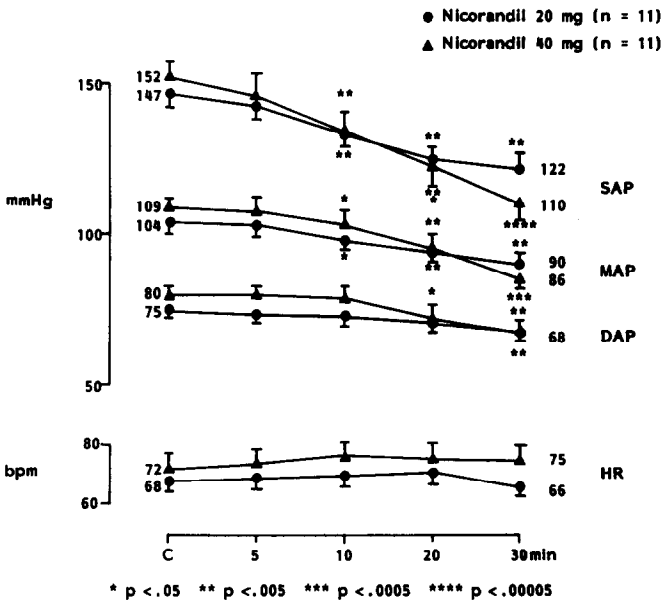

FIGURE 2. Systemic responses after administration of nicorandil. C = control state; DAP = diastolic aortic pressure; HR = heart rate; MAP = mean aortic pressure; SAP = systolic aortic pressure.

TABLE III Coronary Hemodynamics After 40 mg of Nicorandil (n = 11)

	Control	5 minutes	10 minutes	20 minutes	30 minutes
CSBF (ml/min)	93 ± 12	94 ± 11	109 ± 13	112 ± 17	92 ± 14
CVR (mmHg/ml/min)	1.3 ± 0.2	1.3 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2
AO O_2 content (ml %)	18.8 ± 0.5	18.8 ± 0.5	18.8 ± 0.5	18.8 ± 0.5	18.8 ± 0.5
CS O_2 content (ml %)	9.5 ± 0.5	10.2 ± 0.4	10.6 ± 0.6*	11.1 ± 0.5†	11.1 ± 0.5†
(AO-CS) O_2 diff (ml %)	9.1 ± 0.4	8.8 ± 0.4	8.1 ± 0.3*	7.6 ± 0.3‡	7.6 ± 0.3†
MVO_2 (ml/min)	9.0 ± 1.1	8.2 ± 1.0	8.7 ± 1.1	8.5 ± 1.3	7.0 ± 1.1*
Pressure-rate product (mm Hg × beats/min)	10,866 ± 741	10,824 ± 907	10,395 ± 952	9,444 ± 908*	8,290 ± 784†

* $p < 0.05$; † $p < 0.002$; ‡ $p < 0.0005$.
Abbreviations as in Table II.

after 20 mg and 21% after 40 mg nicorandil, the calculated coronary vascular resistance decreased but did not reach statistical significance. The mean arteriocoronary sinus oxygen content difference decreased significantly in both groups by 8% ($p < 0.01$) and by 16% ($p < 0.002$), respectively. This significant decrease in arteriocoronary sinus oxygen difference, not associated with an increase in coronary sinus blood flow, resulted in a decrease in myocardial oxygen consumption by 14% in group 1 and 22% in group 2 (Table II and III). The decrease in the myocardial oxygen consumption is consistent with a significant decrease in the calculated pressure-rate product of 19% ($p < 0.0005$) and 24% ($p < 0.002$), respectively.

Quantitative coronary angiograms: A total of 103 coronary segments, including 17 stenotic segments, of the left coronary artery were analyzed. The mean absolute diameters (in mm) of the coronary segments, as measured during the 2 consecutive angiographies, are presented in Table IV and Figure 3. Thirty minutes after 20 mg of nicorandil, an increase of the mean diameter was observed in the proximal (+9%, $p < 0.003$), midportion (+10%, $p < 0.08$) and distal (+15%, $p < 0.0006$) parts of the left anterior descending coronary artery. Corresponding values for the proximal and distal segments of the circumflex artery were 13% and 10% ($p < 0.003$ for each). These significant changes in the mean coronary diameter were also observed to a similar extent after 40 mg of nicorandil. Among the 103 coronary segments analyzed, 17 stenotic segments were measured (Table V). After nicorandil, an increase in the obstruction diameter was observed in all but 3 of the stenotic lesions (Figure 3).

Discussion

The general profile of response of nicorandil, a nicotinamide nitrate (ester), is partly similar to that of the related substance, nitroglycerin. Both belong to a group of nitroesters, suggesting similar effects on the systemic and coronary hemodynamics. However, the differences between both drugs have been investigated.[4,15,20] Nicorandil, unlike conventional nitrates, is probably slowly metabolized by the liver during passage through the portal system, and therefore easily enters the general circulation, resulting in greater bioavailability after oral dosing.[2] Kinoshita et al[21] indicated that nicorandil exerts beneficial effects on exercise capacity in patients with chronic stable angina pectoris 30 minutes after oral administration. Preliminary study has shown that plasma levels reach the highest value at that time.[22]

Chronotropic effect: In the route and doses used in the present study, the heart rate did not change significantly despite decreased aortic pressure. This finding is consistent with a number of animal[1,3,11,12,23,24] and clinical[25,26] studies. However, in a systemic and coronary hemodynamic experimental study, Mizukami et al[4] demonstrated a dose-related increase of heart rate due to a baroreflex tachycardia after an abrupt decrease in arterial pressure after administration of nicorandil. These findings were essentially consistent with the results observed in a clinical study.[6] In this study, all cardiac medications, including β-blockade agents, were discontinued 24 hours before catheterization. It could be speculated that some of the longer lasting effects of β-blockers may have partly contributed to

TABLE IV Effect of Nicorandil on the Absolute Coronary Artery Diameter (mm) of All Analyzed Segments

	Nicorandil 20 mg					Nicorandil 40 mg				
	n	Before	After	Δ	p Value	n	Before	After	Δ	p Value
LAD-proximal	11	2.42 ± 0.19	2.64 ± 0.21	+9%	0.003	11	2.53 ± 0.18	2.71 ± 0.20	+7%	0.002
LAD-mid	6	2.29 ± 0.21	2.51 ± 0.26	+10%	0.08	9	1.94 ± 0.12	2.16 ± 0.11	+11%	0.001
LAD-distal	11	1.84 ± 0.10	2.11 ± 0.12	+15%	0.0006	11	1.64 ± 0.08	1.85 ± 0.07	+13%	0.0002
LC-proximal	11	2.44 ± 0.16	2.75 ± 0.15	+13%	0.002	11	2.58 ± 0.18	2.85 ± 0.18	+10%	0.00005
LC-distal	11	2.09 ± 0.12	2.29 ± 0.15	+10%	0.003	11	1.97 ± 0.17	2.27 ± 0.19	+15%	0.00008

Values are expressed as mean ± standard error of the mean.
LAD = left anterior descending coronary artery; LC = left circumflex.

TABLE V Effects of Nicorandil on the Stenotic Segments

	Nicorandil 20 mg (n = 7)			Nicorandil 40 mg (n = 10)		
	Before	After	Δ	Before	After	Δ
Extent obstruction (mm)	6.46 ± 1.25	6.92 ± 1.35	+7%	5.03 ± 0.45	4.73 ± 0.41	−6%
Obstruction diameter (mm)	1.43 ± 0.10	1.58 ± 0.13	+10%	1.29 ± 0.14	1.44 ± 0.16	+12%*
Obstruction area (mm^2)	1.86 ± 0.45	2.20 ± 0.60	+18%	1.34 ± 0.27	1.78 ± 0.39	+33%*
Diameter stenosis (%)	43.1 ± 2.8	41.7 ± 3.1	−3%	48.9 ± 3.1	41.7 ± 4.5	−15%*
Area stenosis (%)	70.3 ± 4.6	62.4 ± 7.3	−11%	73.4 ± 4.0	67.7 ± 5.0	−8%
Symmetry index	0.47 ± 0.10	0.49 ± 0.12	+4%	0.58 ± 0.10	0.58 ± 0.10	0
Reference diameter (mm)	2.50 ± 0.18	2.83 ± 0.16	+13%†	2.22 ± 0.11	2.39 ± 0.12	+8%*
Reference area (mm^2)	5.09 ± 0.75	6.45 ± 0.75	+27%†	3.95 ± 0.39	4.57 ± 0.43	+16%*

Values are expressed as mean ± standard error of the mean.
Only p values of <0.05 are reported: * p <0.03; † p <0.005.

the effect on heart rate and to the observed increases in coronary artery dimensions. β-blockers used alone produce a reduction in myocardial oxygen consumption, increase coronary vascular resistance and reduce coronary sinus blood flow,[27,28] which may have increased the sensitivity to the vasodilator effects of nicorandil. However, the resting heart rates of our study population suggest minimal β-blockade effect at the initiation of the study. Thus, we conclude that the observed increases in coronary dimensions are indeed the result of the administration of nicorandil.

Effect on coronary hemodynamics: Verdouw et al[14] reported that after nicorandil, although left ventricular transmural blood flow was not affected, its distribution over the myocardium changed in favor of the subepicardial layers. Flow to the subendocardium decreased by 30%, whereas that to the subepicardium increased by 65%, which is in agreement with the observation of Preuss et al.[15] As a result the endocardial-epicardial blood flow ratio decreases. However, if the decrease in aortic pressure after nicorandil is prevented by use of a cuff around the descending thoracic aorta, collateral blood flow to the subendocardial layers of an ischemic area increases to a similar extent as that to the subepicardial layers.[9,10] Using the intracoronary route of administration, in order to minimize systemic responses, nicorandil selectively increased epicardial blood flow suggesting a preferential susceptibility of the epicardium to the vasodilator action of nicorandil.[14]

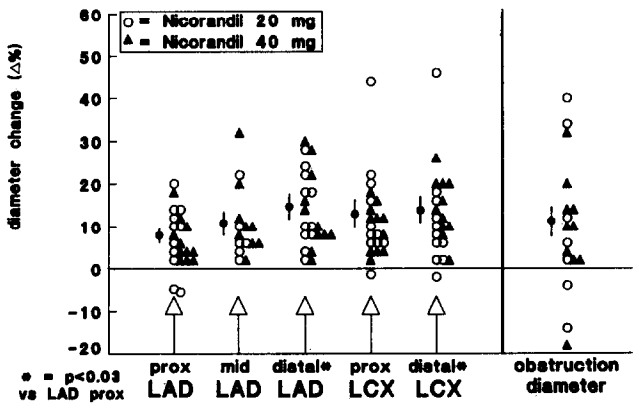

FIGURE 3. ***Left,*** **percentual changes (Δ%) in coronary artery diameter in the proximal (prox), midportion (mid) and distal parts of the left anterior descending (LAD), and proximal and distal parts of circumflex (LCX) coronary artery. The increase in the coronary artery diameter was more pronounced in the distal segments when compared to the proximal segments (*p <0.03 vs LAD prox).** ***Right,*** **percentual changes (Δ%) in the obstruction diameter.**

The coronary sinus blood flow, as measured by thermodilution in this study, is a mixture of flow coming from the region supplied by normal and stenotic coronary artery, and the results should be interpreted with this in mind. In the doses used in this study, coronary sinus blood flow remained unchanged, despite the nicorandil-induced hypotension. Therefore, coronary vasodilation must have taken place, although the decrease in coronary vascular resistance did not reach statistical significance. There was a slight decrease in myocardial oxygen consumption (−14% and −22%, respectively) reflected by a significant decrease in arteriocoronary sinus oxygen difference (−8% and −16%, respectively, p <0.01), as coronary sinus oxygen content increased significantly. This was consistent with a significant decrease in the calculated pressure-rate product. The finding is in agreement with an animal experimental study.[14]

Quantitative coronary angiography: When performing pharmacologic interventions during coronary angiography, 2 different approaches may be used: either repeated angiography in the same single view without altering the x-ray setting or use of multiple angiographic views. In the first case, if the coronary segment is nonaxisymmetric, induced vasodilation may accentuate the asymmetry of the lumen by preferentially relaxing the nonatherosclerotic part of the arterial wall. Consequently, the use of a single angiographic view will be misleading. It therefore follows that the effects of a vasodilatory agent will be better quantified if multiple projections are obtained. This will increase the accuracy of diameter measurements and will better reflect the true luminal cross-sectional area.

Our results demonstrate that nicorandil causes a significant vasodilatation in the normal coronary segments, as well as in the majority of the stenotic segments. In fact, the percentage of increase in the diame-

ter of the nonobstructed segments was more pronounced in the distal segments when compared with the proximal segments as shown in Figure 3. This more pronounced distal vasodilation was also observed with other vasodilatory agents.[29]

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