JACC Vol. 13, No. 2
February 1989:428–33

Effect of Cutaneous Nitroglycerin Patches on Coronary Artery Diameter: Issues Concerning Development of Tolerance

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The coronary dilative and systemic responses to graded doses of intracoronary nitroglycerin were studied in 53 patients undergoing diagnostic coronary arteriography, 43 of whom had received a cutaneous nitroglycerin patch. During coronary arteriography, graded doses of 50, 100 and 200 μg of intracoronary nitroglycerin were given 5 min apart. An arteriogram and hemodynamic measurements were obtained after each dose. In the control group (n = 10) cumulative intracoronary nitroglycerin doses of 50, 150 and 350 μg caused an increase in coronary diameter in the left anterior descending artery of 20 ± 4%, 21 ± 3% and 22 ± 7%, respectively, and in the circumflex artery of 18 ± 6%, 23 ± 8% and 18 ± 5% ($p < 0.01$ versus values in untreated group).

In Group 1 (15 patients given a 5 mg/24 h nitroglycerin patch 2 to 12 h before coronary arteriography), the same intracoronary nitroglycerin doses increased the left anterior descending artery diameter by 6 ± 2%, 7 ± 2% and 7 ± 2%, respectively, and the circumflex artery diameter by 3 ± 2%, 3 ± 2% and 1 ± 3%. All values were statistically different from control ($p < 0.05$). An even more pronounced blunting ($p < 0.01$) of the coronary dilative response was observed in Group 2 (14 patients given a 15 mg/24 h nitroglycerin patch 2 to 12 h before arteriography). The diameter responses to intracoronary nitroglycerin observed in Group 3 (seven patients given a 5 mg/24 h nitroglycerin patch 24 h before arteriography) and Group 4 (seven patients given a 15 mg/24 h nitroglycerin patch 24 h before arteriography) were not significantly different from those of the control group.

The results demonstrate that a nitroglycerin patch administered a few hours before coronary arteriography caused significant coronary artery dilation and that the incremental dilation due to the intracoronary nitroglycerin was small. On the other hand, 24 h after arteriography, the coronary dilative effect of the patch was attenuated (suggesting development of tolerance) and the increment in diameter induced by intracoronary nitroglycerin was much larger.

(J Am Coll Cardiol 1989;13:428–33)

The use of nitroglycerin patches has aroused both interest and controversy. The introduction of transdermal patches with release of nitroglycerin at a constant rate for ≥24 h was greeted with enthusiasm, but investigators have since questioned their efficacy. The possibility of early nitrate tolerance or "attenuation" of their effects has been raised and therefore the clinical usefulness of these patches has come under question (1–6).

Measurements of coronary artery diameter are useful for quantitating coronary responses to interventions (7). Investigations (8,9) have shown a dose-response relation between coronary artery dilation and the dose of nitroglycerin administered. In this investigation we studied the degree of coronary artery dilation resulting from increasing doses of intracoronary nitroglycerin in patients who had received a nitroglycerin patch (Nitro-Dur, Key Pharmaceutical) 2 to 24 h before coronary arteriography.

Methods

Patient selection. Fifty-three patients undergoing cardiac catheterization for evaluation of chest pain were studied after giving informed consent. Patients with acute myocardial infarction, unstable angina or symptoms suggesting variant angina were excluded.

Cardiac catheterization. Left heart catheterization and coronary arteriography were performed with the Judkins technique. All coronary vasodilators were withheld 48 h before catheterization. The patients were in a postabsorptive

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Manuscript received March 28, 1988; revised manuscript received August 8, 1988, accepted September 5, 1988.

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0735-1097/89/$3.50

Table 1. Patient Characteristics

	No.	M/F	Age (yr) (mean ± SD; range)	Coronary Artery Disease (>50% diameter stenosis)			
				Normal	1 V	2 V	3 V
Control group	10	7/3	51.1 ± 7.9; 35 to 60	4	1	3	2
Group 1	15	9/6	55.1 ± 10.3; 38 to 70	4	4	5	2
Group 2	14	9/5	58.6 ± 11.3; 38 to 74	4	3	2	5
Group 3	7	3/4	53.6 ± 8.7; 39 to 65	1	2	4	—
Group 4	7	6/1	62.4 ± 11.7; 42 to 75	2	2	2	1

F = female; M = male; V = vessel.

state with mild sedation (diazepam, 10 mg intermuscularly) when catheterized. Ten patients who did not receive a nitroglycerin patch served as the control group. Fifteen patients received a 5 mg/24 h nitroglycerin patch (Group 1) and 14 patients a 15 mg/24 h patch (Group 2) 2 to 12 h before coronary arteriography (median for Group 1, 6 h and for Group 2, 7 h). In addition, seven patients received a 5 mg/24 h nitroglycerin patch (Group 3) and seven patients a 15 mg/24 h (Group 4) 24 h before the procedure.

Multiple views of the left coronary artery were obtained with use of an appropriate left Judkins catheter. The right anterior oblique view (10 to 30°) was chosen to optimize visualization of both left anterior descending and circumflex systems. Renografin-76, 6 to 8 ml per angiogram injected manually, was used as contrast medium. The filming rate was 30 frames/s with 12.5 cm image intensification and 1.2 mm focal spot. After the control angiogram and hemodynamic measurements (systolic, diastolic and mean aortic pressures and heart rate) were obtained, graded doses of 50 μg, 100 μg (cumulative dose 150 μg) and 200 μg (total cumulative dose 350 μg) of intracoronary nitroglycerin were given 5 min apart. An arteriogram and hemodynamic measurements were obtained 3 min after each dose. The patient's position was maintained constant throughout the study. In addition, the relation between the focal spot, patient and height of the image tube was kept constant. At each dose, cineangiographic frames obtained at end of diastole were analyzed. Midcoronary segments free of disease were selected for the measurement. To ensure that the same segments were examined with each dose, coronary branch points were used as reference points. To assess the effect of contrast material on coronary artery diameter, five additional patients had four successive coronary arteriograms with the omission of nitroglycerin. Measurements of coronary diameters in these angiograms showed either minimal (<5%) or no detectable changes.

Measurements of coronary artery diameter. The selected angiographic frames were enlarged to 203 × 254 mm hard copies and coded for analysis in a blinded fashion. Measurements of the coronary artery diameter were made by a single observer using an electronic caliper (DEC, Prodical 1101, Accurex). The precision and accuracy of this measuring technique for stenosis assessment has been well described (10). The intra- and interobserver variability of the techniques in measuring the diameter of normal coronary segments was tested in seven patients by four observers unaware of other patient data. The intraobserver variability was tested by repeated (10) diameter measurements of a normal coronary segment. The coefficient of variation for intra- and interobserver variability ranged from 1.4 to 4.3%. In addition, to assure an unbiased measurement of arterial diameter, observers had no knowledge of the sequence, control or treatment group or nitroglycerin dose. Actual coronary artery diameter (in millimeters) was calculated by reference to the catheter tip (1.81 mm). Percent increases in diameter from baseline were calculated for each subject and averaged to provide the mean increase in arterial diameter.

Statistical analysis. Changes in coronary artery diameter, mean arterial pressure and heart rate were grouped for each patient according to intracoronary nitroglycerin dose. Mean values and SEM were calculated. Data were analyzed by analysis of variance (repeated measures design) with use of the SAS general linear models procedure (SAS Statistics Guide for Personal Computers, SAS Institute). Arterial diameters in each group at baseline were compared by one-way analysis of variance. Duncan's multiple range test was used to identify significant differences between levels of the independent variable.

Results

Patient data (Table 1). The study group consisted of 53 patients. Fifteen patients had normal coronary arteries and 38 patients had coronary artery disease as defined by ≥50% stenosis in one or more vessels. Only angiographically

Table 2. Effect of 50, 100 and 200 μg Intracoronary Nitroglycerin on Diameter (mm) of Midsegments of Left Anterior Descending and Circumflex Arteries (mean ± SD)

Groups	Left Anterior Descending Artery				Left Circumflex Artery			
	Baseline	50 μg	100 μg	200 μg	Baseline	50 μg	100 μg	200 μg
No patch: control (n = 10)	2.08 ± 0.51	* 2.46 ± 0.42	* 2.49 ± 0.54	* 2.56 ± 0.72	2.11 ± 0.53	* 2.45 ± 0.53	* 2.53 ± 0.52	* 2.51 ± 0.55
5 mg/24 h patch 2 to 12 h before art.: Group 1 (n = 15)	2.26 ± 0.45	† 2.37 ± 0.43	† 2.40 ± 0.44	† 2.39 ± 0.45	2.70 ± 0.61	NS 2.80 ± 0.68	NS 2.78 ± 0.68	NS 2.76 ± 0.62
15 mg/24 h patch 2 to 12 h before art.: Group 2 (n = 14)	‡ 2.69 ± 0.38	NS 2.65 ± 0.34	NS 2.78 ± 0.33	NS 2.69 ± 0.31	‡ 3.05 ± 0.64	NS 3.24 ± 0.37	NS 3.05 ± 0.51	NS 3.14 ± 0.51
5 mg/24 h patch 24 h before art.: Group 3 (n = 7)	2.02 ± 0.58	* 2.29 ± 0.56	* 2.39 ± 0.55	* 2.45 ± 0.48	2.44 ± 0.87	† 2.72 ± 0.82	† 2.79 ± 0.75	† 2.78 ± 0.74
15 mg/24 h patch 24 h before art.: Group 4 (n = 7)	2.42 ± 0.42	* 2.66 ± 0.32	* 2.73 ± 0.34	* 2.75 ± 0.40	2.69 ± 0.32	† 2.93 ± 0.55	† 2.99 ± 0.44	† 3.00 ± 0.63

* = $p < 0.01$ from baseline; † = $p < 0.05$ from baseline; art. = coronary arteriography; ‡ = different ($p < 0.05$) from baseline diameter in corresponding control group; NS = no significant difference from baseline.

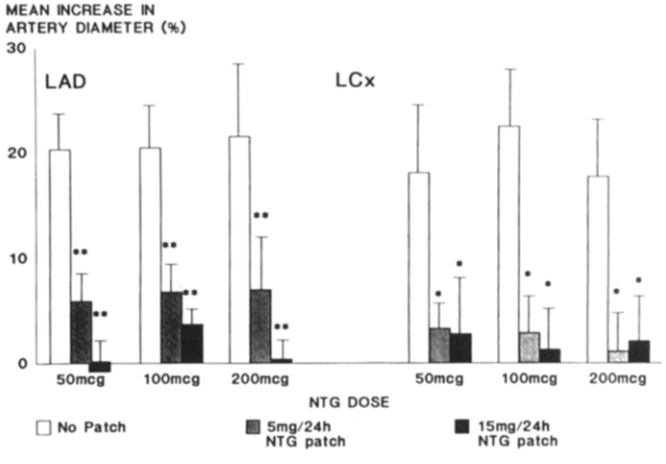
normal segments of vessels were examined. Patient characteristics in each group are described in Table 1.

Effect of intracoronary nitroglycerin in diameter of midsegments of left anterior descending and circumflex arteries (Table 2). In the control group, increasing doses of intracoronary nitroglycerin (50, 100 and 200 μg) evoked an important increase in diameter in both left anterior descending and circumflex coronary arteries. This type of response was not observed in Groups 1 and 2, except for left anterior descending artery segments in Group 1. It should be noted that the percent changes of these segments (left anterior descending artery, Group 1) were significantly smaller from those in the control group (Fig. 1). A significant increase in coronary artery segment diameter was again observed in Groups 3 and 4. Baseline diameters for the left anterior descending and circumflex arteries in the treatment groups were not statistically different from those in the control group except in Group 2.

Dilation of coronary artery midsegments after cumulative doses of intracoronary nitroglycerin. *Control group.* Diameter responses of the left anterior descending and circumflex arteries to intracoronary nitroglycerin are shown in Figure 1. At a dose of 50 μg, left anterior descending artery diameter increased by 20 ± 4% and circumflex coronary artery diameter increased by 18 ± 6%. At a dose of 100 μg (150 μg cumulative), left anterior descending artery diameter increased by 21 ± 3% and circumflex artery diameter by 23 ± 8%. At a dose of 200 μg (350 μg cumulative), left anterior descending artery diameter increased by 22 ± 7% and circumflex artery diameter by 18 ± 5%. All values were significantly different ($p < 0.01$ from the untreated values).

Coronary artery dilation in patients who received 5 mg/24 h patch (Group 1) and 15 mg/24 h patch (Group 2), 2 to 12 h before coronary arteriography (Fig. 1). Intracoronary nitroglycerin doses of 50, 100 and 200 μg in the left coronary artery in Group 1 patients, who had received a 5 mg/24 h nitroglycerin patch, caused an increase in diameter of the left anterior descending artery of 6 ± 2%, 7 ± 2% and 7 ± 2%, respectively, and in the circumflex artery of 3 ± 2%, 3 ± 2% and 1 ± 3%, respectively. For Group 2 patients, who had received a 15 mg/24 h nitroglycerin patch, the changes induced by the same intracoronary nitroglycerin doses in coronary diameter were −2 ± 3%, 4 ± 1% and 0 ± 2%, respectively, for the left anterior descending artery and 3 ±

Figure 1. Effect of graded doses of intracoronary nitroglycerin (NTG) (50, 100, 200 μg) on coronary artery dilation in patients who had received a nitroglycerin patch 2 to 12 h before coronary arteriography. * = $p < 0.05$; ** = $p < 0.01$ compared with values in control group (no patch); LAD = left anterior descending artery; LCx = left circumflex artery.



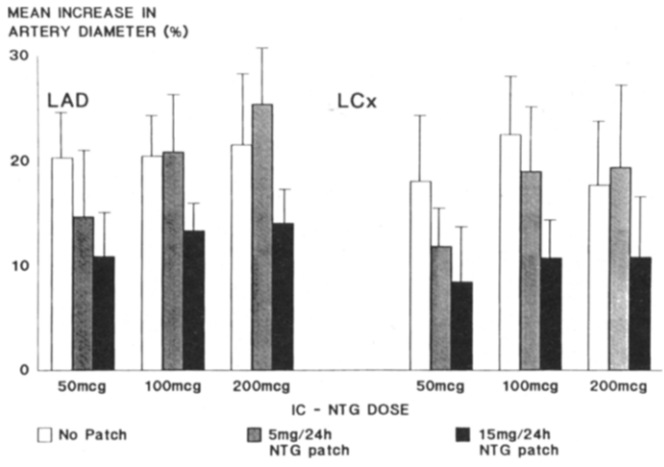


Figure 2. Effect of graded doses of intracoronary (50, 100, 200 μg) nitroglycerin (IC-NTG) on coronary artery diameter in patients who had received a nitroglycerin patch 24 h before coronary arteriography. The mean increase in arterial diameter was not statistically different from values in the control group (no patch). Abbreviations as in Figure 1.

5%, 1 ± 4% and 2 ± 4%, respectively, for the circumflex artery. The blunting of the coronary dilator response to intracoronary nitroglycerin was statistically significant for all doses in both arteries.

Coronary artery dilation in patients who received 5 mg/24 h (Group 3) and 15 mg/24 h (Group 4) 24 h before coronary arteriography (Fig. 2). The response to intracoronary nitroglycerin in Group 3 patients, who received a small dose patch (5 mg/24 h), was not significantly different from that of the control group; in the left anterior descending artery the dilation was 15 ± 7% for the 50 μg dose, 21 ± 7% for the 100 μg dose and 25 ± 7% for the 200 μg dose. The corresponding increases in the circumflex artery diameter were 12 ± 3%, 19 ± 7% and 20 ± 8%, respectively.

In the Group 4 patients, who received a large dose patch (15 mg/24 h), the dilative response to the same grade doses of intracoronary nitroglycerin (50, 100 to 200 μg) for the left anterior descending artery was 11 ± 4%, 13 ± 3% and 14.3%, respectively, and for the circumflex artery 8 ± 4%, 11 ± 3% and 11 ± 6%, respectively. Although a trend toward a "blunting" of the dilative response of the coronary arteries was observed, these responses in arterial diameter were not statistically different from those of the control group.

Effect of cumulative doses of intracoronary nitroglycerin on heart rate and aortic pressure (Table 3). In the control group, as well as in the study groups, there was a gradual decrease in mean arterial blood pressure. At the highest cumulative dose of 350 μg of intracoronary nitroglycerin, mean blood pressure decreased in the control group by 11 ± 5 mm Hg, in Group 1 by 12 ± 9 ± mm Hg, in Group 2 by 7 ± 5 mm Hg, in Group 3 by 15 ± 6 mm Hg, and in Group 4 by 8 ± 5 mm Hg. Differences between the control and study groups at each intracoronary nitroglycerin dose level were not statistically significant at the 0.05 level.

There was a small (−1 ± 6 beats) change in heart rate in the control group at the maximal cumulative nitroglycerin dose. Similarly, in different study groups, there were only small changes in heart rate (Group 1, 5 ± 8 beats; Group 2, 1 ± 4 beats; Group 3, 6 ± 8 beats; Group 4, 0 ± 7 beats. Differences in heart rate between the control and study groups at each intracoronary nitroglycerin dose level were not statistically significant.

Discussion

Tolerance to organic nitrates. There is still controversy about the occurrence and characteristics of tolerance to organic nitrates in patients with coronary artery disease (11–13). In patients with congestive heart failure, tolerance has been demonstrated several times by continued hemodynamic monitoring (14–16). In patients with angina, several investigators (1,4) have presented data consistent with tolerance to organic nitrates using treadmill exercise testing as an endpoint. However, the variability of the time on the treadmill decreases the reproducibility of the measurements.

Table 3. Changes in Heart Rate and Mean Blood Pressure From the Rest State With Graded Doses of 50, 100 and 200 μg Intracoronary Nitroglycerin (mean ± SD)

	Heart Rate			Mean Blood Pressure		
	50 μg	100 μg	200 μg	50 μg	100 μg	200 μg
Control group (no patch)	−1 ± 4	0 ± 6	−1 ± 6	−4 ± 5	−7 ± 5	−11 ± 5
5 mg/24 h patch 2 to 12 h before art. (Group 1)	1 ± 4	3 ± 5	5 ± 8	−5 ± 9	−8 ± 10	−12 ± 9
15 mg/24 h patch 2 to 12 h before art. (Group 2)	0 ± 4	0 ± 4	1 ± 4	−2 ± 3	−4 ± 5	−7 ± 5
5 mg/24 h patch 24 h before art. (Group 3)	3 ± 3	4 ± 6	6 ± 8	−3 ± 2	−9 ± 5	−15 ± 6
15 mg/24 h patch 24 h before art. (Group 4)	−2 ± 5	1 ± 5	0 ± 7	−6 ± 5	−6 ± 5	−8 ± 5

art. = coronary arteriography; NTG = nitroglycerin.

JACC Vol. 13, No. 2
February 1989:428–33

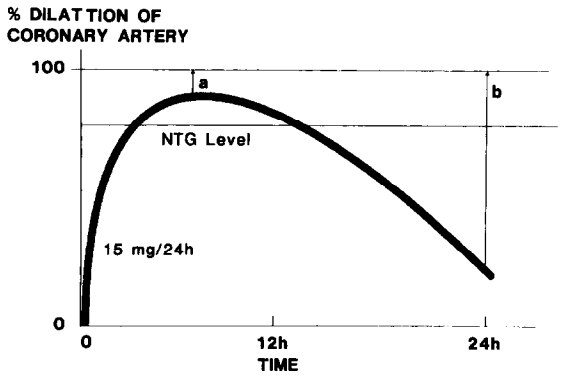


Figure 3. Hypothesis of development of tolerance to nitroglycerin as measured by coronary artery dilative response to intracoronary nitroglycerin (NTG). The **vertical axis** represents percent dilation of the epicardial coronary artery (increase in coronary artery diameter) induced by nitroglycerin. A constant nitroglycerin blood level caused by the patch is assumed ("nitroglycerin level"). The **horizontal axis** represents time (in hours). After application of the patch (zero time), the coronary arteries dilate. With the passage of time, nitroglycerin tolerance develops and this dilative effect decays **(thick line)** despite constant nitroglycerin blood levels. High dose intracoronary nitroglycerin brings the dilation to 100% of possible nitroglycerin-induced dilation **(top horizontal line)** causing a small additional dilation early after the application of the patch **(arrow a)** and greater dilation 24 h after the patch **(arrow b)**.

In addition, one study (14) suggested that tolerance to nitrates is more pronounced or occurs only in the arterial system rather than the venous system. Because the effects of nitrates in patients with coronary artery disease occur at several sites including the coronary arteries, we have investigated the occurrence of tolerance to organic nitrates by direct measurement of coronary artery diameter as visualized by coronary arteriography.

Intracoronary nitroglycerin to assess tolerance to transdermal nitroglycerin patches. Our method is based on measuring the dose-dependent dilation of epicardial branches of the coronary arteries after incremental doses of intracoronary nitroglycerin. Our conclusions are based on the assumption that the powerful dilative response evoked by intracoronary nitroglycerin is manifested even in the presence of tolerance. There is circumstantial evidence that this may be true, because in patients with angina pectoris sublingual nitroglycerin has been shown to overcome tolerance (17). We found that when a nitroglycerin patch was administered a few hours before the test it caused significant coronary artery dilation and that the incremental dilation due to the intracoronary nitroglycerin was small (Fig. 3). On the other hand, 24 h after administration of intracoronary nitroglycerin the coronary dilative effect of the patch was attenuated because tolerance and the increment in diameter induced by intracoronary nitroglycerin was much larger (implying that the effect of the transdermal patch was smaller). Feldman et al. (7) showed that percent dilation is less in large coronary arteries than in smaller vessels. One may argue that in our study the groups with less dilation were the ones with larger baseline diameter. However, within this diameter range the reported dilation is 15 to 20%. Moreover, an average percent dilation of 5 to 9% after intracoronary nitroglycerin has been reported only for coronary segments with an average diameter of ≥3.13 mm (8). In this study, in the group with the largest baseline diameter (Group 2, circumflex artery mean diameter 3.05 mm) the percent dilation was only 1 to 3%, a value much lower than would be expected. We believe that the larger arterial diameters observed in Groups 1 and 2 at baseline probably reflect a dilative effect by nitroglycerin patches administered a few hours before arteriography.

Our results may be explained by the following alternative theories: 1) The patches may not deliver constant nitroglycerin blood levels for 24 h. This does not appear to be the case, as repeated trials of these patches have demonstrated constant blood levels throughout the day (18,19). 2) The effect of intracoronary nitroglycerin may be blunted early after administration of the patch or accentuated 24 h later. This "reverse tolerance" does not appear likely.

Limitations of study. We believe that the data demonstrate tolerance. In any case, they demonstrate that the response to intracoronary nitroglycerin is altered by the 24 h patch. A limitation of this study is that nitroglycerin blood levels were not actually measured. As mentioned before, blood level data showed that patches release nitroglycerin at a constant rate. On the basis of this premise, studies of antianginal effects (1,4) suggested development of tolerance within 24 h of the application of cutaneous nitroglycerin patches. Rose et al. (20) reported absence of differential effect of intracoronary nitroglycerin on coronary artery diameter in patients who had received it intravenously. It is difficult to explain the discrepancy. Our study was done in a blinded fashion and all data were analyzed without knowledge of treatment and group assignment, and those of intracoronary or patch by a single observer.

Change in heart rate and mean blood pressure. Similarly to Feldman et al. (9), we observed that with the smallest dose of intracoronary nitroglycerin a significant (near maximal) dilation of coronary arteries in the control group and minimal change in blood pressure and heart rate were present. At a maximal cumulative dose (350 μg nitroglycerin) there was a slight decrease in mean arterial pressure (range of means from 7 to 15 mm Hg) with only minimal changes in heart rate. There was no difference in the systemic response between untreated patients and those who had received a nitroglycerin patch. This lack of hemodynamic attenuation perhaps can be explained by attenuation of the arterial (including coronary) dilative effect being more prominent than attenuation of the venodilating effect (14).

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