JACC Vol. 25, No. 2
February 1995:349–55

Intermittent Transdermal Nitrates Do Not Improve Ischemia in Patients Taking Beta-Blockers or Calcium Antagonists: Potential Role of Rebound Ischemia During the Nitrate-Free Period

S. BEN FREEDMAN, MB, PHD, FRACP, FACC, BIPIN V. DAXINI, MD, DM, DIANA NOYCE, BA, DAVID T. KELLY, MB, FRACP, FACC

Sydney, Australia

Objectives. **This study was conducted to determine whether rebound ischemia occurs during nitrate-free periods with intermittent cutaneous nitroglycerin therapy in patients with angina pectoris who are receiving background antianginal therapy.**

Background. **Rebound angina has been suggested to be a complication of the nitrate-free period with long-term cutaneous nitroglycerin therapy given intermittently to prevent tolerance.**

Methods. **Fifty-two patients with stable effort angina taking either a beta-adrenergic blocking agent (n = 25) or diltiazem (n = 22) or their combination (n = 5) completed a randomized, double-blind, placebo-controlled crossover study of cutaneous nitroglycerin patches (50 mg). Active or placebo patches were worn for 1 week, applied at 8 AM and removed at 10 PM to provide a 10-h daily nitrate-free (or placebo-free) period. During the last 48 h of each study phase, a Holter monitor was used to detect ischemia.**

Results. **Only 31 patients experienced ischemia during either phase of the study (23 during the patch-off period). A total of 463 ischemic episodes were recorded: 246 during placebo and 217 during nitroglycerin (p = 0.8, for per patient comparison). The majority (88%) of ischemic episodes were silent. Mean (±SEM) duration of ischemia during the total 48-h period was similar during active and placebo phases (35.5 ± 15.0 min/24 h for active therapy vs. 29.7 ± 9.8 for placebo, p = 0.8). This was due to an increase in duration of ischemia with active therapy during the patch-off period (46.9 ± 17.9 min/24 h for active therapy vs. 22.5 ± 9.2 for placebo, p = 0.07) and a decrease during the patch-on period (27.5 ± 14.0 min/24 h for active therapy vs. 34.5 ± 11.0 min/24 h for placebo, p = 0.16). The pattern of diurnal distribution of ischemic episodes differed between active and placebo phases. During placebo there was a nadir in the incidence of ischemia in the overnight patch-off period, with a significantly lower incidence between midnight and 6 AM (25 episodes) compared with the mean number of episodes during the three other 6-h periods (73 episodes, p < 0.001). During the nitroglycerin patch-off period, there was a loss of this overnight nadir, with the same incidence of ischemia between midnight and 6 AM (53 episodes) as the mean number of episodes for the three other 6-h periods (54 episodes).**

Conclusions. **The majority of patients taking background antianginal therapy experienced no ischemia during the patch-off period. In the 44% of patients with ischemia during this period, there was a nonsignificant increase in the duration of ischemia with active therapy. Although this result was statistically inconclusive, the change in the distribution of diurnal ischemia offers suggestive evidence that rebound ischemia may be a problem with regard to intermittent cutaneous nitroglycerin.**

(J Am Coll Cardiol 1995;25:349–55)

Since the classic articles of William Murrell describing the actions of nitroglycerin and its use in effort angina in 1879 (1), short-acting formulations of this drug have become the mainstay of acute therapy for anginal attacks. Transcutaneous delivery systems (patches and disks) were recently developed to provide a more sustained action for prophylaxis of angina, but the steady nitroglycerin plasma concentrations that they deliver rapidly induce tolerance or attenuation of the therapeutic effect (2–10). Intermittent application of patches to allow for an 8- to 12-h daily nitrate-free period has been shown to avoid tolerance (2–5,11–14), but patients are unprotected during this period.

Another potential problem of intermittent therapy with nitroglycerin is the development of rebound ischemia, similar to that initially described in workers after industrial nitrate exposure (15). Recent studies of intermittent nitroglycerin found increased angina in the daily nitrate-free period after patch removal (5,12), although a variable proportion of the patients were not receiving background therapy with another antianginal drug to cover this period. Other studies did not report increased ischemia in the patch-off period, although most did not use ambulatory electrocardiographic (ECG) recordings (2–4,11,13,14). Because silent ischemia occurs

From the Hallstrom Institute of Cardiology, University of Sydney, Royal Prince Alfred Hospital, Sydney, Australia. Dr. Freedman is supported by the Medical Foundation of the University of Sydney, Sydney, Australia. The study was supported by a grant from Ciba-Geigy, Sydney, Australia.

Manuscript received May 5, 1994; revised manuscript received September 14, 1994, accepted September 22, 1994.

Address for correspondence: Dr. S. Ben Freedman, Associate Professor, Hallstrom Institute of Cardiology, Royal Prince Alfred Hospital, Missenden Road, Camperdown, New South Wales 2050, Australia.

0735-1097/95/$9.50
0735-1097(94)00416-N

JACC Vol. 25, No. 2
February 1995:349–55

more frequently than symptomatic ischemia in patients with effort-related angina (16–20), a technique to detect it, such as ambulatory electrocardiography, is required to investigate the problem. In this study, ambulatory electrocardiography was used to determine whether rebound ischemia occurs in the daily nitrate-free period during intermittent nitroglycerin patch therapy when patients are receiving background antianginal therapy with either a beta-adrenergic blocking agent or diltiazem.

Methods

Patient selection. Patients were eligible for study if they had a history of stable effort-related angina pectoris and either angiographic documentation of coronary artery disease or demonstration of ischemia on exercise electrocardiography or stress thallium scintigraphy. All patients were required to be taking a stable dose of either a $beta_1$-selective beta-blocker (atenolol or metoprolol) or diltiazem in a dose of at least 60 mg three times daily throughout the study period. Additional entry criteria were 1) ECG interpretable for ischemia; 2) not hypersensitive to a nitroglycerin patch; 3) no contraindication to nitroglycerin therapy. All patients gave written informed consent for the study, which was approved by the institutional Ethics Review Committee.

A total of 58 patients were enrolled in the study. Six patients did not complete the study: two because of headache, one because of noncompliance, and three were withdrawn (one because of development of rate-dependent left bundle branch block, one with no significant stenosis at subsequent coronary angiography and one because the dose of diltiazem was <60 mg every 8 h), leaving 52 patients who completed the study (40 men, 12 women, mean [±SD] age 62 ± 9 years).

Coronary angiography was performed in 47 of the patients, and revealed significant stenosis (≥70% lumen diameter reduction) in all: 20 had one-vessel disease; 14 had two-vessel disease; and 13 three-vessel disease. Of the remaining five patients, four had a positive result on exercise electrocardiography, and one had a reversible perfusion abnormality on dipyridamole thallium scintigraphy.

Study design. The study was a randomized, double-blind crossover design of intermittent transcutaneous nitroglycerin (50-mg nitroglycerin patch delivering 10 mg/24 h) (Ciba-Geigy) or matching placebo. During the screening phase, all but the first nine patients were given an open-label 50-mg nitroglycerin patch for 24 h if they had not previously been exposed to nitrates to ensure that they could tolerate the trial medication. This became necessary because two of the initial nine patients, given only 2 h of open-label patch, developed a severe headache during the study necessitating their withdrawal from the trial. A 12-lead exercise ECG using a bicycle ergometer, as previously described (11), was obtained during the screening phase, primarily to optimize selection of leads for ambulatory ECG recording. The total exercise duration, time to angina and time to 1-mm ST segment depression were recorded for each patient.

Patients then entered the double-blind phase and were given daily patches to be applied at 8 AM and removed at 10 PM for 7 days. At the end of the first 7-day trial phase on active drug or placebo, there was a 2-day washout period, followed by a second 7-day trial phase with crossover to the alternative treatment. In the last 2 days of each trial phase, patients underwent 48-h ambulatory ECG recording and were given a diary in which to record anginal symptoms.

Concomitant therapy. By design, all patients were taking background antianginal therapy in a fixed dose throughout the study. Twenty-five patients were taking a beta-blocker alone; 22 were taking diltiazem alone; and 5 were taking both a beta-blocker and diltiazem. No long- or short-acting oral nitrate preparations were allowed during the study or in the 48 h before commencement of the study, although sublingual nitrates or nitroglycerin spray was allowed ad libitum.

Ambulatory ECG recording. Ambulatory monitoring of two leads was performed for 48 h using QMED TC350 recorders, which we have previously validated for recording of ischemic ST segment changes (21). The leads chosen were the two leads showing the greatest ST segment depression on the exercise ECG. When the exercise ECG was negative for ischemia, lead CM_5 and an inferior lead were chosen for ambulatory recording. Sample ECGs in supine, right and left lateral decubitus, sitting and standing positions were recorded to exclude positional ST segment changes.

The ambulatory recorder was programmed to detect ischemic episodes of ST segment depression ≥1 mm lasting for at least 40 s. All episodes of ischemia detected by the recorder were verified by inspection of the stored ECG and the ST segment level versus time plots. Episodes of ischemia separated by <8 min were counted as a single episode (this cutoff was predicated by the resolution of the ST segment trend plot). The ambulatory ECG variables analyzed were the duration of ischemia and the number of episodes of ischemia.

Angina diary. Each patient was given a diary and asked to record the occurrence and time of anginal symptoms. Diaries were referenced to the ambulatory ECG recordings to determine whether ischemic episodes were symptomatic or silent.

Trial end points. The primary end point in this study was the duration of ischemia in the nitrate-free (patch-off) period. Secondary end points included the number of episodes of ischemia, the number of anginal attacks and the proportion of patients with >5 min of ischemia in the patch-off period.

Statistical analysis. Differences between active and placebo phases in duration of ischemia, number of episodes of ischemia and number of anginal attacks were analyzed by paired *t* tests. The Shapiro-Wilks test (22) was used to determine whether the differences were normally distributed. Nonparametric Mann-Whitney tests and sign tests were used when the differences were not normally distributed, which was the case for most of the differences in duration and frequency of ischemia. Differences in proportions were analyzed using the exact conditional binomial test. Tests were conducted with a two-tailed level of significance of 0.05. The trial number of 50 patients was chosen to provide 80% power to show a 50%

increase in the duration of ischemia in the patch-off period with an alpha level of 0.05. It was decided a priori to analyze separately the patients taking beta-blockers and those taking diltiazem.

The diurnal variation of ischemic episodes in the four 6-h periods (0 to 6, 6 to 12, 12 to 18, 18 to 24) was examined by chi-square test for goodness of fit (23). If this showed a significant variation, the period with the lowest frequency of ischemic episodes was tested to evaluate its difference from the average of the other periods. Because multiple tests were performed, p values were reported for critical values of chi-square using three degrees of freedom. All analyses with this more stringent test indicated significance at the $p < 0.01$ level.

Results

Exercise stress testing. The results of the exercise stress test performed during background antianginal therapy (beta-blocker or diltiazem, or both) were positive for ischemia in 33 of 52 patients. The mean time to 1-mm ST segment depression was 5.2 ± 2.1 min.

Ischemia on ambulatory recording. During the two 48-h recording periods (both active and placebo nitroglycerin patch phases), 31 patients had one or more episodes of ischemia, although only 23 patients had ischemia in both phases. Ambulatory ischemia occurred in 28 (85%) of 33 patients with positive exercise ECG results compared with only 3 (16%) of 19 with negative exercise test results ($p < 0.01$). A total of 463 episodes of ischemia were recorded in the 31 patients: 246 episodes during placebo and 217 during the active therapy phase. The majority (88%) of ischemic episodes were silent. The proportion of silent episodes was similar during the placebo and active phases (92% and 84% respectively, p = NS). Thirty-two patients experienced angina during either 48-h ambulatory recording phase (some patients experienced angina without ischemic ST segment changes).

Duration and frequency of ischemia (Fig. 1 and 2, Tables 1 and 2). In all of the following comparisons, the duration and frequency of ischemia are expressed in minutes or number of episodes/24 h. For the 14-h daily patch-on period and the 10-h daily patch-off period, values are normalized to minutes of ischemia or number of episodes/24 h for ease of comparison. For the 2 × 10-h patch-off periods in each 48-h recording, the normalized duration in min/24 h was as follows: (Total ischemia duration in 20 h ÷ 20) × 24. For the 2 × 14-h patch-on periods, the normalized duration in min/24 h was as follows: (Total duration in 28 h ÷ 28) × 24. No order or period effect for any variable was seen for any of the time periods. The mean duration of ischemia for the whole 48-h period was similar during placebo and active phases 29.7 + 9.8 vs. 35.5 ± 15.0 min/24 h, respectively, p = 0.8) (Fig. 1). During the patch-on period, there was a reduction in the duration of ischemia with active therapy that did not reach statistical significance (34.5 ± 11.0 vs. 27.5 ± 14.0 min/24 h, p = 0.16). However, in the patch-off period there was a trend for the duration of ischemia

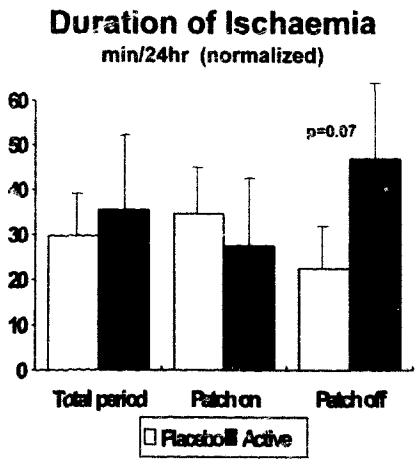

Figure 1. Duration of ischemia on ambulatory monitoring during placebo and active therapy. Values are mean duration with **standard error bars**. There was an increase in duration of ischemia in the nitrate-free (patch-off) period. **p value** refers to Mann-Whitney and sign tests.

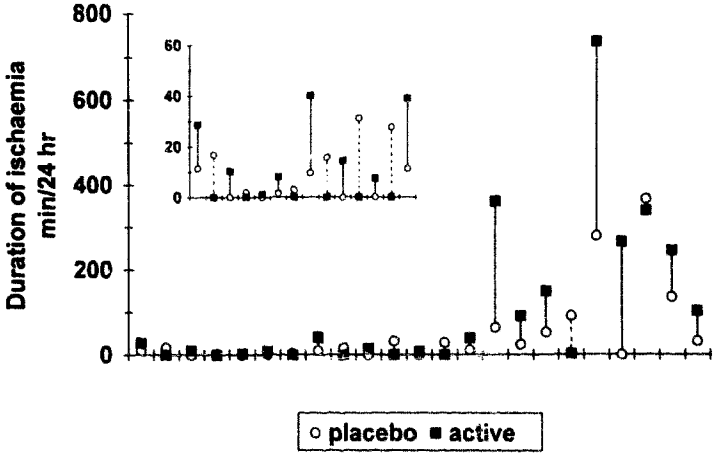

Figure 2. Plot of individual ischemic duration in all 23 patients who experienced ischemia during the patch-off period (10 PM to 8 AM). Patients with ischemic duration <60 min/24 h were replotted on the expanded axis shown in the **inset. Solid lines** = patients with greater ischemic duration on active therapy; **dashed lines** = patients with greater ischemic duration on placebo therapy.

JACC Vol. 25, No. 2
February 1995:349-55

Table 1. Duration of Ischemia During the Patch-Off Period

	No. of Pts	Duration of Ischemia (min/24 h) Placebo	Active Therapy	p Value
All pts	52	23 ± 9	47 ± 18	0.07
Beta-blockers	30	29 ± 15	54 ± 28	0.7
Diltiazem	22	13 ± 7	37 ± 20	0.5

*All values were normalized to mean duration/24 h for ease of comparison. Data presented are mean value ± SEM. Pts (pts) = patients.

during active therapy to be increased compared with that during placebo (22.5 ± 9.2 vs. 46.9 ± 17.9 min/24 h, p = 0.07) (Fig. 1, Table 1). The differences in duration of ischemia for individual patients during the patch-off period are shown in Figure 2. Because the differences were skewed, the paired *t* test was not appropriate, and a Mann-Whitney test was used. The differences in duration of ischemia during the patch-off period were directionally similar in the 30 patients taking a beta-blocker and in the 22 taking diltiazem alone (Table 1).

Only 23 of the patients experienced ischemia during the overnight patch-off period during either the placebo or the active phase, whereas the remaining 29 experienced no ischemia during this period. Of these 23 patients, 17 experienced ischemia during the active and 18 during the placebo phase (some patients had ischemia during only one of the phases). In 15 patients the duration of ischemia during the patch-off period was greater during the active than the placebo phase, whereas in 8 the duration was greater during the placebo phase (p = 0.07). The proportion of patients experiencing >5 min of ischemia during the patch-off period was the same (15 of 23) for both active and placebo phases.

The number of episodes of ischemia during the entire 48 h was similar for placebo and active therapy (Table 2). However, in the patch-on period during active therapy there was a significant reduction in the number of episodes of ischemia consistent with a treatment effect, whereas during the patch-off period, there was a nonsignificant increase in the number of episodes. Ischemic episodes occurred during the patch-on period in 29 patients during either the placebo or the active

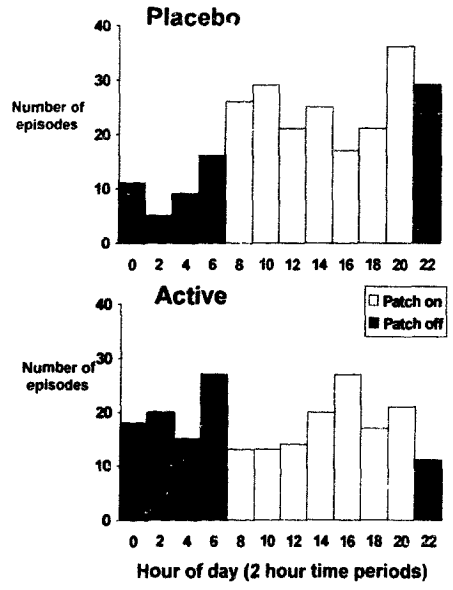

Figure 3. Diurnal distribution of ischemic episodes during placebo and active therapy. Episode onset is grouped into 2-h time periods, starting at 00:00 to 02:00, up to 22:00 to 24:00. **Solid bars** = patch-off (nitrate-free) period between 22:00 and 08:00. There is a loss of the normal diurnal nadir of ischemic episodes in the overnight period during active therapy.

phase: 20 of these patients experienced fewer episodes during the active than during the placebo phase, and 8 experienced fewer episodes during the placebo phase (p < 0.05; 1 patient had the same number of episodes in both phases).

Diurnal distribution of ischemic episodes (Fig. 3 and 4). All ischemic episodes were plotted according to the time of onset of ischemia (Fig. 3), and this was related to the timing of patch application (8 AM) and patch removal (10 PM). The times of episode onset were grouped into twelve 2-h periods for both placebo and active phases. During the placebo phase, there was a clear nadir in the incidence of ischemia in the overnight patch-off period when patients were asleep. The chi-square test showed a significant difference in frequency of ischemic episodes in the four 6-h periods (p < 0.001), and a significantly lower incidence in the period midnight to 6 AM (25 episodes)

Table 2. Number of Episodes of Ischemia and Angina

	No. of Episodes of Ischemia/24 h Placebo	Active Therapy	p Value	No. of Episodes of Angina/24 h Placebo	Active Therapy	p Value
Total 48-h period (8 AM–8 AM)	2.4 ± 0.6	2.1 ± 0.5	0.8	0.89 ± 0.18	0.67 ± 0.13	0.3
Patch-on period (8 AM–10 PM)	2.9 ± 0.7	2.0 ± 0.5*	0.05	1.20 ± 0.26	0.78 ± 0.20	0.12
Patch-off period (10 PM–8 AM)	1.7 ± 0.5	2.2 ± 0.7	0.2	0.39 ± 0.12	0.51 ± 0.15	0.6

*p = 0.05, active therapy versus placebo. All values were normalized to mean number of episodes/24 h for ease of comparison. Data presented are mean value ± SEM.

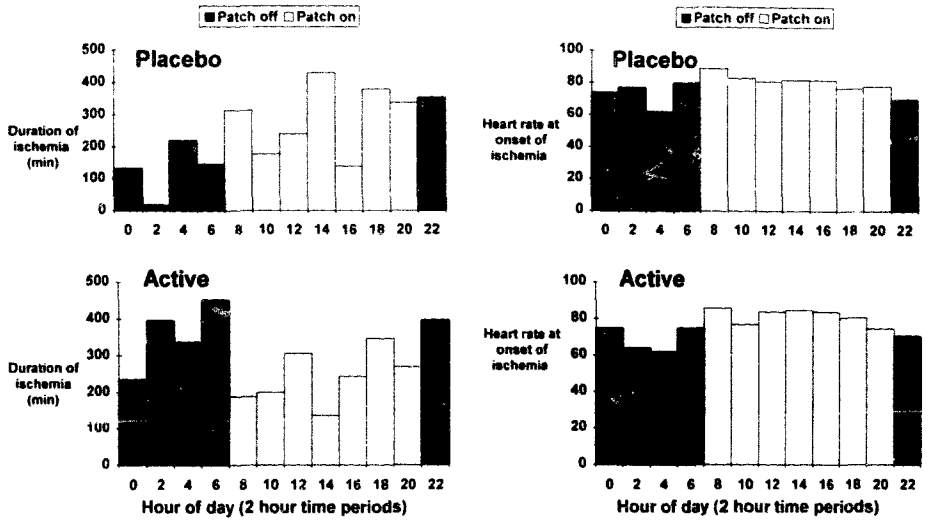

Figure 4. Left, diurnal distribution of duration of ischemic episodes during placebo and active therapy. Episode onset is grouped into 2-h time periods, starting at 00:00 to 02:00, up to 22:00 to 24:00. **Solid bars** = patch-off (nitrate-free) period between 22:00 and 08:00. The pattern is similar to that seen with a number of ischemic episodes (Fig. 3). **Right,** diurnal distribution of heart rate at onset of ischemia. During active therapy, the usual dip in heart rate at onset in the overnight period is preserved.

compared with the mean frequency in the other three periods (73 episodes) and the normalized mean frequency in the 14-h patch-on period (75 episodes) ($p < 0.001$). In contrast, during active therapy, the chi-square test showed no difference in ischemic frequency over the 24-h (53 episodes between midnight and 6 AM vs. a mean frequency of 54 episodes for the other three 6-h periods), consistent with a loss of the overnight nadir. These differences in diurnal distribution pattern between placebo and active phases remained when patients were grouped according to those taking beta-blockers and those taking diltiazem alone. Similar differences were seen in the diurnal distribution of duration of ischemia (Fig. 4), but there was no loss of the usual dip in heart rate at onset of ischemia in the overnight period during active nitroglycerin therapy (Fig. 4).

Occurrence of angina (Table 1). Overall, patients experienced slightly fewer anginal attacks during active therapy than placebo, but the difference was not significant. There were fewer anginal attacks in the patch-on period during active therapy than during placebo ($p = 0.1$) and slightly more anginal attacks in the patch-off period during active therapy ($p = 0.6$), but the differences were not significant.

Discussion

The results of ambulatory ECG recording in this study indicated that in patients taking intermittent cutaneous nitroglycerin therapy in addition to concomitant antianginal drugs, there was an increase in the duration of ischemia during the overnight nitrate-free period that did not reach statistical significance ($p = 0.07$). For the majority of patients (29 of 52), no ischemia was observed in the overnight patch-off period during either active therapy or placebo, and for such patients, rebound ischemia is not an issue. However, for the 23 patients with ischemia during this period, the possibility of an important rebound effect cannot be excluded.

Previous studies suggesting rebound ischemia. A rebound effect after nitrate withdrawal was first described in munitions workers exposed during the week to industrial concentrations of nitroglycerin, with angina, myocardial infarction and even death occurring in the weekend period after removal from exposure (15). Although this is clearly different to removal of a nitrate patch, two early studies of nitroglycerin patches suggested the possibility of rebound angina (24,25). These studies utilized a repetitive cycle of 2 days of continuous patch followed by 2 days of no nitroglycerin. Both studies showed a consistent increase in anginal attacks and sublingual nitroglycerin use on the first day after patch removal. A more recent study reported increased nocturnal angina during the evening patch-off period with intermittent cutaneous nitroglycerin (12), although none of the patients were taking concomitant antianginal therapy. In one other large controlled trial (5) there was an increase in angina and ischemic events during the patch-off period, although concomitant therapy was not specified.

Studies documenting silent ischemia. Because silent ischemia usually predominates over angina in symptomatic patients with coronary artery disease (16–20), a number of studies of cutaneous nitroglycerin have used ambulatory ECG monitoring (4,11,26–30). This addresses the problem of predominantly silent ischemia, but in these studies no increase in ischemia during the nitrate-free period was found. In two studies (26,30), patients were withdrawn from antianginal drugs. In five of the studies (4,11,27–29), results were based on <10 patients who developed ischemia in the nitrate-free period, although larger numbers had been enrolled (in one study [26] numbers were not specified). These small numbers reduce the power to detect an increase in ischemia during this period. In three of the studies (4,11,28), ambulatory recording was performed for only 24 h, which may be too brief to show a difference. In the present study, a longer recording time of 48 h and larger patient numbers partly overcame the problem of

sample size, which is important if rebound ischemia is a phenomenon that affects a relatively small proportion of patients, but the large number of patients with no ischemia in either phase resulted in the study still being underpowered.

Diurnal distribution of ischemia. An important finding of this study was the alteration in diurnal distribution of ischemic episodes by intermittent cutaneous nitroglycerin therapy. A number of previous studies (26,31–36) have shown that when patients with angina are monitored without active therapy or with placebo, there is an overnight nadir in ischemic episodes, followed by morning and evening peaks of ischemia. This pattern is not altered by monotherapy with calcium antagonists, including diltiazem and nifedipine (32,35), or cutaneous nitroglycerin (26). Monotherapy with beta-blockers preserves the overnight nadir, but the daytime peaks are reduced or abolished, particularly the morning peak (32,34). In the present study, the expected diurnal pattern was observed while patients were taking background antianginal therapy plus placebo, in contrast to the loss of overnight nadir during active therapy. These differences were observed regardless of whether the concomitant antianginal drug was a beta-blocker or diltiazem. This alteration in the diurnal pattern of ischemia with loss of the overnight nadir is further evidence to suggest the possibility of rebound ischemia with intermittent cutaneous nitroglycerin despite concomitant antianginal therapy.

There were no significant differences in the overall duration and number of episodes of ischemia between the active and placebo phases. This was probably because the modest reduction in ischemia during the patch-on period was offset by an increase during the patch-off period. This is consistent with previous studies showing no overall reduction in silent ischemia with intermittent nitroglycerin therapy (26,28,30).

Possible mechanisms of rebound ischemia. Potential mechanisms of rebound ischemia include counterregulatory vasoconstriction and reflex sympathetic activation, which are unopposed when nitrate concentrations decrease rapidly. This could give rise to hypertension, tachycardia and unopposed vasoconstrictor activity in the coronary artery bed. Reeves et al. (37) reported coronary artery spasm in rabbits after abrupt withdrawal of nitroglycerin, and in some of the patients who developed ischemic complications after industrial exposure, there was no coronary atheroma, suggesting that spasm may have played a role (15). Some neurohumoral activation has been reported during nitroglycerin therapy in patients and volunteers (38,39), although evidence is conflicting (40).

Limitations of the study. More than 50% of the patients in this study had no ischemia during the patch-off period according to ambulatory ECG recordings in either phase while taking background therapy. Our results are therefore based on the 44% of patients who developed ischemia during this period in the study. This is a problem for study design in trials using ambulatory monitoring because even larger patient numbers must be recruited to provide enough patients with ischemia during this period, otherwise there is insufficient power to obtain a definitive answer as to the occurrence and magnitude of rebound. Although the difference between active therapy and placebo in duration of ischemia during the nitrate-free period in this study was not statistically significant, the null hypothesis cannot be rejected, and rebound ischemia remains a possible explanation for the results. Moreover, the change in diurnal pattern of ischemia offers suggestive evidence that such a phenomenon may be clinically important.

We acknowledge the invaluable assistance of Phillipa Sobb in data management and analysis and Tyron Johnson for checking the data.

References

1. Murrell W. Nitro-glycerine as a remedy for angina pectoris. Lancet 1879;1: 80–1, 113–5, 151–2, 225–7.
2. Luke R, Sharpe N, Coxon R. Transdermal nitroglycerin in angina pectoris: efficacy of intermittent application. J Am Coll Cardiol 1987;10:624–6.
3. Cowan JC, Bourke JP, Reid DS, Julian DG. Prevention of tolerance to nitroglycerin patches by overnight removal. Am J Cardiol 1987;60:271–5.
4. Schaer DH, Buff LA, Katz RJ. Sustained antianginal efficacy of transdermal nitroglycerin patches using an overnight 10-hour nitrate-free interval. Am J Cardiol 1988;61:46–50.
5. De Mots H, Glasser SP. Intermittent transdermal nitroglycerin therapy in the treatment of chronic stable angina. J Am Coll Cardiol 1989;13:786–95.
6. Parker JO, Fung HL. Transdermal nitroglycerin in angina pectoris. Am J Cardiol 1984;54:471–6.
7. Thadani U, Hamilton SF, Olson E, et al. Transdermal nitroglycerin patches in angina pectoris. Dose titration, duration of effect, and rapid tolerance. Ann Intern Med 1986;105:485–92.
8. Waters DD, Juneau M, Gossard D, Choquette G, Brien M. Limited usefulness of intermittent nitroglycerin patches in stable angina. J Am Coll Cardiol 1989;13:421–5.
9. Crean PA, Ribeiro P, Crea F, Davies GJ, Ratcliffe D, Maseri A. Failure of transdermal nitroglycerin to improve chronic stable angina: a randomized, placebo controlled, double-blind, double crossover trial. Am Heart J 1984; 108:1494–500.
10. Abrams J. The brief saga of transdermal nitroglycerin discs: paradise lost? Am J Cardiol 1984;54:220–4.
11. Gumbrielle T, Freedman SB, Fogarty L, Ogasawara S, Sobb P, Kelly DT. Efficacy, safety and duration of nitrate-free interval to prevent tolerance to transdermal nitroglycerin in effort angina. Eur Heart J 1992;13:671–8.
12. Ferratini M, Pirelli S, Merlini P, Silva P, Pollavini G. Intermittent transdermal nitroglycerin monotherapy in stable exercise-induced angina: a comparison with a continuous schedule. Eur Heart J 1989;10:998–1002.
13. de Milliano PA, Koster RW, Bar FW, et al. Long-term efficacy of continuous and intermittent use of transdermal nitroglycerin in stable angina pectoris. Am J Cardiol 1991;68:857–62.
14. Abrams J. Interval therapy to avoid nitrate tolerance: paradise regained? Am J Cardiol 1989;64:931–4.
15. Lange RL, Reid MS, Tresch DD, Keelan MH, Bernhard M, Coolidge G. Nonatheromatous ischemic heart disease following withdrawal from chronic industrial nitroglycerin exposure. Circulation 1972;46:666–78.
16. Schang SJ, Pepine CJ. Transient asymptomatic ST segment depression during daily activity. Am J Cardiol 1977;39:396–402.
17. Deanfield JE, Maseri A, Selwyn AP, et al. Myocardial ischemia during daily life in patients with stable angina: its relation to symptoms and heart rate changes. Lancet 1983;2:753–8.
18. Chierchia S, Lazzari M, Freedman SB, Brunelli C, Maseri A. Impairment of myocardial perfusion and function during painless myocardial ischemia. J Am Coll Cardiol 1983;1:924–30.
19. Nabel EG, Rocco MB, Barry J, Campbell S, Selwyn AP. Asymptomatic ischemia in patients with coronary artery disease. JAMA 1987;257:1923–8.
20. Cohn PF. Should silent ischemia be treated in asymptomatic individuals? Circulation 1990;82:149–54.
21. Jamal SM, Mitra-Duncan L, Kelly DT, Freedman SB. Validation of a real-time electrocardiographic monitor for detection of myocardial ischemia secondary to coronary artery disease. Am J Cardiol 1987;60:525–7.

22. Royston J. An extension of the Shapiro and Wilk's W test for normality to large samples. Appl Stats 1982;31:115–24.
23. Muller JE, Stone PH, Turi ZG, et al. and the MILIS Study Group. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 1985;313:1315–22.
24. Terland O, Eidsaunet W. A double-blind multicenter, crossover general practice study of glyceryltrinitrate delivered by a transdermal therapeutic system angina pectoris. Curr Therap Res 1986;39:214–22.
25. Dickstein K, Knutsen H. A double-blind multiple crossover trial evaluating a transdermal nitroglycerin system vs placebo. Eur Heart J 1985;6:50–6.
26. Fox KM, Dargie HJ, Deanfield J, Maseri A. Avoidance of tolerance and lack of rebound with intermittent dose titrated transdermal glyceryl trinitrate. The Transdermal Nitrate Investigators. Br Heart J 1991;66:151–5.
27. Hamer AW. Placebo effect of nitrate monotherapy for myocardial ischemia. Am J Cardiol 1992;70:1238–42.
28. Rossetti E, Luca C, Bonetti F, Chierchia SL. Transdermal nitroglycerin reduces the frequency of anginal attacks but fails to prevent silent ischemia. J Am Coll Cardiol 1993;21:337–42.
29. Juhani Knuuti M, Wahl M, Wiklund I, et al. Acute and long-term effects on myocardial ischemia of intermittent and continuous transdermal nitrate therapy in stable angina. Am J Cardiol 1992;69:1525–32.
30. Nabel EG, Barry J, Rocco MB, Mead K, Selwyn AP. Effects of dosing intervals on the development of tolerance to high dose transdermal nitroglycerin. Am J Cardiol 1989;63:663–9.
31. Imperi GA, Lambert CR, Coy K, Lopez L, Pepine CJ. Effects of titrated beta blockade (metoprolol) on silent myocardial ischemia in ambulatory patients with coronary artery disease. Am J Cardiol 1987;60:519–24.
32. Mulcahy D, Keegan J, Cunningham D, et al. Circadian variation of total ischemic burden and its alteration with anti-anginal agents. Lancet 1988;2: 755–9.
33. Nademanee K, Intarachot V, Josephson MA, Singh BN. Circadian variation in occurrence of transient overt and silent myocardial ischemia in chronic stable angina and comparison with Prinzmetal angina in men. Am J Cardiol 1987;60:494–8.
34. Benhorin J, Banai S, Moriel M, et al. Circadian variations in ischemic threshold and their relation to the occurrence of ischemic episodes. Circulation 1993;87:808–14.
35. Theroux P, Baird M, Juneau M, et al. Effect of diltiazem on symptomatic and asymptomatic episodes of ST segment depression occurring during daily life and during exercise. Circulation 1991;84:15–22.
36. Willich SN, Pohjola-Sintonen S, Bhatia SJ, et al. Suppression of silent ischemia by metoprolol without alteration of morning increase of platelet aggregability in patients with stable coronary artery disease. Circulation 1989;79:557–65.
37. Reeves WC, Cook L, Wood MA, Whitesall L. Coronary artery spasm after abrupt withdrawal of nitroglycerin in rabbits. Am J Cardiol 1985;55:1066–9.
38. Dupuis J, Lalonde G, Lemieux R, Rouleau JL. Tolerance to intravenous nitroglycerin in patients with congestive heart failure: role of increased intravascular volume, neurohumoral activation and lack of prevention with N-acetylcysteine. J Am Coll Cardiol 1990;16:923–31.
39. Parker JD, Farrell B, Fenton T, Cohanim M, Parker JO. Counter-regulatory responses to continuous and intermittent therapy with nitroglycerin. Circulation 1991;84:2336–45.
40. Packer M. What causes tolerance to nitroglycerin? The 100 year old mystery continues. J Am Coll Cardiol 1990;16:932–5.