Acute effects of oral alprenolol on exercise tolerance in patients with angina pectoris

A dose-response study

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Ten trained patients with typical angina pectoris took part in a double-blind cross-over study to assess the effects on exercise tolerance of 50 and 100 mg alprenolol and placebo, on three successive days. On the fourth day, a known dose of 200 mg alprenolol was given.

Analysis of the results showed that there was a dose-dependent reduction of exercise-induced tachycardia and rise in systolic blood pressure at times of comparable work, such effects being greatest after the administration of the 200 mg dose, presumably proportional to the degree of adrenergic beta-blockade.

The greatest increase of total work was generally seen after the 100 mg dose. In addition, the appearance of angina was delayed to a greater degree after this dose than any other. Possible reasons for these observations in relation to the known pharmacological actions of beta-receptor blocking drugs are discussed. It is concluded that though the 100 mg dose generally is the most effective dose, the optimal dose range may vary from 50 to 200 mg.

Adrenergic beta-blocking drugs have been widely used in the prophylactic treatment of angina pectoris in the last few years. Alprenolol² is a recently introduced beta-blocking drug (Brändström *et al.*, 1966) possessing a moderate beta-stimulating effect (Åblad, Brogård, and Ek, 1967a), which has been shown to be effective in reducing the frequency of anginal attacks, reducing nitroglycerin consumption (Björntorp, 1967, 1968; Aubert *et al.*, 1970; Hickie, 1970), and increasing exercise tolerance (Arstila, Iisalo, and Kallio, 1969; Adolfsson, Areskog, and Rasmuson, 1971).

In a previously reported double-blind cross-over study, alprenolol given intravenously to trained patients with angina pectoris, who subsequently performed exercise tests on a bicycle ergometer, was found to increase effort capacity and delay the appearance of angina pectoris in most subjects (Sealey *et al.*, 1969). The present study was undertaken to assess the effects of various doses of oral

alprenolol compared to placebo on effort capacity in trained subjects with angina pectoris by means of ergometry. Placebo, 50, and 100 mg tablets of alprenolol were given in a random order in a double-blind cross-over manner on three successive days, and on the fourth day a known dose of 200 mg alprenolol was given to each patient. The reason not to include the 200 mg dose in the double-blind allocation was that no previous experiences of a single first oral dose of that size in angina patients were at hand.

Despite the fact that many studies on beta-blocking drugs have been reported previously, we have been unable to find an account of a similar dose-response study. Most of the patients who took part in the previous intravenous study also agreed to participate in the present study during their hospital stay, whereby a comparison between oral and intravenous doses was also made.

Subjects and methods

Ten male patients between the ages of 44 and 69 (mean age 60) years were studied. Body weights ranged from 70 to 93 (mean 81) kg. All had typical exertional angina pectoris while walking at normal

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speed on the level, and in some cases at rest or while getting dressed, for at least one year. None had established diastolic hypertension, valvular heart disease, heart failure, or cardiac infarction within three months. Three patients had a verified history of previous myocardial infarction. Anti-anginal drugs other than sublingual nitroglycerin were not used two weeks before the study. The patients were studied as inpatients in hospital and tested at the same time of the day. They abstained from tobacco before testing and were instructed not to take nitroglycerin later than 2 hours before the exercise tests.

Between 3 and 9 exercise tests were performed on a mechanically braked bicycle ergometer (Monark, Varberg, Sweden) according to a standard procedure, with stepwise increasing work loads until anginal pain according to Sjöstrand (1967). In this way, the patients became familiarized with the experimental procedure. On the basis of these control tests, a work load which could be expected not to produce unendurable anginal pain before 6 to 12 minutes was chosen for each individual patient. Two patients (Cases 3 and 7) were found to have great difficulties if the starting work load was too large. In these patients, a rather low starting load was chosen and increased in a stepwise manner at 6-minute intervals (cf. Table 1). One or two control runs were performed on the work loads chosen before the trial proper. In addition, all patients except Cases 8 and 10 participated in the exercise study using intravenous alprenolol mentioned above.

The patients had been trained to exercise until forced to stop because of pain similar in degree to that experienced in everyday activities. We consider this to be the most relevant end-point in assessing exercise tolerance in this type of patients, and sufficiently safe when performed under controlled laboratory conditions with facilities at hand to cope with the complications that might occur during exercise in coronary arteriosclerotic patients.

The exercise tests were performed in the morning on consecutive days, and started 1½ hours after intake (after a light breakfast) of 2 tablets from bottles coded A–D. Bottles A, B, and C contained placebo and alprenolol tablets in the following combinations: one placebo + one 50 mg tablet, two 50 mg tablets, and two placebo tablets. These combinations were allocated to the patients in random order in a double-blind manner. Bottle D always contained two 100 mg tablets. All tablets were identical in appearance and taste. The order of therapy in the individual patients is given in Table 1.

Electrocardiograms were constantly monitored during the exercise, and leads V₂, V₄, and V₆ were recorded, reference electrodes being placed on the left and right shoulders and the sacral area. The following parameters were also recorded: systolic blood pressure by the cuff method (diastolic blood pressure being uncertain during work with this method), respiratory rate, total work load, times for angina appearance, maximal degree of pain, and disappearance of pain. The type, degree, and time of appearance and disappearance of electrocardiographic abnormalities were subsequently noted. Heart rate was calculated from electrocardiograms.

For statistical evaluation, Student's *t* test for paired differences has been used, two-tailed.

Results

No harmful sequelae resulted from the test procedure.

Average results Table 2 shows the mean results with regard to exercise tolerance (total work), pain appearance and disappearance time, time for electrocardiogram to return to pre-exercise level (normalization time), heart rate, and systolic blood pressure at various points of exercise, on the various dose levels

TABLE 1 Work loads, order of therapy, and total work

Case No.	Work load	Order of therapy	Total work (kp m) placebo	Difference from placebo on		
				50 mg	100 mg	200 mg
1	900	50–0–100	4500	+4500	+4500	+2700
2	900	100–50–0	6300	+1700	+1700	+900
3	300–450*	0–100–50	3150	–1350	+2250	± 0
4	750	0–100–50	4500	± 0	+1500	± 0
5	600	0–50–100	6000	± 0	+2400	+2400
6	900	50–100–0	7200	± 0	± 0	+1800
7	300–450–600*	50–100–0	3600	+1800	+1500	+3300
8	600	50–0–100	6000	± 0	+300	+1200
9	450	100–50–0	5400	–900	–1800	–1800
10	600	100–0–50	7200	–2100	± 0	–1350
$\bar{X}$			5385	+465	+1335	+915
S.E.M.			446	629	561	539
<i>t</i>				0.73	2.37	1.69
<i>P</i>				<0.50	<0.05	<0.20

* Stepwise increase after 6 minutes on each work load.

tested. After alprenolol intake, the appearance time for angina during exercise was prolonged and the total work performed increased. The effect was most pronounced after the 100 mg dose, which increased the pain appearance time by 31 per cent over the placebo value ($P < 0.025$), and significantly larger than after the 50 mg dose ($P < 0.025$), the effect of which was not different from placebo. The 200 mg dose produced a prolongation of the pain appearance time of 24 per cent ($P < 0.05$), slightly less than after 100 mg. The duration of pain after end of exercise was not significantly influenced by alprenolol at any dose level.

Total work increased by 25 per cent over the placebo value on the 100 mg dose ($P < 0.05$). On the other dose levels, the total work values increased less and were statistically insignificant.

Mean ST depression level did not change significantly on the various dose levels, mainly due to one patient (Case 9) showing much larger ST depression on all dose levels of alprenolol than on placebo. Table 3 gives the number of patients having less, equal, and more ST depression at various times during the exercise on the different dose levels. With increasing dose and increasing amount of work performed, the number of patients having less ST depression than on placebo increases, indicating a decrease of cardiac ischaemia in a larger number of patients. The electrocardiographic normalization time is also shortened after alprenolol, the mean reduction being 27 per cent after the 100 mg dose and 48 per cent after the 200 mg dose.

Alprenolol produced a dose-dependent reduction of heart rate and systolic blood pressure after 4 minutes' exercise. At the onset of anginal pain and at the end of exercise, 200 mg alprenolol produced a significantly larger reduction of heart rate ($P < 0.01$) and systolic blood pressure ($P < 0.02$) than did the 100 mg dose. At rest (sitting on the bicycle) there is a small but statistically significant reduction of heart rate (5–10 beats/minute) on all dose levels, whereas systolic blood pressure at rest is insignificantly influenced.

All mean values are given in Table 2.

Individual results Eight patients improved (see Table 1). All these patients had a fall in heart rate and systolic blood pressure at the end of exercise. Two patients could not increase their exercise tolerance on any dose of alprenolol compared to placebo. One of these patients (Case 10) had on placebo a resting heart rate of 48 beats a minute and the comparatively low heart rate of 95 beats a minute

TABLE 2 Mean values, standard errors, and significance limits < 0.05 two-tailed for differences between various dose levels of recorded variables

	Mean	S.E.M.	P values below 0.05 for differences			
			Plac-drug	50-100	50-200	100-200
<i>Total work (kpm)</i>						
P (placebo)	5385	446.34	—			
50 (50 mg alprenolol)	5850	687.38				
100 (100 mg alprenolol)	6720	562.49	< 0.05			
200 (200 mg alprenolol)	6300	627.89				
<i>Pain appearance time (min)</i>						
P	5.85	0.39	—			
50	5.85	0.28		< 0.025		
100	7.65	0.67	< 0.025		< 0.005	
200	7.05	0.46	< 0.05			
<i>Duration of angina pectoris after end of exercise (min)</i>						
P	3.10	0.78				
50	3.55	0.85				
100	2.80	0.62				
200	2.95	0.89				
<i>Electrocardiogram normalization time (min)</i>						
P	8.40	1.02	—			
50	7.70	1.08				
100	6.10	1.06	< 0.005			
200	4.40	0.93	< 0.01		< 0.005	
<i>Heart rate before exercise, sitting on bicycle (beats/min)</i>						
P	68.4	3.88	—			
50	63.7	3.86	< 0.025	< 0.05		
100	58.9	2.75	< 0.001			
200	59.8	3.86	< 0.001			
<i>Heart rate at 4 minutes' exercise</i>						
P	117.6	6.83	—			
50	108.4	6.01	< 0.001	< 0.001		
100	99.5	5.19	< 0.001		< 0.005	
200	94.8	4.07	< 0.001			
<i>Heart rate when angina pectoris develops</i>						
P	122.0	6.33	—			
50	111.0	5.42	< 0.05	< 0.01		< 0.01
100	104.8	4.85	< 0.001		< 0.005	
200	98.2	4.47	< 0.001			
<i>Heart rate at stopping moment</i>						
P	126.0	6.40	—			
50	114.5	5.70	< 0.005	< 0.01		< 0.025
100	108.1	4.29	< 0.001		< 0.005	
200	100.8	4.88	< 0.001			
<i>Systolic blood pressure before exercise, sitting on bicycle (mmHg)</i>						
P	145.5	7.43				
50	142.0	8.34				
100	141.5	8.43				
200	139.0	6.94				
<i>Systolic blood pressure at 4 minutes' exercise</i>						
P	187.8	6.90	—			
50	177.0	9.64	< 0.05	< 0.05		< 0.05
100	168.5	6.67	< 0.001		< 0.005	
200	156.6	7.37	< 0.001			
<i>Blood pressure when angina pectoris develops</i>						
P	188.5	8.17	—			
50	182.5	9.49				
100	176.0	7.48	< 0.005			< 0.01
200	162.0	8.37	< 0.001		< 0.005	
<i>Blood pressure at stopping moment</i>						
P	191.5	10.41	—			
50	185.0	9.83				
100	179.5	8.18	< 0.025			< 0.025
200	164.5	8.58	< 0.001		< 0.005	

when angina appeared after 6 minutes' exercise on a load of 600 kpm/min. This heart rate was little changed by alprenolol treatment. The other patient (Case 9) had at appearance of angina on placebo a heart rate of 115 beats a minute and a systolic blood pressure of 155 mmHg. His heart rate responded in the expected way to the various doses of alprenolol but the systolic blood pressure was not reduced even after 200 mg alprenolol. This patient was the only one of the group who had significantly more ST depression during exercise after alprenolol on all three dose levels. He was also the only patient with lower exercise tolerance on all alprenolol dose levels than on placebo.

In 2 patients (Cases 1 and 2), the 50 mg dose was as effective as the 100 mg dose. These 2 patients showed a much larger reduction of heart rate on the 50 mg dose than the rest of the alprenolol responders. At 4 minutes' exercise, the heart rate of Case 1 decreased from 125 to 108 beats/minute and that of Case 2 decreased from 125 to 100 beats/minute on the 50 mg dose, whereas the corresponding mean change for the remaining 6 alprenolol responders on the 50 mg dose was from 120 ± 11 to 115 ± 9 beats/minute (N.S.).

Four patients showed less improvement of exercise tolerance after the 200 mg dose than after the 100 mg dose. Three of these patients (Cases 2, 3, and 4) had a considerably greater reduction in systolic blood pressure during exercise after 200 mg alprenolol than the other responders. The difference from the 100 mg value at the end of exercise for these 3 patients was 30, 35, and 40 mmHg respectively, whereas the corresponding mean difference for the remaining 5 alprenolol responders was 7 ± 4.3 mmHg.

Comparison with effects of intravenous alprenolol For the 8 patients who also took part in the previous intravenous study, mean values for heart rate and systolic blood pressure at 4 minutes' work, time until pain appeared, electrocardiographic normalization time, and total work have been summarized in Table 4 for the intravenous study (active drug and placebo) and the present study (100 mg dose and placebo). The placebo values in the two studies for the variables mentioned do not differ significantly from one another, and the changes induced by intravenous alprenolol (mean dose 8.2 mg) are not significantly different from the changes induced by 100 mg oral alprenolol.

Discussion

The present results show that an oral dose of 100 mg alprenolol, in comparison to placebo,

TABLE 3 ST depression changes on various dose levels (figures indicate number of patients)

Time of exercise	Dose								
	50 mg			100 mg			200 mg		
	-	o	+	-	o	+	-	o	+
At 4 minutes exercise	3	6	1	2	8	0	1	6	3
At time of comparable work	3	4	3	4	5	1	6	3	1
At end of exercise	3	3	4	5	4	1	7	1	2
Maximum depression during or after exercise	2	4	4	4	5	1	6	1	3

- = less ST depression than placebo; o = same ST depression as placebo; + = more ST depression than placebo.

caused a statistically significant delay of the appearance of anginal pain during standardized exercise and an increase of the total work performed. Alprenolol did not influence the duration of pain after end of exercise but reduced significantly the duration of ST depression.

The present results with 100 mg alprenolol are in general agreement with those reported by Adolfsson *et al.* (1971). These authors found on the average a greater increase of exercise tolerance after alprenolol than in the present study. This difference might be related to the fact that the patients of Adolfsson *et al.* could endure significantly less exercise after placebo than our patients.

After 50 mg alprenolol, some patients improved in the present study, but statistically the mean exercise tolerance and electrocardiographic changes were not significantly different from placebo.

The exercise studies were carried out 1½ hours after administration of the tablets, at which time the beta-blocking action of orally given alprenolol reaches its peak (Åblad *et al.*, 1967b). Studies in healthy students of the effect of orally given alprenolol on the tachycardia response to repeated exercise indicate that the beta-blocking action of 100 mg alprenolol persists for more than 7 hours, while that of 50 mg is weaker and is of shorter duration (Åblad *et al.*, 1971).

On the basis of these human pharmacological data and the present clinical investigation, alprenolol in a dose of 100 mg q.i.d. should be of therapeutic value in the long-term treatment of angina pectoris, while a dose of 50 mg q.i.d. should have little effect in most cases. This hypothesis is supported by the results from some studies where the clinical effects of alprenolol, given over 2 to 4 weeks, were compared with placebo with double-blind cross-over technique.

TABLE 4 Mean values and per cent changes from placebo after 100 mg alprenolol orally and 0.1 mg/kg i.v. for 8 patients

	Oral (100 mg)				Intravenous (mean dose 8.2 mg)			
	placebo	active	per cent change	P	placebo	active	per cent change	P
Heart rate at 4 minutes of exercise (beats/min)	123.6	102.4	-17.2	<0.001	122.5	103.3	-15.7	<0.001
Systolic BP at 4 minutes of exercise (mmHg)	183.5	164.4	-10.4	<0.001	182.0	166.5	-8.5	<0.01
Time until onset of anginal pain (min)	5.8	7.2	+24.2	<0.10	5.3	6.5	+22.6	<0.02
Electrocardiogram normalization time (min)	8.25	5.63	-31.8	<0.01	7.5	4.5	-40.0	<0.01
Total work (kp m)	5081	6713	+32.2	<0.05	4913	6563	+33.6	<0.05

In four studies comprising 97 patients, alprenolol in a dose of 100 mg q.i.d. was found to reduce the attack rate and the nitroglycerin consumption (Björntorp, 1967, 1968; Aubert *et al.*, 1970; Hickie, 1970). Similar studies with alprenolol in doses of 50 mg q.i.d. or 75 mg t.i.d. showed, on the other hand, none or only a marginal effect on these parameters (W. T. L. Ohlsson and L. Sandberg, 1968, personal communication; Arstila *et al.*, 1969).

As 8 of the 10 patients in the present series also took part in a previous intravenous alprenolol study, it is of interest to compare the results in these 8 patients in the two trials. The effect of 100 mg alprenolol orally was not significantly different from 0.1 mg/kg i.v. (mean total dose 8.2 mg) with regard to increase of total work and reduction of exercise heart rate. This is approximately in accordance with previous studies on dose-effect relations between orally and intravenously given alprenolol as regards antagonism to isoprenaline-induced tachycardia in healthy volunteers (Johnsson, Norrby, and Sölvell, 1967).

The relevance of the data obtained after 200 mg alprenolol in the present study should be judged with caution as this dose was deliberately given on the last day of the trial in each patient. Certain facts, however, justify the inclusion of the effects of the 200 mg dose in an overall comparison between the various doses. The patients had carried out 6 to 9 exercise tests shortly before the present study. In the 8 patients who took part both in the present trial and the previous study with intravenous alprenolol, the mean total work performed on placebo in the two investigations was practically the same. Furthermore, the sums of total work performed in each of the three consecutive exercise days with randomized drug administration in the present trial scarcely differed.

Thus, factors such as physical training or unfamiliarity with the test procedure could not have influenced the variation between tests much.

The mean results obtained after 200 mg alprenolol indicate that this dose produced about the same reduction of ST depression as 100 mg alprenolol, but exercise tolerance improved, if anything, less than on the 100 mg dose.

It thus appears that alprenolol had on an average its most pronounced positive effect on exercise tolerance in a dose of 100 mg in this type of study. However, the data indicate that there may be individual variations as regards the optimal dose. Of the 10 patients, 2 showed an optimum improvement of exercise tolerance after 50 mg, and 3 others after 200 mg alprenolol. So far no long-term studies have been published about the anti-anginal effect of alprenolol in doses above 100 mg q.i.d.

The therapeutic effect of alprenolol in angina pectoris is probably due to the beta-blocking activity of the drug (Björntorp, 1968). Beta-blockers, such as alprenolol and propranolol, reduce the myocardial oxygen demand in situations with increased adrenergic activity in the dog heart (Ek and Åblad, 1970). This effect is probably mainly a consequence of inhibition of the adrenergic control of cardiac rate and contractility (Epstein and Braunwald, 1966). Such inhibition leads to decreased heart rate and arterial blood pressure, which should result in reduced cardiac work, in turn leading to diminished myocardial oxygen consumption. Adrenergic blockade of cardiac chronotropic and inotropic stimuli further influences myocardial oxygen demand in several other ways, both reducing it, for example through a decrease of the speed of ventricular contraction, and increasing it, for example through an enlargement of cardiac size (Epstein and Braunwald, 1966).

While the therapeutic effect of beta-blockers in angina pectoris has hitherto largely been discussed as a matter of interference with the oxygen demand of the myocardium, secondarily to its function as a pump, it should be kept in mind that the agents may also influence the delivery of oxygen to the myocardium. A decrease of coronary blood flow has been observed after propranolol both in animals (McKenna *et al.*, 1966; Parratt, 1967; Stein *et al.*, 1968) and in man (Wolfson and Gorlin, 1969). It is likely that this increase of coronary vascular resistance is mainly a consequence of the reduced myocardial oxygen demand (Lucchesi and Whitsitt, 1969), but in part it may be an expression of alpha-receptor mediated adrenergic vasoconstrictor activity on the coronary resistance vessels (Feigl, 1967; Parratt, 1967). In some studies the arteriovenous myocardial oxygen difference has been found to be increased after propranolol (McKenna *et al.*, 1966; Wolfson and Gorlin, 1969), and it has been suggested that propranolol reduces the myocardial oxygen supply more than it decreases the myocardial requirement for oxygen in the heart as a whole (Parratt and Grayson, 1966). Some recently reported studies with propranolol on dogs with regional myocardial ischaemia have yielded results (Craven and Pitt, 1968; Becker *et al.*, 1969a; Becker, Fortuin, and Pitt, 1969b) that may be pertinent to the therapeutic effect of beta-blockade in angina pectoris. These studies showed that propranolol reduced blood flow to normal myocardium but not to areas of ischaemia. This selective maintenance of flow after beta-blockade may imply an improvement in the relation between oxygen delivery and demand in the ischaemic regions, provided the myocardial oxygen requirements are reduced by beta-blockade in the ischaemic areas as in the rest of the myocardium. The mechanism behind the described redistribution of coronary blood flow after propranolol has not yet been elucidated.

Animal studies indicate that beta-blockade may also influence the oxygen economy of the myocardium through a direct interference with its cellular metabolism. Propranolol has been found to reduce myocardial uptake of free fatty acids with a consequent relative rise in the myocardial carbohydrate utilization (Marchetti, Merlo, and Nosedà, 1968; Masters and Glaviano, 1969). This should be expected to raise the cardiac respiratory quotient (cf. McKenna *et al.*, 1966), indicating an oxygen-saving shift of myocardial energy metabolism. A decreased metabolism of free fatty acids in the myocardium may further

improve the oxygen economy of the myocardium, because these substrates may induce a primary 'metabolic' increase of oxygen consumption (Challoner and Steinberg, 1966).

While the relative importance of the above discussed factors is so far incompletely elucidated, it seems evident that the integrated response to beta-blockade in most angina patients is an improvement of the relation between myocardial oxygen demand and delivery. It would otherwise be difficult to explain the well-documented therapeutic effect of the drugs, whether expressed as increase of exercise tolerance, reduction of ST depression during exercise, or decrease of attack rate under long-term administration. The beta-blockers should be expected to be particularly effective in angina patients where the attack-producing imbalance of the oxygen economy of the myocardium is mainly due to activation of the cardiac beta-receptors. Patients with hyperkinetic circulation appear to be characterized by such a reaction pattern (Frohlich, Dustan, and Page, 1966) and the beta-blockers have been found to be especially effective in angina patients with a hyperkinetic response to standing (Furberg and Jacobsson, 1967) and exercise (Cullhed, 1971).

The heart rate and systolic blood pressure are the most simply measured parameters reflecting cardiac beta-receptor blockade. From the foregoing discussion one would not expect to find any simple correlation between the effects of alprenolol on exercise tolerance on the one hand, and on exercise heart rate and systolic blood pressure on the other. That some correlation exists, however, is suggested by the study of Kimura, Yoshida, and Ushiyama (1967). These authors investigated propranolol and pronethalol in angina pectoris, by means of exercise tolerance tests, and concluded that when one of the drugs was effective, the product of systolic pressure and heart rate during angina decreased compared to the control value, whereas when this product did not decrease, the patient had no improvement of the angina.

The present results show on the average no direct correlation between the anti-anginal effect of alprenolol and its reduction of the heart rate and blood pressure. While the dose-responsive curve as regards the effect of alprenolol on exercise tolerance seemed to reach a peak at a dose of 100 mg on average, the drug-induced reduction of exercise heart rate and systolic blood pressure followed a different pattern, the 200 mg dose being most effective. An examination of the individual cases revealed, however, some interesting relations between the effects on exercise

tolerance and on heart rate – blood pressure. Of the 2 patients whose exercise tolerance worsened or was unchanged after alprenolol, one showed practically no decrease of exercise heart rate, while the other showed no decrease of exercise systolic blood pressure after any dose of alprenolol. The remaining 8 patients whose exercise tolerance improved on alprenolol all responded to the drug with a distinct reduction of the heart rate and blood pressure. The 2 patients showing most obvious improvement of exercise tolerance after 50 mg alprenolol also had the most pronounced reduction of exercise heart rate of all patients on this dose.

Three patients had a much more pronounced reduction of systolic blood pressure after 200 mg alprenolol than after 100 mg, but their exercise tolerance was lower after the higher dose. This finding represents the most obvious deviation from a direct correlation between the anti-anginal effect and the blood pressure reduction. The mechanism behind this finding is not clear. One possibility is that the oxygen delivery to the myocardium was critically lowered because of the decreased arterial pressure. Another possible factor is that the hypotensive reaction created a deficient blood flow to the exercising muscles, so that the patients had to stop exercise, in part, because of tiredness in the legs. Though this was not spontaneously reported by the patients, the latter hypothesis is supported by the fact that the decreased exercise tolerance was not accompanied by more pronounced ST depression.

Like previous acute and more prolonged studies of the effect of alprenolol in angina pectoris patients, the present investigation indicates that the drug, when given in proper doses, is an effective and safe therapeutic agent in the majority of patients. It appears important to analyse whether acute exercise tests, as made in the present study, could be of value in predicting therapeutic response and optimal dosage during long-term treatment with beta-blockade in the individual angina patient. Positive findings in this regard imply a more rational basis for therapy than the patients' subjective impressions, which are now the most widely used therapeutic criteria in the routine assessment of these agents.

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