Antiangiastic effects of atenolol and pindolol in patients with stable effort angina pectoris

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Abstract A double blind, randomised crossover study with 22 patients was performed to compare the antiangiastic effects of atenolol 100 mg once daily and pindolol 5 mg thrice daily. After a placebo run-in period, 2 treatments were given for 2 wk each. The number of anginal attacks and the nitroglycerin (NTG) consumption were determined. During bicycle exercise testing, the systolic blood pressure (BP), heart rate (HR), double product and exercise tolerance were measured. Both drugs reduced the number of anginal attacks and NTG consumption relative to the placebo, with atenolol being more effective than pindolol. During exercise, both β-blockers produced a slight increase in BP and HR compared to the placebo. HR attained with atenolol was lower than pindolol at the same workload. The total duration of exercise and the maximal tolerated workload were greater in atenolol than pindolol experiment. The special properties of β-blockers, such as cardioselectivity or intrinsic sympathomimetic activity (ISA), may have clinical importance in the treatment of angina pectoris.

Key words atenolol; pindolol; angina pectoris; exercise test; clinical trial; blood pressure; heart rate; electrocardiograph; sympathomimetics

Beta-blockers with marked ISA produce a higher resting HR, however, the level of increase in HR on exercise is similar to that during treatment with other β-blockers with no ISA. It has been demonstrated that in patients with severe angina pectoris, the reduction in resting HR is an important factor in reducing the frequency and severity of myocardial ischemia and it may raise the question of risk–benefit consideration of the ISA(4,5). The aim of this study was to compare the antiangiastic and circulatory effects of 2 β-blockers having different pharmacological properties—pindolol, a non-cardioselective drug with strong ISA and atenolol, a cardioselective drug with no ISA.

Materials and methods

Patients Twenty patients (5 female, 15 male; aged 24–70 yr) were studied. They had had chronic, stable effort angina pectoris for at least 6 months and 5 attacks/wk without any treatment or nitrates. There were no changes in their symptoms for the 6 wk prior to the study. The resting ECGs were normal. During exercise, an ST segment depression of 0.1 mV which lasted 80 ms after point J was seen in all patients. There were no spontaneous anginal attacks and none developed angina or ST segment depression after prolonged hyperventilation.

Significant coronary artery disease was confirmed by coronaryography except for 2 patients in whom the localized perfusion defects were verified by thallium 201 exercise scintigraphy.

Study design A double blind, randomized crossover. Fixed dose study was organized on an outpatient basis. After a washout period (1 wk) during which all medications were discontinued, the patients were given placebo for 2 wk (run-in period). At the start and end of this period, the patients underwent a clinical examina-
tion. BP and HR measurements and an exercise test was performed. No significant differences between these 2 evaluations were observed. After assuming that the entry criteria were satisfied, the patient were given at random either atenolol 100 mg once a day at 8:00 AM or pindolol 5 mg tid at 7:00 AM, 1:00 and 8:00 PM. The first treatment period lasted for 14 d. Patients then entered a wash-out period (1 wk) prior to being crossed over to the alternative treatment period (2nd period). 1) placebo-pindolol place- atenolol. 2) placebo-atenolol-placebo– pindolol.

Clinical examinations and exercise tests were performed at the end of each period. All examinations were performed about 3 h after the last dose. At each examination, the number of angina attacks, NTG tablets, drug tolerance and side effects were recorded. Subjective assessment of any anginal episodes and NTG consumption were analyzed by a special "angina diary" in which the patients wrote their experiences.

The exercise test was performed on an electrically braked bicycle ergometer (Medion Erg 22) beginning at 30 W and progressively increasing the workload by 30 W every 3 min to the following end points: anginal pain, dyspnea, fatigue, maximal HR.

During exercise the maximal tolerated workload, total duration of exercise duration to chest pain, to significant ST depression (1 mm or more occurring 80 ms after point J and lasting for at least 3 consecutive beats) and to the end of exercise were analyzed. HR and systolic BP were recorded just prior to exercise, at the onsets of ST segment depression, chest pain and cessation of exercise, and immediately after the completion of exercise.

Statistical analysis Data are presented as X ±SD. Linear regression and t-tests were used for statistical evaluation. Data and parameter changes in the treatment and placebo periods were compared.

Results Effects of treatment on anginal attacks and nitroglycerin consumption All 20 patients completed the crossover trial. Both atenolol and pindolol significantly reduced the number of anginal attacks and NTG tablets after 14 d of treatment. Compared with pindolol, atenolol resulted in a greater reduction in the number of anginal attacks and in NTG consumption at the end of each treatment period (Fig 1).

![Graph A](image1)

![Graph B](image2)

Fig 1. A) Number of anginal attacks with placebo and the two β-blockers. B) Consumption of nitroglycerin (NTG) tablets on placebo and the two β-blockers. *P<0.05. **P<0.01. ***P<0.001. G1 = group 1, G2 = group 2.

Circulatory changes at rest 1 Atenolol slightly reduced systolic BP when compared to the placebo. Pindolol did not cause significant changes in systolic BP. There were no differences in the effects of the drugs on BP measured in
standing and supine positions.

2 Atenolol significantly reduced the HR with respect to placebo, while pindolol showed no such effect (Fig 2).

Circulatory and ECG changes during exercise test

1 Systolic BP Both atenolol and pindolol attenuated the usual increase in systolic BP during all 3 phases of exercise compared to the placebo. Atenolol produced a greater reduction than pindolol, however, the differences were not statistically significant.

2 HR Both atenolol and pindolol reduced the increase in HR during exercise when compared with the placebo. The effect on HR was greater in the patients treated with atenolol than with pindolol (Fig 3).

3 HR x systolic BP product The double product was maintained at a significantly lower level at the end of exercise by both β-blocking drugs compared with the placebo. Within the 2 treatment periods, atenolol produced a significantly lower double product value than pindolol for the same level of exercise (Fig 4).

4 Effects of treatment on exercise tolerance The β-blocker therapy with both drugs increased the exercise tolerance in both treatment periods. Atenolol allowed a longer time of exercise (7±6 and 10±6) and a greater maximal tolerated workload

Fig 2, Standing heart rate or placebo and the two β-blockers at rest, *P<0.05, ***P<0.01.

Fig 3, Changes in heart rate during exercise, ST—appearance time of ST depression, Pain—appearance time of anginal pain, Stop—stopping time of exercise, **P<0.05, ***P<0.01.

Fig 4, Heart rate x systolic pressure product, □ = number of patients, *P<0.05, **P<0.01, (**±16 W, P<0.001) than did pindolol (Fig 5).

5 Side-effects No side effect serious enough to warrant discontinuation of the medication was observed, and no changes in laboratory parameters were seen at the end of the trial.

Discussion

Several studies with atenolol and pindolol have confirmed the efficacy of these drugs for the treatment of stable angina pectoris**. However, it is not yet clear
whether ISA or cardioselectivity can offer advantages in treatment of angina pectoris. β-blockers with ISA, such as pindolol, may offer protection against worsening airway obstruction, thereby resulting in a higher resting HR than that induced by agents which do not possess this activity. The β-blockade is evident during exercise or when the resting HR is high. It has been suggested that ISA decreases the antianginal activity of β-blockers. 

It seems that cardioselectivity does not influence the effect of a β-blocker on HR and BP during exercise. Atenolol as a cardioselective β-blocker without ISA has a longer half-life and therapeutic activity, allowing a single daily dose. It results in a strong decrease in the resting HR.

The widely accepted explanation of the antianginal effect and the increased exercise tolerance produced by β-blockers in patients with effort angina is a reduction in HR. Some investigators have observed that the reduction in HR during exercise seen in patients taking β-blockers without ISA was greater than in those taking β-blockers with ISA.

Both β-blockers increased the exercise tolerance; however, the total duration of exercise and the maximal tolerated work load were greater with atenolol than with pindolol. Patients taking pindolol reached their threshold of angina sooner. At the dose used, both atenolol and pindolol were well tolerated and no side effects were observed.

The special properties of β-blockers, such as cardioselectivity and ISA, may have some clinical importance in the treatment of patients with unstable effort angina pectoris.

References
8. Schwartz JB. Atenolol in the treatment
阿普洛尔和吲哚洛尔对定期发作心绞痛病人
的作用

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摘要 选 20 例慢性心绞痛病人（病史至少半年，每周发作 5 次以上），用安慰剂、吲哚洛尔及阿普洛尔，比较阿普洛尔 100 mg qd 及吲哚洛尔 5 mg tid po 的疗效作用。在服用安慰剂后，2 周内服吲哚洛尔 2 wk，记录心绞痛发作次数和硝酸甘油（NTG）的消耗量。在有行为性心绞痛发作期间，测定 BP、HR，以及两次的轻微和剧烈运动的超极量试验，与安慰剂期相比较。2 周后吲哚洛尔减少心绞痛发作次数和 NTG 的消耗量，阿普洛尔比吲哚洛尔更有效。在运动期间，3 个 T 试验则均能导致 BP 和 HR 的轻微上升，与吲哚洛尔期相比较，阿普洛尔期 HR 增高。阿普洛尔与吲哚洛尔相比，根据病人的总体活动量更大，明显饱受心绞痛之苦，两药所含有的 β 阻滞剂的特性，如心肌选择性和延性，使交感激动性（USJ），可能在治疗心绞痛中有重要的临床意义。

关键词 阿普洛尔；吲哚洛尔；心绞痛；运动试验；心电图反应；心电图记录；和交感激动性