Treatment of stable angina pectoris with verapamil hydrochloride: a double blind cross-over study

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Verapamil hydrochloride, a calcium antagonist, has been recommended for the treatment of angina pectoris. The effectiveness of 3×120 mg verapamil was tested in 33 male patients with stable angina pectoris. The drug reduced the incidence of anginal episodes from 15 (1–98) to two (0–85) in four weeks (median, range); $P < 0.01$. The nitroglycerin consumption was similarly reduced. Exercise tolerance on a bicycle ergometer improved on the average by 10 W ($P < 0.05$). No side effects were observed.

It is concluded that verapamil is an effective drug in the treatment of stable angina pectoris.

Verapamil hydrochloride is used widely in the treatment of supraventricular arrhythmias[1,2]. In addition this drug has certain actions which may improve the balance between myocardial oxygen requirements and oxygen supply in patients with coronary disease. Verapamil has a negative inotropic effect on the myocardium through either a reduction of calcium transport through the cell membrane[3,4,5] or interference with the interaction between actin and myosin[6]. Furthermore, it reduces myocardial oxygen consumption through arterial vasodilatation which results in reduction of the rate-pressure product at rest and during exercise[7,8]. Finally some studies indicate that verapamil has a direct vasodilatory action on the coronary arteries[9,10]. Several clinical trials have been published which support the efficacy of verapamil in the treatment of angina pectoris. However, in the European and American literature, little data are available on the effect on exercise tolerance of chronic administration of the drug[11]. Therefore we performed a clinical trial with a double blind cross-over design to test the value of verapamil (3×120 mg) in stable angina pectoris. Work tolerance was assessed by symptom limited exercise tests with computer assisted ECG interpretation[12]. In addition the frequency of

anginal episodes and nitroglycerin consumption was measured.

Patient selection

Forty male patients with stable angina pectoris participated in the present study, which was conducted at the outpatient clinic of the Thoraxcenter. The patients were informed about the goals and details of the study, and gave their consent. All patients had stable angina pectoris of at least three months duration, which was not sufficiently controlled by beta-blocking agents and/or nitrates. At the initial examination they reported a minimum of five episodes of chest pain a week. All patients developed typical chest pain during the exercise test which was part of the screening procedure. Exercise induced chest pain or ST segment changes or both improved when the stress test was repeated 1 h later after the administration of 0.5 to 1.0 mg nitroglycerin.

During the study period, the patients did not use beta-blocking agents or long-acting nitrates. Nitroglycerin could be taken freely, but prophylactic use of nitroglycerin was not encouraged.

Design of the study

The study consisted of three periods of four weeks each. During the first period, which was single blind, all patients received placebo. During the second and third periods either a sustained

release tablet containing 120 mg verapamil hydro-chloride (Isoptin retard[R]) or an identical placebo was administered three times daily according to a double blind random cross-over design.

Before entry into the study and after each period of four weeks, the following investigations were done: history and physical examination; urine and blood tests, including electrolytes, alkaline phosphatase and serum transaminase, serum creatinine, hemoglobin, hematocrit, thrombocyte and leucocyte counts with differential; pulmonary function tests (vital capacity and 1 s expiratory capacity); electrocardiogram, vectorcardiogram and exercise test. During the initial screening evaluation the exercise test was repeated 1 h later after administration of 0·5 or 1·0 mg nitroglycerin, depending on the patient's normal use of this drug.

The patients were seen in a special clinic by the same physician throughout the study. The stress tests were performed in the same laboratory with the same attending physician and technician.

Patients were instructed to keep a diary of episodes of chest pain as well as the use of any drugs including nitroglycerin and the tablets which were administered throughout the study. Prophylactic use of nitroglycerin was not encouraged. At the end of each four-week period, the study tablets as well as the nitroglycerin were returned and counted.

Exercise tests were performed at the end of each treatment period. Each patient was tested at the same hour in the morning throughout the study, between 2 and 4 h after the last medication. A calibrated, electrically braked bicycle ergometer was used with stepwise workload increments of 10 W per minute. The bicycle was controlled by a computer system which also performed quantitative analysis of the ECG during each minute of the test[12]. The corrected orthogonal Frank lead system was used. Computer measurements included ST amplitudes and ST slopes at fixed intervals after the end of QRS, which were corrected for heart rate during the test[13]. Blood pressure was measured with a cuff and stethoscope every other minute. All patients had been familiarized with the protocol before the trial. They were encouraged to continue until the development of moderate chest pain or fatigue. None of the tests had to be terminated for abnormal heartrate or blood pressure responses[14], excessive ST changes or arrhythmias. After termination of the highest workload, patients continued cycling for 4 min at a low load. The ECG was monitored until all changes had disappeared.

Statistical analysis was done with the Wilcoxon rank sign test[15].

Results

Forty patients were selected and entered into the study. Seven of these had to be withdrawn for different reasons. One patient developed unstable angina pectoris during the first placebo period. One other patient suffered from cardiac failure after withdrawal of digoxin within the first month of the study. A third patient refused further participation since he did not observe any improvement during the second treatment period. Two patients appeared to have insufficient complaints in spite of the selection procedure. They reported respectively one and two episodes of chest pain during the 12 weeks of the trial and had no chest pain during the stress tests. One patient appeared to be very unreliable in the consumption of his medication as well as in the presentation of his complaints. It was found that he suffered from a psychiatric disorder and he should not have been admitted to the study. Part of the data of the seventh patient was lost. One patient developed ventricular fibrillation during an exercise test before he actually entered the study. This patient had volunteered for the study, and beta-adrenergic blocking drugs had gradually been withdrawn. He was successfully defibrillated and recovered. Thirty-three patients completed the study without unwanted effects. Their ages ranged from 38 to 73 years; the median was 57 years.

The presence of coronary disease was documented by selective coronary arteriography in 15 patients. Five of these as well as 10 others had suffered a myocardial infarction, four months or more prior to the study. All 33 patients had a typical history of angina pectoris as well as an abnormal stress test before entry into the study. In 18 patients beta-adrenergic blocking drugs were withdrawn prior to the study. None of the patients suffered from other significant cardiovascular, hepatic, renal or metabolic disease; specifically none of the patients had chronic cardiac failure. No abnormalities were observed in the laboratory data or pulmonary function tests, either at entry or during the study.

Seventeen patients received placebo – verapamil – placebo and the 16 others received placebo – placebo – verapamil.

No differences were observed between the data from patients who received verapamil in the second treatment period and those who received the

*Table 1   Episodes of chest pain and nitroglycerin consumption during each period of four weeks. Given are the median value and the range in 33 patients. ** = P < 0·01; statistical significance of the difference between placebo period II and verapamil*

	Placebo I	Placebo II		Verapamil
No. of episodes	15 (1–98)	14 (0–85)	**	2 (0–85)
Nitroglycerin consumption (mg)	4·5 (0–49)	4·5 (0–28)	**	1 (0–26)

Table 2   Reasons for termination of the exercise tests at the end of each treatment period

	Placebo I	Placebo II	Verapamil
Chest pain	23	22	15
Dyspnea	1	1	3
Fatigue	8	9	15
Other	1	1	

sequence placebo – placebo – verapamil. Therefore the data from these two series were combined in the final analysis.

The frequency of occurrence of chest pain as well as the nitroglycerin consumption was similar in the
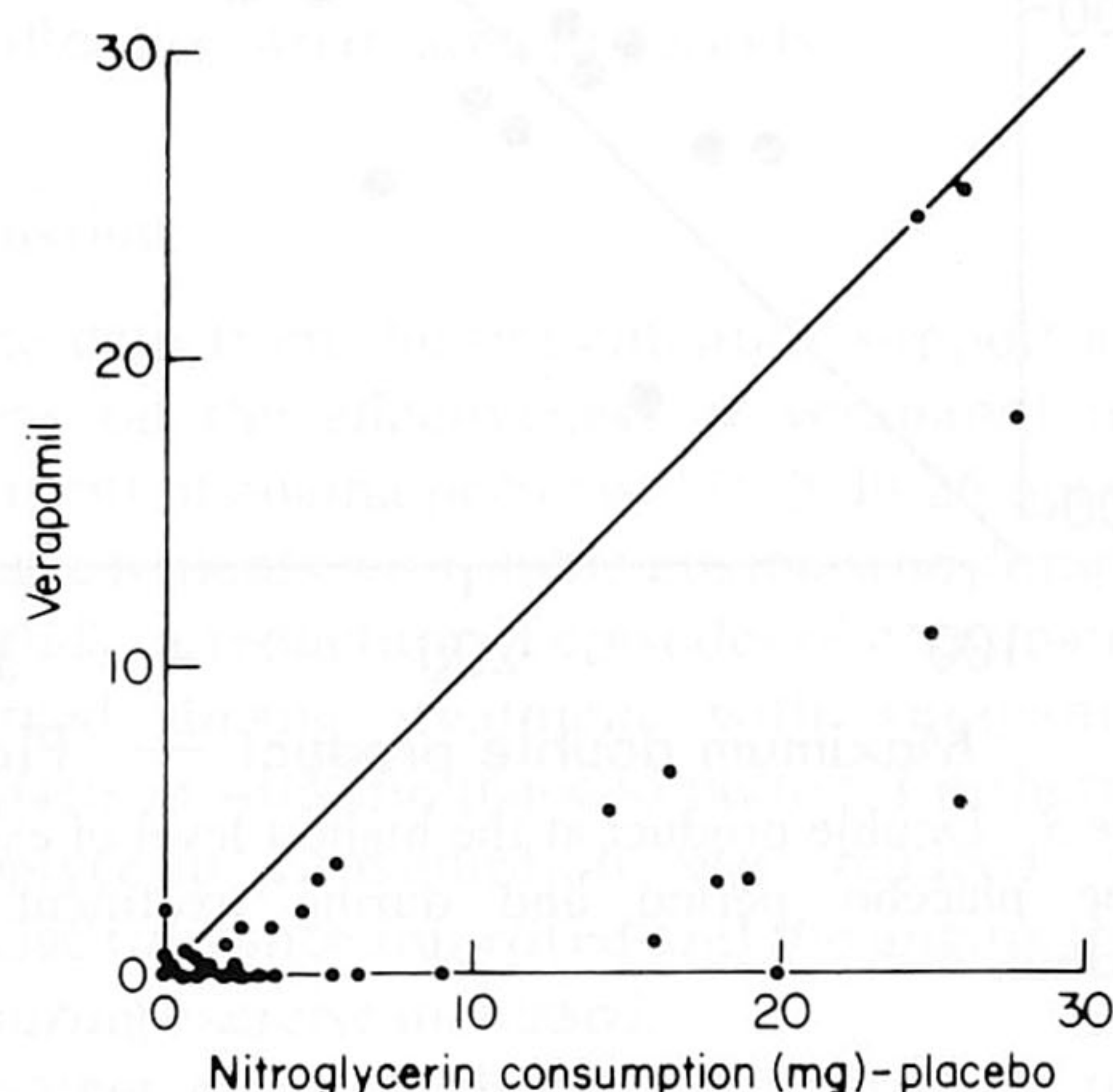

Figure 1   Nitroglycerin consumption (mg during four weeks) in the placebo period and during treatment with verapamil 3 × 120 mg.

two placebo periods (Table 1). During verapamil therapy, 26 out of the 33 patients reported a reduction in the number of episodes of chest pain; two patients had more episodes with verapamil than on placebo and five patients reported no difference between the two periods. The median of the differences between the two periods was eight episodes, the individual differences ranged from a reduction of 54 episodes to an increase of two episodes ($P < 0·01$). Similarly the nitroglycerin consumption was reduced in 27 patients. The median reduction was 2 mg, ranging from 20 to -2, as illustrated in Fig. 1 ($P < 0·01$).

At the end of the trial all patients were asked which treatment period gave the best results. Seven patients observed no differences between verapamil and placebo. 25 patients preferred verapamil and one patient preferred the placebo period ($P < 0·01$). The latter patient had two episodes of chest pain during the second treatment period (verapamil) and no episodes in the third period (placebo).

No differences were observed between the exercise tests at the end of the two placebo periods as shown in Tables 2, 3 and 4. After four weeks

*Table 3   Median values and ranges of exercise tolerance (W) at the end of each treatment period. The highest workload without chest pain was considered to be the maximum workload when no chest pain occurred during the test. * = P < 0·05; statistical significance of the difference between placebo period II and verapamil*

	Placebo I	Placebo II		Verapamil
Highest workload	110 (90–190)	110 (80–200)	*	120 (100–190)
Highest workload without chest pain	90 (50–140)	100 (40–160)	*	110 (50–150)

Table 4   Median values and ranges of heart rate (beats/min) and blood pressure (mmHg) during exercise tests at the end of each treatment period. * = P < 0·05; statistical significance of the difference between placebo period II and verapamil

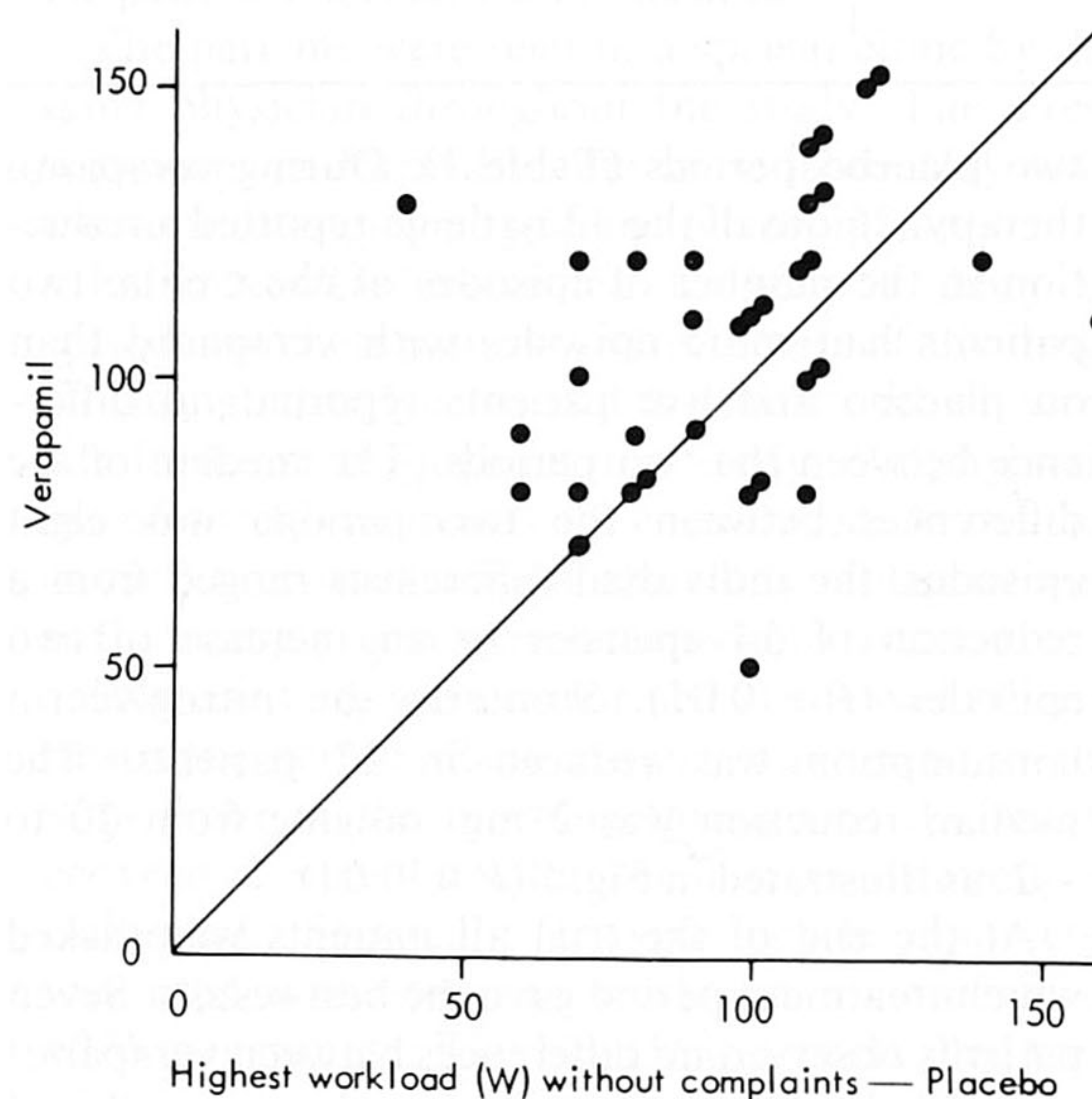|	Placebo I	Placebo II		Verapamil
Rest				
Heart rate	70 (48– 84)	69 (51– 94)		68 (48– 89)
Systolic pressure	140 (110–170)	140 (105–180)		140 (100–190)
Rate-pressure product	108 (76–136)	102 (54–154)	*	83 (56–146)
Highest workload				
Heart rate	126 (95–166)	125 (89–161)		123 (94–161)
Systolic pressure	185 (130–230)	190 (110–240)		185 (110–225)
Rate-pressure product	244 (149–348)	246 (140–315)		223 (122–305)

Figure 2   Highest level of work without dyspnea or chest discomfort in the placebo period and during treatment with verapamil.
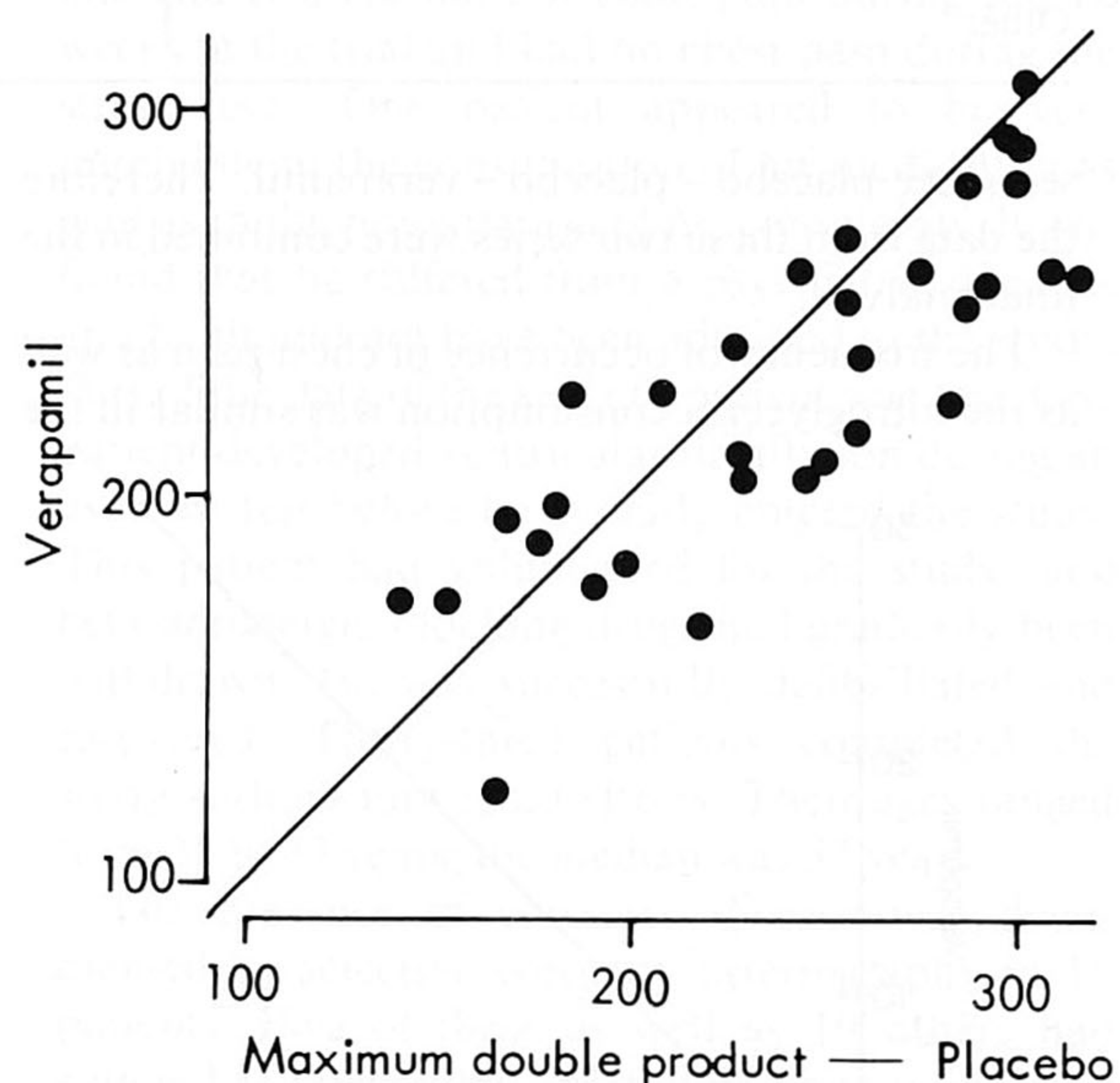

Figure 3   Double product at the highest level of exercise in the placebo period and during treatment with verapamil.

treatment with verapamil fewer patients developed chest pain (Table 2). The load which was tolerated without chest pain, as well as the highest workload increased by a median of 10 W. The individual differences ranged from an improvement of 90 to a reduction of 50 W (Fig. 2 and Table 3; $P < 0·05$).

No differences were found between heart rates and blood pressure either at rest, or at the highest workload. However, the rate-pressure product (double product) at rest was lower after verapamil than in the placebo period ($P < 0·05$). Also the highest rate-pressure product tended to be lower after verapamil ($P = 0·06$). When we compared the

tests of each individual patient, 20 out of the 33 reached a higher workload, 21 increased their threshold for chest pain during exercise (Fig. 2), and 21 patients terminated the test at a lower double product (Fig. 3).

Quantitative analysis of the ECG changes during exercise[8] yielded no difference between the probabilities of exercise-induced myocardial ischaemia after verapamil or placebo at the highest workload (Fig. 4). This corresponded with the results of visual reading of the ECG tracings. Finally, no systematic difference was observed between the incidence of premature ventricular complexes or
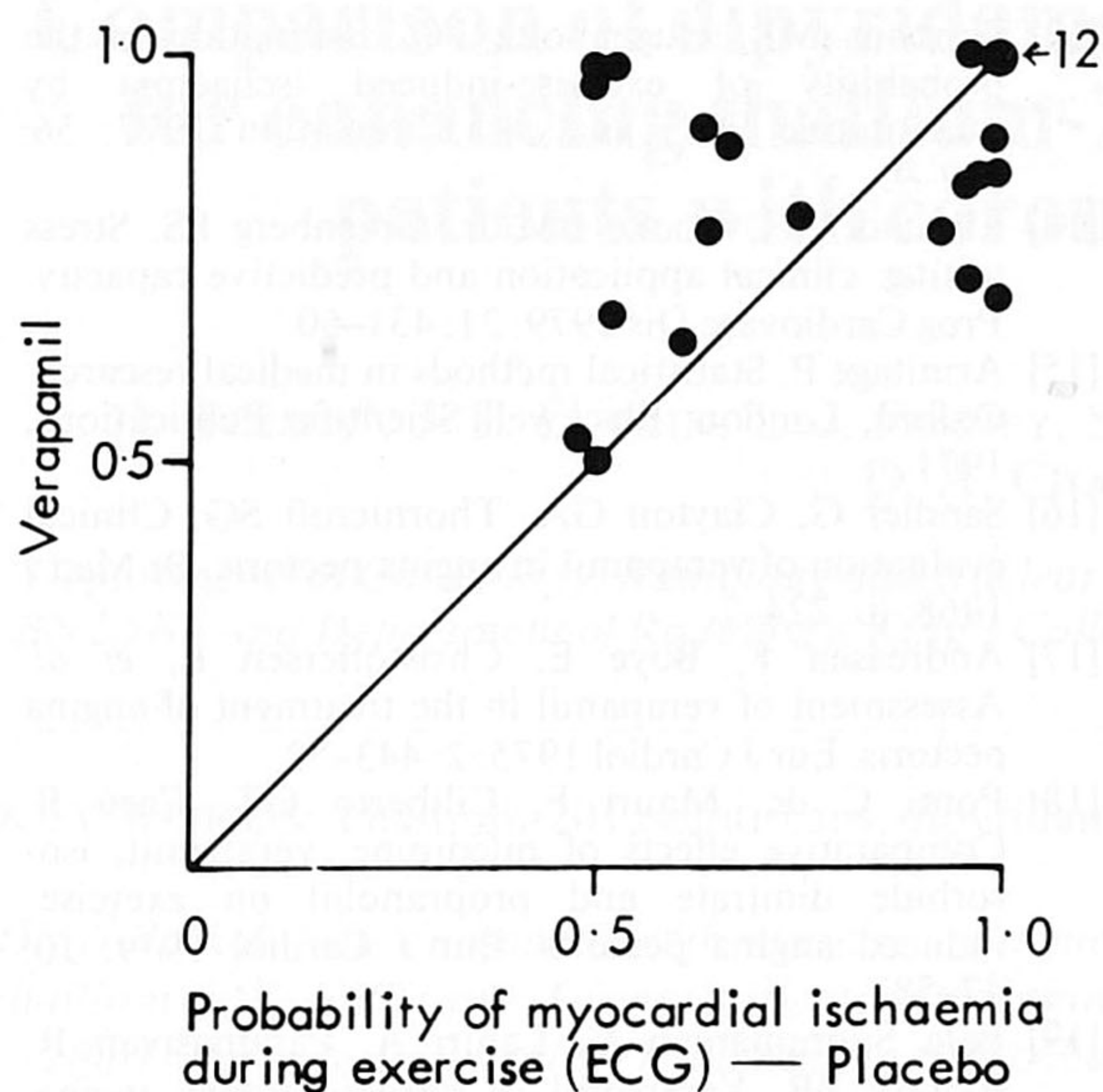
Figure 4 Probability of an abnormal ECG response at the highest level of exercise in the placebo period and during treatment with verapamil. The prior-probability was assumed to be 0·50[13].

premature supraventricular complexes during exercise after the two treatment periods.

Discussion

The data from the present study support earlier reports on the effectiveness of verapamil in the treatment of angina pectoris[11,16,17]. In 26 out of the 33 male patients with stable angina who completed the study, a reduction of episodes of chest pain was observed during treatment with verapamil in comparison with the placebo period. Furthermore, nitroglycerin consumption was reduced, mean exercise tolerance improved and the angina threshold during exercise increased.

Another recent study[19] reported similar results in 28 patients with the same dosage of verapamil, while lower dosages were not consistently effective[11]. In the present study, the improvement in symptoms and nitroglycerin consumption was more pronounced than the improvement in exercise tolerance. In comparison, Bala Subramanian *et al.*[19] observed greater improvement during exercise. This difference may be due to the exercise protocols and to patient selection since in the latter study patients had twice as many episodes of chest pain. Furthermore, it should be realized that all patients had stable angina for at least three months, so that it is likely that the patients had adjusted

their daily activities to a level which resulted in few episodes of chest pain. When we assume that their level of activities remained the same throughout the trial, it may be appreciated that the slightly improved exercise tolerance during drug treatment considerably reduced the symptoms. The improvement of the exercise tolerance after four weeks of verapamil was similar to the improvement immediately after nitroglycerin.

No comparison with other drugs was performed in the present study. Data from other studies[11,16,18] suggest that efficacy of verapamil 120 mg t.d.s. is comparable to that of beta-adrenergic blockade, such as propranolol 100 mg t.d.s.

The mechanism of the effect of verapamil in stable angina is not completely understood[1,3-6]; nevertheless it appears that verapamil, 360 mg daily, is an effective anti-anginal agent. It will be of particular value in patients in whom beta-adrenergic blockade has an insufficient effect and in patients with contra-indications to treatment with beta-adrenergic blockade such as chronic pulmonary disease. Since the mode of action of verapamil differs from beta-adrenergic blockade, both drugs might be combined theoretically. However, in patients with impaired left ventricular function, deterioration has been reported after combination of intravenous verapamil and practolol[7]. Thus such combination should be avoided, and patients in whom both drugs are prescribed should be monitored for signs of heart failure.

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