β Blockade and intermittent claudication: placebo controlled trial of atenolol and nifedipine and their combination

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Abstract

Objective—To determine the effects of the β_1 selective adrenoceptor blocker atenolol, the dihydropyridine calcium antagonist nifedipine, and the combination of atenolol plus nifedipine on objective and subjective measures of walking performance and foot temperature in patients with intermittent claudication.

Design—Randomised controlled double blind four way crossover trial.

Setting—Royal Hallamshire Hospital, Sheffield.

Subjects—49 patients (40 men) aged 39-70 with chronic stable intermittent claudication.

Interventions—Atenolol 50 mg twice daily; slow release nifedipine 20 mg twice daily; atenolol 50 mg plus slow release nifedipine 20 mg twice daily; placebo. Each treatment was given for four weeks with no washout interval between treatments.

Main outcome measures—Claudication and walking distances on treadmill; skin temperature of feet as measured by thermistor and probe; blood pressure before and after exercise; subjective assessments of walking difficulty and foot coldness with visual analogue scales.

Results—Atenolol did not significantly alter claudication distance (mean change −6%; 95% confidence interval 1% to −13%), walking distance (−2%; 4% to −8%), or foot temperature. Nifedipine did not alter claudication distance (−4%; 3% to −11%), walking distance (−4%; 3% to −10%), or foot temperature. Atenolol plus nifedipine did not alter claudication distance but significantly reduced walking distance (−9%; −3% to −15% ($p<0.003$)) and skin temperature of the more affected foot (−1·1°C; 0 to −2·2°C ($p=0.05$)). These effects on walking distance and foot temperature seemed unrelated to blood pressure changes.

Conclusions—There was no evidence of adverse or beneficial effects of atenolol or nifedipine, when given singly, on peripheral vascular disease. The combined treatment, however, affected walking ability and foot temperature adversely. This may have been due to β blockade plus reduced vascular resistance, which might also explain the reported adverse effects of pindolol and labetalol on claudication.

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Introduction

Patients with intermittent claudication commonly have coexistent angina or hypertension[1-3] and are therefore often candidates for β adrenoceptor blockers. Several uncontrolled observations have suggested that β blockers may cause or worsen the symptoms of peripheral vascular disease,[4-9] and intermittent claudication is widely regarded as a contraindication to β blockers in ordinary practice. Formal studies of the effect of β blockers on intermittent claudication are summarised in table I.[10-15] Most of the studies found no adverse effect, but most were too small to allow adequate assessment[16] and some were imperfectly controlled.

We report a double blind placebo controlled crossover trial of atenolol, the dihydropyridine calcium antagonist nifedipine, and both drugs in combination in patients with intermittent claudication. We studied atenolol because it remains unclear from the findings of Roberts *et al* whether this β blocker worsens intermittent claudication.[15] Nifedipine, which acts as an arteriolar vasodilator, was included because little information is available on its effect in peripheral vascular disease. In the only placebo controlled study reported nifedipine did not alter exercise tolerance, as measured by pedal ergometry, or subjective walking ability.[17] A major concern in that study was that six of 33 patients developed critical ischaemia after randomisation, but no information was given on the relation of deterioration to nifedipine or placebo.[17] Atenolol and nifedipine have additive antihypertensive[18] and antianginal[19] effects and are therefore often prescribed together. Patients with intermittent claudication are commonly treated with the two drugs simultaneously because of the frequent coexistence of hypertension, ischaemic heart disease, and peripheral vascular disease.[1-3] Nifedipine might counteract coldness of the peripheries associated with β blockade as it seems to increase skin temperature in peripheral vascular disease.[20]

Patients and methods

We recruited patients with stable intermittent claudication of at least six months' duration. All had leg claudication within 500 m of walking, absent or diminished peripheral pulses, and an ankle to brachial systolic pressure index <0·9 (mean 0·76 and 0·67 in right and left legs respectively) by Doppler ultrasonography at rest. Angiography was not required for entry.[16] We excluded patients with rest pain, angina which limited exercise before claudication, recent myocardial infarction, insulin dependent diabetes, serum creatine concentrations >200 μmol/l, any contraindication to β blockade, and coprescription of peripheral vasodilators, angiotensin converting enzyme inhibitors, or calcium antagonists. Treatment at constant dosage with diuretics, antiplatelet drugs, and other antihypertensive agents was allowed. Patients were asked to keep smoking habit, alcohol intake, diet, and exercise constant during the study.

Forty nine patients (40 men) aged 39-70 met the study criteria. The mean duration of claudication was 32 months (range 6-180), and 31 patients had bilateral and 18 unilateral peripheral vascular disease. The site of disease was superficial femoral in 45 limbs and aortoiliac plus femoral in 19 patients. Twenty had angina and 10 hypertension. Twenty nine patients were current cigarette smokers and 19 former smokers. All patients gave written informed consent, and the study was approved by the hospital ethics committee.

Study design and treatments—The study was a randomised placebo controlled double blind four period crossover trial comparing atenolol 50 mg twice daily, slow release nifedipine 20 mg twice daily, atenolol 50 mg plus slow release nifedipine 20 mg twice daily, and placebo. After a four week single blind placebo run in period patients were allocated study

numbers sequentially to provide a prerandomised treatment order, receiving each treatment for four weeks. Treatment periods were not separated by a washout interval. Trial drugs were dispensed as identical capsules to be taken one twice daily.

Exercise testing—Treadmill exercise tests were performed at entry, at two week intervals during the run in period, and at the end of each four week treatment period. After 30 minutes of acclimatisation treadmill exercise testing was performed on a Powerjog M4 treadmill (Sports Engineering, United Kingdom) at a gradient of 10%. The maximum comfortable walking speed for each patient was determined at the pre-entry test and then held constant throughout. The mean walking speed was 2·9 (range 2·0-4·5) km/h. Continuous electrocardiographic monitoring was performed during each test. Exercise tests were performed at the same time of day two to four hours after the morning dose of trial drug. The distance walked until the onset of pain was recorded as the claudication distance, and the distance walked until pain caused the patient to stop was recorded as the walking distance.

Measurements—Pre-exercise blood pressure was measured by a single observer (LP) as the mean of three readings supine (after five minutes' rest) and standing (for two minutes) using a Hawksley random zero sphygmomanometer on the right arm supported at heart level and recording phase V diastolic pressure. Post-exercise standing blood pressure was the mean of two readings taken two minutes after completion of exercise. The skin temperature of the plantar aspect of both big toes was measured at each visit with a thermistor and probe (models 4708 and 4700/4, Digitron Instrumentation, United Kingdom) after 30 minutes of acclimatisation. Subjective measurements of foot coldness, tiredness of legs, and difficulty in walking during the preceding treatment period were made with 10 cm calibrated horizontal visual analogue scales. Compliance was assessed by counting capsules returned and averaged 95% of those dispensed. There was no difference between treatments. Body weight and changes in smoking habit were recorded at each visit and showed no important change.

Statistics—The sample size was calculated to provide a power of 80% to show as significant at the 5% level a 20% difference in claudication distance between treatments.[16] Analysis of variance was used to examine the variance related to patients (df=48), visit (df=3), treatment (df=3), and carryover (df=3). The residual variance was n−58, where n=the number of observations; n was 196 with complete data but was usually 190. No adjustment was made in the analysis to allow for missing observations. Patients who withdrew from the study were included in the analysis up to the time of withdrawal. The significance of the carryover and treatment effects was assessed by the F test, and no evidence suggested that carryover effects were present. When treatments differed in the F test at $p<0·1$ pairs of treatments were compared by Student's paired t test. Data from the treadmill tests were log transformed to satisfy the model assumptions, and this transformation was shown to be appropriate by residual and normal plots. The data are presented untransformed for clarity. One patient responded particularly badly to nifedipine on treadmill testing but the results had no overwhelming effect on the analysis and were retained. Standard errors of the mean were derived from the analysis of variance and were almost identical in the four treatment groups. For simplicity only those in the placebo group are shown in the tables.

Results

Withdrawals after randomisation—Three of the 49 patients withdrew after randomisation. One developed left ventricular failure during placebo treatment. Another suffered subjective worsening of claudication, lethargy, insomnia, and cold extremities while taking atenolol in the second study phase and had to discontinue treatment. Treadmill testing was performed after two weeks of treatment (before she stopped taking atenolol), and these results are included in the analysis. A third patient stopped taking combined treatment with atenolol plus nifedipine because of rest pain and cold extremities. No treadmill data were available for that treatment, and the analysis is therefore biased slightly in favour of combined treatment.

Claudication distance—The results for claudication and walking distances and subjective measurements of walking difficulty and tiredness of legs are shown in table II. During placebo treatment the mean distance walked to claudication was 66·8 (SEM 1·0) m and the total walking distance 113·1 (1·0) m. When compared with placebo treatment atenolol, nifedipine, and the two drugs in combination shortened claudication distance slightly but not significantly. The mean reductions in claudication distance (95% confidence interval) were 6% (−1% to 13%) with atenolol, 4% (−3% to 11%) with nifedipine, and 6% (−2% to 13%) with atenolol plus nifedipine. The three active treatments did not differ significantly. Direct comparison of atenolol with nifedipine showed a non-significant 2% advantage for nifedipine. The effect of treatments on claudication distance was unrelated to the severity of claudication. In particular, there was no evidence of an adverse effect in those most severely afflicted as judged by claudication distance during placebo treatment. Patients in the lowest quartile had a mean claudication distance of 38 m (range 27-46 m; n=12) during placebo treatment. The mean changes in claudication distance in this group were +4% for atenolol, +1% for nifedipine, and −2% for combined treatment.

Total walking distance—For total walking distance atenolol and nifedipine caused slight but non-significant reductions from placebo values, averaging 2% (95% confidence interval −4% to 8%) and 4% (−3% to 10%) respectively (table II). Direct comparison of atenolol with nifedipine showed a 2% advantage for atenolol, which was not significant. The combination of atenolol plus nifedipine reduced total walking

TABLE I—*Formal studies of influence of β blockers in patients with intermittent claudication*

Reference	No of patients	β Blocker	Daily dose (mg)	Duration (weeks)	Trial	Claudication distance
Reichert *et al*[10]	7	Propranolol	240-1600	2	Crossover, double blind	No change
Lepantalo *et al*[13]	28	Various	Various	4	Parallel group, open	No change
Bogaert and Clement[12]	10	Propranolol	160	8	Crossover, double blind	No change
	10	Metoprolol	200	8	Crossover, double blind	No change
Hiatt *et al*[11]	19	Propranolol	120	2	Crossover, double blind	No change
	19	Metoprolol	150	2	Crossover, double blind	No change
Svendsen *et al*[14]	14	Metoprolol	200	8	Crossover, open	No change
	11	Acebutolol	400	8	Crossover, open	No change
Roberts *et al*[15]	20	Atenolol	100	4	Crossover, observer blind	No change
	20	Pindolol	20	4	Crossover, observer blind	Reduced
	20	Labetalol	400	4	Crossover, observer blind	Reduced

TABLE II—*Mean (SEM) results for objective and subjective measures of walking performance and temperature in patients with intermittent claudication*

	Placebo	Atenolol	Nifedipine	Atenolol + nifedipine
No of patients	48	49	46	47
Claudication distance (m)	66·8 (1·0)	62·6	63·9	62·9
Walking distance (m)	113·1 (1·0)	110·8	109·0	102·4*
Tired legs by visual analogue scale (mm)	46·1 (2·4)	52·8†	54·0‡	50·9
Walking worse by visual analogue scale (mm)	45·4 (2·2)	50·8	46·7	46·4
Temperature (°C):				
Left foot	25·5 (0·4)	24·5	24·7	24·6
Right foot	25·8 (0·3)	25·0	25·0	24·5§
Worse foot‖	25·6 (0·4)	24·9	24·7	24·5†
Better foot	25·8 (0·4)	25·3	25·2	24·9

*p<0·003 *v* placebo; p<0·02 *v* atenolol; p=0·06 *v* nifedipine. †p=0·05 *v* placebo. ‡p<0·02 *v* placebo. §p<0·01 *v* placebo. ‖Foot of more affected limb as determined by Doppler studies (n=42-44).

TABLE III—*Mean (SEM) results for blood pressure and heart rate before and two minutes after treadmill exercise tests in patients with intermittent claudication*

	Placebo	Atenolol	Nifedipine	Atenolol + nifedipine
No of patients	48	49	47	47
Pre-exercise supine:				
Systolic blood pressure (mm Hg)	142·2 (1·6)	132·3*	137·3†‡	132·1*
Diastolic blood pressure (mm Hg)	84·8 (1·1)	77·9*‡	81·7†§	74·8*
Heart rate (beats/min)	82·1 (1·1)	66·6*	84·5§	69·6*
Pre-exercise standing:				
Systolic blood pressure (mm Hg)	136·6 (1·6)	127·5*‖	126·9*‡	121·1*
Diastolic blood pressure (mm Hg)	86·4 (0·9)	79·1*§	81·6*§	73·8*
Heart rate (beats/min)	84·7 (1·1)	68·6*	87·4§	71·1*
Post-exercise standing:				
Systolic blood pressure (mm Hg)	163·1 (2·3)	156·4†§	151·1*‖	141·8*
Diastolic blood pressure (mm Hg)	87·1 (1·0)	82·4¶§	82·2*§	74·4*
Heart rate (beats/min)	107·8 (1·4)	83·1*	111·8†§	84·8*

*p<0·001 *v* placebo.
†p<0·05 *v* placebo.
‡p<0·05 *v* atenolol + nifedipine.
‖p<0·1 *v* atenolol + nifedipine.
¶p<0·01 *v* placebo.

distance significantly by 9% (3% to 15%; p<0·003). Walking distance was reduced more by the combination than by atenolol alone (by 8%; 2% to 13% (p<0·02)) or nifedipine alone (by 6%; 0 to 12% (p=0·06)).

Subjective walking ability—In the subjective assessments of walking ability both atenolol and nifedipine increased tiredness of the legs as measured by visual analogue scale (p=0·05 and p<0·02 respectively; table II) with no significant difference between the treatments. Atenolol plus nifedipine when combined had no significant effect on leg tiredness despite the significant shortening of walking distance. There were no significant differences among treatments in difficulty in walking as measured by visual analogue scale.

Temperature changes—When compared with placebo, atenolol and nifedipine reduced the skin temperature of the toes slightly but not significantly (table II). Atenolol and nifedipine in combination reduced the temperature of the right foot by 1·3°C (95% confidence interval 0·3 to 2·2°C; p<0·01) and in the left foot by 0·9°C (−0·1 to 1·9°C; p>0·05). Differences among the active treatments were not significant. When the skin temperature was analysed in the better and worse limbs, as judged by Doppler studies, combined treatment reduced the temperature of the worse limb by 1·1°C (0 to 2·2°C; p=0·05) and in the better limb by 0·9°C (−0·2 to 1·9°C; p>0·05). The difference between worse and better limbs was not significant, and temperature changes with combined treatment did not differ significantly from those with atenolol and nifedipine given singly. Subjective coldness of the feet assessed by visual analogue scale showed no significant differences among treatments for either foot or for the better or worse foot. The objective reduction in temperature of the right foot with combined treatment was not paralleled by increased subjective coldness.

Blood pressure and heart rate—When compared with placebo, atenolol and nifedipine each reduced systolic and diastolic blood pressures when supine and standing before exercise and when standing after exercise (table III). These changes were similar with the two treatments and were generally highly significant when compared with placebo. Combined treatment with atenolol plus nifedipine decreased blood pressure further, both before and after exercise (table III). The falls in blood pressure with combined treatment were generally significantly larger than those with the drugs taken singly (table III). When compared with atenolol and nifedipine alone combined treatment reduced post-exercise systolic blood pressure by 15 (95% confidence interval 8 to 21; p<0·0001) and 9 (3 to 16; p<0·01) mm Hg respectively and post-exercise diastolic pressure by 8 (5 to 11; p<0·0001) and 8 (5 to 11; p<0·0001) mm Hg respectively. Heart rate was reduced highly significantly by atenolol alone and in combination with nifedipine (table III). Nifedipine alone did not significantly change supine or standing heart rate before exercise but significantly increased the post-exercise heart rate when compared with placebo (table III).

Blood pressure and walking performance—The relations between post-exercise blood pressure, objective and subjective measures of walking ability, and objective and subjective measures of foot temperature during treatment with atenolol plus nifedipine in combination are shown in table IV as correlation matrices using absolute values and changes from placebo values. There were no important relations of post-exercise blood pressure with claudication or walking distance or measures of temperature. The only significant correlation was between change in systolic pressure and subjective leg tiredness ($r=0·40$; p<0·02), patients with smaller falls in systolic pressure having increased leg tiredness. This may have been a spurious significant finding given the number of tests performed. There was no correlation between treadmill walking distance and foot temperature, the two variables affected adversely by combined treatment. Of note was the lack of correlation between objective and subjective assessments. There were no significant relations between walking distance and subjective leg tiredness or between foot temperature and subjective coldness.

TABLE IV—*Relations between post-exercise blood pressure and objective and subjective measures of walking ability during treatment with atenolol plus nifedipine in combination expressed as correlation matrices using absolute values and changes from placebo values*

	Claudication distance	Walking distance	Tired legs*	Temperature of right foot	Cold right foot*
		Absolute values			
Systolic blood pressure	0·27	0·30	−0·14	−0·15	0·12
Diastolic blood pressure	0·07	0·08	0·07	−0·16	0·04
Claudication distance		0·86†	−0·10	0·21	0·02
Walking distance			−0·03	0·26	0·10
Tired legs*				0·13	0·43‡
Temperature of right foot					0·14
		Changes from placebo values			
Systolic blood pressure	0·15	−0·07	0·40‡	0·03	−0·07
Diastolic blood pressure	0·20	0·03	0·17	0·08	0·09
Claudication distance		0·31	−0·04	0·00	−0·02
Walking distance			−0·08	0·19	−0·22
Tired legs*				0·08	0·23
Temperature of right foot					−0·11

*Visual analogue scale. †p<0·002; df=45. ‡p<0·02; df=45.

The dissociation was evident also when examining changes between treatments (table II). Significant subjective leg tiredness was observed with atenolol and nifedipine treatments with no change in walking distance, whereas the significant reduction of walking distance by combined treatment was not paralleled by increased leg tiredness.

Discussion

The β_1 selective blocker atenolol had no significant adverse effect on the claudication or total walking distance in these patients with peripheral vascular disease. The 95% confidence intervals precluded reductions greater than 13% for claudication distance and 8% for walking distance. There was no evidence of an adverse effect even in patients in the lowest quartile for claudication distance—that is, those with most severe peripheral vascular disease. Our findings for claudication distance were consistent with those of Roberts *et al*, who reported that atenolol caused no significant reduction in the distance to claudication.[15] However, we were unable to confirm the significant reduction in total walking distance of about 17% observed with atenolol in their study, and the 95% confidence interval in our study was inconsistent with an effect of that magnitude.

The reason for the different outcome in the two studies, which were similar in design and dosage of atenolol, is unclear. However, Roberts *et al* may have overestimated any effect of atenolol on walking distance because of their smaller sample size. The only adverse effect of atenolol observed in our study was a significant increase in subjective leg tiredness measured by visual analogue scale, but this finding is not specific to patients with peripheral vascular disease.[21,22] Leg tiredness of a similar degree was observed with nifedipine. Atenolol caused a slight but non-significant reduction in peripheral skin temperature and a non-significant increase in subjective coldness of the feet. Our overall conclusion, however, is that atenolol had no important adverse effect on the symptoms of peripheral vascular disease. Results of the studies summarised in table I suggest that this conclusion may also hold for another β_1 selective blocker, metoprolol. We emphasise, however, that our study, with a sample size far larger than that in any previous study, was unable to exclude with confidence a reduction in claudication distance as large as 13% with atenolol. Other studies have generally been far too small to settle the question adequately.[16]

There have been suggestions that the dihydropyridine calcium antagonist nifedipine might improve[20,23] or worsen[24,25] intermittent claudication. Its effects have been examined in only one controlled trial, which showed no significant change in intermittent claudication or subjective walking ability.[17] Our study also showed no evidence for any beneficial or adverse effect of nifedipine on walking ability, and the 95% confidence intervals precluded changes in claudication or walking distance larger than a 3% improvement or 11% worsening. The significant increase in subjective leg tiredness was unexpected. An increase in skin temperature and improvement in subjective coldness of the feet might have been anticipated as nifedipine increases skin temperature[20] and commonly causes flushing and hotness of the skin. However, there was a non-significant reduction in skin temperature equivalent to that observed with atenolol. The overall conclusion for nifedipine is that it had no important negative or positive effect on the symptoms of peripheral vascular disease. Moreover, there is no support for the suggestion[17] that it has an advantage over β blockers, or at least over atenolol, in patients with peripheral vascular disease. The effects of nifedipine and atenolol on claudication and walking distances, foot temperature, and leg tiredness were virtually identical.

Combined treatment with atenolol plus nifedipine caused significantly larger falls in blood pressure before and after exercise than did the two drugs given singly. The combination caused a non-significant 6% reduction in claudication distance, and the 95% confidence interval precluded a reduction greater than 13%. There was a significant reduction in walking distance averaging 9%, with a 95% confidence interval of 3% to 15%. The effect of combined treatment on walking distance was significantly greater than that of atenolol alone, and the difference from nifedipine alone approached significance. Atenolol plus nifedipine in combination also caused a significant reduction in skin temperature, which was slightly but not significantly more pronounced in the more affected limb. The only patient to develop critical ischaemia during the trial did so during treatment with the drugs in combination. The reductions in walking distance and skin temperature with combined treatment did not correlate with blood pressure or change in blood pressure after exercise. There was a pronounced dissociation between the findings of objective and subjective methods of assessment. Reduction in skin temperature was not paralleled by increased subjective coldness, and the significant reduction in walking distance was not associated with a noticeable increase in subjective leg tiredness. Subjective leg tiredness was less prominent with combined treatment than it was with atenolol or nifedipine given alone.

CONCLUSIONS FROM AVAILABLE EVIDENCE

What conclusions can be drawn from this study, previous clinical studies (table I), and experimental evidence concerning the effects of β blockade on peripheral vascular disease? β Blockers reduce maximal muscle blood flow in subjects without peripheral vascular disease.[26,27] This is observed alike with non-selective and β_1 selective blockers[27] and is therefore unlikely to be caused by β_2 blockade in muscle vessels.[27,28] However, pindolol, which has substantial partial agonist activity, maintains maximum muscle blood flow,[29] presumably through stimulation of β_2 receptors in muscle vasculature. Similar effects of β blockade have been observed in the less affected limb of patients with peripheral vascular disease,[30] including maintained maximal muscle blood flow with pindolol.[31]

The situation, however, seems different in the more severely affected limb of patients with peripheral vascular disease. β Blockade has reduced maximal muscle blood flow in some studies[30] but not in others.[31] Differences between studies are possibly related to the method of inducing maximal flow or to the severity of vascular obstruction.[31] In advanced disease the degree of arterial insufficiency itself probably becomes the main modulator of muscle blood flow[31] as the reduction in flow is independent of ancillary properties of β blockers such as β_1 selectivity,[30] partial agonist activity,[30,31] or additional α blockade.[31] These observations suggest that reduced maximum muscle blood flow in peripheral vascular disease is not a consequence of β blockade locally in the ischaemic limb. This is supported by evidence that methyldopa reduces maximum muscle blood flow to the same extent as metoprolol in patients with peripheral vascular disease.[32]

It has been suggested, therefore, that any adverse effect of β blockers on symptoms of peripheral vascular disease is likely due to reduction in cardiac output by β blockade[27] or to reduction of blood pressure regardless of the mechanism.[32] Clinical studies (table I) and our study do not support this interpretation. Unequivocal worsening of intermittent claudication has been

observed only with pindolol and labetalol.[15] In our study only the combination of atenolol plus nifedipine had a significant adverse effect on walking distance, and this effect was significantly different from that of atenolol alone. These three treatments—pindolol, labetalol, and atenolol plus nifedipine—have in common their combination of β blockade with a reduction in peripheral vascular resistance. The reduced vascular resistance is caused respectively by β_2 agonist activity,[33] α blockade, and non-specific arteriolar vasodilatation. These treatments cause less reduction in cardiac output than does β blockade with no additional vasodilatation.[19 33] The view that reduced cardiac output is the important factor in worsening walking performance is therefore difficult to sustain.

Blood pressure reduction is also unlikely to be the critical influence. In this study atenolol plus nifedipine combined had a significant added hypotensive effect, as expected.[18] However, there was no relation between blood pressure or blood pressure change and the deterioration of walking performance with combined treatment. In the study of Roberts *et al* blood pressure reductions were similar with pindolol, labetalol, atenolol, and captopril, yet only pindolol and labetalol reduced claudication distance significantly.[15] Reduction in blood pressure does not therefore seem to be the proximate cause of symptomatic deterioration in patients with peripheral vascular disease.

We propose that adding vasodilatation to β blockade, whether through partial agonist activity, α blockade, or non-specific vasodilatation, may be the key factor in symptomatic worsening of peripheral vascular disease. Reduction in vascular resistance in unaffected or less affected vascular beds may lead to a local "steal" phenomenon[34] and reduce perfusion of limbs with obstructive arterial disease without affecting the blood pressure recorded at the brachial artery. In the case of pindolol the steal may be to unaffected muscle, mediated by β_2 receptor stimulation,[31] and in the case of labetalol mainly to the skin through α blockade.[31] In this study a significant reduction in skin temperature with atenolol plus nifedipine, particularly in the more affected leg, lends indirect support to this hypothesis. The corollary of the hypothesis is that the increase in vascular resistance observed with β blockers which have no additional partial agonist activity, α blockade, or vasodilator action[27] may actually be necessary to maintain local blood flow and prevent symptomatic deterioration in patients with peripheral vascular disease.

What are the implications of these observations for ordinary medical practice? We conclude that the β_1 selective blocker atenolol can generally be used safely in patients with intermittent claudication, and this may also be true for other β_1 selective blockers such as metoprolol. There is insufficient evidence to draw any firm conclusion on the safety or otherwise of propranolol and other non-selective β blockers without partial agonist activity. Nifedipine seems to offer no advantage over atenolol in patients with peripheral vascular disease. The combination of atenolol plus nifedipine worsens walking distance and reduces skin temperature significantly in patients with intermittent claudication. β Blockers which also reduce vascular resistance, whether by partial agonist activity, additonal α blocking activity, or non-specific vasodilatation, should probably be avoided in patients with peripheral vascular disease until further evidence on their safety becomes available.

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