ALTERNATIVES TO β -BLOCKADE IN THERAPY OF HYPERTENSION WITH ANGINA PECTORIS: ROLE OF NIFEDIPINE OR OF LABETALOL

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- 1 Patients with combined hypertension and angina pectoris may represent a therapeutic dilemma, with the angina being refractory to conventional β -blockade.
- 2 The added benefit of peripheral vasodilation in control of blood pressure is documented in the case of nifedipine.
- 3 Improved blood pressure control by added nifedipine may not be accompanied by decreased severity of angina pectoris, emphasizing the complex causation of the angina in such patients.
- 4 The clinically proven added α -blocking activity of labetalol distinguishes labetalol from other β -blockers. However, the suggested benefits of the added α -activity in patients with hypertension and angina remain to be proven by further trials in patients.

Introduction

Considerable evidence points to a role for vascular hyper-reactivity in the initiation and maintenance of high arterial pressure. Patients with borderline hypertension have a neural-dependent mechanism, whereas those with sustained hypertension have an increased total peripheral resistance (Safar *et al.*, 1977). In the developing phase of hypertension, the peripheral resistance rises while the initially high cardiac output normalizes (Kilcoyne, 1980). Hypertensive patients who react to a coldpressor test with exaggerated rises in the arterial pressure have a poorer prognosis than others (Hines, 1940; Keys *et al.*, 1977). Borderline hypertensive patients react to the stress of mental arithmetic with an increased rise in arterial pressure (Nestel, 1969), which is accompanied by increased urinary values of adrenaline and noradrenaline. Recent evidence also suggests that α -mediated vasoconstriction can play a role in coronary artery spasm (Leven & Freeman, 1976; Ricci *et al.*, 1979), one of the causes of angina at rest. In occasional patients, coronary spasm may also be exercise-induced. The intolerance to cold found in some patients with angina is associated with increased blood pressures at rest and during exercise, presumably reflecting an increased peripheral vascular resistance (Lassvik & Areskog, 1979). Therefore, the potential therapeutic role of

α -blockade becomes readily understandable in patients with both hypertension and angina pectoris.

Similar arguments hold for the assessment of the possible therapeutic role of calcium antagonist agents, such as nifedipine, which both reduce the afterload (Olivari *et al.*, 1979) and reduce coronary arterial tone (Himori *et al.*, 1976). For these reasons, therapeutic trials have been undertaken with nifedipine as an example of a calcium-antagonist agent, and with labetalol, which has combined α - and β -blocking activity.

Use of nifedipine

In combination with propranolol, nifedipine reduces ST-segment deviations in monitored patients with exertional angina (Lynch *et al.*, 1980). A combination of β -adrenoceptor blockade and nifedipine should, therefore, be especially effective in treating coexisting hypertension and angina. We studied 15 patients with stable effort angina and hypertension who were treated with nifedipine in addition to pre-existing treatment with a β -adrenoceptor blockade and a diuretic. One of our patients has been reported in detail (Opie & White, 1980).

Quantification of angina pectoris (Lubbe & White, 1978)

- Score 5: severe attacks on effort > four daily; angina at rest; severely limited (nitrate consumption > four tablets daily).
- Score 4: angina only on effort, one to four attacks daily, somewhat limited (nitrate consumption one to four tablets daily).
- Score 3: angina inconsistently on effort; minimal limitation (nitrate consumption none to one daily).
- Score 2: attacks occasionally but definable as angina (nitrate required, but sporadically).
- Score 1: pain only on marked effort and not severe; no nitrate required.
- Score 0: unlimited ordinary activity without chest pain.

After an initial run-in period of 2-6 weeks to establish compliance, initial control blood pressure readings were done in the sitting (mean of two blood pressure values 2 min apart after 10 min of rest), standing after 30 s, standing just after walking a measured distance of 60 m, during hand-grip of 60 s to half maximal pressure (using a Medicon dynamometer graduated in arbitrary units), and after 30 s of cold-immersion (hand up to mid-arm in bucket of ice-cold water). Blood pressure was taken on the right arm with a standard mercury sphygmomanometer, with a cuff with bladder, 24 cm in length and 13 cm in width, and the disappearance of the sounds (Korotkoff sound 5) was taken as the diastolic value, always using the same machine and same cuff throughout. Readings were taken at 1000-1100, that is, 3-4 h after the morning dose of drugs.

Table 1 Effect of nifedipine on blood pressures (mm Hg mean $\pm$ s.e.mean) in patients with hypertension and angina pectoris

		Sitting	Standing	After walking	During isometric exercise	During cold exposure
Admission	(15) <i>P</i>	162 ± 7/108 ± 4 NS <0.005	161 ± 7/105 ± 4 NS	157 ± 7/99 ± 3 NS	188 ± 8/127 ± 3 NS	181 ± 7/120 ± 3 NS
First placebo period	(15) <i>P</i>	165 ± 7/102 ± 3 <0.001 <0.001	160 ± 7/104 ± 3 <0.005 <0.001	157 ± 6/100 ± 3 <0.005 =0.05	189 ± 7/125 ± 3 <0.005 <0.001	183 ± 8/119 ± 3 <0.005 <0.005
Nifedipine	(15) <i>P</i>	148 ± 6/94 ± 3 <0.01 <0.005	146 ± 5/96 ± 3 <0.005 <0.001	143 ± 5/87 ± 7 <0.005 <0.01	174 ± 5/116 ± 3 <0.01 <0.005	166 ± 5/111 ± 3 <0.05 <0.005
Second placebo period	(14)	161 ± 6/104 ± 3	162 ± 7/107 ± 3	159 ± 7/99 ± 9	188 ± 6/126 ± 3	177 ± 6/121 ± 3

Number of patients in brackets.

Trial design

The nifedipine placebo (one capsule twice daily) was added to the pre-existing therapy for a period of 6 weeks, with all the blood pressure measurements repeated thrice at 2 week intervals. For purposes of calculation, the mean of the three blood pressure values was taken as a single reading.

Thereafter nifedipine placebo was substituted by active nifedipine 10 mg twice daily in 12 patients for a further 6 weeks and all the above measurements repeated. Finally, active nifedipine was replaced by nifedipine placebo (one capsule twice daily) and all the blood pressure readings were repeated after 2 weeks and 1 month, as was the exercise test.

Two treadmill exercise tests were undertaken during the initial placebo period (after 2 and 4 weeks) with the Naughton protocol (Naughton & Haider, 1973) at a constant speed of 2 m.p.h. and an increasing elevation. End points were ECG ST-depression, fatigue onset of chest pain or ventricular arrhythmias. A further treadmill test was undertaken between 2 and 4 weeks of active nifedipine.

Deviations from trial design

Two unexpected reactions led to deviations from the trial design. In one patient (Opie & White, 1980) severe hypertension developing on combined atenolol and nifedipine led to inability to undertake the exercise test during the nifedipine period. Another patient, described in more detail under the Results section, did not complete the second placebo period because of the striking improvement (from unstable angina and effort-induced ST-elevation) in response to nifedipine. Her results for the angina score are shown separately (Table 2). Other deviations from the design are given under the Results of exercise testing section.

Results of addition of nifedipine

Nifedipine was an active hypotensive agent, even in the presence of β -blockade and was superior to placebo in reducing the sitting, standing and post-exercise blood pressures as well as the cold pressure response (Table 1). Mean sitting pressures were as follows (mmHg $\pm$ s.e. mean): initial therapy $162 \pm 7/108 \pm 4$; same therapy plus nifedipine placebo $165 \pm 7/102 \pm 3$; same therapy plus active nifedipine, $148 \pm 6/94 \pm 3$; same plus placebo and nifedipine $164 \pm 7/105 \pm 4$ ($P < 0.005$ for all comparisons between active nifedipine and placebo). There were certain deviations from the

Table 2 Effect of nifedipine on angina score in patients with hypertension and angina pectoris

	Placebo	Nifedipine	Placebo
Patients who completed trial (14)	2.79 ± 0.24	2.91 ± 0.34	2.71 ± 0.27
Single patient who did not complete trial	5.0	0	—

protocol (see next section) which do not alter the comparisons between the active nifedipine period and the final placebo period. The values for these comparisons are based on a paired *t* test, omitting the values of the patient who dramatically improved on nifedipine and in whom it was not ethically justifiable to revert to placebo therapy. The addition of nifedipine did not change the severity of the angina as judged by a subjective scoring system, except in one patient with exertional angina which was due to coronary artery spasm (Table 2). In the patient, there was a dramatic response to nifedipine and it was this patient who was excluded from the final part of the trial. Nifedipine addition did not change the heart rate (Table 3), nor the PR-interval, nor the cardiothoracic ratio (data not shown).

Results of exercise testing in patients treated with nifedipine

Exercise testing was performed in 13 patients, two being deemed clinically unsuitable because of excess hypertension or hypotension. When taking all our 13 patients together, there was a persistent increase in the distance that these patients could exercise (Table 4), before reaching the endpoint which was one of the following: ST depression (five), fatigue (five), anginal pain (four), dyspnoea (three), blood pressure fall (one), ST-elevation and ventricular arrhythmias (one).

When active nifedipine was introduced in six patients of this single-blind study, it was noted that in these patients the blood pressure fell rather markedly and concurrent therapy had to be reduced or altered. That was to avoid the sort of adverse hypotensive interaction between nifedipine and β -blockade recently described by Opie & White (1980). Thus in six of the patients, the dose of prazosin was stopped, while in two perhexilene was ceased (the patients no longer requiring the perhexilene).

For these reasons, the results of the exercise test are difficult to interpret on six of the 13 patients. In the remaining seven patients, the results on nifedipine again showed an improvement in the

Table 3 Effect of nifedipine on heart rate (beats min⁻¹; mean $\pm$ s.e.mean)

	<i>Sitting</i>	<i>After isotonic exercise</i>	<i>During isometric exercise</i>
Admission heart rate	60.5 $\pm$ 1.8 (15)	65.2 $\pm$ 2.6 (15)	65.9 $\pm$ 2.7 (15)
First placebo period	60.4 $\pm$ 1.9 (15)	66.5 $\pm$ 2.2 (15)	67.5 $\pm$ 2.8 (15)
Active nifedipine	63.1 $\pm$ 2.4 (15)	67.1 $\pm$ 2.9 (15)	67.9 $\pm$ 2.8 (15)
Second placebo period	63.7 $\pm$ 2.2 (14)	67.2 $\pm$ 2.6 (13)	69.2 $\pm$ 2.4 (13)

P values for comparison between nifedipine and both placebo periods — not significant

walking distance but the results were not of statistical significance, possibly because of the smaller numbers.

Conclusions: nifedipine plus β -blockade

The major consistent finding of the study was that nifedipine was an active hypotensive agent when added to β -blockade. Subjectively, the anginal score did not change, but there was inconclusive evidence of an objective improvement in effort tolerance. We cannot exclude that nifedipine acted to improve cardiac output by coronary vasodilation, but the combination of unaltered anginal scores and the tendency of improved exercise tolerance where the endpoint was generally fatigue, suggests a major peripheral site of action for nifedipine in these patients. The adverse interaction between nifedipine and β -blockade could result from (a) additive hypotensive effects (Opie & White, 1980), or (b) additive negative inotropic effects (Anastassides, 1980).

Arguments for labetalol

Although labetalol is widely held to have a much more major β - than α -blocking effect (Brittain & Levy, 1976), such animal pharmacology tests tell us little about the actual effects on the blood pressure in man. Nor is the relatively low binding of labetalol to α -receptors, when compared with phentolamine (Greenslade *et al.*, 1979), of direct clinical importance. Thus, if the arterial pressure is in reality very actively controlled by a relatively "small" but "active" α -input, then even a relatively mild α -blocking agent should be effective. Attention to the role of the α -adrenoceptor in the production

and perpetuation of hypertension has also been focused by the widespread use of prazosin as an effective agent for the management of hypertension, as well as for afterload and pre-load reduction in the therapy of congestive heart failure. Lund-Johansen (1979) found that the haemodynamic effects of labetalol (mean daily dose 423 mg) were similar to those of combined α - and β -blockade with prazosin (mean daily dose 4 mg) and tolamolol (mean daily dose 200 mg which equalled 17.5 mg timolol). Johnsen (1976) could also show that labetalol 400–600 mg gave at least as good control of hypertension in 11 subjects with initial mean supine values of 188/109 mmHg, as did the combination of oxprenolol 480 mg daily and phentolamine 60 mg daily. Especially noteworthy is that the early studies by Richards *et al.* (1977) showed that the infusion of labetalol to normal subjects was accompanied by a rapid drop in arterial pressure within 2 min, in contrast to the intravenous infusion of β -blocking agents such as atenolol which caused no fall in arterial pressure at 15 min and significant falls only after 1–3 h in the case of the diastolic pressure (Fitzgerald *et al.*, 1978). Similarly, infusion of labetalol led to no changes in the pulse rate or a slight increase (Richards *et al.*, 1977), whereas infusion of β -blocking agents led to a decrease in the heart rate (Fitzgerald *et al.*, 1978). In severely hypertensive subjects, labetalol (100–125 mg intravenous bolus) was compared with propranolol (10 mg intravenous bolus); within 5 min labetalol had had a hypotensive effect which was sustained for 3 h, whereas propranolol did not decrease the pressure at all (Trust *et al.*, 1976). Another difference between labetalol and other β -blockers lies in the effect in the cardiac output, which may be unchanged (Mehta & Cohn, 1976) even at doses which reduce the arterial blood pressure, presumably because the indirect positive inotropic

Table 4 Effect of nifedipine treatment added to β -blockade on effort testing in patients with hypertension and angina pectoris (values at cessation of test; mean $\pm$ s.e. mean)

<i>All patients (including deviations from protocol)</i>	<i>Treadmill elevation</i>	<i>Heart rate (beats/min)</i>	<i>Blood pressure (mmHg)</i>	<i>Double product</i>	<i>Exercise time (min)</i>
Placebo (n=13)	8.6 $\pm$ 1.3	88.8 $\pm$ 4.4	163 $\pm$ 7/105 $\pm$ 5	14685 $\pm$ 1238	7.15 $\pm$ 0.77
Nifedipine (n=13)	11.6 $\pm$ 1.3	96.2 $\pm$ 5.1	162 $\pm$ 5/105 $\pm$ 3	15824 $\pm$ 1257	8.77 $\pm$ 0.77
P	<0.025	<0.01	NS	<0.05	<0.03
Percentage change	+35	+8	0	8	+23
<i>Patients (without deviations from protocol)</i>					
Placebo (n=7)	8.5 $\pm$ 2.0	92.0 $\pm$ 5.1	165 $\pm$ 8/107 $\pm$ 4	15274 $\pm$ 1385	7.29 $\pm$ 1.23
Nifedipine (n=7)	10.0 $\pm$ 1.6	97.4 $\pm$ 5.8	160 $\pm$ 8/109 $\pm$ 4	15789 $\pm$ 1581	8.21 $\pm$ 1.00
P	NS	NS	NS	NS	NS
Percentage change	+18	+6	-3	3	+13

effect of the afterload reduction (α -blockade) counters the direct negative inotropic effect of the β -blockade.

The inescapable conclusion is, therefore, that the peripheral vasodilating activities of labetalol are of significance with intravenous dosing, and that such peripheral vasodilation fundamentally separates labetalol from conventional β -antagonist agents.

These fundamental differences between labetalol and conventional β -antagonist agents seem to have been overlooked by those clinicians who argue that the α -blocking activity is slight. If, however, the above data are given full weight, then labetalol can be expected to play a significant role in the therapy of those conditions where increased sympathetic tone with increased α -activity is of special significance, with resultant increase in peripheral or coronary vascular resistance. Such conditions would include (a) early hypertension or labile hypertension; (b) sustained severe hypertension; (c) angina at rest; and (d) at least some patients with effort angina, especially when mediated by cold exposure. Whereas the induction of spasm-mediated pain in exertional angina appears to be unusual (except possibly during cold exposure), the increase in blood pressure associated with exercise is at least in part mediated by α -induced peripheral vasoconstriction (Fagard *et al.*, 1979). Furthermore, emotional stress causes a reduction in coronary blood flow, probably mediated by

coronary spasm (Schiffer *et al.*, 1980) and therefore presumably α -mediated. For all these reasons, it is particularly instructive to refer to a study undertaken by Lubbe and White (1978) who compared labetalol with other agents in the therapy of hypertension and angina.

Labetalol for angina pectoris: published data

Lubbe and White (1978) studied six patients with established hypertension and angina who were treated with one of a variety of β -blocking agents as well as nitroglycerin. They substituted the existing β -blocking agent by labetalol in an increasing dose, using an average daily dose of 600 mg. They assessed the angina pectoris largely by a subjective scoring system and found a significant improvement during the labetalol period. There was improved blood pressure control during labetalol (Table 5); hence this trial can be criticized because there was no report of a titration period for the conventional β -blockers. It seems likely that labetalol was acting as a peripheral vasodilator. The added possibility that labetalol was also a coronary vasodilator could not be excluded.

Several of Lubbe and White's (1978) patients were also part of our nifedipine trial and, on the whole, the patients showed a more marked subjective improvement with labetalol than with nifedipine. It must be emphasized that the

Table 5 Blood pressure, pulse rates and angina scores of patients during initial phase (2 months of existing medications including β -blockers with labetalol-placebo), titration phase of labetalol (2 months), maintenance phase of labetalol (2 months) and the final phase of resubstituting labetalol-placebo for 2 months together with the medications (including β -blockers) used in the initial phase

<i>N = 17 patients</i>	<i>Initial phase</i>	<i>Titration period</i>	<i>Labetalol maintenance</i>	<i>Final period</i>
Pulse rate (per min)	68 $\pm$ 3	72 $\pm$ 3	71 $\pm$ 3	66 $\pm$ 3
Resting blood pressure (mmHg)	165 $\pm$ 7 106 $\pm$ 4	166 $\pm$ 7 108 $\pm$ 3	159 $\pm$ 6 103 $\pm$ 4	166 $\pm$ 8 101 $\pm$ 4
Exercise blood pressure	160 $\pm$ 6 102 $\pm$ 4	161 $\pm$ 7 104 $\pm$ 3	156 $\pm$ 6 99 $\pm$ 4	157 $\pm$ 10 98 $\pm$ 5
Angina score	2.9 $\pm$ 0.4	1.9 $\pm$ 0.3*	1.4 $\pm$ 0.3**	2.3 $\pm$ 0.3

* $P < 0.05$; ** $P < 0.001$

Resting blood pressure was obtained in the sitting position, exercise blood pressure was obtained in the upright position after walking 60 metres.

conditions of the two trials were different, and no direct comparison between nifedipine and labetalol was undertaken.

Boakes and Prichard (1973) studied the effect of acute injections of propranolol, pindolol and labetalol on exercise tolerance of patients with angina pectoris. All these agents gave approximately similar increases in exercise tolerance, but the patients did not have hypertension.

Halprin *et al.* (1980) studied six patients with stable angina and systemic hypertension. At a mean peak labetalol dose of 950 mg daily, there was a marked reduction in systolic and diastolic blood pressures, both lying and standing, whereas the exercise time increased substantially, with a decreased peak systolic blood pressure during exercise. As they point out, labetalol was safe and effective for reducing spontaneous attacks of angina pectoris, but double-blind studies need to be initiated in patients with angina pectoris, comparing labetalol to other β -adrenoceptor-blocking agents, nitrates and placebos. The effects of labetalol on left ventricular function also need assessment.

In an open study, Besterman and Spencer (1979) found that a mean dose of labetalol 810 mg daily reduced blood pressure in supine and standing positions and also during exercise; exercise tolerance was improved and angina disappeared or decreased.

A study of the circulatory effects of labetalol was carried out by Fagard *et al.* (1979). They gave labetalol to 18 hypertensive patients with an average final dose of 1659 mgs (Fagard *et al.*, 1979). It must be emphasized that these patients did not have angina. Particular attention was paid to the role of the α -effects of labetalol. At rest, labetalol did not

change the systemic vascular resistance, but labetalol did reduce the increase in resistance obtained by phenylephrine and by exercise. They concluded that the anti-hypertensive action of labetalol was mainly based on its β -receptor-blocking properties at rest, and both its α - and β -receptor-blocking effects while sitting and during exercise. Interestingly, they also noted that the phenylephrine-induced increase in pulmonary vascular resistance was not altered and therefore labetalol did not influence the resistance of the pulmonary arteries.

Side-effects of labetalol

Side-effects found in some of the above studies are summarised in Table 6. The critical point is that none of the above studies compare side-effects with those of conventional β -blockade. In such a double-blind study, McNeil and Louis (1979) found that labetalol had effects very similar to those of conventional β -blocking agents (Table 7). Other studies suggest a somewhat higher incidence of side-effects (Table 6). For example, tingling of the scalp has been reported (Bailey, 1979); postural hypotension and difficulty with micturition are reminiscent of the side-effects of prazosin, another α -blocker.

Conclusions

Patients with hypertension and angina may represent a therapeutic dilemma, especially in view of the possible occurrence of hypertrophic

Table 6 Comparative side-effects of labetalol and other β -blocking agents in the therapy of mild to moderate hypertension (data taken from McNeill & Louis, 1979)

<i>Agent</i>	<i>Labetalol</i>	<i>Pindolol</i>	<i>Metoprolol</i>	<i>Atenolol</i>
Mean daily dose (mg)	308	24%	234	138
Lack of energy	23%	31%	34%	31%
Dry mouth	23%	14%	24%	23%
Cold extremities	15%	10%	17%	19%
Depression	15%	7%	10%	8%
Insomnia	12%	31%	21%	15%
Blocked nose	12%	10%	7%	19%
Abnormal dreams	8%	31%	14%	19%

cardiomyopathy and late-stage congestive cardiomyopathy (Richardson and Hill, 1979), in addition to the classical coronary artery disease. It is a well-established clinical fact that better control of the hypertension may improve the angina. Hence, conventionally, β -blocking agents are the first line of choice in therapy. In patients in whom the angina persists, further therapy may include either the calcium antagonist agent nifedipine or the replacement of conventional β -blockade by labetalol.

There is published evidence to suggest that added afterload reduction either by added α -blockade or by a calcium antagonist agent such as nifedipine can be expected to improve blood pressure control. The added α -blockade or calcium antagonism should be especially useful in further reducing systemic vascular resistance during exercise. Hence, it might be anticipated that combined afterload reduction and β -blockade will be more effective in the therapy of hypertension with angina than β -blockade alone.

Although there are good data showing that such added α -blockade or calcium antagonism gives

improved control of blood pressure, in the case of the associated angina there is less firm evidence that nifedipine or labetalol can induce significant added improvement in the angina symptoms of these patients. The results of double-blind trials now being undertaken should answer these questions.

In summary, peripheral vasodilation achieved by nifedipine when added to β -blockade, improves blood pressure control in patients with hypertension and angina. In a similar way, labetalol, which is an agent significantly different from other β -blocking drugs, merits special therapeutic evaluation in those many clinical situations where α -mediated vasoconstriction is likely to be important, and where peripheral vasodilation is desirable. The results of animal experiments on isolated hearts suggest that labetalol can also have direct cardiac effects on the severity of ischaemia in the absence of any peripheral effects (Hamm & Opie, unpublished). However, high doses of labetalol may be needed when the drug is given orally to achieve significant α -blockade.

Table 7 Effects and side-effects of labetalol when used for patients with hypertension and angina

<i>Authors</i>	<i>Mean daily dose of labetalol (mg)</i>	<i>Effects</i>	<i>Side-effects</i>
Lubbe & White (1978)	570	Apparently superior to conventional β -blockade; no strict comparisons; no effort test data	Not reported
Besterman & Spencer (1979)	810	Decreased blood pressure; increased effort tolerance; decreased anginal pains no comparisons—open trial	Reduced tear flow 6/18 General fatigue 1/18 Libido reduced 2/18 Failure of erection 1/18
Halprin <i>et al.</i> (1980)	950	Decreased blood pressure and heart rate; increased effort tolerance; decreased anginal pains and nitroglycerin consumption; no comparison—single-blind trial	Mild fatigue 1/6 Decreased libido 1/6

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