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Effect of long-term oral nifedipine therapy on left ventricular regional wall function at rest and during supine bicycle exercise

R. J. BOS, P. W. SERRUYS, R. W. BROWER, H. J. TEN KATEN, G. VANHALEWEYK, P. G. HUGENHOLTZ

Catheterization Laboratory, Thoraxcenter, Erasmus University Hospital, Rotterdam, The Netherlands

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15 patients, 1 to 3 year after coronary bypass surgery, underwent symptom limited supine bicycle exercise tests without nifedipine and after acute and chronic (3 months) administration of the drug. Haemodynamic variables were monitored as was epicardial marker motion, using biplane cineradiography during exercise, the markers having been implanted at the time of surgery. We found significant ($P<0{\cdot}001$) reductions in end-diastolic and end-systolic regional dimensions at maximal exercise after oral nifedipine, associated with a significant reduction in exertional angina, which persisted during long-term treatment. No adverse effects of the drug were observed.

Introduction

The short-term effects of the calcium antagonist nifedipine are well documented both in terms of its direct action on the cardiac cell and the coronary system as well as on the systemic circulation[1–8]. The long-term effects of oral nifedipine on left ventricular function are, however, less well documented, especially with regard to exercise tolerance. As this medication is now finding widespread use in the practice of cardiology, it is pertinent to demonstrate whether there is an important functional adaptation to the drug, and whether cumulative effects occur or significant toxic effects are noted in the longer term. This study reports on immediate and long-term left ventricular performance, as measured from implanted epicardial markers, in patients studied under resting and maximal exercise conditions before and after 3 months of therapy.

Methods and patient material

Fifteen adult patients (42–60 years of age, 14 males, 1 female) were requested to participate in this study one to three years after uncomplicated coronary artery bypass surgery (Table 1). All had pairs of platinum epicardial markers implanted at the time of surgery. All gave informed consent. In the preceding three months, eight patients had been free of angina pectoris, four had reported anginal attacks occurring infrequently, while three reported 1 to 5 attacks per day on exertion.

Eight were in NYHA class I, five in NYHA II and two in NYHA III. All had undergone cardiac catheterization 1 to 3 months prior to inclusion in this study as part of routine follow-up after bypass graft surgery. On average 3·4 grafts were placed per patient. Mean EF was 0·51 (range 0·24 to 0·79). Mean EDV was 88·6 ml m^{-2} (range 37 to 124). A complete medical history as well as a routine physical examination was obtained from all patients on entering the study. Measurements were obtained in the supine position, since marker motion had to be filmed in orthogonal projections with our conventional biplane cineangiographic equipment. These consisted of heart rate, blood pressure, ergometric time and workload, while a biplane X-ray cine film of radiopaque marker motion was recorded before and after a maximum exercise test was performed.

The exercise protocol consisted of increasing loads of 25 W every 3 min to maximum sustainable work load. All patients maintained a speed of at least 60 revolutions per minute. All tests were performed at the same hour of day. Since it has been demonstrated that the compound reaches a significant level in 10–15 min after oral and even more rapidly after sublingual administration, we gave 10 mg nifedipine sublingually together with 10 mg orally after the first exercise run[9]. The patients rested for an average of 20 min until their heart

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Address for correspondence: Patrick W. Serruys, MD, Catheterization Laboratory, Thoraxcenter, Erasmus University, Dr Molenwaterplein 40, 3015 GD Rotterdam, The Netherlands.

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Table 1 Patients entered into the study

No.	Sex	Age (yrs)	EDV ml m^{-2}	EF	Vessel disease	Coronary anastomosis	NYHA class	Angina in last 3 months	Marker pairs
1	M	50	61	0·67	3	4	2	+	3
2	M	42	98	0·50	2	4	3	+	3
3	M	48	124	0·41	3	1	1	–	3
4	M	53	102	0·39	3	5	1	–	3
5	F	42	91	0·24	3	3	2	+	3
6	M	48	81	0·72	2	2	1	–	3
7	M	52	86	0·45	3	3	2	+	3
8	M	60	92	0·56	3	5	3	+	3
9	M	48	120	0·30	1	1	1	–	2
10	M	49	93	0·58	3	4	2	+	3
11	M	58	47	0·79	3	3	1	–	3
12	M	54	109	0·34	3	5	1	–	3
13	M	48	70	0·62	2	2	2	+	3
14	M	46	70	0·59	3	4	1	–	3
15	M	47	79	0·56	3	3	1	–	3

EDV: end diastolic volume index; EF: ejection fraction; M: male; F: female; NYHA: New York Heart Association Class.

rate reached control levels prior to a repeated exercise session. An additional film was recorded when the heart rate reached the same level as in the control test. All patients were then asked to take 4 × 10 mg of nifedipine daily for 3 months. They were seen at regular intervals. At the end of the three months the same protocol as described above was repeated. No patient reported adverse effects of the drug, except for one who complained of two days of headache which disappeared spontaneously. All confirmed having taken the medication as prescibed, although no adherence testing was carried out.

Regional marker motion

Regional myocardial shortening was determined from radiopaque markers implanted during surgery on the LV epicardium in each bypassed region, in pairs 2 cm apart and located from 1–3 cm distal to the coronary anastomosis[5,10,11] (Fig. 1). Five consecutive beats were recorded on synchronized biplane cinefilms (50 frames per s^{-1}) at 30° right anterior oblique and 60° left anterior oblique direction.

Correction for X-ray and optical distortion was performed to give true anatomic dimensions. Because the biplane technique was employed, the small errors due to lateral and transverse rotation of the heart were eliminated as well as the potential wall motion artefacts due to motion of the thorax during exercise[12]. The position of the Roentgen apparatus was not changed during sequential recordings. As shown in Fig. 2, separation of marker pairs was plotted with regard to the onset

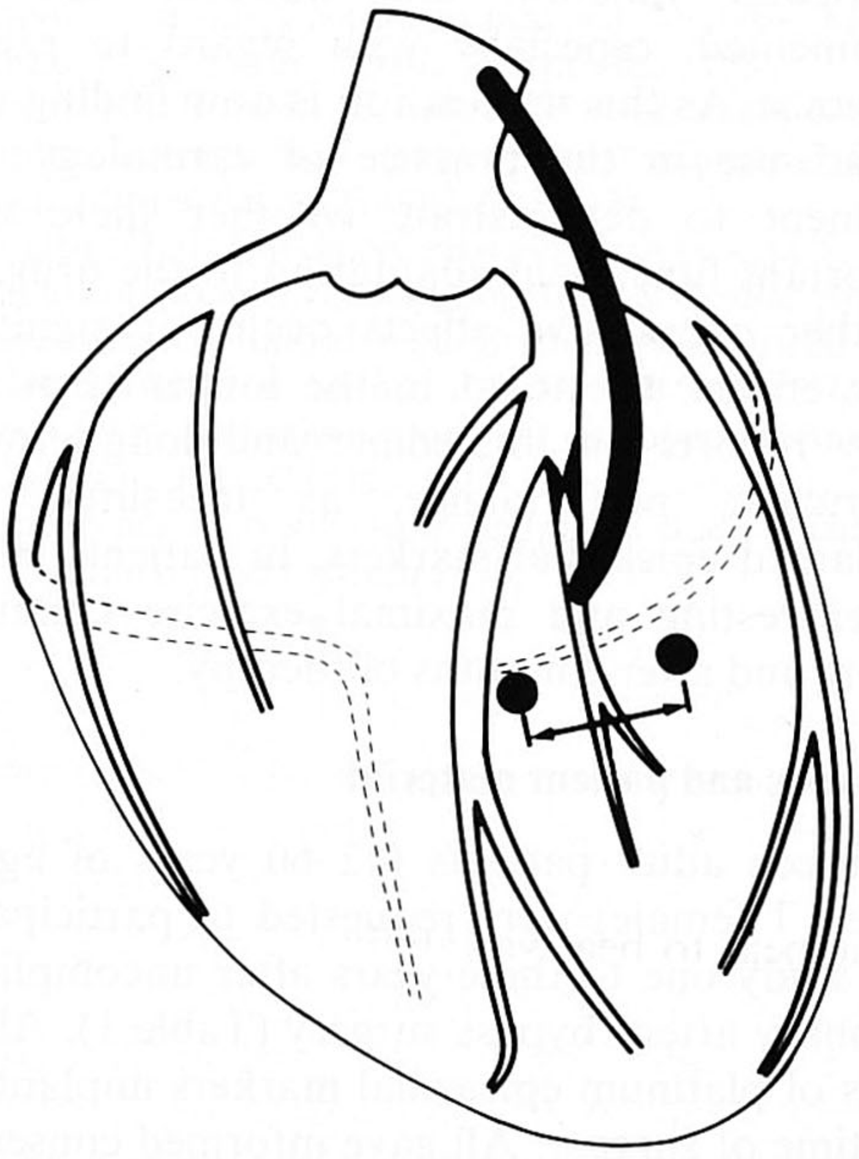

Figure 1 Radiopaque epicardial marker pairs were placed about 2 cm apart and from 1 to 3 cm distal to the coronary anastomosis in the region perfused by the graft. When possible an additional pair was placed in apparently normally perfused control regions.

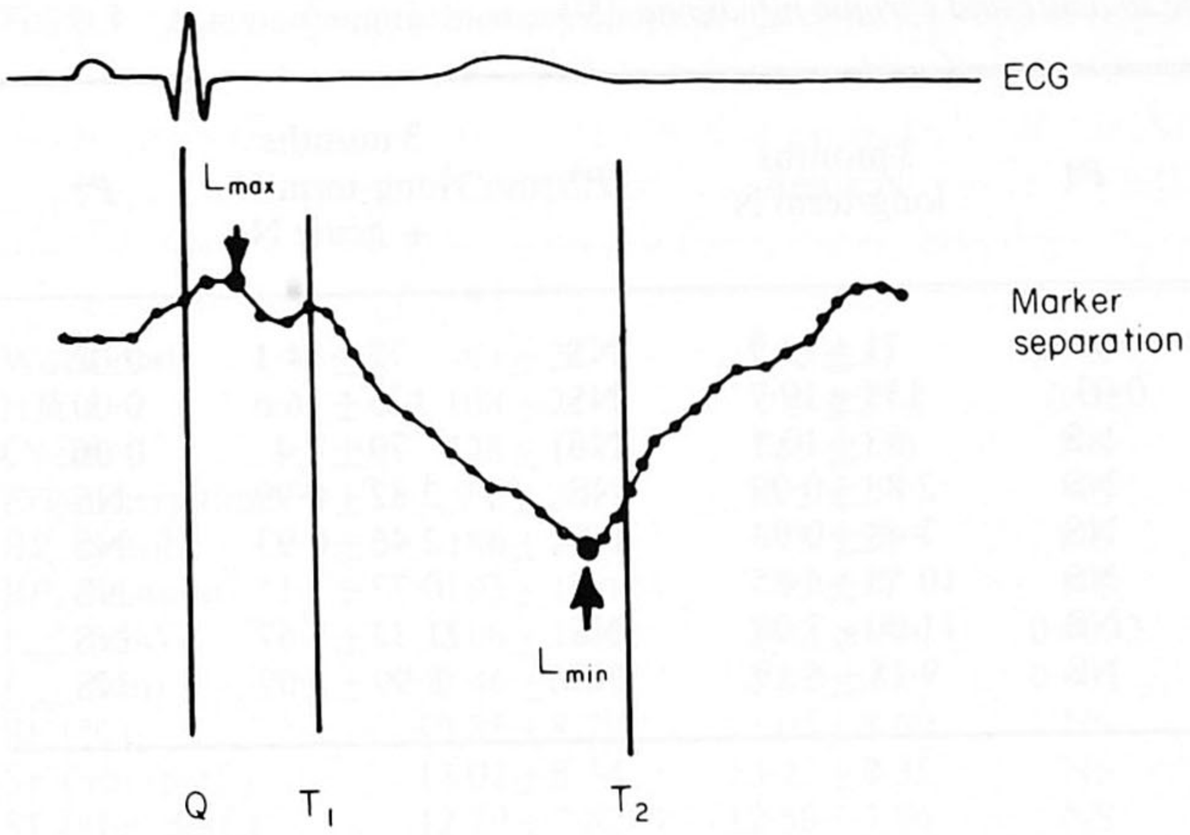

Figure 2 The marker motion was filmed biplane. After digitization and correction for image amplification and distortion, marker separation was plotted for at least 5 beats. The resulting myocardial shortening pattern was quantified from either the maximum and minimum marker separation of the respective separation required to compute the shortening contribution to ejection (see text).

of electrical activity. L_{max} and L_{min} are defined as the maximal and minimal marker separations. The shortening fraction calculated between these two points is given by $SF_{max}=(L_{max}-L_{min})/L_{max}$ and expressed as a percentage. Because SF_{max} does not necessarily represent the shortening contribution to ejection, shortening was also quantified in a way to represent ejection events more directly.

That is, $SF_{ej}=(Le_j-L_{es})/L_{ej}$ where L_{ej} is the maximal marker separation measured prior to aortic valve opening (T_1) and L_{es} is the minimal marker separation measured prior to aortic valve closure (T_2). Both the moment of valve opening (T_1) and closure (T_2) were estimated from standard formulae based on systolic time intervals[13] $T_1=131-0{\cdot}4\times HR$ (in ms), $T_2=T_1+143-1{\cdot}7\times HR$ (in ms).

Because marker filming at each exercise test was performed without repositioning the equipment or the patient, the measurement error is primarily due to the beat to beat variability, which is defined as the pooled standard deviation in L_{max} divided by L_{max} and expressed as a percentage. For biplane recording this averaged 0·6%. Given a L_{max} of 20 mm, a change of more than 0·26 mm for any heart beat can be measured with 95% confidence. As we averaged the results of 5 beats, the 95% confidence band of the mean is less than 0·13 mm[5]. Observer variability (inter and intra) has been previously published[10] and is briefly described in the Appendix.

Results

CLINICAL RESULTS OF THE EXERCISE TEST

There was a clear subjective benefit in terms of anginal complaints during the time course of the study. At the entry six patients reported pain during maximal exercise, three of whom responded to acute nifedipine on the second test. Three months after chronic nifedipine, three patients still complained of pain during maximal exercise while two of them responded to a further increased dose of nifedipine during the second test.

RESTING HAEMODYNAMICS AND REGIONAL EPICARDIAL DIMENSIONS AND SHORTENING

The haemodynamic results obtained from the 15 patients at rest are summarized in Table 2 and Fig. 3. The response to acute administration of oral nifedipine (column 2) shows a drop in systolic blood pressure and a significant increase in heart rate, as expected. After 3 months of long-term nifedipine (column 3) heart rate remains unchanged. However, the acute response to nifedipine at 3 months (column 4) is slightly less, a 6 bpm increase *vs* the 11 bpm increase at the beginning of the study.

Table 2 Haemodynamic measurements at rest in response to acute and chronic nifedipine (N)

	Control	Acute N	P*	3 months long-term N	P*	3 months long-term N + acute N	P†
HR	68 ± 13·8	79 ± 13·9	0·0006	71 ± 13·9	NS	77 ± 14·1	0·02
BP, systolic	140 ± 16·5	131 ± 22·1	0·03	135 ± 19·7	NS	126 ± 16·6	0·003
BP, diastolic	85 ± 5·8	84 ± 7·7	NS	83 ± 10·1	NS	79 ± 7·4	0·06
L_{max} (cm)	2·86 ± 1·02	2·84 ± 1·02	NS	2·83 ± 0·99	NS	2·82 ± 0·99	NS
L_{min} (cm)	2·49 + 0·94	2·49 ± 0·95	NS	2·48 ± 0·93	NS	2·46 ± 0·93	NS
SF (%)	10·97 ± 6·53	10·68 ± 6·91	NS	10·56 ± 6·85	nS	10·77 ± 7·15	NS
SF (nor. perf.)	11·58 ± 6·50	11·32 ± 7·18	NS	11·00 ± 7·08	NS	11·32 ± 7·67	NS
SF (abn. perf.)	9·07 ± 6·64	8·61 ± 5·81	NS	9·18 ± 6·19	NS	8·99 ± 5·09	NS

Values are mean ± SD.
*Student's paired t-test with regard to controls.
†Student's paired t-test with regard to 3 months chronic nifedipine.
Nor. perf.—normally perfused; abn. perf.—abnormally perfused.

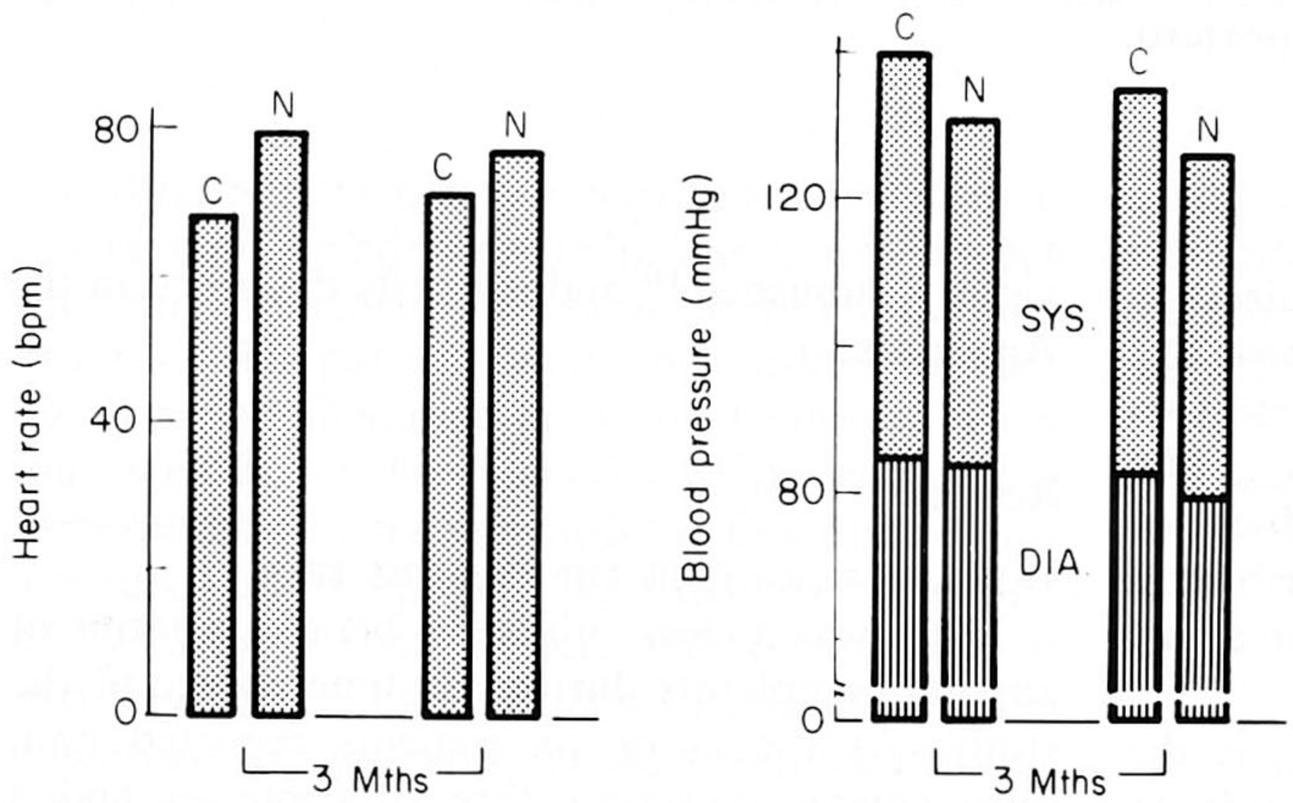

Figure 3 Changes in HR and blood pressure at rest before (C) and after (N) acute nifedipine and 20 mg oral nifedipine.

Systolic blood pressure demonstrated a 9 mmHg drop in the control period after acute nifedipine; after long-term nifedipine a 5 mmHg drop was seen. However, at 3 months the acute response to nifedipine remained unchanged with a 9 mmHg decrease in systolic pressure.

MAXIMAL EXERCISE

At these dosage levels, diastolic blood pressure showed a small but statistically non-significant response to the drug. There was no clear effect of L_{max}, L_{min}, or SF at rest during the entire follow-up period (see Fig. 5). Neither could a difference in the response of normally perfused *vs* abnormally perfused regions be demonstrated in their shortening fraction response, while SF in the abnormally perfused regions was consistently lower than in normally perfused regions. We conclude that, at rest and at these clinical dosage levels, nifedipine has little effect on LV shortening, with no important accumulative or adaptive effects at three months.

EXERCISE HAEMODYNAMICS AND REGIONAL EPICARDIAL DIMENSIONS AND SHORTENING

Nifedipine did not affect the maximum work load achieved at any point in the study (Table 3), although there was a discernible tendency to

Table 3 Haemodynamic measurements at maximal exercise in response to acute and chronic nifedipine (N)

	Control	Acute N	*P**	3 months long-term N	*P**	3 months long-term N + acute N	*P*†
Workload	61 ± 22	65 ± 21	NS	60 ± 18	NS	62 ± 19	NS
HR	108 ± 21·1	116 ± 25·2	0·02	112 ± 21·9	NS	116 ± 20·3	NS
Cycles	538 ± 182	589 ± 158	NS	581 ± 153	NS	547 ± 142	NS
Ergometry time	9·8 ± 2·8	10·1 ± 2·7	NS	9·9 ± 2·6	NS	9·8 ± 2·2	NS
BP, systolic	186 ± 29·5	178 ± 28·5	NS	180 ± 31·2	NS	179 ± 40·7	NS
BP, diastolic	95 ± 13	93 ± 17	NS	93 ± 12·8	NS	89 ± 13·3	NS
L_{max} (cm)	2·86 ± 1·01	2·82 ± 1·00	0·0002	2·83 ± 0·97	0·03	2·82 ± 1·01	NS
L_{min} (cm)	2·46 ± 0·91	2·42 ± 0·89	0·001	2·41 ± 0·86	0·003	2·41 ± 0·90	NS
SF (%)	12·85 ± 8·28	13·05 ± 8·09	NS	13·20 ± 8·53	NS	13·67 ± 8·10	NS
SF (nor. perf.)	13·02 ± 8·54	13·22 ± 8·35	NS	13·53 ± 9·07	NS	14·12 ± 8·40	NS
SF (abn. perf.)	12·29 ± 7·82	12·50 ± 7·56	NS	12·14 ± 6·81	NS	12·22 ± 7·27	NS

Values are mean ± SD.
*Student's paired t-test with regard to controls.
†Student's paired t-test with regard to 3 months chronic nifedipine.
Nor. perf—normally perfused; abn. perf.—abnormally perfused.

achieve a higher workload immediately after nifedipine. Neither did the total number of revolutions of the ergometer or total duration of the tests show a significant change during acute or long-term nifedipine.

The heart rate response to nifedipine during maximal exercise paralleled the response at rest, both during acute and long-term administration (Fig. 4). However, neither systolic nor diastolic blood pressure showed a significant change (Fig. 4). The lack of significance here reflects more the increase in the standard deviation during the test rather than the magnitude of the changes actually observed, which follow the pattern measured at rest.

Shortening fraction showed a tendency to increase after both acute and long-term nifedipine, but these increases were not significant. SF in abnormally perfused regions were consistently lower than values measured in normally perfused

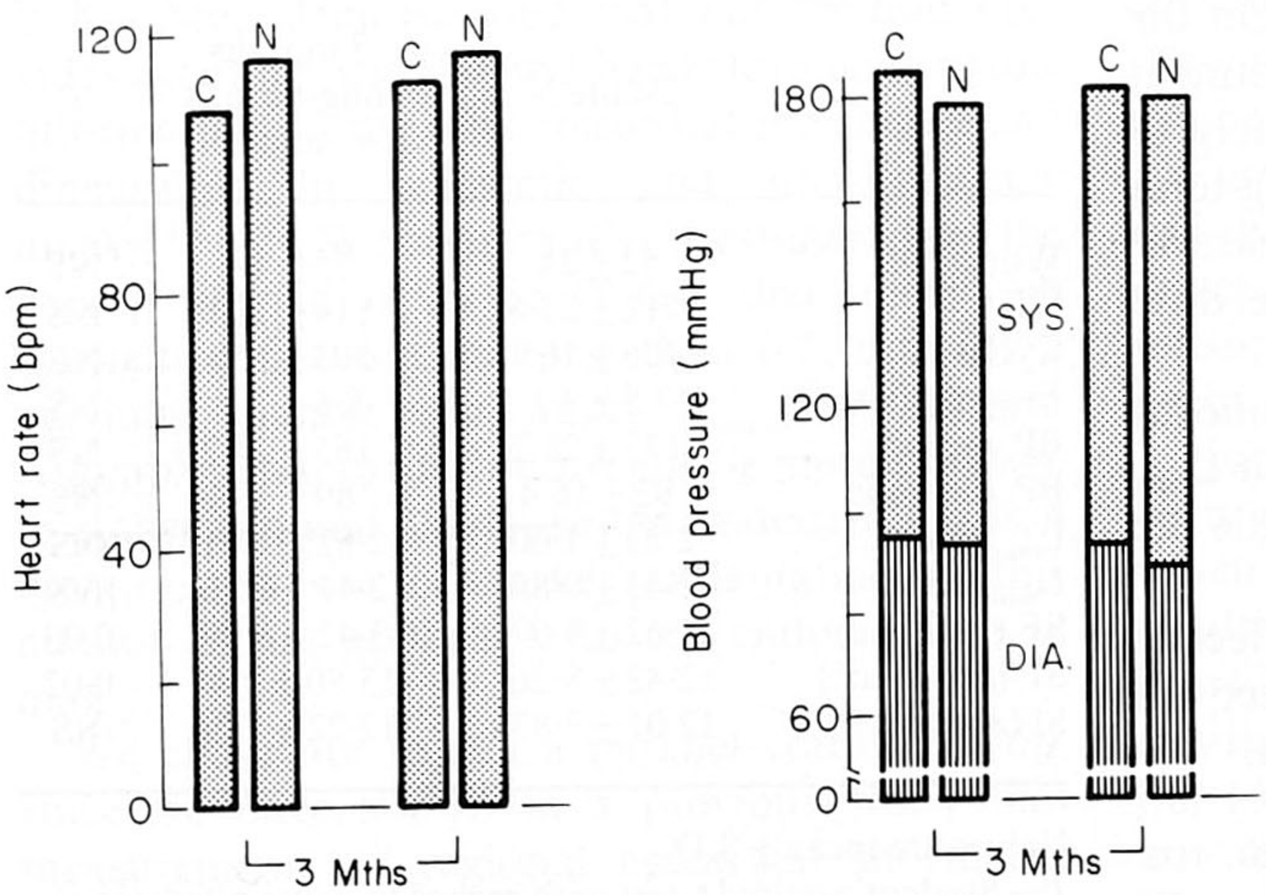

Figure 4 Changes in HR and blood pressure at maximal exercise before (C) and after (N) 20 mg of oral nifedipine.

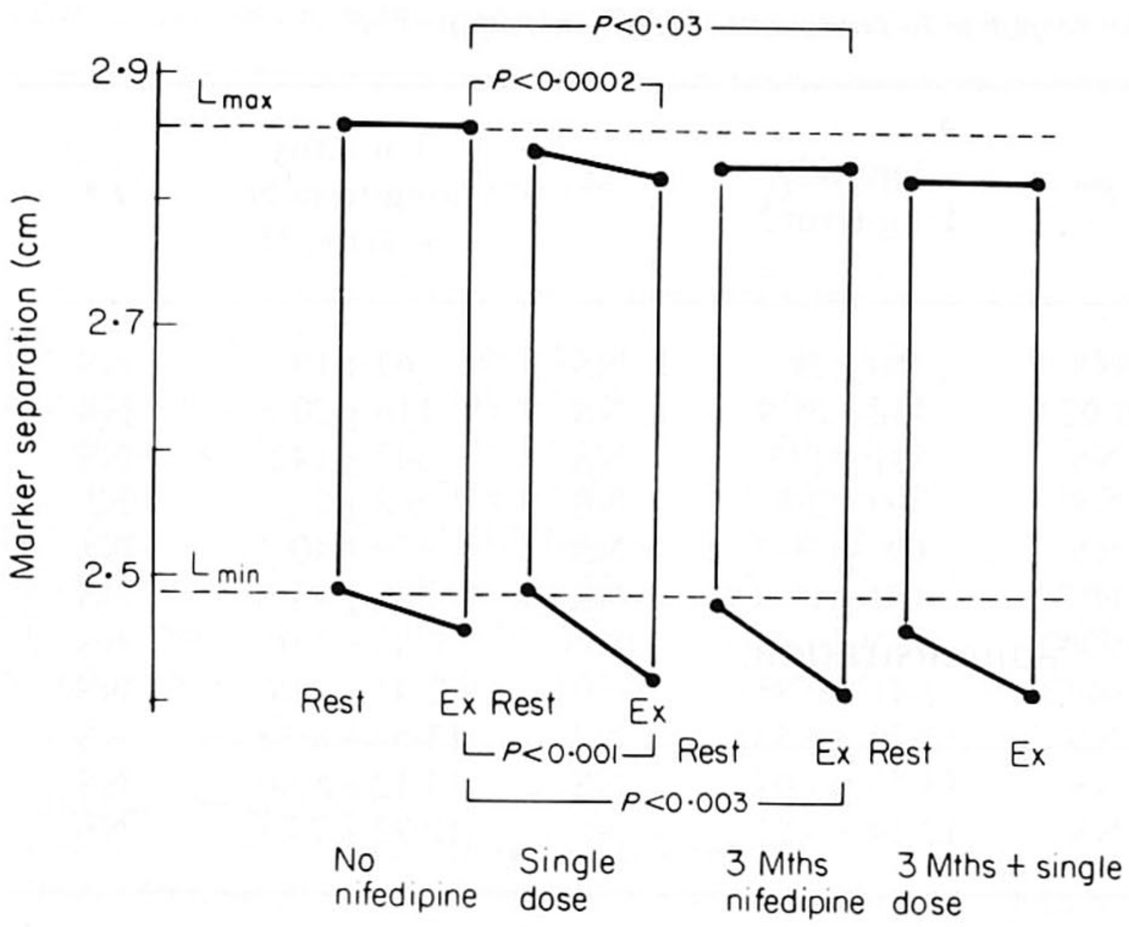

Figure 5 Changes in maxial (L_{max}) and minimal (L_{min}) marker separation during the study. A clear and significant decrease of L_{max} and L_{min} is shown after a single dose of 20 mg nifedipine. This reaction remained stable during chronic treatment with 40 mg nifedipine daily with loss of the ability to respond to extra nifedipine (see text).

regions, but neither showed a significant change in response to nifedipine during any stage of the study.

Although there were significant changes in SF following acute or long-term nifedipine, there were no significant changes in the absolute marker separation at ED and ES. Both L_{max} and L_{min} decreased following acute nifedipine at the beginning of the study. After 3 months of long-term nifedipine treatment, dimensions were virtually identical to those measured during the first acute administration of nifedipine and they remained significantly below control levels (Fig. 5). On the other hand, after 3 months of long-term treatment with nifedipine, the ability to respond acutely to nifedipine was abolished. Possibly the long-term administration of nifedipine achieved whatever gain was to be obtained, so that an acute dose could achieve nothing further.

It is clear that the reason why no significant change in SF was obtained was because both L_{max} and L_{min} decrease in parallel, resulting in little net change of the quantity $L_{max} - L_{min}$.

During maximal exercise, the long-term effect of nifedipine is predictable from the acute effect; no cumulative or adaptive effect could be shown.

SUBMAXIMAL EXERCISE

In order to unravel more carefully the confounding effects of exercise on heart rate, which might indirectly affect SF and the dimensions L_{max} and L_{min}, two measurements were made after acute nifedipine during submaximal exercise when the heart rate reached the same level as that obtained during the maximal control exercise stress test. These tests were performed both at the beginning of the study and at 3 months (see Table 4).

Table 4 Haemodynamic measurements during submaximal exercise in response to acute and chronic nifedipine (N)

	Acute N	3 months long-term N + acute N	*P*
Workload	52 ± 24	55 ± 19	NS
HR	112 ± 23·6	114 ± 17·9	NS
Cycles	486 ± 165	503 ± 150	NS
Ergometry time	7·8 ± 3·1	8·6 ± 2·5	NS
BP, systolic	173 ± 28·2	165 ± 24·2	NS
BP, diastolic	92 ± 16·4	89 ± 13·0	NS
L_{max} (cm)	2·83 ± 1·00	2·82 ± 1·01	NS
L_{min} (cm)	2·43 ± 0·89	2·41 ± 0·90	NS
SF (%)	12·62 ± 8·07	13·42 ± 8·09	0·03
SF (nor. perf.)	12·82 ± 8·26	13·80 ± 8·41	0·02
Sf (abn. perf.)	12·01 ± 7·83	12·22 ± 7·26	NS

Values are mean ± S.D.
P—Student's paired t-test with regard to acute nifedipine.
Nor. perf.—normally perfused; Abn. perf.—abnormally perfused.

There was no significant difference in the workload during the submaximal recordings, nor were there significant differences in the number of revolutions (cycles) or duration of exercise up to the moment of recording (ergometry time) after 3 months of long-term nifedipine. Systolic blood pressure response to acute nifedipine fell by 8 mmHg over the 3 month period, similar to the findings at maximal exercise, but this again was not sufficiently large in relation to the SD to register as a significant drop.

The pattern of regional myocardial shortening is however altered with submaximal testing. SF, for all regions, showed a significant increase after acute nifedipine primarily from the normally perfused regions however. The abnormally perfused regions showed a lesser increase which was not significant. It would appear that long-term nifedipine actually enhances the ability of the myocardium to respond acutely to nifedipine. While at the time of the measurements, blood pressure was slightly lower than at the beginning of the study, it is conceivable that the long-term unloading of the heart had a beneficial effect especially on the normally perfused regions.

Discussion

Regional myocardial function, particularly in patients with coronary artery disease, has been assessed by two-dimensional and M-mode echocardiography, by contrast and by radionuclide ventriculography. None of these methods can accurately assess transverse epicardial shortening. It has been demonstrated that our method provides accurate, specific and heretofore unavailable information on regional epicardial shortening and dimensions in ischaemic and non-ischaemic areas[5,10–12]. We conservatively estimate that the overall margin of error is less than 0·66% in shortening fraction and less than 0·13 mm for a maximal marker separation (L_{max}) of 20 mm. Arguably, endocardial shortening is more sensitive to ischaemia and therefore the endocardium is a more optimal site for marker implantation but this method is not applicable to the endocardium in man.

We chose not to run a parallel control group, since we have shown in a previous study that measurements of regional epicardial shortening remain stable during a 6 month period in patients without intercurrent cardiac events. Therefore it was reasoned that each patient could serve as his or her own control.

The mechanism of action of long-term oral nifedipine upon left ventricular regional wall motion at rest or during exercise is not yet fully understood.

The present study did not demonstrate changes in systolic and diastolic regional dimensions at rest after nifedipine, but showed a reduction in systolic and diastolic regional dimensions during exercise after acute as well as after long-term oral administration.

It has been demonstrated by Majid *et al.*[8] that nifedipine reverses the exercise-induced or atrial pacing-induced haemodynamic disturbances which were observed prior to the administration of nifedipine, such as increases in the LVEDP, end-diastolic and end-systolic volumes and impaired ejection fraction. A decrease in left ventricular filling pressures and an increase in cardiac output during exercise or atrial pacing after nifedipine has been consistently found[14–17]. Lydtin *et al.*[14] observed that the beneficial effect of nifedipine on exercise pulmonary capillary wedge pressure persisted after 3 weeks of chronic treatment.

Several possible mechanisms for the beneficial effect of chronic nifedipine administration on exercise left ventricular end-systolic and end-diastolic dimensions may be considered. Nifedipine has a potent vasodilatory effect which leads to afterload reduction[18]. As a consequence better emptying of the heart would be expected, attended by a decrease in end-systolic and end-diastolic dimensions. As we demonstrated that the significant reduction in dimensions lasts up to 3 months without a comparable reduction of systemic blood pressure, we do not feel that afterload reduction can be the sole mechanism of action.

Furthermore, the reduction in end-systolic and end-diastolic dimensions cannot be explained by a direct positive inotropic effect of the drug, as nifedipine is intrinsically a negative inotropic agent.

However, the decrease in blood pressure has been shown to trigger the baroreceptor reflex, which induces a release of catecholamines with a resultant indirect positive inotropic action on the heart[5,19]. Beta-blocking agents might antagonize this reaction partly, as was shown earlier. Yet 6 of our 15 patients used beta blockers; their results did not differ significantly from the other patients. Thus, this mechanism probably plays a minor role.

Venous pooling and a reduction of preload, as a

possible cause for the reduction in regional myocardial wall dimensions, has not been convincingly demonstrated after nifedipine and therefore appears unlikely. A more attractive hypothesis is that nifedipine in this type of patient with severe coronary artery disease and (intermittent) ischaemia, has a potent anti-ischaemic effect. It has been shown that this anti-ischaemic effect is associated with increased systolic emptying of the heart. Zacca *et al.*[20] assessed the effect of sublingual nifedipine on left ventricular global function and regional myocardial perfusion, using radionuclide ventriculography and exercise thallium scintigraphy. While exercise tolerance after nifedipine increased, the peak exercise double product remained essentially unchanged. Ejection fraction improved at peak exercise from 42 to 47% and nifedipine administration resulted in an improved segmental wall score. Improved exercise myocardial perfusion occurred in 5 of 11 patients and in 7 of 28 segments with reversible hypoperfusion. A beneficial effect of nifedipine on regional wall function may be accounted for, at least in part, by improvement in myocardial perfusion. Furthermore, nifedipine administration results in an increase in coronary blood flow and a decrease in coronary vascular resistance at rest. An increase in total coronary blood flow during atrial pacing or exercise is usually not seen. However, Engel *et al.*[15] observed during atrial pacing a tendency towards an increase in blood flow in post-stenotic areas and a decrease in normal areas, using the Xenon clearance technique. Thus, blood redistribution during atrial pacing appeared to become more homogeneous.

Recently, Specchia *et al.*[21] investigated the mechanism by which nifedipine improves exercise tolerance in patients with stable exertional angina and left anterior descending disease. Half of the patients studied had prolonged exercise duration and less ST segment depression at peak exercise after nifedipine. In this group of patients nifedipine significantly increased great cardiac vein blood flow by 67% and decreased anterior regional coronary resistance at peak exercise, while a significant increase in double product occurred. Thus, in an important subgroup of patients, local coronary blood flow may increase during exercise after nifedipine in regions of the myocardium supplied by stenotic coronary arteries.

The beneficial effect of nifedipine on exercise left ventricular dimensions appears to be multifactorial. Besides peripheral mechanisms, an anti-ischaemic effect together with improved coronary blood flow leading to a better mechanical emptying of the heart, may best explain our results.

Our study did not reveal any serious adverse reaction to the prolonged use of nifedipine.

As mentioned above, a decrease in L_{max} and L_{min} was found after long-term and acute nifedipine administration during maximal exercise. No additional reduction in regional dimensions could be measured with acute oral nifedipine administration after 3 months' use of the drug. This suggests that a sustainable therapeutic effect, which is reflected in haemodynamic improvement, is achieved by 40 mg oral nifedipine daily.

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Appendix: observer variability

Intraobserver variability: Three observers measured 150 projected marker pair distances equally divided among the different shapes. Each frame was remeasured independently 10 times. The standard deviation for each frame for repeated measurements was determined and the standard deviations pooled. This was corrected for anatomic dimensions (scale factor = 2·0 projected/anatomic). The pooled standard deviation for observer A was 0·049 mm, for observer B (no previous experience) 0·052 mm and for observer C (most experienced) 0·038 mm. This variability was independent of marker type and of distance between markers. The 95% confidence limits for intraobserver variability was $\pm 0{\cdot}092$ mm (averaged for all observers).

Interobserver variability: The same data base was used for determining interobserver variability. The repeated measurements of a frame (10 measurements per frame) were averaged for each observer to yield his best estimate of marker separation of that frame. This was repeated for all frames. Linear regression between observers showed no significant difference in the calculated shortening fraction. The 95% confidence interval derived from the standard error of the estimate (from regression analysis) is 0·11 mm.