EFFECTS AND MECHANISM OF NIFEDIPINE AFTER ORAL, SUBLINGUAL, INTRAVENOUS AND INTRACORONARY ADMINISTRATION. SURVEY ON CLINICAL RESULTS

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Clinical investigations over 13 years have created a picture of the substance which agrees with the hypothesis of calcium antagonism as the basis and common biochemical mechanism, but leaves questions still open and under discussion.

I would like to give a brief survey of the relevant clinical findings and discuss with you the possible underlying mechanism.

Angina pectoris under load

Numerous controlled and double-blind studies were carried out to establish the efficacy of nifedipine in anginal patients under load [1,2].

The single doses were 10, 20 or 30 mg and the number of patients in these trials is 351. In controlled short and long-term trials the daily dose was 30, 40 or 60 mg. Seven hundred and seventy eight patients were examined during the therapy which lasted between 14 to 70 days.

There is no doubt about the efficacy. The increase in angina pectoris. threshold is between 20 and 50% of the control values. It was established that the effect of a single dose of 20 mg was maintained for about 6. 5 hours.

We carried out this investigation (fig. 1) on 18 patients with exertional angina in an ergometer test. The study was a placebo controlled cross-over test.

The ordinate shows the increase of angina pectoris-threshold in percent and the abscissa, the time of the load test. The patients performed the first ergometer test at 8.00 a.m. The test was repeated at 11.00 a.m. , 2.00 and 5.00 pm. The bottom curve shows the average angina pectoris-threshold on the first day without any medication.

There was an increase of about 80% after the second ergometer test and I would consider this as an adaptation, as the patients had not been trained beforehand. After munch there was a considerable drop, however, angina pectoris-threshold was approximately 45% above the zero level of the morning.

On the second day the same procedure was performed.

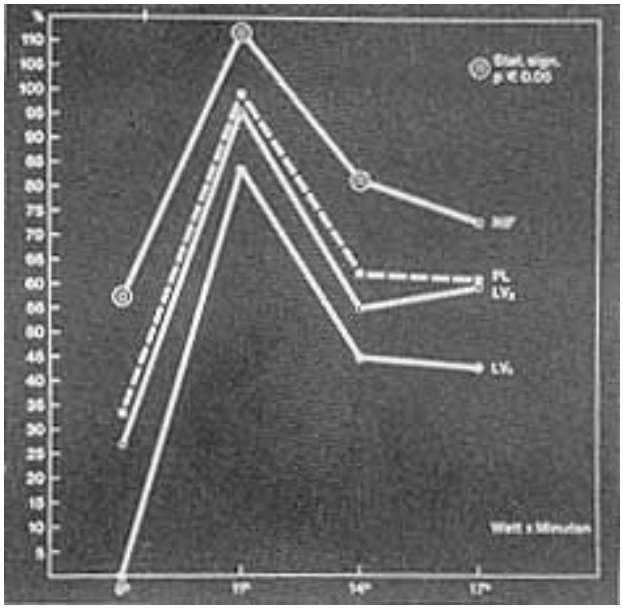

Fig. 1

Without any medication the group of patients showed a higher baseline level of 25% compared to the first test. Interestingly enough, the group of patients showed the same behaviour with the peak before lunch.

Day 3 and 4 tests were carried out under double-blind cross-over conditions against placebo, the patients received the medication at 7. 30 in the morning and performed the ergometer test as on the days before.

The third curve is slightly higher than the second one and shows a placebo-effect of about 5%. The difference under test. medication was statistically significant at 8 o'clock, 11.00 o'clock and 2.00 o'clock.

No tachyphylasis was found in long-term trials. Figure 2 demonstrates ischemic ST-depression during the treadmill-test, carried out by Menna and coworkers[2] in Buenos Aires. After 4 and 8 weeks, the group of patients showed a placebo effect of 19 and 22% respectively, compared to the pre-treatment va-

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lues. After switching over to 20 mg nifedipine thrice daily the angina pectoris- threshold increased to 40% after 4 weeks and to 52% after 8 weeks of active medication. The second group of patients, who started with nifedipine, also showed a significant reduction of depressed ST-segments of 27 and 37% respectively under nifedipine and a placebo-effect of 19 and 15%, again compared to pre-treatment values.

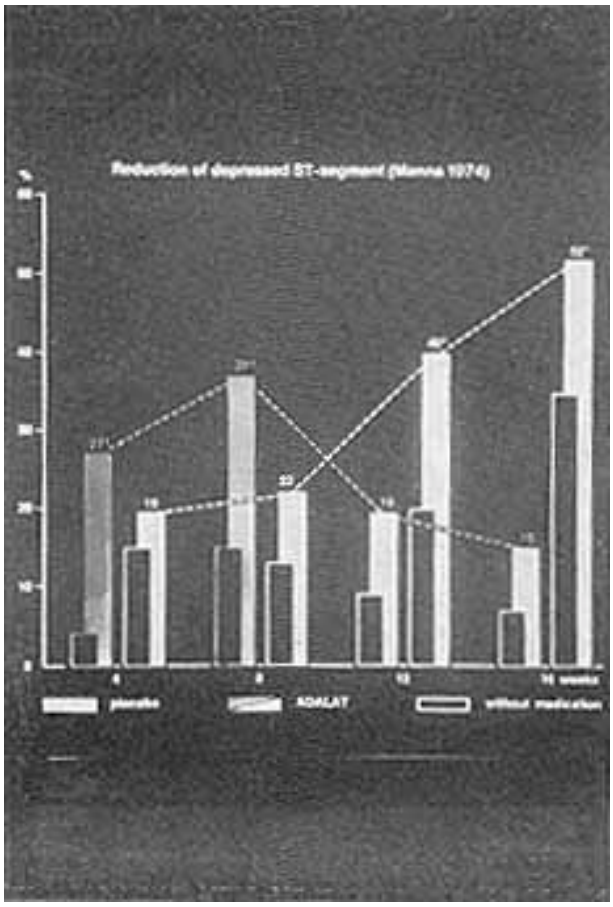

Fig. 2

In most of these clinical tests nifedipine was given prior to provoked ischemia. Ischemic symptoms were reduced or even abolished and onset of ischemia delayed.

However, it is obvious from all the relevant hemodynamic measurements, that in normotensive patients the afterload reduction is limited and very small. Heart rate under load is unchanged or slightly above control values. Therefore the pressure-rate product in most cases does not differ significantly from the control. However, there is a shift from pressure-work into volume-work, as demonstrated by the increased stroke volume, but certainly more important, its is observed a significant and less pronounced increase of left filling pressures. And I should add, no negative-inotropic effect was found after oral administration of nifedipine.

These results are pointing to a direct myocardial action of nifedipine not caused by afterload reduction alone.

Therefore, Kaltenbach and co-workers[3] tried to differentiate between the peripheral effects and cardiac effects by giving nifedipine intracoronary (i.c.) to patients with coronary heart disease, and then subjecting them to an ergometer test up to angina. They gave 1 mg intravenously or 0.1 mg i. c. and found a clear anti-anginal effect after both routes (fig. 3).

The ST-depression under no medication was expressed as 100% After nifedipine, 0,1 mg i.c. , there was a significant reduction to 34% and after 1 mg intravenously (i. v.) the values dropped to 21% of pre-treatment values.

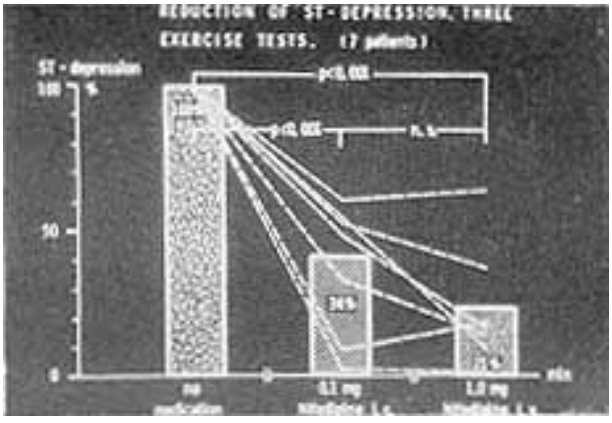

Fig. 3

Both the tests were carried out 20 and 30 minutes respectively after administration of nifedipine, at a time, where no significant hemodynamic effect was observed.

There is no doubt about the anti-anginal effect of inifedipine, after i.c. administration as well. However, it is still unclear, if this effect is present, as long as hemodynamic changes are visible and how much they contribute to the anti-anginal effect. One could speculate that the calcium overload is reduced under ischemia by nifedipine and therefore wall-stiffness is reduced by this direct action of nifedipine.

This aspect is supported by investigations, recently published by Weintraub and co-workers[4]. Data regarding open-chest dogs which underwent carotid-to-left anterior coronary artery bypass were presented. Perfusion pressure, segment length (by ultrasonic Christmas) and continuously myocardial blood flow (by mycrospheres) were measured. Ischemia was produced by a partial coronary occlusion. Two groups of dogs were investigated. Each of 10 dogs received an i.c. bolus. dose of 10 μg and each of 13 dogs received 3 μg per kg nifedipine per minute by 15 minutes i.v.

Here I must emphasize that nifedipine was given 5 minutes after onset of ischemia.

Nifedipine induced an increase in ischemic segmental shortening after i. v. and i.c. administration as well. As in Kaltenbach's findings i.v. nifedipine was slightly more effective than i.c. nifedipine.

The improvement in the function of ischemic tissue, after i.c. administration could not be explained by the after-load reduction because after-load reduction was not found, and diastolic pressure was not affected, normal zone-shortening was not influenced. Neither i.v. nor i. c. nifedipine affected ischemic zone blood flow.

Thus, nifedipine appears to have an effect on intramyocardial and mytochondrial calcium compartments during ischemia. The explanation for the improved ventricular function may lie in the reduced calcium overload of mitochondria and in an ATP saving effect, which reduces ischemia. induced wall stiffness.

Angina pectoris at rest

The effect of nifedipine on angina pectoris at rest was found very early in the clinical investigations. Endo[5] in Japan reported that nifedipine had a rapid and dramatic effect on variant angina and angina at rest. In the meantime, numerous studies were carried out and representative for all I would like to present an interesting case, published by Dunn[6] and co-workers from Sidney, Australia.

The patient, a 60-year old truck driver and smoker was admitted to hospital because of recurrent chest pain and syncope with chest pain. Propranolol was ineffective. During cardiac catheterization. minor coronary lesions were found in LAD, in the right and in the circumflex coronary arteries In the first diagonal branch there was a 85% obstruction. Provocation with ergonovine (0 25 mg ergonovin maleate), repeated 12-mead ECG and repeated thallium. scan gave coincidence for spasm of the right coronary artery, and 7 weeks later, spasm of the left anterior descending coronary artery. Therapy, consisting of ISDN, NTG-ointment, verapamil and phenoxybenzaminie could not stop chest pain complicated with ventricular fibrillation (fig. 4).

After introduction of nifedipine, 20 mg every 6 hours, chest pain was abolished and at follow-up 5 months after admission he was well with no further angina.

The overall results show that approximately 65% of patients became painless and only very few did not respond to nifedipine. These open studies were recently confirmed by Schick and co-workers[7] in a randomized double-blind study.

These results can be quite satisfactorily explained on the basis of a concept of increased vasomotor tone and reduced coronary flow as the underlying pathogenic mechanism of this type of angina. As already reported by Vater and co-workers in 1970, nifedipine has clear antispasmodic properties. However, to achieve a

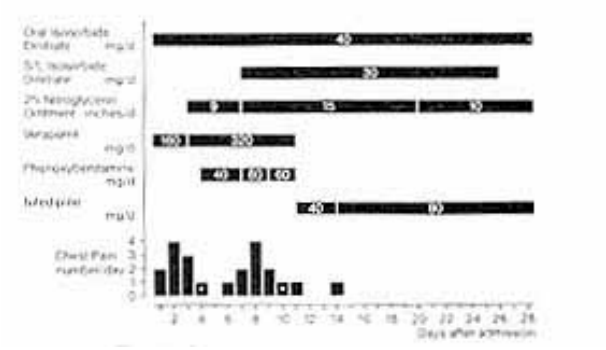

Fig. 4 - Multivessel coronary artery spasm.

satisfactory therapy, the individual dose must be higher than in angina under load, e.i., around 80 to 120 mg per day.

Unstable angina

Nifedipine is also very effective in unstable angina. Serruya[8], from the group of Hugenholtz in Rotterdam, reported a cooling off in severe unstable angina within 48 hours in 60% of patients by adding nifedipine to pre-treatment with nitrates and betablockers. This open trail was recently confirmed by Gerstenbmith[9] from the Weisfeldt group in Baltimore.

This randomized double-blind trail was carried out on 138 patients. They did not respond satisfactorily to nitrates and propranolol. However, this pretreatment was retained as concomitant medication with nifedipine or placebo (fig. 5).

Anginal pain at rest was accompanied by ischemic ST-changes. The groups were homogenious with regard to age, previous myocardial infarction or other risk factors. Treatment was considered to be a

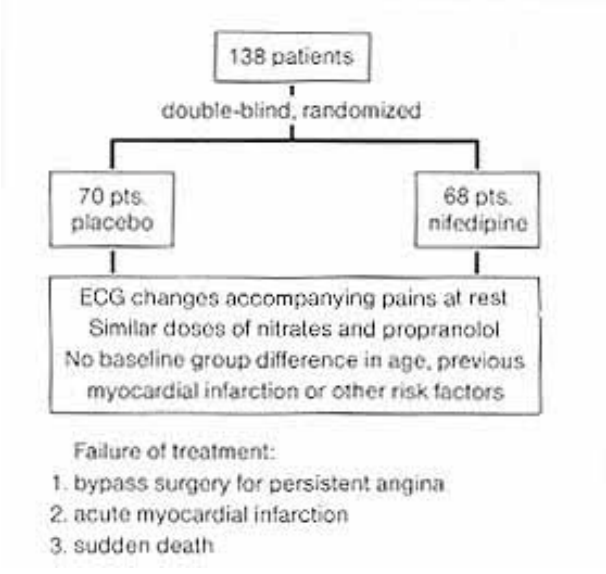

Fig. 5 - Nifedipine in unstable angina double-blind randomized trial (following Gerstenblith et al., 1981/Eb., Fr., 1982).

failure when patients underwent bypass surgery because of persistent angina or acute myocardial infarction occurred, or sudden death.

One hundred and thirty eight patients were randomized into 2 groups, 5 patients were withdrawn because of side-effects, and 6 were withdrawn by their physicians. One was most to follow-up (fig. 6).

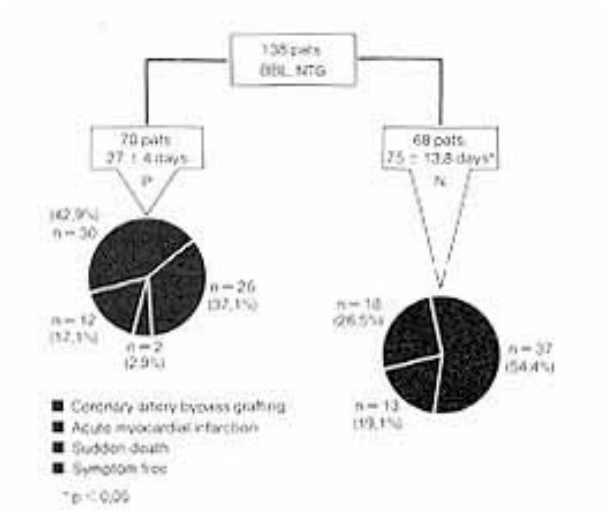

Fig. 6 – Nifedipine in unstable angina double-blind randomized trial (following Gerstenblith et al., 1981/Eb., Do., Fr., 1982).

There was a striking difference between the follow-up of patients to their end. points: 27 days in the placebo group and 75 days in the nifedipine group. This difference was statistically significant.

Forty three percent of the patients in the placebo and 26% in the nifedipine group underwent bypass surgery for persistent angina. The difference was significant with 0.06 by the chisquare test. Thirty seven percent became painless under additional placebo and 54% under additional nifedipine. Despite the fact that more patients in the nifedipine group were at risk of infarction or death because of the greater number of bypass operations performed in the placebo group, the numbers of sudden death and of myocardial infarctions did not differ in the 2 groups.

Several explanations could be found: the atherosclerotic plaque in the coronary vessel wall is not always concentric and fixed, therefore parts of vessel could change vasomotor tone induced by pharmacological interventions. A few studies show nifedipine actually dilates the coronary artery at the point of the stenotic lesions and could change pre and poststenotic diameter. But it is not fully understood if changes in vasomotor tone persist longer than the hemodynamic changes and how long coronary arteries became less sensitive to vasoconstricting stimuli.

What platelet aggregation is concerned, nifedipine may partly reduce angina pectoris by preventing platelet clumping[10]. However, effects were only found in patients, not in healthy volunteers, and under exercise induced ischemia, not at rest.

Hypertension

Nifedipine is also used in hypertension. It is interesting to note, that this effect is dependent on initial values, i. e. it is substantially greater in patients with elevated pressures than in normotensive subjects, according to Aoki and others[11].

An overview of findings is presented here[11, 18] (table I). In these investigations the patients received single doses of 10, 20 or 30 mg. Despite the fact that this summary includes several groups from different investigators, the fall in systolic blood pressure seems to show a dose-dependency. The results show that the systolic blood pressure is very rapidly lowered, the onset of effects occurs after 5 to 10 minutes and a peak effect between 10 and 120 minutes. Duration of hypotension was observed for 2 to 8 hours and in most patients heart-rate showed a slight upward trend after onset of therapy.

TABLE I

NIFEDIPINE IN ESSENTIAL HYPERTENSION
(SINGLE DOSE EFFECT)

n = 544

10mg	SBP up to DBP up to	48 mm Hg (23%) 31 mm Hg (27%)
20 mg	SBP up to DBP up to	51 mm Hg (26%) 37 mm Hg (32%)
30 mg	SBP up to DBP up to	58 mm Hg (32%) 32 mm Hg (28%)

Duration of hypotension 2-8 hrs.
HR shows slight increase from 1 to 22 beats/minute.

Corea and co-workers [19] published data on nifedipine in hypertensive acute pulmonary edema (table II). The nifedipine therapy was compared with conventional therapy, which consisted of 40 to 80 mg furosemide i.v., 10 mg morphine and continuous intranasal oxygen; 20 mg of nifedipine were given 6 hourly.

After 24 hours of therapy the results were a statistically significant drop of systolic blood pressure from 189 to 135 and in diastolic blood pressure from 112 to 81 mm Hg. The heart rate which was initially 104 beats per minute dropped to 92 and there was no change in serum. sodium or serum-potassium.

The use of calcium-antagonists is quite an interesting approach to the therapy of hypertension. The mechanism could be controversial. However, a possible hypothesis published by Blaustein[2O] is the as-

TABLE II

Nifedipine in Hypertensive Acute Pulmorary Edema
(n = 2 x 7)

		APE (nifedipine)	Δ %	APE (diuretics, morphine, oxygen)	Δ %
SBP (mmHg)	Basal	189 ± 8.4		182 ± 7.5	
	24h.	135 ± 7.2**	28.5	149 ± 9.4**	18.1
DBP (mmHg)	Basal	112 ± 6.1		108 ± 9.4	
	24 h.	81 ± 7.1	27.7	94 ± 6.6*	12.9
MAP (mmHg)	Basal	137 ± 6.8		132 ± 8.7	
	24 h.	99 ± 7.1	27.7	112 ± 7.5*	15.1
HR (b/min)	Basal	104 ± 11.2		98 ± 9.4	
	24 h.	92 ± 7.9	11.5	91 ± 9.2	7.1
Na+ (mEq/1)	Basal	141 ± 1.5		141 ± 1.3	
	24 h.	142 ± 1.2		140 ± 1.7	
K+ (mEq/1)	Basal	4.3 ± 0.8		3.8 ± 0.8	
	24 h.	4.0 ± 0.6		3.5 ± 1.0	
Diuresis (ml/24 h.)	Basal	—		—	
	24 h.	2022 ± 251		2216 ± 352	

**p 0.01 *p 0.05

(following Corea Let at/ Acta Therap. 6 (1980) pp 303/313)

TABLE III

NIFEDIPINE and BETA-BLOCKERS

AUTHORS	CASE HISTORY	PRETREATMENT	NIFEDIPINE	REPORTED EFFECT
ANASTASSIADES (B.M.J. 1980, 1982)	72a ♂ severe angina myoc. infarction	alprenolol 2 x 200 mg for 2 years	3 x 10 mg for 15 days	dyspnoea heart failure
	58a ♂ severe angina triple vessel disease impaired left vent. f. dyskinetic areas	alprenolol several months → propranolol 3 x 40 mg	3 x 10 mg for 6 days	dyspnoea slight heart failure (2 x)
	50a ♂ myoc. infarct. akinetic areas, unstable angina	metoprolol 3 x 50 mg for 1 year	3 x 10 mg for 14 days	signs of heart failure
OPIE/WHITE (B.M.J. 1981)	longstanding hypertension + A. pectoris	atenolol 100 mg diuretic prazosin >6 weeks	2 x 10 mg for 3 weeks	hypotension (withdrawal of atenolol caused withdr. syndr.)
STAFFURTH/ EMERY (B.M.J. 1981)	47a ♂ longstanding hypertension + renal failure (s. creatinine 5.6—4.8 mg .%) triple vessel disease + 5 M.I. exacerb. of a. pect.	propranolol 4 x 160 mg hydrochlorothi. 50 mg ISDN 4 x 10 mg for 2 years	3 x 10 mg for 18 days	severe drop in blood pressure heart 48/min dev. myoc. inf.
ROBSON/ VISHWANATH (B.M.J. 1981)	60a severe triple vessel disease, M.I. impaired left ventric. function, severe unst. a. pect. 2 years	metoprolol, ISDN for 2 years atenolol 100 mg frusemide 40 mg spironolactone 100 mg	3 x 20 mg for 5 days	heart failure (2 x)

sociation of intracellular sodium and free intracellular calcium concentrations via a linked pump. The increase in free intracellular calcium will increase smooth muscle-contractility and hence peripheral resistance and blood pressure. However, one must add that there is no direct evidence that the vascular smooth muscle membrane of hypertensive patients shares the electrolyte abnormality which has been demonstrated in their blood cells, nor that such smooth muscle contains a higher concentration of free intracellular calcium. However, drugs which specifically reduce the influx of calcium into the cell through the cell membrane and from bound sites within the cells have an anti- hypertensive, vasodilator action.

Nifedipine and beta-blockers

The last part of my presentation is focused on the combination of nifedipine with beta-blockers in angina pectoris and in hypertension because this combination is very often used[21,22] (table III).

The single doses of nifedipine varied from 10 to 30 mg orally and 7. 5 µg per kg i. v. and was combined with various single doses of beta-blockers; 351 patients were included. Multiple dose studies were carried out in 700 patients and nifedipine was given daily doses of 30 or 60 mg. The longest duration of therapy was 14 and 365 days and highest doses used were for, propranolol 120, 480 to 500 mg, combined with 60 mg of nifedipine. The doses given for hypertension do not differ considerably.

Although documents and reports on approximately 2500 patients are available and this combination is given to many patients, the literature reports only 6 cases which have some evidence of a negative interaction of beta-blockade and nifedipine. Three cases were reported by Anastasiades[23] and one each by Opie[24], Stafford[25] and Robson[26].

All these cases, except the one reported by Opie[24], were high-risk cases with severe angina pectoris, triple vessel disease, myocardial infarctions in the case-history and impaired left ventricular function, showing dyskinetic or akinetic areas in the ventriculogram. All patients had been on beta-blockade for many months or years.

Because of the worsening of angina pectoris they also received nifedipine, usually 10 mg 3 tines a day. Within 5 to 21 days, they developed dyspnea and heart-failure symptoms. It is not clear how often this was caused by the progression of the disease or by a hemodynamic interplay between vasoactive drugs. However, in 2 cases, a re-challenge induced signs of heart failure again.

A possible explanation for this may be a more pronounced fall in peripheral blood pressure without heart rate increase due to the beta-blockade. However, some additional facts are necessary for a full explanation. One can speculate that a pronounced fall in aortic pressure induced a reduction in perfusion pressure in or around hypokinetic zones.

To summarize this topic: in some high risk patients suffering from triple vessel disease and impaired left ventricular function and on beta-blockade, nifedipine may have contributed to the cardiac failure. Analysis of results obtained by a great number of investigators, however, have shown this combination to be a useful and effective anti-anginal and an anti-hypertensive regimen and in most cases more effective than the components alone.

Some other nifedipine effects are of greater interest: there are no negative interactions with car-

diac glycosides, or with antidiabetic agents; nifedipine does not decrease insulin secretion.

Possibly there is an interaction with smoking. In a study published recently[27], during smoking, nifedipine effect in exercise angina was reduced. This result could be explained by an increased catecholamine secretion and hence, higher heart rates. And there is some evidence that catecholamines could overcome calcium-induced effects.

However, another group of investigators[28] who looked for the antihypertensive effect of nifedipine under cigarette smoking, found nifedipine capable for blocking cigarette smoking induced peripheral vasoconstriction and hence, a greater efficacy of nifedipine. Additional experiments have to be done to explain if there are different cardiac and peripheral effects and to clarify these contradicting preliminary findings.

In summary, nifedipine is a potent adjunct to therapy of angina pectoris and hypertension with a broad biological activity and without any severe toxic effects.

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