Peter H Stone
James E Muller
Zoltah G. Turi
Edward Geltman
Allan S. Jaffe
Eugene Braunwald

EFFICACY OF NIFEDIPINE THERAPY IN PATIENTS WITH REFRACTORY ANGINA PECTORIS: SIGNIFICANCE OF THE PRESENCE OF CORONARY VASOSPASM

Nifedipine is an effective anti-anginal agent, but its efficacy in patients with angina refractory to maximally tolerated conventional therapy has not been well studied We reviewed the experience using nifedipine in an unblinded manner in 716 patients with refractory angina, all of whom underwent cardiac catheterization. Patients were treated with nifedipine when maximally tolerated conventional therapy was inadequate to control angina. Patients were divided into three mutually exclusive clinical groups based on the presumed pathophysiologic mechanism responsible for angina. Group I consisted of 389 patients with Prinzmetal's angina and coronary vasospasm documented by the observation of spontaneous angina with ST segment elevation and/or vasospasm observed during coronary angiography. Group II was composed of 292 patients with "mixed angina", defined as those patients who exhibited evidence of both classic exertional angina as well as possible superimposed coronary vasospasm. None of these patients had documented coronary vasopasm or ST segment elevation with angina. Group III included 35 patients with classic stable exertional angina, without rest pain of ST segment elevation associated with episodes of ischemia. Angina frequency and nitroglycerin use were compared on conventional therapy before and after the addition of nifedipine. Mean duration of nifedipine therapy was 6.5 months. The addition of nifedipine (median dose 60 mg1day, range 10-200 mg) significantly decreased the mean frequency of angina attacks1week in group I from 14 .4 to 3 .0 ($p < 0$ .0001), in group II from 19. 9 to 5.9 ($p < 0$ .0001), and in group III from 11. 3 to 7.1 ($p < 0$ .3). Complete prevention of angina was most frequent in patients with documented vasospasm (42% of group I patients), intermediate in those clinically suspected of, but no proven to have, vasospasm (20% of group 11 patients), and least frequent in patients with classic exertional angina alone (3% of group III patients) ($p < 0$ .001). In 78% of the 716 patients the weekly angina rate decreased by = 50% of base line values obtained during maximally tolerated conventional therapy, but the degree of improvement was significantly better in patients with either suspected or documented vasospasm. Treatment with nifedipine was associated with an increase of angina frequency in 13-29% of the 716 patients: this increase was most frequently observed in those with no evidence of vasospasm (group III). Nifedipine efficacy did not vary on the basis of the presence or absence of fixed obstructive coronary disease.

These results suggest that nifedipine is efficacious for patients with angina refractory to maximally tolerated conventional therapy, and that efficacy may be greatest when coronary vasospasm is also present.

The calcium (Ca++) channel blocking agents are a new class of drugs with widespread application for the treatment of cardiovascular disorders[1,2]. Nifedipine, one of this new class of agents, is a potent inhibitor of the excitation contraction process in myocardial cells and in vascular smooth muscle cells[3] and has been used successfully in relieving myocardial ischemia due to a variety of pathogenetic mechanisms. Different mechanisms may contribute to a variable degree to produce episodes of myocardial ischemia[4]. In patients whose angina pectoris is due to coronary vasospasm or increases in coronary vasomotor tone, nifedipine is effective by preventing episodes of coronary vasoconstriction[5-10], and myocardial oxygen supply is thereby maximized. On the other hand, in patients whose angina is due to fixed

From the Departament of Medicine, Cardiovascular Division, Brigham and Women's Hospital Harvard Medical School. Boston, MASS., and the Departament of Medicine, Cardiovascular Division, Barnes Hospital, Washington University School of Medicine, St. Louis, MI.

obstructive coronary lesions without e superimposed component of coronary vasospasm, nifedipine is effective primarily by decreasing myocardial oxygen demand through its effect on decreasing arterial pressure[11-15]. Nifedipine has been shown to be efficacious inpatients with classic exertional angina as single agent therapy[13,15,18] and also in combination therapy with nitrate preparations and/or beta-adrenergic blocking agents[19,23]. Its use in patients with angina refractory to conventional anti anginal agents, however, has mot been extensively studied. In this report we describe experience with nifedipine in the treatment of refractory angina pectoris due to a variety of possible pathogenic mechanisms: 1) patients with Prinzmetal's variant angina and documented coronary vasospasm; 2) patients with "mixed" angina, defined as those patients who exhibit evidence of both exertional angina as well as possible superimposed coronary vasospasm; and 3) patients with stable classic exertional angina whose symptoms are presumed to be due to fixed obstructive lesions alone.

METHODS

This report represents the multicenter experience of open label treatment with nifedipime before the drug was approved by the Food and Drug Administration, when nifedipine therapy was available on an experimental basis for patients with angina pectoris, in whom conventional therapy with nitrates and/or betablocking agents was found to be ineffective, only partly effective, or not well tolerated. Physicians with patients meeting these criteria were supplied with nifedipine in the form of 10 mg light-protected capsules to be taken orally (provided by the Pfizer Pharmaceutical Corp., New York). Baseline information and follow-up data were collected on standardized forms by Pfizer Pharmaceutical Corporation. This report presents the experience of 716 patients with angina pectoris refractory to maximally tolerated conventional therapy who were treated with nifedipine. All patients underwent diagnostic cardiac catheterization and coronary arteriography. Written informed consent was obtained in all cases with forms that had been approved by institutional review committees.

The response to nifedipine was evaluated by comparing the number of anginal attacks and nitroglycerin tablets used per week during the two-week period prior to the initiation of nifedipine and the most recent two-week period of follow-up. Neither the patient por the physician was blinded.

To determine if the type of anginal pattern influenced nifedipine's efficacy to relieve angina, the patients were divided into three mutually exclusive categories based on both the clinical and laboratory manifestations of ischemic heart disease (table I). Group I is composed of 389 patients with Prinzmetal's variant angina and coronary vasospasm documented by the observation of angina at rest with ST-segment elevation in 56% of the patients, spontaneous vasospasm observed during coronary angiography in 26%, and ergonovine-induced coronary vasospasm in 33%. Among the 389 patients with documented vasospasm, 98% of the patients experienced some episodes of angina at rest. Thirty-six percent of the patients demonstrated rest angina alone, the remainder experienced angina both at rest and during exertion.

Group II is composed of 292 patients with "mixed angina", defined as patients who exhibited evidence of both classic exertional angina, defined below, as well as possible superimposed coronary vasospasm, manifested by either occasional episodes of rest angina or a variable and inconsistent threshold for the provocation of exertional angina. None of these patients demonstrated ST-segment elevation with pain, however, or any other documented evidence of coronary vasospasm.

Group III is composed of 35 patients with classic exertional angina that was provoked by

TABLE I - Baseline characteristics of 716 patients treated with nifedipine

	Prinzmetal's Variant Angina (group I)	Mixed Angina (group II)	Classic Enxertional Angina (group III)
n	389	292	35
Male: female ratio	1.1:1	1:6:1	7.8:1
Mean age (years)	53	57	56
Mean duration of angina (months)	30	48	39
Patients with fixed obstructive CAD	39%	87%	91%
History of previous MI	26%	58%	49%
Patients with NYHA Class III or IV angina	65%	86%	79%
Previous treatment with nitrates	99%	99%	98%
Previous treatment with β-blockers	80%	94%	94%
Patterns of Angina Provocation			
consistent exertional threshold	15%	22%	100%
variable exertional threshold	49%	65%	0%
rest angina only	36%	13%	0%
ST-segment response during angina:			
ST-segment elevation	75%	0	0
ST-segment depression or T inversion	18%	62%	57%
No ST-T segment change	7%	38%	43%
Exercise Treadmill Test			
Positive	36%	44%	66%
Negative	31%	17%	17%
Non-diagnostic	33%	39%	17%
Exertional ST elevation	12%	5%	0%
Mean number angina attacks/week	14.4%	19.9	11.3
Mean number NTG consumed/week	19.5	27.2	10.7

CAD = coronary artery disease; MI = myocardial infarction; NTG = nitroglycerin.

a stable, consistent, and predictable exertional threshold. None of these patients had rest pain or ST segment elevation recorded during an episode of exertional pain. These patients were considered to represent a group in which angina was likely to be the result of fixed atherosclerotic obstruction. Relatively few patients with classic exertional angina are included in this study because most physicians requested use of the drug for patients with refractory coronary vasospasm during this open label protocol.

Table I illustrates the baseline characteristics of all patients in the study. All patients underwent cardiac catheterization and coronary arteriography. Most of the patients with classic exertional angina were male. Patients with either classic exertional angina or mixed angina had a much higher incidence of fixed atherosclerotic coronary obstructions (≥ 50% luminal cross-sectional narrowing of at least one major coronary artery) and a history of a previous myocardial infarction (MI) compared to patients with Prinzmetal's variant angina. The majority of patients in all 3 clinical groups were severely limited by their angina pectoris, i .e , they were in functional class III or IV of the New York Heart Association, despite therapy with nitrate preparations and/or betaadrenergic blocking agents.

As described above, patients with classic exertional angina (group III), by definition, exhibited a stable and consistent exertional threshold for angina. The majority of patients with either mixed angina or Prinzmetal's angina exhibited a variable and inconsistent exertional threshold for the provocation of angina.

There were characteristic differences among the 3 groups in the ST segment response during an episode of angina (table I). Among the patients with classic exertional angina or mixed angina (groups II and III), almost two-thirds demonstrated ST segment depression or T wave inversion with pain while the remainder demonstrated no ST segment changes. In contrast, only 18% of the patients with Prinzmetal's angina (group I) demonstrated ST segment depression with pain.

Exercise stress tests were performed on 323 patients (166 patients in group I, 133 patients in group 11, 24 patients in group III).Two-thirds of the patients in group III had a positive ST-segment response, defined as ≥ 1.0 mm horizontal or downsloping ST segment depression, and less than 20% had a negative test, defined as achievement of ≥ 85% of maximal predicted heart rate for age and < 1 mm of horizontal or downsloping ST segment depression. On the other hand, only one third of the patients with Prinzmetal's variant angina (group I) had a positive test and almost one third had a negative test. Exercise-induced ST segment elevation ≥ 1 mm in a lead without a pre-existing Q-wave was observed in 19 patients (12%) in group I, in 8 patients (5%) in group II, and in none of the patients in group III.

The heart rate and blood pressure, determinants of myocardial oxygen demand, were controlled with conventional anti-anginal agents at rest in almost all patients (table II). In spite of this, the mean weekly anginal attack rate was high, ranging from 11.3 ± 2 .0 in patients in group III to 19.9 ± 1.6 (± S.E.M) in patients in group II. Mean weekly nitroglycerin consumption ranged from 10.7 ± 1.9 tablets for patients in Group III to 27.2 ± 2 .1 tablets for patents in group II.

Statistical analysis of the nifedipine efficacy data within groups was performed using a paired two-tailed t-test, and comparison between groups using am unpaired two tailed t-test.

TABLE II - Effect of nifedipine on resting heart rate and arterial blood pressure

Patient Group	Conventional Therapy	Conventional Therapy Plus Nifedipine	P
Prinzmetal's Variant Angina (group I)			
Systolic Pressure (mmHg)	124.4 ± 1.8	127.8 ± 2.0	NS
Diastolic Pressure (mmHg)	77.5 ± 1.2	79.0 ± 1.6	NS
Heart Rate (beats/min)	70.3 ± 1.2	76.3 ± 1.4	0.0001
Mixed Angina (group II)			
Systolic Pressure (mmHg)	124.3 ± 1.9	127.4 ± 2.1	NS
Diastolic Pressure (mmHg)	75.2 ± 1.2	84.0 ± 9.3	NS
Heart Rate (beats/min)	65.7 ± 1.2	69.0 ± 1.4	0.01
Classic Exertional Angina (group III)			
Systolic Pressure (mmHg)	122.2 ± 4.0	115.4 ± 4.2	NS
Diastolic Pressure (mmHg)	75.6 ± 2.5	76.0 ± 2.1	NS
Heart Rate (beats/min)	69.9 ± 3.4	75.3 ± 6.8	NS

data displayed as mean ± SEM

RESULTS

The daily dose of nifedipine ranged from 10 to 200 mg, with a median daily dose of 60 mg for patients in all three patient subsets. Although some patients in each group noted a decrease in angina frequency while receiving 40 mg/day or less, most required higher doses. These findings indicate that different patients require markedly different total daily doses to achieve a similar degree of efficacy.

Patients were followed for an average of 6 .5 months on nifedipine therapy (range 1-43 months). The addition of nifedipine to the conventional anti-anginal regimen was associated with a small, but statistically significant increase in the resting heart rate in the patients with Prinzmetal's angina (group I) and in those with mixed angina (group II), but not in the patients with classic exertional angina (group III) (table II). None of the patient groups exhibited a significant change in the systolic or diastolic blood pressure at rest when nifedipine was added to the regimen.

In general, nifedipine was well tolerated (tables III and IV). Only 3.5% of the 716 patients discontinued the drug because of an inadequate response, and only 18 patients (2.5%) discontinued the drug because of adverse experiences.

Table III - Status of nifedipine use at time of follow-up

	n	(%)
Total Patients	716	(100)
Nifedipine discontinued because of:		
adverse experience	18	(2.5)
inadequate response	25	(3-5)
death	6	(0-8)
myocardial infarction	3	(0-4)
coronary bypass surgery	15	(2.1)

Table IV - Tolerance of nifedipine

		n	(%)
Total patients treated		716	(100)
Nifedipine discontinued because of adverse experiences		18	(2.5)
GI distress	5		
Fatigue	5		
Headache	2		
Dizziness	2		
Ankle edema	2		
reflex tachycardia	1		
digital dysesthesias	1		

The reduction in weekly angina attack rate at the latest follow-up visit while on nifedipine - was compared to the 2-week period just prior to initiation of nifedipine (fig. 1). Patients in each of the three clinical groups experienced a significant improvement in angina frequency when nifedipine was added to the regimen of conventional therapy, although patients with either Prinzmetal's variant angina or mixed angina exhibited a significantly more favorable response than patients with classic exertional angina ($p < 0.05$). A similar improvement was observed In weekly nitroglycerin consumption for patients In each of the three groups (fig 2). The distribution of response to nifedipine is shown in figures 3-5 and illustrates important differences among the three clinical groups. The addition of nifedipine therapy was associated with complete prevention of angina more frequently in patients with Primzmetal's angina (42% of group I patients), and those with mixed angina (20% of group II patients), than in. Patients with classic exertional angina (3% of groups III patients) (p, < 0 001) (fig. 3). The majority of patients in each of the three clinical groups experienced an improvement in weekly angina rate to less than 50% of the base-line angina frequency when nifedipine was added to their conventional regimen. Such improvement in angina frequency was greatest in those patients with either suspected or documented coronary vasospasm (83% of group I patients, 76% of group II patients, and 51% of group III patients; $p < 0.001$) (fig. 4). These responses include an unknown placebo effect and spontaneous variations in the course of the disease.

Among the 716 patients treated in this series, a total of 100 patients experienced an increase in angina frequency during treatment with nifedipine (fig. 5). However, an

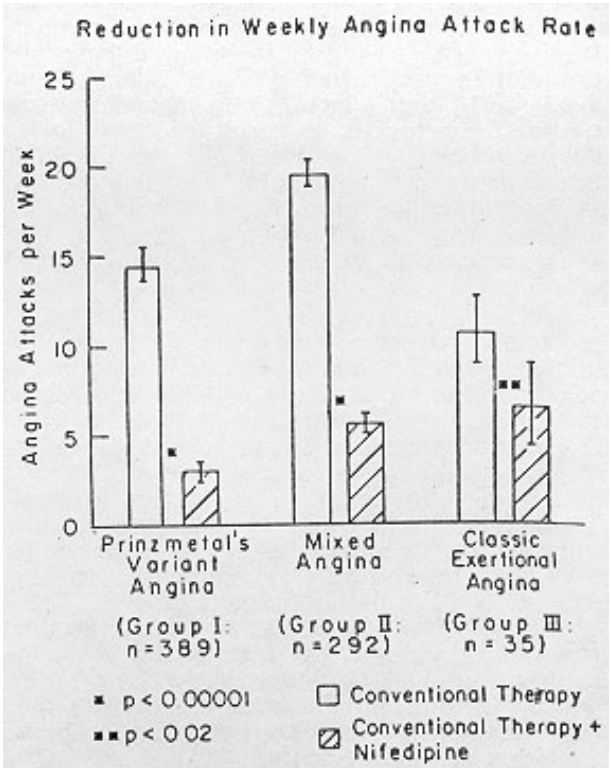

Fig. 1 - Weekly angina attack rate on maximally tolerated conventional therapy compared with the attack rate after the addition of nifedipine. Although patients in each of 3 groups experienced a significant reduction in angina frequency when nifedipine was added to the conventional regimen, patients with either Prinzmetal's variant angina or mixed angina experienced a more favorable response than patients with classic exertional angina ($p < 0.05$).

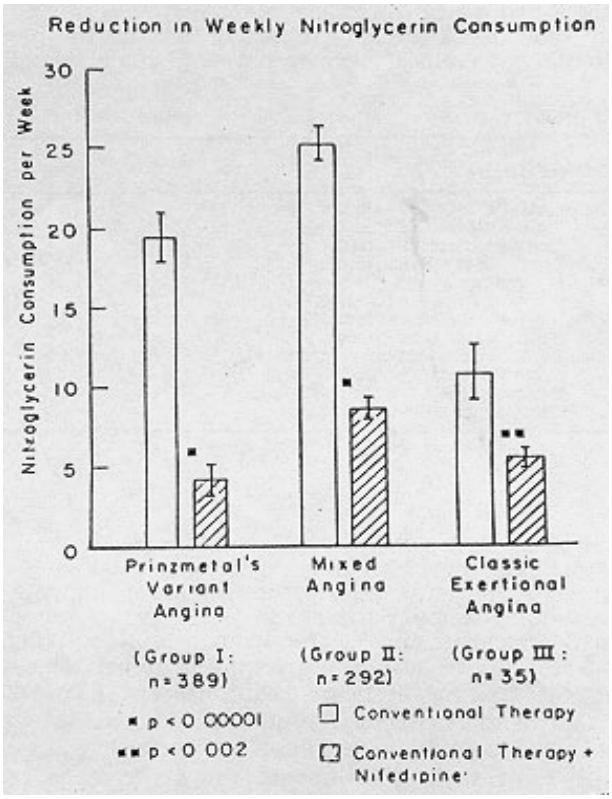

Fig. 2 - Weekly nitroglicerin consumption after the addition of nifedipine.

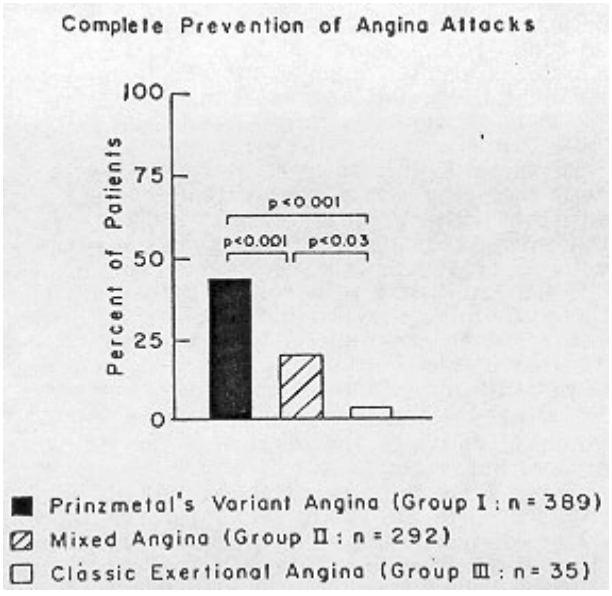

Fig. 3 - The percent of patients in each group who experienced complete prevention of angina attacks when nifedipine was added to the conventional regimen.

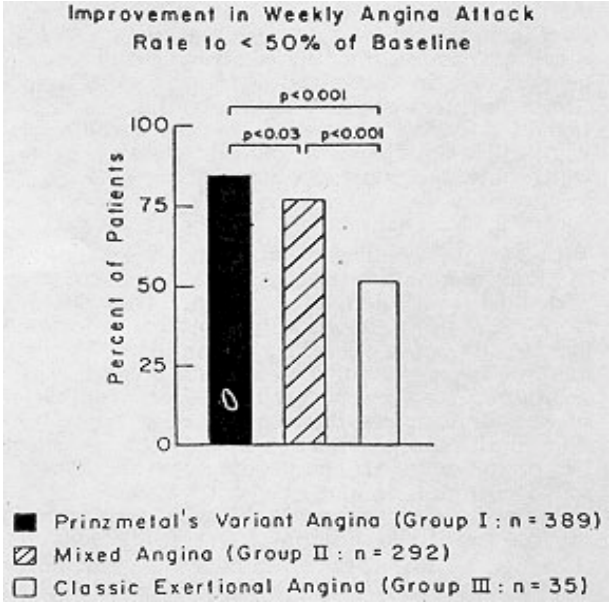

Fig. 4 - The percent of patients in each group who experienced an improvement in weekly angina attack rate when nifedipine was added to their conventional regimen to less than 50% of the baseline angine attack frequency on conventional therapy. Although the majority of patients in each of the 3 groups experienced a beneficial response, the percentage of patients with documented vasospasm (group I) or suspected vasospasm (group II), than in those considered not to have vasospasm (group III).

exacerbation of anginal symptoms was more common in patients with classic exertional angina (29% of group III patients) than in patients with either mixed angina (13% of group II patients) or in patients with Prinzmetal's angina (14% of group I patients) ($p < 0.03$).

Patients were further subdivided into those with fixed atherosclerotic coronary artery obstructions determined from coronary arteriography and those without fixed obstructions. We speculated that patients whose ischemia

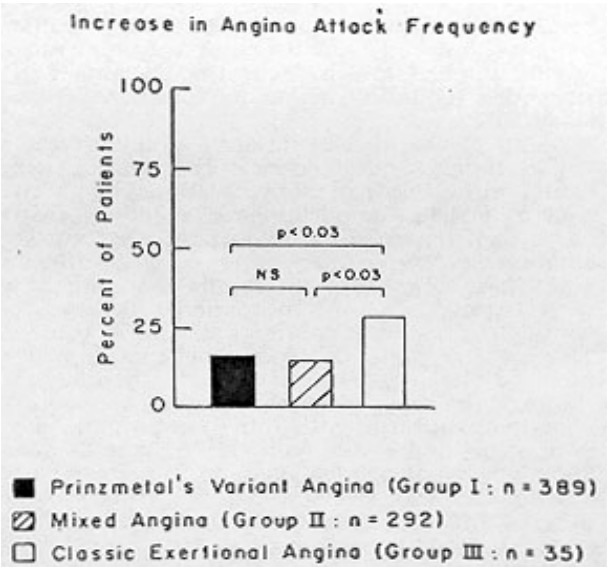

Fig. 5 - The percent of patients in each group who experienced an increase in angina attack frequency when nifedipine was added to the conventional regimen.

was due primarily to fixed obstructions might have a different therapeutic response to nifedipine than patients whose angina was due primarily to alterations in coronary vasomotor tone. We observed that patients with either Prinzmetal's variant angina or mixed angina experienced a significant improvement in angina frequency and nitroglycerin consumption regardless of the presence or absence of fixed coronary obstructions. Since only 3 patients with symptoms of classic exertional angina did not have fixed obstructive coronary disease a meaningful analysis of efficacy could not be made in this group.

DISCUSSION

These observations suggest that patients with severely limiting angina pectoris that is refractory to maximally tolerated doses of conventional medication may experience a significant benefit in anginal symptoms when nifedipime Is added the conventional regimen.

The efficacy of nifedipine to treat refractory documented coronary vasospasm and Prinzmetal's variant angina in a large series of patients in this country was first described by Antman et al[7]. In a smaller subset of 38 of these patients nifedipine was used in a double-blind, placebo-controlled trial[24] that confirmed the efficacy initially observed with the open label use. This present report expands Antman's initial observations of 127 patients to include 389 patients with Prinzinetal's variant angina (group I), and again illustrates that nifedipine is effective in reducting episodes of angina. In this current larger series 42% of the 389 patients experienced complete relief of their anginal pain following the addition of nifedipine therapy, and a total of 83% of the patients experienced a reduction of angina episodes to less than half of the baseline frequency prior to initiation of nifedipine. This experience is similar to that reported in the initial

series by Antman et al. in which 63% of 127 patients responded with complete control of angina attacks and 87% of the patients experienced a reduction in anginal frequency by at least 50%.

The group of 292 patients with refractory "mixed angina", defined as those patients who exhibited evidence of both exertional angina as well as possible superimposed coronary vasospasm or heightened vasomotor tome (group II), also experienced am impressive reduction in angina frequency when nifedipine was added to their regimen: 20% of the patients experienced complete prevention of angina, and a total of 76% of the patients experienced am improvement to an angina frequency less than 50% of the pre-nifedipine baseline- The mechanism of beneficial action of nifedipine for patients with both effort and rest angina may include decreasing myocardial oxygen demands by decreasing afterload as well as maximizing coronary blood flow by preventing increases in coronary vasomotor tone or vasospasm.

Although only one (3%) of the 35 patients with severe classic exertional angina (group III), experienced complete prevention of anginal episodes when nifedipine was added to the anti-anginal regimen, it is nevertheless significant that 51% of these patients, most of whom were treated with maximally tolerated doses of nitrate preparations and bet43,blookers, experienced a 50% or greater reduction in angina frequency. The number of patients with classic exertional angina in this. series is small, however, and conclusions concerning efficacy in this group are suggestive only. It has previously been shown that nifedipine can be safely added to anti-anginal regimens consisting of nitrates or beta-blockers[22,23,25], but the additional benefit from nifedipine in patients who are already maximally treated with both of these drugs has not previously been reported. The explanation of the beneficial effect of nifedipine in these patients with refractory classic angina is mot clear, but, as in patients in group II, it may be due to a decrease in myocardial oxygen demand and/or to an increase in coronary flow and myocardial oxygen supply. Most investigators have noted that the beneficial effect of nifedipine in patients with stable exertional angina is not associated with an improved double product at the onset of angina (an index of myocardial oxygen supply), and therefore appears not to be due to an increased oxygen delivery to the ischemic myocardium, but rather is due to a decrease in myocardial oxygen demand [13,15]. On the other hand, patients with classic exertional angina may often demonstrate a heightened coronary vasoconstrictive response to provocative measures such as the cold pressor test[26] and nifedipine may Prevent Such coronary constriction[27]. In addition, nifedipine increases coronary blood flow both at, rest and after rapid atrial pacing in normal as well as obstructed vessels[28]. Thus, the mechanism of nifedipine's anti-anginal effectiveness in patients in group III is not clear.

Our study was not designed to determine the mechanism of beneficial effect from the addition of nifedipine therapy and we do not have data concerning the heart rate, blood pressure, or double product during exercise in our patients. Nifedipine e decreased the mean systolic blood pressure at rest in our patients with classic exertional angina, but this change did not achieve statistical significance (table II).

It is particularly noteworthy that patients with Prinzmetal's angina or mixed angina experienced a significantly greater therapeutic benefit from the addition of nifedipine than did patients with classic exertional angina. It is likely that the angina episodes in the patients with either Primmetal's or mixed angina were due in large part to coronary vasospasm and that nifedipine may be more spasmolytic than conventional therapy[29,30]. Alternatively, the difference may be due to bias in the selection of patients for nifedipine therapy.

A placebo effect must be considered as a potential cause of the decreased symptoms - of myocardial ischemia in this entire group of 716 patients since there was not a randomly selected placebo control group. However, this reported experience is not entirely uncontrolled since the period in which there was inadequate response to conventional therapy provided for each patient a control level of attack frequency that was then compared with the attack frequency observed during nifedipine therapy. Furthermore, it is unlikely that placebo effect alone accounted for such a striking and sustain ed decrease in such a large number of patients. These features suggest strongly that nifedipine provided additional relief of myocardial ischemia in patients with angina pectoris beyond that obtained with conventional anti-anginal medication.

It is significant that 13 to 29% of patients with refractory angina experienced an increase in their angina frequency when nifedipine was added to their medical regimen. This observation has been noted anecdotally before31-33, but its incidence in a large number of patients has not been previously reported. The increase in anginal frequency may represent progression of the underlying disease or may have been due to nifedipine therapy itself. This exacerbation of anginal symptoms was significantly more common in patients with classic exertional angina than in patients with Prinzmmetal's angina or mixed angina. The study was not designed to investigate the cause of the increase in anginal symptoms noted in some patients, but one can speculate that the difference in response between the different clinical groups may be related, to the respective underlying pathophysiologic mechanism of the ischemia and the mechanism of action of the anti-anginal regimen. If the beneficial action of nifedipine in the treatment of classic exertional angina is to decrease ox1gygen demand by decreasing afterload, nifedipine's additive effect may be relative trivial when added to a maximally tolerated conventional regimen that may have already achieved an optimal decrease in myocardial-oxygen demand. Use of nifedipine in some maximally treated patients, therefore, may not lead to a further decrease in myocardial oxygen demand, but, instead, to a paradoxical increase in myocardial oxygen demand because of the reflex-mediated increases in contractility and heart rate. Alternatively, nifedipine may have induced an imbalance in the myocardial oxygen supply: demand ra-

tio in some patients by decreasing peripheral vascular resistance excessively so that coronary perfusion pressure and flow across the obstruction decreased. Other coronary vasodilators such as nitrates and dipyramidole have been demonstrated to cause a "coronary i teal" phenomenon[34,35], but this has not been demonstrated with nifedipine[28] .Fewer patients with Prinzmetal's angina or mixed angina, i.e , those whose ischemic episodes may have been due to coronary vasospasm, appeared to experience an increase in their anginal frequency when compared with the patients with classic exertional anginal. The enhanced efficacy of nifedipine in these two groups of patients may be because nifedipine may be more efficacious than conventional therapy to prevent vasospasm, and reflex-mediated increases in myocardial o e demand, if they developed, would be of less pathophysiological significance.

In summary, we observed that nifedipine is highly efficacious in decreasing the frequency of anginal episodes and nitroglycerin consumption in patients with Prinzmetal's variant angina and mixed angina that is refractory to maximally tolerated doses of conventional antianginal therapy. It may also be of benefit in patients with classic exertional angina, but the decrease in anginal attack rate and nitroglycerin consumption was significantly less marked. The mechanism of beneficial response in patients with refractory angina pectoris is unclear, but may be due to additional decreases in after and myocardial oxygen demand, or, in some patients, to the prevention of decreases in myocardial oxygen supply caused by coronary vasoconstriction. Since this study reflects experience using nifedipine in an unblinded and non-controlled manner, these efficacy results should be considered to have generated a hypothesis that must now be tested prospectively with a randomized, double-blind, and placebo-controlled study design.

RESUMO

Receberam nifedipina, quando a terapia convencional máxima tolerada se tomou inadequada para controlar angina, 716 pacientes que foram divididos em 3 grupos mutuamente exclusivos de acordo com os mecanismos fisiopatológicos presumidos para a angina. 0 grupo 1 consistiu de 389 pacientes com angina de Prinzmetal e vasoespasmo coronário, documentado pela observação de angina espontânea com elevação do segmento ST e/ou vasoespasmo observado durante angiografia coronária. 0 grupo 2 compõe-se de 292 com "angina mista". pacientes que exibiam tanto angina clássica de exercício como possível espasmo coronário sobreposto. Nenhum desses pacientes apresentava espasmo coronário documentado ou elevação do segmento ST com angina. 0 grupo 3 incluiu 35 pacientes com angina clássica de exercício, estável, sem dor de repouso ou elevação do segmento ST associada com episódio de Isquemia. A freqüência de angina e de utilização de nitroglicerina foram comparadas sob a terapia convencional, antes e depois da adição de nifedipina. A duração média da terapêutica com nifedipina, foi 6,5 meses. A adição de nifedipina, (dose média de 60 mg/dia, 10 a 2W mg) significativamente diminuiu a freqüência de ataques de angina por semana no grupo 1, de 14,4 para 3,0 ($p < 0,0001$), no grupo 2, de 19,9 para 5,9 ($p < 0,0001$) e no grupo 3, de 11,3 para 7,1 ($p < 0,03$). Prevenção completa da angina foi mais freqüente nos pacientes com va soespasmo documentado (42% dos pacientes do grupo 1), intermediária naqueles clinicamente suspeitos de vasoespasmo, porém não provado (20% dos pacientes do grupo 2) e menos freqüente nos pacientes com angina clássica de exercício 0% dos pacientes do grupo 3) ($p < 0,0001$). Em 78% dos 716 pacientes, a freqüência semanal de angina diminuiu em mais de 5001o dos valores obtidos durante o tempo de terapêutica convencional máxima tolerada. Entretanto, o grau de melhora foi significativamente maior em pacientes com espasmo ou suspeito ou documenlado. 0 tratamento com nifedipina esteve associado com aumento da freqüência da angina em 13-29% dos 716 pacientes: este aumento foi mais fre;qüentemente observado naqueles sem evidência de vasoespasmo (grupo 3). A eficácia da nifedipina não variou em função da presença ou ausência da doença coronária obstrutiva fixa. Esses resultados sugerem que nifedipina é eficaz para os pacientes com angina refratária à terapia convencional máxima tolerada e que a sua eficácia pode ser maior quando o espasmo coronário está presente.

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