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A Randomized, Double-Blind Comparison of Lercanidipine 10 and 20 mg in Patients with Stable Effort Angina

Clinical Evaluation of Cardiac Function by Ambulatory Ventricular Scintigraphic Monitoring

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We evaluated the antiischemic action and the effects on left ventricular response to exercise of lercanidipine, a long-acting dihydropyridine calcium antagonist, in 23 patients with stable effort angina in a randomized, double-blind, parallel trial. Left ventricular function was assessed during upright bicycle exercise using an ambulatory radionuclide detector for continuous noninvasive monitoring of cardiac function. Exercise was performed under control conditions before (run-in placebo period) and after 2-week treatment with lercanidipine 10 or 20 mg once daily. During the placebo run-in period and at the study end, patients underwent clinical examination, ECG, exercise tests, ambulatory ventricular scintigraphic monitoring (VEST). Results showed that both drug doses increased time to onset of ST segment depression ≥1 mm and peak ST segment depression, with improvement of total exercise duration. Heart rate, blood pressure, and the rate-pressure product did not significantly change with respect to pretreatment value. The left ventricular ejection fraction, indicating contractility state of myocardium, was unchanged at rest and during exercise after both lercanidipine doses. In conclusion, lercanidipine is safe and effective in reducing ischemia in patients with stable effort angina without any deterioration of cardiac function.

Keywords: calcium channel blocker, lercanidipine, stable effort angina, ambulatory ventricular scintigraphic monitoring (VEST), myocardial ischemia, exercise tests

INTRODUCTION

Monitoring of exercise-induced hemodynamic parameters may be a better index for the detection of ischemia: Actually, changes in the ejection fraction occur earlier than ECG changes or symptoms in patients with myocardial ischemia.[1–10] However, hemodynamic measurements during a stress test and in response to drug administration are difficult to apply over a prolonged period.[11–14] Continuous hemodynamic and ECG recording of cardiac function may be performed by means of radionuclide ambulatory ventricular function monitoring (VEST). Combined ECG and radionuclide monitoring is able to provide a more thorough evaluation of ischemia, drug, and training effects.[15–21]

Calcium antagonists are widely used in the treatment of patients with hypertension and angina pectoris. In spite of the therapeutic success of several calcium channel blockers, their use is still limited because of class-specific side effects. Calcium antagonists improve exercise time and reduce anginal frequency in patients with stable effort angina.[22–29] Their therapeutic effects are related to a reduction in myocardial oxygen demand and to an increase in coronary blood flow.[30] Until now, no calcium antagonist has the

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combined characteristics of high bioavailability, once-daily dosage regimen, absence of reflex tachycardia, and lack of negative inotropic effect. Lercanidipine is a new calcium channel blocker structurally related to the 1,4-dihydropyridines. Lercanidipine's characteristics include high lipophilicity, long biologic half-life, absence of reflex increases in neurohormones, and sympathetic activity.[31–36] The results of clinical trials have clearly established the efficacy and safety in patients with hypertension and stable effort angina of once-daily treatment with lercanidipine 5, 10, 20, and 40 mg.[37,38]

On the basis of these favorable properties, we evaluated the antiischemic action and the effects on the left ventricular response to physical exercise of lercanidipine in a randomized, placebo-controlled, double-blind, parallel-designed, dose-response trial in patients with chronic stable angina pectoris.

METHODS

Patients selection

Patients were selected from a larger population referred to our department for evaluation of angina.

Inclusion criteria for the present study were stable effort angina for at least 3 months, reproducible exercise tests (tests were considered reproducible when they showed a difference of less than 10% on 3 different assessments during the placebo run-in period), angina and ST segment depression ≥2 mm 80 milliseconds after the J point at a work load not lower than 50 W on exercise test, a reversible perfusion defect at exercise ^{201}Tl myocardial scintigraphy in at least 1 segment of left ventricle, availability of a quantitative coronary arteriography in the 3 months preceding the study entry to assess the number of diseased vessels with more than 70% luminal diameter narrowing, and the ability to follow the prescribed therapy and to report the number of angina attacks and the possible side effects.

We excluded from the study patients with unstable anginal; recent myocardial infarction (in the past 3 months); repolarization abnormalities on ECGs at rest, after positional changes, or during hyperventilation; hypertension; atrial fibrillation; electronically paced rhythm; significant valvular disease; heart failure; severe arrhythmias; sinus node dysfunction; atrioventricular conduction disturbances; left bundle branch block; preexcitation syndrome; left ventricular hypertrophy; digoxin treatment; significant renal, thyroid, hepatic, or hematologic disorders; and debilitating systemic diseases.

Twenty-three sedentary patients met selection criteria. All patients gave their informed consent, and the protocol was approved by the Salvatore Maugeri Foundation's Ethics Committee. The study was conducted according to "Good Clinical Practice" rules.

Study design

The double-blind, randomized, parallel study consisted first of a 1-week washout period, during which previous antianginal medications (β-adrenergic blocking agents, long-acting nitrates, and calcium channel blockers) were gradually discontinued after screening. Then patients entered a 2-week, single-blind, placebo run-in period, after which they were randomized to receive a single daily dose of lercanidipine, 10- or 20-mg tablet, for 2 weeks. Clinical examination, ECG, exercise tests, and VEST monitoring were performed in the placebo run-in phase and at the study end (Fig. 1). The use of sublingual nitroglycerin was allowed to relieve angina throughout the study.

Angina was defined as the occurrence of substernal or precordial chest discomfort that was fairly reproducible, was induced by effort, and relieved by its cessation or by sublingual nitroglycerin assumption. Adverse events were recorded throughout the study.

Exercise test

Stress tests were performed in a thermostatically controlled room with a bicycle ergometer in the upright sitting position. Instructions were given to the patients before and during all the exercise tests. The starting load was 30 W, with increments of 20 W every 2 minutes. Patients were asked to cycle at a constant rate of 50 rpm and to report the onset of angina.

Leads V_4, V_5, and V_6 were continuously monitored during the test. ECG and blood pressure were obtained at baseline, every minute of exercise until interruption, and every minute of recovery until the third minute.

Tests were stopped in case of angina, when it was recognized as usual by the patient, and ST segment depression ≥2 mm at 80 milliseconds from the J point

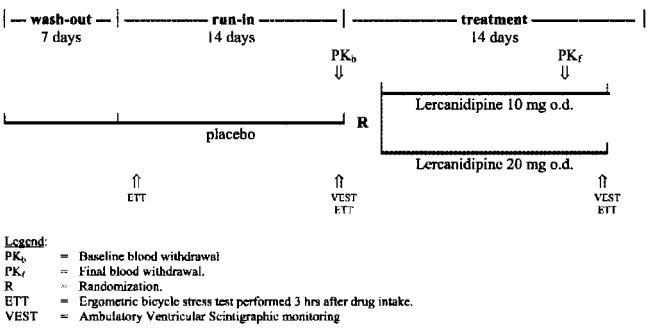

FIGURE 1. Study design.

or muscular exhaustion. Tests were also interrupted in case of severe arrhythmias, lack of increase in blood pressure, blood pressure >250/120 mm Hg, or dyspnea.

Stress tests were performed by the same physician, blinded to the treatment given to the patients, throughout the whole study. The following ergometric variables were considered: heart rate (beats per minute), systolic blood pressure (mm Hg) and rate-pressure product (heart rate × systolic blood pressure) at rest and peak exercise, ST segment depression (millimeters) at peak exercise, total exercise duration, and time to onset of ST segment depression ≥1 mm and to development of angina (seconds). Electrocardiographic analysis was carried out in V_4, V_5, and V_6 leads and the mean value of measurements made in these leads was used for statistical analysis.

Radionuclide ambulatory left ventricular function monitoring

Left ventricular function at rest and during exercise was evaluated by VEST, which records 2 channels of the ECG in analog form (frequency response >300 Hz) and a beat-to-beat left ventricular time-activity curve. Data were recorded on a cassette tape. At the end of monitoring, the tape was read into a dedicated computer (PDP-11/73, DEC; IBM PC/RT, IBM, Armonk, NY) for analysis, with a temporal resolution of 7.8 seconds.

The patients were asked to avoid strenuous physical activity for at least 24 hours before the study. Alcohol, caffeine, and smoking were all prohibited within 24 hours of the study. After an overnight fast, the study was begun at 8 AM with the subject in a comfortable sitting position. The temperature (22°C) and the light of the study room were maintained at constant levels. The in vivo labeling of red blood cells was performed with 555 MBq (15 mCi) of ^{99m}Tc. In each patient, equilibrium radionuclide angiography was then obtained to determine the basal peak filling rate and global and regional left ventricular ejection fraction. Immediately after radionuclide angiography, the VEST garment was placed over the subjects' chest and tightened to ensure stable contact. The VEST detector (Capintec, Inc.) was positioned under gamma camera control (Kayden 1990). A 2-minute static gamma camera image was obtained to confirm the adequacy of the VEST detector position. Measurements in the resting condition were obtained after the subjects had been sitting quietly for at least 10 minutes. Thereafter, they underwent bicycle cardiopulmonary exercise and simultaneous assessment of left ventricular function. For analysis, we considered the values at rest (2 minutes to the beginning of the exercise test) and throughout the exercise period. The exercise level was expressed as the percentage of maximal effort.

Radionuclide angiography was analyzed with standard commercial software (General Electric). The left ventricular ejection fraction was computed on the raw time-activity curve, while the peak filling rate was calculated after a Fourier expansion with 4 expansions. At the end of monitoring, data were reviewed for technical adequacy. The average count rate (decay-corrected) of the entire study was displayed: If the curve had <10% deviation from straight line, the VEST study was considered adequate. Radionuclide and ECG data were analyzed beat by beat and summed for 30-second intervals. Excellent agreement between VEST and radionuclide angiography in measuring ejection fraction and peak filling rate was found for 60-second time averaging. The relative end-diastolic volume (EDV) was considered to be 100% at the beginning of the study and was subsequently expressed relative to this initial value. The end-systolic volume (ESV) was expressed relative to EDV. The ejection fraction was computed as the stroke counts divided by the background-corrected end-diastolic counts. Background was determined by matching the initial resting VEST ejection fraction value to that obtained by the gamma camera. This background value was then used throughout the remainder of each individual's VEST data analysis.

The accuracy and reproducibility of this technique have been validated in our laboratory. In particular, at the beginning of the study, the correlation coefficients between the measurements of the ejection fraction and the peak filling rate obtained with radionuclide angiography and with VEST were 0.98 and 0.82 ($P < 0.01$), respectively; similar values were obtained at the end of the monitoring period. VEST assessment of the ejection fraction and the peak filling rate within the same patients under steady-state conditions on different days of observation also showed significant correlation ($r = 0.94$ and $r = 0.74$, respectively, both $P < 0.05$).

Tolerability assessment

Each adverse change from the patients' baseline conditions was considered as an adverse event and classified as mild, moderate, or severe. Mild adverse events were defined as events able to cause discomfort but not interfering with the patient's normal daily activities; moderate adverse events were considered events interfering with the normal daily activities; severe adverse events were defined as events not compatible with normal daily activities. Investigators judged the possible relation of the adverse events with the administration of the test drug.

Statistical analysis

Comparison of baseline data of the groups was performed by an unpaired t test, Wilcoxon rank test, or χ^2 analysis, as appropriate. The statistical analysis was carried out by means of a split-plot design of analysis of variance applied to quantitative variables, including treatment (10 and 20 mg lercanidipine) and time (baseline and end of study) in the model.

A repeated measures analysis of variance was then applied to investigate the following main effects: left ventricular ejection fraction (at rest and during the exercise test), heart rate (at rest and during the exercise test), stroke volume (at rest and during the exercise test), and cardiac output (at rest and during the exercise test). The interactions of these main effects with treatment and time were also tested.

The rank, log, or square root transformation was applied when the departure of the original data from the normal distribution was significant (Shapiro-Wilks test).

The χ^2 test was applied to compare the percentage of patients with angina before and after treatment.

All hypothesis tests were performed using a significance level of 0.05. All P values were 2-sided. All analyses were carried out with the SAS software package (SAS Inc., Vers. 6.12).

RESULTS

Patients characteristics

Twenty-three patients were randomized to 1 of the treatment groups (lercanidipine 10 mg, 12 patients; lercanidipine 20 mg, 12 patients). Clinical and angiographic characteristics of the 2 groups are shown in Table 1. No difference was seen in the distribution of baseline characteristics between the 2 lercanidipine dose groups.

Exercise test

The rate-pressure product variations at peak exercise between the 2 tests performed during the run-in period were 3.0%.

No difference was found at rest or at peak exercise in heart rate, systolic blood pressure, and rate-pressure product in both treatment groups with respect to the placebo phase (Table 2).

Both 10 and 20 mg lercanidipine reduced ST segment depression at peak exercise.

Exercise test duration and time to onset of ST segment depression ≥1 mm was significantly increased by both doses with respect to placebo (Table 2).

The exercise test was interrupted for angina in 1 patient in the 10-mg lercanidipine group and in 2 patients in the 20-mg lercanidipine group.

Variability of the ejection fraction at rest

Variability in VEST determinations of left ventricular ejection fraction at rest without change in position or blood pressure status was determined by a weighted average of the changes in the ejection fraction. Consecutive 1-minute collections of ejection fraction data during 15 minutes at rest were averaged for each patient with the initial stable baseline ejection fraction used as the reference value. The mean changes in the ejection fraction during this period of observation at rest were minimal (1.6 ± 0.5%) in all experimental study groups.

Left ventricular function during exercise by VEST

Baseline measurements of each left ventricular function variable were similar in the patients treated with 10 and 20 mg lercanidipine. In the 2 treatment groups, rest and peak exercise left ventricular ejection fraction, peak end-diastolic volume, end-systolic volume, stroke volume, and cardiac output were unchanged

Table 1. Patient characteristics.

	Lercanidipine 10 mg (N = 12)	Lercanidipine 20 mg (N = 12)	Total (N = 24)
Age (years)	61 ± 11	61 ± 9	61 ± 10
Male/Female	11/1	12/0	24/1
Diagnosis of angina (months)	17 ± 7	19 ± 24	18 ± 17
Weekly angina frequency	3.3 ± 0.5	3.6 ± 0.5	3.4 ± 0.5
Previous myocardial infarction	8	2	10
Previous Coronary by-pass	8	6	14
Previous PTCA	1	2	3
Radionuclide LVEF (%)	42 ± 10	50 ± 10	46 ± 10

LVEF = Left ventricular ejection fraction.

Table 2. Exercise test variables after placebo, 10 and 20 mg lercanidipine treatment.

	Lercanidipine 10 mg		Lercanidipine 20 mg	
	Baseline	Day 14	Baseline	Day 14
Rest HR (bpm)	75 ± 6	75 ± 4	75 ± 5	72 ± 3
Rest SBP (mmHg)	126 ± 4	126 ± 6	127 ± 5	127 ± 4
Rest RPP ($Ux10^{-3}$)	9.4 ± 0.8	9.4 ± 0.7	9.5 ± 0.9	9.2 ± 0.6
Peak HR (bpm)	131 ± 18	133 ± 19	133 ± 15	136 ± 26
Peak SBP (mmHg)	188 ± 27	184 ± 31	206 ± 24	195 ± 23
Peak RPP ($Ux10^{-3}$)	24.9 ± 6.3	24.8 ± 7.1	27.4 ± 4.7	26.8 ± 7.1
Peak ST ↓ (mm)	−1.08 ± 0.5	−0.08 ± 0.3°	−1.20 ± 0.3	−0.20 ± 0.5°
Exercise duration (sec)	477 ± 171	527 ± 171°	533 ± 74	552 ± 67°
Onset ST ↓≥1 mm (sec)	441 ± 185	527 ± 171*	515 ± 71	546 ± 68*
Patients with angina (n)	11	1	12	2

Split-plot ANOVA: *$P < 0.005$ vs. baseline; °$P < 0.001$ vs. baseline.
Data expressed as means ± SD.

after 2 weeks of both 10 and 20 mg lercanidipine administration (Table 3). In the patients treated with 20 mg lercanidipine, the left ventricular ejection fraction during exercise increased after the 2-week treatment (Fig. 2). Chronotropic responses to exercise were characterized by a progressive increase in heart rate in the patients treated with 10 and 20 mg lercanidipine (Fig. 3). However, the slope of the ratio obtained by dividing the ejection fraction by the square root of the RR interval did not change significantly at rest or during exercise in patients on lercanidipine treatment ($r = 0.116$; P = NS). This finding suggests that the increase in the ejection fraction was due to the small increment in heart rate and not to an increase in the contractility state, expressed as myocardial contractility reserve (Fig. 4).

Stroke volume reached the peak value at 60% of maximal effort with a significant improvement only in patients treated with 20 mg lercanidipine (Fig. 5). In these patients, cardiac output during exercise increased significantly (Fig. 6).

No significant ECG abnormalities were revealed after lercanidipine administration. Laboratory values remained stable throughout the study. No patient reported adverse effects.

DISCUSSION

A major finding of the present study was that the calcium channel blocker lercanidipine did not cause any evidence of worsening heart function at rest and during exercise in patients with stable effort angina. In our study, administration of lercanidipine 10 and 20 mg induced a significant improvement in total exercise duration, time to onset of ST-segment depression, and peak ST segment depression. Rate-pressure product did not change with respect to the pretreatment value. The left ventricular ejection fraction, indicating a contractility state of the myocardium, was unchanged at rest and during exercise after both lercanidipine doses.

The effects of lercanidipine at peak exercise appear to be a result of both reduced oxygen consumption and increased oxygen supply. Actually, after lercanidipine administration, the rate-pressure product

Table 3. Cardiac response to lercanidipine administration.

	Lercanidipine 10 mg			Lercanidipine 20 mg		
	Baseline	Day 14	*P* Value	Baseline	Day 14	*P* Value
Resting LVEF, %	42 ± 9	49 ± 7	<0.01	50 ± 10	54 ± 7	<0.01
Peak LVEF, %	38 ± 11	42 ± 6	<0.05	48 ± 15	55 ± 17	<0.05
Peak EDV, %	91 ± 20	100 ± 18	ns	97 ± 17	100 ± 10	ns
Peak ESV, %	51 ± 9	58 ± 11	ns	46 ± 14	44 ± 8	ns
Peak SV, %	35 ± 13	44 ± 7	<0.01	46 ± 18	55 ± 17	<0.01
Peak CO, %	44 ± 14	56 ± 13	<0.01	56 ± 23	71 ± 17	<0.01

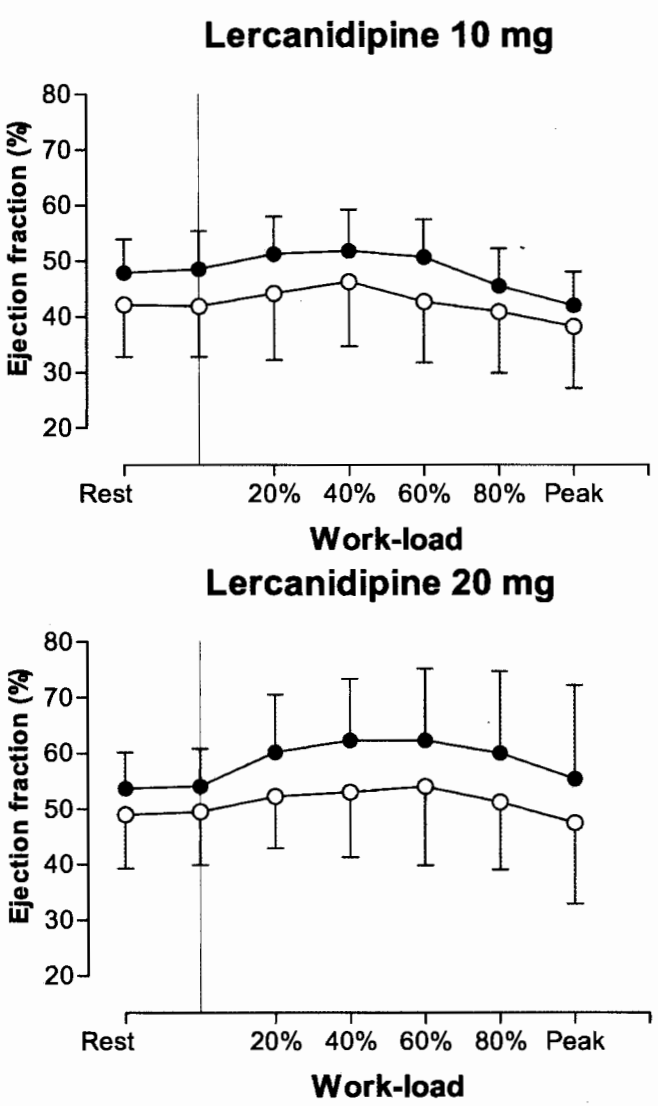

FIGURE 2. Graphs showing continuos VEST monitoring of left ventricle ejection fraction during exercise tests before (open circles) and after (closed circles) 2-week lercanidipine treatment. Rest indicates pre-exercise phase. Vertical dashed lines correspond to the beginning of exercise test. The F value was calculated by three-factor repeated analysis of variance of the responses to exercise in the two conditions and in the two lercanidipine regimens [Effect of Lercanidipine, F = 18.15, $P < 0.01$; Effect of doses, F = 7.49, $P = <0.05$; Effect of work-load, F = 8.80, $P < 0.01$; Interaction (Lercanidipine*Doses*Work-load), F = 1.36, P = ns].

at higher workload was similar to that obtained at baseline.

The reduction in ST segment depression at peak exercise after lercanidipine was not accompanied by significant changes in the left ventricular ejection fraction. In agreement with previous investigations, this observation could suggest that lercanidipine plays a role in controlling other factors responsible for myocardial ischemia. During ischemia, lercanidipine could preserve ATP cellular content through a reduction of intracellular calcium concentration and oxygen saving[39,40] and increase endothelin-dependent vasodilation by restoring nitric oxide availability and preventing hyperpolarization, an effect probably determined by antioxidant activity.[41]

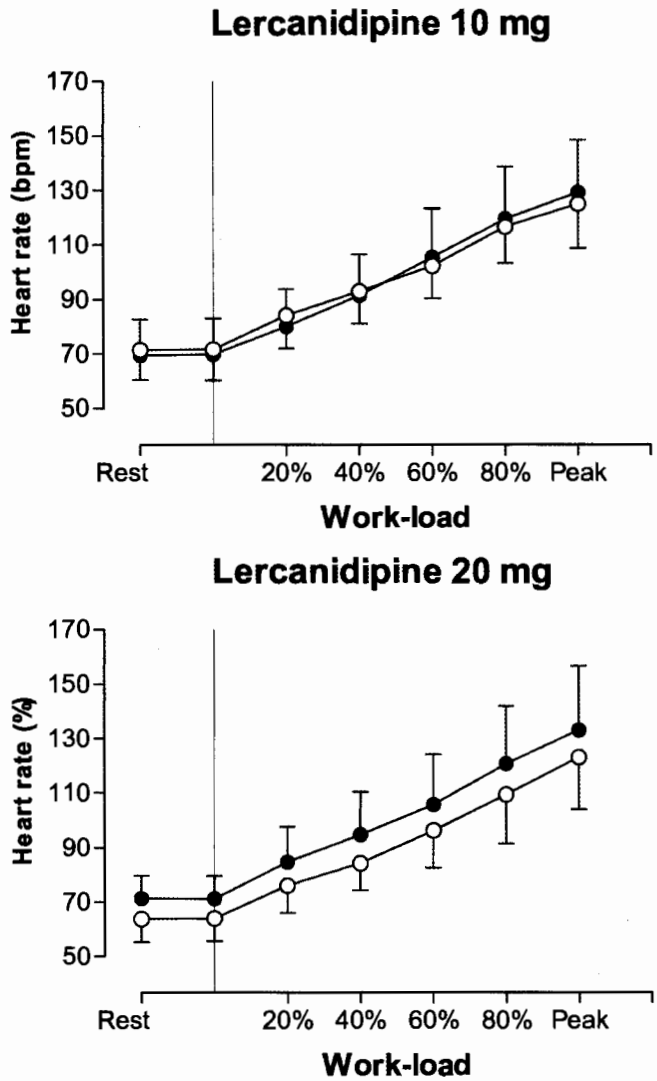

FIGURE 3. Graphs showing continuos heart rate monitoring during exercise tests before (open circles) and after (closed circles) 2-week lercanidipine treatment. Rest indicates pre-exercise phase. Vertical dashed lines correspond to the beginning of exercise test. The F value was calculated by three-factor repeated analysis of variance of the responses to exercise in the two conditions and in the two lercanidipine doses [Effect of Lercanidipine, F = 4.35, $P < 0.05$; Effect of doses, F = 0.17, P = ns; Effect of work-load, F = 286.19, $P < 0.01$; Interaction (Lercanidipine*Doses*Work-load), F = 1.15, P = ns].

The safety of calcium antagonists in the treatment of cardiovascular disorders has became a controversial issue.[22] Numerous clinical trials have shown that calcium antagonists provide effective therapy for patients with effort angina. It is not too difficult to see why calcium antagonists relieve the symptoms of effort angina because they dilate the peripheral vasculature; moreover, verapamil and diltiazem decrease the oxygen requirement of the heart by reducing heart rate.[27–29]

With 1 or 2 exceptions, the beneficial effect of calcium antagonists in patients with effort angina is dose dependent.[42,43] However, in the case of the dihydropyridines, increasing the dose is not always advantageous. For example, relatively high doses of nifedipine can actually aggravate the anginal condition,[44,45] likely because the excessive decrease in blood pressure triggers a reflex-induced increase in heart rate and causes further underperfusion of the myocardium.[44,45] The result can be a decrease in coronary perfusion, accompanied by an increase in cardiac work. A similar situation has been described for nicardipine and nisoldipine.[46–49] Gheorghiade et al[47] reported that oral administration of nicardipine at dose of 40 mg was associated with an improvement in exercise performance and a decrease in exercise-induced ischemia in patients with stable effort angina; however, these favorable results were associated with a significant increase in heart rate and decreased blood pressure levels at rest. Thadani et al[49] found that during 2 weeks of therapy with nisoldipine, 6 of 167 patients with stable coronary disease had a myocardial infarction or unstable angina. No coronary events occurred in the placebo group. In the Holland Interuniversity Nifedipine/Metoprolol Trial, the risk of myocardial infarction within 48 hours was 2 times higher among the patients with unstable angina on nifedipine treatment than among those assigned to placebo.[29] A decrease in blood pressure and an increase in heart rate are responsible for cardiac events in short- and long-term trials with higher dihydropyridines doses. Theoretically, a powerful systemic and coronary vasodilator such as nisoldipine or nicardipine may prevent

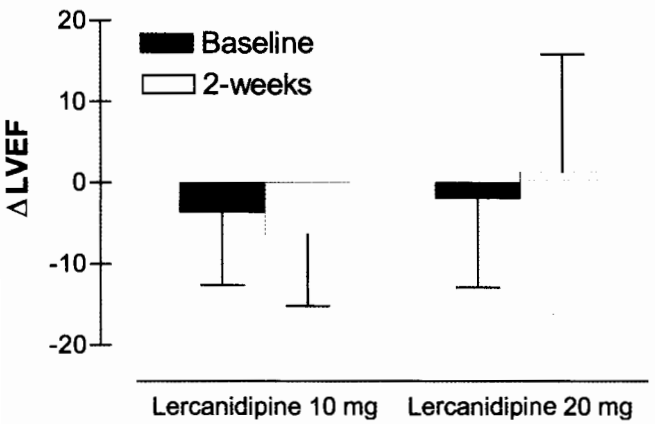

FIGURE 4. Graphs showing myocardial contractility reserve (ΔLVEF) assessed as left ventricular ejection fraction (LVEF) during peak exercise minus LVEF at rest during VEST monitoring.

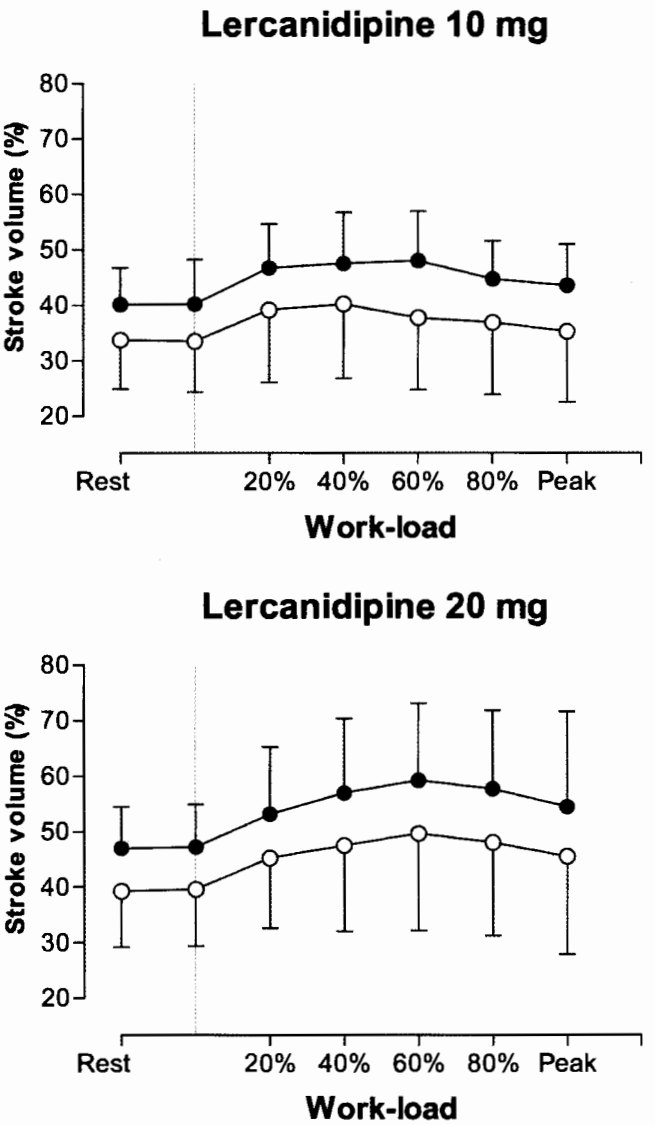

FIGURE 5. Graphs showing continuos VEST monitoring of relative stroke volume of the left ventricle during exercise tests before (open circles) and after (closed circles) 2-week lercanidipine treatment. Rest indicates pre-exercise phase. Vertical dashed lines correspond to the beginning of exercise test. The F value was calculated by three-factor repeated analysis of variance of the responses to exercise in the two conditions and in the two lercanidipine doses [Effect of Lercanidipine, F = 14.56, $P < 0.01$; Effect of doses, F = 4.96, $P < 0.05$; Effect of work-load, F = 12.01, $P < 0.01$; Interaction (Lercanidipine*Doses* Work-load), F = 0.13, P = ns].

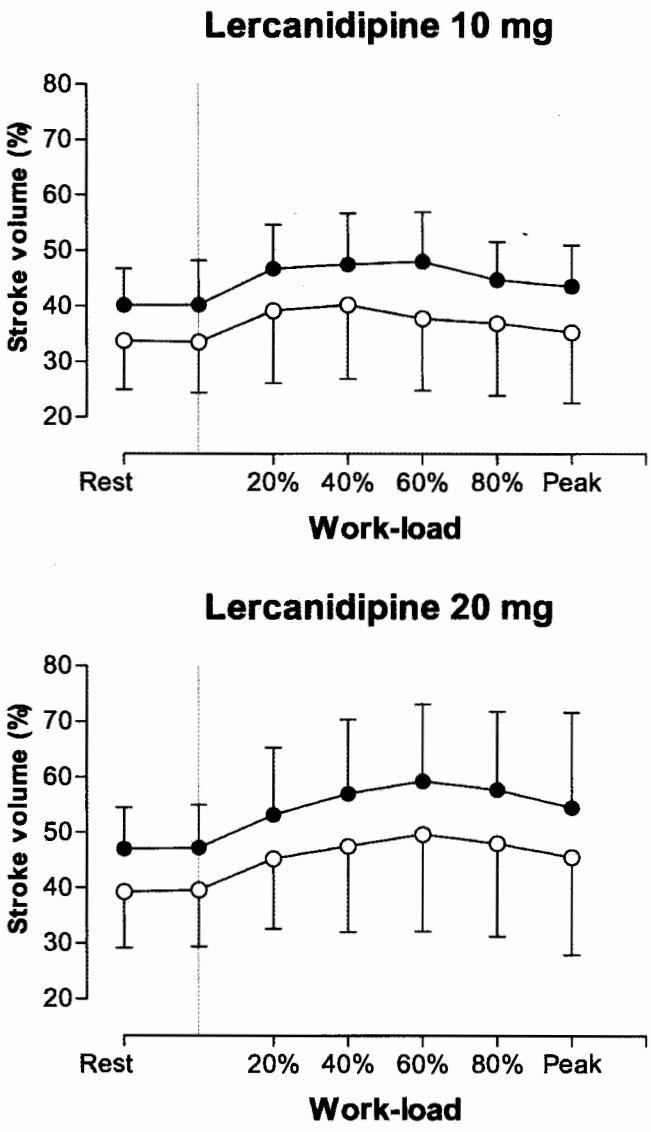

FIGURE 6. Graphs showing continuos VEST monitoring of relative cardiac output of the left ventricle during exercise tests before before (open circles) and after (closed circles) 2-week lercanidipine treatment. Rest indicates pre-exercise phase. Vertical dashed lines correspond to the beginning of exercise test. The F value was calculated by three-factor repeated analysis of variance of the responses to exercise in the two conditions and in the two lercanidipine doses [Effect of Lercanidipine, F = 15.14, $P < 0.01$; Effect of doses, F = 4.46, $P < 0.05$; Effect of workload, F = 97.64, $P < 0.01$; Interaction (Lercanidipine*Doses* Work-load), F = 0.24, P = ns].

ischemia during exercise by increasing coronary blood flow[50] and decreasing the cardiac workload. At rest, these drugs can cause ischemia by reflex activation of the sympathetic system with a resultant increase in myocardial contractility and heart rate, and thus myocardial oxygen consumption. In a recent study, we demonstrated that lercanidipine did not cause adrenergic activation, which is the main mechanism hypothesized to explain the negative effect on cardiovascular mortality assigned to dihydropyridines calcium channel blockers.[38]

In the present study, increasing doses were not accompanied by increases in heart rate, left ventricular ejection fraction, and contractility reserve or with a decrease in blood pressure. Lercanidipine was effective in reducing signs and symptoms of myocardial ischemia in patients with stable effort angina without any deterioration of cardiac function.

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