In 10 patients with moderate to severe hypertension, the hemodynamic effects of ergometric exercise and nicardipine, a dihydropyridine calcium channel antagonist, were characterized under basal conditions and after 1 week of therapy. The responses of plasma renin activity and catecholamines were also assessed. Nicardipine induced significant reductions of systolic, diastolic and mean blood pressure under conditions of rest and peak exercise \((p < 0.001)\), mediated by reversal of vasoconstriction \((p < 0.001)\). Overall, cardiac index and stroke volume index responses were not significantly altered by nicardipine. Although rest pulmonary wedge pressure was unchanged \((6 \pm 3 \text{ to } 5 \pm 4 \text{ mm Hg})\), peak exercise pulmonary wedge pressure decreased from \(24 \pm 22 \text{ to } 7 \pm 5 \text{ mm Hg} \) \((p < 0.001)\) with nicardipine therapy. This effect of nicardipine on pulmonary wedge pressure was present across all work loads studied, and was accompanied by reduction of peak exercise pulmonary artery pressure from \(43 \pm 10 \text{ to } 25 \pm 7 \text{ mm Hg} \) \((p < 0.001)\). Oxygen consumption was unchanged, associated with reduction of arteriovenous oxygen difference \((p < 0.02)\). Both plasma renin activity \((p < 0.05)\) and norepinephrine \((p < 0.005)\) were significantly increased with nicardipine therapy.

Thus, nicardipine produced significant blood pressure reduction by reversal of vasoconstriction in patients with essential hypertension. The preservation of cardiac output, with markedly reduced pulmonary wedge pressure, indicated that nicardipine improved ventricular performance in response to reversal of vasoconstriction.

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dipine therapy in patients with moderate to severe systemic hypertension.

Methods

Study patients. The study group comprised 10 patients with moderate to severe hypertension. There were seven men and three women, ranging from 27 to 76 years of age. All patients had essential hypertension, on the basis of standard screening criteria, documented during outpatient visits over at least 2 years. All patients had been receiving one or more combinations of medical therapy with unsatisfactory blood pressure control. No patient manifested accelerated or malignant hypertension or had clinical evidence of congestive heart failure or chronic lung disease. Funduscopic changes ranged from grade I through III hypertensive retinopathy. Occlusive carotid disease was excluded by physical examination and Doppler ultrasound evaluation. No patient provided a history of angina or myocardial infarction, had ever been treated with an antianginal regimen or had electrocardiographic (ECG) evidence of myocardial infarction.

Previous medications were tapered and discontinued in the 1 to 3 week period before admission to the hospital to avoid carryover effects of previous therapy. All patients were admitted to the Adult Clinical Research Center of New York Hospital-Cornell Medical Center for the study and were maintained on a 100 mEq sodium diet. Informed written consent was given, and the study was approved by the Committee on Human Rights in Research.

Overall study design. After admission to the Clinical Research Center, patients were observed for 3 to 5 days of stabilization. They then underwent two exercise hemodynamic studies performed 1 week apart. During the first hemodynamic study, exercise responses in the baseline untreated state were obtained. The second study was performed after 1 week of oral nicardipine therapy. All hemodynamic studies were performed in the morning, after an overnight fast. Patients were brought to the hemodynamic procedure room, where a right heart catheter was placed percutaneously from either an arm vein or an internal jugular vein, and a cannula was placed percutaneously into a brachial artery. A 1 to 2 hour equilibration period ensued, followed by the baseline upright exercise. After baseline study, oral therapy with nicardipine was initiated at a dose of 30 mg administered every 8 hours. After 1 week of oral nicardipine therapy, and maintenance of the 100 mEq sodium diet, the patients returned to the procedure room for repeat exercise hemodynamic study, using the contralateral arm for catheter placement.

Exercise hemodynamic protocol. The hemodynamic studies were performed on a table designed for upright exercise as previously described (3). The patients were placed in a seated position in which they could comfortably pedal an electronically braked bicycle ergometer attached to the table. Patients rested in the seated position for 15 minutes and were then connected by a one-way breathing mask to a metabolic cart (Sensor Medics) for continuous analysis of expired gases for oxygen consumption (V\text{O}_2) and carbon dioxide production (V\text{CO}_2). We also measured heart rate, pressures and cardiac output and obtained blood samples for determination of plasma renin activity, norepinephrine and simultaneous arterial and pulmonary artery oxygen saturation. After these baseline values were obtained, exercise began at a work load of 25 W and increased by 25 W increments every 3 minutes until limited by exhaustion. Hemodynamic monitoring and analysis of expired gases were performed continuously throughout each stage of exercise with cardiac output determined in the last minute of each stage. Peak exercise was defined as the occurrence of patient exhaustion, provided that the respiratory exchange ratio (V\text{CO}_2/V\text{O}_2) was >0.95, a level consistent with peak aerobic muscle metabolism and maximal exertion (17,18). At the peak exercise response, we also obtained blood samples for plasma renin activity and norepinephrine and simultaneous arterial and mixed venous oxygen saturation. When patients had recovered from exercise, the catheters were removed and the exercise protocol was terminated.

Determination of hemodynamic and respiratory gas variables. Heart rate and all pressures were recorded continuously throughout the study on a multichannel recorder. The heart rate was obtained from a standard limb lead electrocardiogram (ECG). The reference point for pressure transducers was the level of the right atrium in the midaxillary line. Pressures were tracked as both phasic and electronically filtered mean recordings, with use of the latter for calculation of derived indexes. Arterial blood pressure was recorded as systolic, diastolic and mean. The heart rate-systolic blood pressure product was also calculated. We also recorded pulmonary arterial and right atrial pressures continuously. Phasic and mean pulmonary wedge pressures were obtained at the end of the rest phase and just before the last minute of each stage of exercise. Cardiac output was determined by thermodilution, in triplicate, using 10 ml of iced dextrose in water injectate, and was expressed as cardiac index (liters/min per m$^2$), correcting for body surface area. Stroke volume index was obtained by dividing cardiac index by the heart rate. Systemic vascular resistance and pulmonary vascular resistance were calculated from standard formulas (19). Expired gases were analyzed on a metabolic cart with Beckman analyzers (SensorMedics).

Blood sample analysis. Plasma renin activity was estimated by radioimmunoassay as previously described (20). Plasma norepinephrine and epinephrine were analyzed by the radioenzymatic method of Peuler and Johnson (21), with values expressed as picograms per milliliter. Analysis of blood oxygen saturation (S\text{a}O_2) was by transmission spectrophotometry, and blood oxygen content (C\text{a}O_2) was calculated from the formula C\text{a}O_2 = S\text{a}O_2 \times h\text{emoglobin} \times 1.34, expressed as volume percent. The arteriovenous ox-
ygen difference was calculated as the difference of arterial and mixed venous oxygen content.

**Statistical analysis.** Statistical analysis for hemodynamic and hormonal data was by two-way analysis of variance (22). We determined the within-group influence of activity (rest versus peak exercise) and treatment (baseline versus nicardipine), as well as potential interactions (23). Differences were considered significant at a level of <0.05. Significance values beyond the <0.001 level were assigned the value of <0.001. For clarity, the analysis results for the nicardipine treatment effect are shown in the figures only, and the activity effect is described only in the text. We also evaluated the effect of nicardipine on pulmonary wedge pressure, over all work loads studied, using paired analyses following the Bonferroni adjustment of the probability (p) value corrected for multiple determinations. All values represent the mean ± 1 SD.

**Results**

**Hemodynamic responses to exercise (Fig. 1 to 3).** In the untreated state, maximal ergometric exercise was associated with an increase of heart rate from 72 ± 13 to 152 ± 17 beats/min and mean arterial pressure increased from 142 ± 18 to 183 ± 23 mm Hg (both p < 0.001). The increase in mean arterial pressure was reflected in both the systolic and diastolic components. Systolic blood pressure increased from 211 ± 35 to 312 ± 56 mm Hg (p < 0.001), and diastolic blood pressure from 111 ± 16 to 124 ± 24 mm Hg (p < 0.03). The rate-pressure product increased from 15,053 ± 3,612 to 46,873 ± 8,401 (p < 0.001; not shown in the figure). The blood pressure response to exercise was accompanied by an increase of right atrial pressure (4 ± 4 to 7 ± 6 mm Hg; p < 0.05), pulmonary artery pressure (17 ± 4 to 43 ± 10 mm Hg; p < 0.001) and pulmonary wedge pressure (6 ± 3 to 24 ± 11 mm Hg; p < 0.001).

In the untreated state, exercise resulted in an increase of cardiac index from 2.44 ± 0.36 to 6.99 ± 1.32 liters/min per m² and of stroke volume index from 35 ± 7 to 47 ± 9 ml/m² (both p < 0.001). Systemic vascular resistance decreased in response to exercise from 2,304 ± 644 to 1,061 ± 434 dynes·s·cm⁻⁵ (p < 0.001), whereas the decrease of pulmonary vascular resistance from 191 ± 101 to 117 ± 63 dynes·s·cm⁻⁵ was not significant.

**Effect of nicardipine on exercise hemodynamics (Fig. 1 to 3).** Heart rate increased from 91 ± 19 to 153 ± 28 beats/min during exercise, with no significant treatment effect. The increase of rest heart rate compared with baseline (72 ± 13 beats/min) was significant (p < 0.03). Mean arterial blood pressure was 108 ± 13 mm Hg at rest, increasing to 142 ± 23 mm Hg at peak exercise; these were significantly decreased compared with pretreatment values.

**Figure 1.** The response of heart rate (HR), systolic blood pressure (SBP), mean arterial pressure (MAP) and diastolic blood pressure (DBP), comparing seated rest (R) and peak exercise (Ex) effects. The significance values shown in this figure and Figures 2 through 4 represent the statistical analysis of the nicardipine (Nic) effect on hemodynamics by two-way analysis of variance; the exercise effect is stated in the text. There was no significant overall effect of nicardipine on heart rate; rest heart rate was increased (p < 0.03) compared with pretreatment. Nicardipine therapy was associated with a marked reduction of systemic, mean and diastolic blood pressures. All values represent mean values ± 1 SD. (●) Baseline; (○) nicardipine.

**Figure 2.** The effect of exercise (Ex) and nicardipine (Nic) on right atrial pressure (RAP), mean pulmonary artery pressure (PAP) and pulmonary wedge pressure (PWP). Nicardipine therapy resulted in marked reduction of exercise pulmonary artery and wedge pressures. R = rest. (●) Baseline; (○) nicardipine.
At rest, increasing to 240 of rest (R) cardiac index (mediated by heart rate) during nicardipine of nicardipine and exercise 011 cardiac index due to the increase Figure3. The response of cardiac index (Cl), stroke volume index (SVI), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) to exercise (Ex) and nicardipine (Nic) therapy. Although there was no significant effect of nicardipine on cardiac index or stroke volume index, there was an interaction (p < 0.02) of nicardipine and exercise on cardiac index due to the increase of rest (R) cardiac index (mediated by heart rate) during nicardipine therapy. The significant reduction of systemic vascular resistance by nicardipine accounted for the reduction of arterial blood pressure. The response of pulmonary resistance was less uniform, so that significance was not achieved. (●) Baseline; (○) nicardipine.

(p < 0.001). The reduction of mean arterial pressure was reflected in systolic blood pressure, which was 175 ± 26 at rest, increasing to 240 ± 51 mm Hg during exercise; likewise, diastolic blood pressure was 84 ± 14, increasing to 96 ± 15 mm Hg. The effect of nicardipine on systolic and diastolic blood pressure was statistically significant (both p < 0.001). The rate-pressure product was 15,675 ± 2,448 (rest) and 35,784 ± 5,833 (exercise), representing a nicardipine effect of p < 0.05.

Right atrial pressure during therapy was 2 ± 3 at rest, increasing to 4 ± 5 mm Hg at peak exercise (p = NS compared with pretreatment value [Fig. 2]). The rest value for pulmonary artery pressure (15 ± 7 mm Hg) was essentially unchanged during nicardipine therapy; during peak exercise, the value increased to 25 ± 7 mm Hg (p < 0.001 compared with baseline, with a significant activity-treatment interaction of p < 0.001). In a similar pattern, pulmonary wedge pressure at rest was 5 ± 4 mm Hg during nicardipine therapy, with a marked reduction to 7 ± 5 mm Hg at peak exercise (p < 0.001 compared with baseline with an activity-treatment interaction of p < 0.001).

The effect of nicardipine therapy on the flow and resistance responses to exercise is shown in Figure 3. There was no overall effect of nicardipine on either cardiac index or stroke volume index, when the treatment value was compared with the baseline value. Cardiac index was 3.30 ± 0.77, increasing to 6.36 ± 0.92 liters/min per m². An activity-treatment interaction (p < 0.02) was observed, representing differences of rest cardiac index comparing baseline (2.44 ± 0.36 liters/min per m²) and nicardipine (3.30 ± 0.77 liters/min per m²) values. Stroke volume index was 37 ± 10 ml/m² at rest, increasing to 43 ± 10 ml/m² at peak exercise (p = NS, compared with pretreatment). In contrast, there was a marked effect of nicardipine therapy on the response of systemic vascular resistance to exercise. At rest, systemic vascular resistance was 1,326 ± 314 dynes-cm⁻⁵, decreasing to 872 ± 212 dynes-cm⁻⁵ during peak exercise. This effect was highly significant (p < 0.001), demonstrating an activity-treatment interaction (p < 0.01). Although there was a modest reduction of pulmonary vascular resistance at rest (143 ± 107 dynes-cm⁻⁵), with a further small reduction during exercise (120 ± 83), this did not achieve statistical significance.

Characteristics of respiratory gas exchange (Fig. 4). In the baseline untreated state, oxygen consumption increased from 281 ± 51 to 1,645 ± 489 ml/min, and carbon dioxide production from 212 ± 40 to 1,797 ± 506 ml/min (both responses p < 0.01). Nicardipine therapy had no significant effect on these values at rest or peak exercise, so that the peak exercise respiratory exchange ratio was not changed. However, there was a reduction of the arterio-
venous oxygen difference at rest (4.8 ± 0.6 to 3.4 ± 0.9 vol%) and during peak exercise (9.0 ± 1.5 to 8.4 ± 1.9 vol%) (p < 0.02).

**Pulmonary wedge pressure response to nicardipine** (Fig. 5). Figure 5 shows rest values, all work load levels studied and the number of patients achieving each work load. With nicardipine therapy, the rest pulmonary wedge pressure was essentially unchanged. However, it was markedly reduced at all ergometric loads, and only minimally increased compared with the rest pretreatment pulmonary wedge pressure.

**Hormonal responses to nicardipine.** Figure 6 summarizes the characteristics of plasma renin activity and plasma norepinephrine during exercise and in response to nicardipine therapy. While plasma renin activity increased from 1.8 ± 2.4 to 3.0 ± 8.6 ng/ml per h during exercise in the untreated state, this effect was not statistically significant. In contrast, during nicardipine therapy, plasma renin activity was increased at both rest (5.9 ± 8.4) and peak exercise (8.4 ± 11 ng/ml per h) (p < 0.05). In the baseline state, plasma norepinephrine increased from 398 ± 232 to 1,427 ± 840 pg/ml (p < 0.001). An effect of nicardipine on norepinephrine was present at rest (913 ± 477) and at peak exercise (2,706 ± 1,586 pg/ml) (p < 0.001). Before treatment, plasma epinephrine (not shown in Fig. 6) was 162 ± 115 pg/ml at rest and 483 ± 651 at peak exercise. After nicardipine, values were 136 ± 117 pg/ml at rest and 715 ± 774 at peak exercise. The effect of exercise was p < 0.03, whereas the nicardipine effect was not significant.

**Side effects.** Clinically, nicardipine was tolerated by all patients in this study. Serum electrolytes, hemogram and liver and renal function were unchanged. Twenty-four hour urinary sodium excretion at baseline (88 ± 12 mEq) was not changed after 1 week of nicardipine (85 ± 13 mEq) therapy. Body weight was also unchanged (90 ± 7 versus 89 ± 7 kg).

**Discussion**

**Hemodynamic response to exercise: hypertension versus normal.** There are few studies regarding the cardiovascular response to exercise in hypertensive individuals that consider changes in cardiac filling pressures, and a similar limitation has accompanied previous studies in normal subjects. However, information regarding the normal response to exercise was recently provided in a rigorous study by Higginbotham et al. (24). The findings of these investigators are particularly relevant in that the exercise protocol they employed was virtually identical to that of the present study, so direct comparisons can be made. In the present study, exercise was associated with a marked increase of both systolic and diastolic blood pressure above the already elevated baseline values. This increase of blood pressure was greater than that observed in normal subjects, but was nonetheless mediated by an increase of cardiac index with contributions of both stroke volume, and to a greater
degree, heart rate. In hypertensive patients, calculated sys-
temic vascular resistance during exercise decreased from
the baseline vasoconstricted state, yet the absolute value
achieved was less than that reported in normal subjects,
suggesting adverse vascular adaptation in severe hyperten-
sion that may compromise the response to exercise. An
additional observation was the response of pulmonary wedge
pressure during exercise; mean levels in hypertensive pa-
tients were at least twofold greater than in normal subjects.
These findings emphasize the importance of ergometric ex-
ercise in hypertensive patients, because the abnormal ex-
ercise increase in wedge pressure and the favorable effect
of nicardipine would have been overlooked had only rest
hemodynamic values been obtained. The magnitude of in-
crease of pulmonary wedge pressure in untreated hyperten-
sive patients was also greater than that previously reported
in patients with less severe hypertension (1).

In the present study stroke volume was mildly decreased
compared with that of normal subjects (24), yet was rela-
tively preserved when compared with that of individuals
who had congestive heart failure (25). Because an increase
of left ventricular filling pressure is necessary to maintain
normal stroke volume index during exercise (24), it is pos-
sible that the observed marked increase of pulmonary wedge
pressure in moderate to severe hypertension reflects the
functional adaptation necessary to maintain stroke volume
in the presence of increased afterload. On the other hand,
the increase of pulmonary wedge pressure during exercise
may reflect a reduction of left ventricular compliance, be-
cause this is one of the earliest changes evoked by long-
standing or severe hypertension (26).

Effect of nicardipine on exercise hemodynamics in
hypertension. The hemodynamic response to nicardipine
was characterized by a marked reduction of blood pressure,
mediated by reversal of vasoconstriction, during rest and
peak exercise conditions. The heart rate response was more
complex, in that the rest heart rate was somewhat higher
during nicardipine therapy, whereas peak exercise heart rate
was unchanged. Because these were patients with severe
hypertension, unloading or disinhibiting arterial barorecep-
tors (27) may have been associated with increased sympa-
thetic nervous system activity that was still manifest at 1
week of therapy. Alternatively, nicardipine may have di-
rectly stimulated catecholamine release, as previously sug-
gested for other calcium channel antagonists (28–31), and
this would be consistent with the rest heart rate and nor-
epinephrine changes at 1 week of therapy. During exercise,
however, the heart rate response was not appreciably altered
despite the increase of norepinephrine, suggesting that the
heart rate response to the stimulus of exercise was predom-
inant when compared with any coexistent drug-induced ef-
fect. The absence of a more positive or negative effect of
nicardipine on cardiac index was similar to findings with
other vasodilators, such as converting enzyme inhibitors
(32), that have no major direct effect on contractility. Thus,
a clinically significant negative inotropic effect of nicardi-
pine could not be identified.

Of additional importance, was the fact that cardiac index,
in response to exercise, was maintained with markedly re-
duced pulmonary wedge pressure during nicardipine ther-
apy. This was associated with some evidence of a favorable
effect on oxygen utilization, in that overall oxygen extrac-
tion was significantly decreased during nicardipine therapy.
To our knowledge, this degree of reduction of pulmonary
wedge pressure during peak exercise has not previously been
reported with drug therapy of hypertension. This magnitude
of response, for instance, was not observed during acute
captopril therapy (1), and the pulmonary wedge pressure
response to verapamil during exercise, previously reported
by our group (3), was relatively small. Compared with the
normal range of pulmonary wedge pressure response to ex-
ercise, reported by Higginbotham et al. (24), nicardipine
induced a normalization of pulmonary wedge pressure in
moderate to severe hypertension.

Mechanisms influencing the hemodynamic response
to nicardipine. Several potential mechanisms may account
for the maintenance of exercise cardiac index at a markedly
reduced pulmonary wedge pressure during nicardipine ther-
apy. First, there is a marked reduction of arterial afterload,
as evidenced by the decrease of systemic vascular resistance.
Second, there is an improvement of ventricular compliance.
This could occur as a consequence of reduced arterial af-
terload or may be a direct consequence of nicardipine. Ven-
tricular compliance is abnormal in hypertension (26,33–36)
and previous studies (11,37,38) have suggested a favorable
effect of calcium channel antagonists on the compliance
changes of the hypertrophied ventricle. Third, preload may
have been reduced during nicardipine therapy. The lack of
change in urinary sodium excretion and body weight sug-
ests that total blood volume was unaltered, but we cannot
exclude a relative shift of cardiopulmonary blood volume
to the periphery during exercise that, in effect, could lower
preload. It is possible that a combination of these factors
accounted for the observed effect; however, the study design
we utilized cannot distinguish among the relative contri-
butions of these mechanisms. We also cannot extrapolate
these findings to patients with mild hypertension, whose
hemodynamic abnormalities may be less pronounced.

Hormonal responses to nicardipine. Reports of the
response of catecholamines and plasma renin activity to
calcium channel antagonists are somewhat divergent
(3,28–31). The observed increase of rest heart rate in our
study may have been a manifestation of increased sympa-
thetic activity. However, there was no evidence to suggest
that an increase of alpha-adrenergic tone interfered with the
favorable effect of nicardipine on both rest and exercise
systemic vascular resistance, because epinephrine was not
increased. The observed increase of plasma renin activity
may represent either a direct or an indirect effect of nicardipine. In vitro studies have demonstrated that calcium channel antagonists will directly induce renin release from juxtaglomerular cells (39), while at the same time suppressing aldosterone release from the zona glomerulosa (40). An indirect release of renin may have been mediated by the observed increase of peripheral norepinephrine in the present study, because increased renal sympathetic activity is a recognized stimulus of renin release.

Conclusion. In patients with moderate to severe essential hypertension, there was a marked increase of blood pressure and pulmonary wedge pressure in response to ergometric exercise, with relative preservation of cardiac index. Nicardipine therapy induced a significant reduction of blood pressure, mediated by reversal of vasoconstriction. Exercise cardiac index was maintained with markedly reduced pulmonary wedge pressure during nicardipine therapy and was associated with reduction of oxygen extraction. The overall favorable effect of nicardipine was most likely mediated by the reversal of vasoconstriction. However, we cannot exclude a direct effect of nicardipine on the abnormal compliance changes that accompany ventricular adaptation to hypertension, or a relative reduction of cardiopulmonary blood volume.

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References


33. Devereux RB, Savage DD, Sachs I, Laragh JH. Relation of hemodynamic load to left ventricular hypertrophy and performance in hypertension. Am J Cardiol 1983;51:171-6.


