Effects of Antihypertensive Agents on Blood Pressure during Exercise

Mikio ARITA, Toshikazu HASHIZUME, Yoshiro WANAKA, Satoshi HANDA, Chigusa NAKAMURA, Setsuko FUJIWARA, and Ichiro NISHIO

The relationship between blood pressure (BP) and cardiovascular morbidity has been appreciated for many years. Casual BP may not be representative of the pressure at other times. It is recognized that BP during exercise may be a more accurate predictor than casual BP. There is, however, little information about the effects of antihypertensive drugs on the BP during exercise. This study was designed to investigate the effects of various antihypertensive agents on BP during exercise. Sixty-four patients (age, 49±10 years) with untreated essential hypertension (WHO I, II) were studied during a supine ergometric exercise regimen. A graded exercise test was started at a workload of 50 W, and the load was increased by 25 W every 3 min. The hemodynamic responses to exercise were evaluated by changes in systolic and diastolic BP (SBP, DBP) and heart rate (HR). Plasma norepinephrine (NE) levels were measured at rest and during submaximal exercise, and before and after 4 weeks of treatment with metoprolol (METO), doxazosin (DOXA), trichlorothiazide (TCTZ), nifedipine (NIFE), amiodipine (AMLO) and temocapril (TEMO) between left ventricular mass index (LVMI) and BP values at rest, during exercise, and during the recovery period after exercise were assessed by multiple regression analysis. The stepwise selection (forward conditional) method showed that LVMI was significantly associated with SBP during submaximal exercise and during the recovery period. All antihypertensive treatments decreased SBP and DBP (p<0.01) at rest. METO, AMLO and TEMO significantly lowered SBP (p<0.05) during exercise, whereas DOXA, TCTZ and NIFE induced no change in SBP. The exercise-induced increase of plasma NE was further enhanced by METO and NIFE but not by AMLO, DOXA, or TCTZ, and it was significantly suppressed by TEMO (p<0.01). These results suggest that BP during exercise is more highly associated with the progression of left ventricular hypertrophy (LVH) than is casual BP. Because antihypertensive agents differ in their effects on exercise hemodynamics, we recommend that hemodynamic factors during exercise be considered when selecting the optimal antihypertensive medication for highly active patients. (Hypertens Res 2001; 24: 671–678)

Key Words: blood pressure during exercise, left ventricular hypertrophy, antihypertensive agents, plasma norepinephrine

Introduction

While it is known that chronic hypertension can produce left ventricular hypertrophy (LVH) (1–3), no clear correlation has been established between LVH and actual blood pressure (BP) values or duration of hypertension. It has been reported that BP, when used alone, is a very weak predictor of cardiovascular risk (4). And while most studies nonetheless rely on casual BP as a predictor of target organ damage, morbidity or mortality, several investigators have suggested that BP measured during exercise may have better predictive value. These studies have mainly been based on basal BP and ambulatory pressure monitoring (5–7). LVH has also been re-
Table 1. Basal Characteristics for the Six Antihypertensive Groups

<table>
<thead>
<tr>
<th>METO</th>
<th>DOXA</th>
<th>TCTZ</th>
<th>NIFE</th>
<th>AMLO</th>
<th>TEMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48±6</td>
<td>50±11</td>
<td>49±10</td>
<td>52±11</td>
<td>51±10</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/3</td>
<td>7/1</td>
<td>6/2</td>
<td>8/2</td>
<td>9/2</td>
</tr>
<tr>
<td>Exercise intensity (W)</td>
<td>89±13</td>
<td>95±11</td>
<td>94±8</td>
<td>90±12</td>
<td>90±13</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.8±2.5</td>
<td>22.6±1.7</td>
<td>22.9±1.9</td>
<td>23.1±2.4</td>
<td>23.2±3.0</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>161±6</td>
<td>162.5</td>
<td>160±8</td>
<td>161±6</td>
<td>166±8</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>99±6</td>
<td>101±6</td>
<td>98±7</td>
<td>97±7</td>
<td>100±5</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>74±7</td>
<td>72±5</td>
<td>69±9</td>
<td>71±8</td>
<td>68±8</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>136±16</td>
<td>126±18</td>
<td>140±23</td>
<td>135±18</td>
<td>136±20</td>
</tr>
<tr>
<td>Plasma NE (ng/ml)</td>
<td>0.27±0.09</td>
<td>0.22±0.08</td>
<td>0.21±0.08</td>
<td>0.25±0.05</td>
<td>0.18±0.06</td>
</tr>
</tbody>
</table>

METO, metoprolol; DOXA, doxazosin; TCTZ, trichlormethiazide; NIFE, nifedipine; AMLO, amlodipine; TEMO, temocapril; BMI, body mass index; SBP, systolic BP; DBP, diastolic BP; HR, heart rate; LVMI, left ventricular mass index; NE, norepinephrine, data are expressed as mean±SD. The differences in baseline characteristics of the 6 antihypertensive groups were non-significant.

ported to be more closely associated with BP during exercise than with casual BP (8±15), although opinions remain divided on this point (16, 17). A recent report has suggested that ambulatory systolic blood pressure during increases in the activity of the sympathetic nervous system is able to infer LV in essential hypertension (18).

In the present study, we used a bicycle ergometer to measure changes in BP during exercise in hypertensive patients and to investigate the correlation between these findings and LVH. We also investigated the effects of various antihypertensive agents on BP, heart rate, and plasma norepinephrine (NE) levels during exercise.

Subjects and Methods

Subjects in this study were 64 outpatients with mild to moderate essential hypertension (WHO stages 1 and II) who were being treated at the Division of Cardiology, Wakayama Medical College. The mean age of subjects was 48.8±10.3 years (mean±SD). In all cases, patients had received no previous treatment with antihypertensive agents, or had discontinued such treatment at least 4 weeks prior to the start of the study. All subjects were outpatients, and all gave their informed consent to participate in this study. After resting for 30 min in a recumbent position, each patient was examined by two-dimensional echocardiography (Aloka, Tokyo, Japan) and B mode or M mode echocardiograms were recorded. Patients then performed exercise stress testing using a supine bicycle ergometer, and BP and heart rate were measured before, during, and after exercise. After 30 min in the supine position, the BP of patients was measured three times by an experienced physician using a mercury sphygmomanometer, and the mean value was defined as the resting BP. Graded exercise was provided by a Siemens bicycle ergometer, starting at a workload of 50 W and increasing by 25-W increments at 3-min intervals until limited by patient symptoms (9). After exercise, patients rested in the supine position for 10 min (recovery period). During the exercise test, patient status was monitored by an electrocardiogram. Left ventricular mass was calculated from factors including echocardiographic findings for ventricular septal thickness, left ventricular posterior wall thickness, and left ventricular end-diastolic diameter using the Penn-convention formula (19).

It is relatively difficult to measure BP during exercise (13). In order to determine the accuracy of BP measurements during exercise, we performed a preliminary study of the correlation between BP findings by cuff measurement and by direct intra-arterial measurement (brachial artery) in 36 patients. The ratio of cuff measurement to direct measurement was r=0.93 for systolic BP, and r=0.91 for diastolic pressure. Because of this close correlation, BP was measured by the cuff method for the remainder of the study.

Next, the subjects were randomly allocated into six groups: a metoprolol group (METO: 40 mg, n=11); a doxazosin group (DOXA: 2 mg, n=8); a trichlormethiazide group (TCTZ: 2 mg, n=8); a nifedipine capsule group (NIFE: 30 mg, n=10); an amlodipine group (AMLO: 5 mg, n=13), and a temocapril group (TEMO: 2 mg, n=9). Each group was treated for a period of 4 weeks. Patient characteristics for the 6 groups are shown in Table 1, with no major differences in patient background noted among the groups. There were no significant differences of exercise intensity or exercise duration among the 6 groups. After completing treatment, patients repeated the same graded exercise tolerance test as performed before the start of treatment. Blood samples were taken through a cannula in the brachial vein before and at the end of exercise. Hemodynamic variables and the plasma NE at rest and during submaximal exercise were compared before and after treatment. Plasma NE levels were measured by high-performance liquid chromatography.

Results are presented as the means±SD. Changes of median values are presented when responses are not normally distributed. Statistical evaluation was performed by repeat-
Table 2. Relation of Left Ventricular Mass Index to Systolic Blood Pressures: the Stepwise Selection (Forward Conditional Method)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Standardized partial regression coefficient</th>
<th>$T$</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP at submaximal exercise</td>
<td>0.455</td>
<td>4.310</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP at recovery</td>
<td>0.364</td>
<td>3.449</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(Constant)</td>
<td></td>
<td>-4.356</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure.

![Graphs of BP response to exercise for Metoprolol, Doxazosin, and Trichlormethiazide](image)

**Fig. 1.** Effects of metoprolol, doxazosin and trichlormethiazide on blood pressure during exercise. All three drugs significantly reduced systolic blood pressure at rest, but during exercise, only metoprolol produced a significant reduction in systolic blood pressure. Results are presented as the means ± SE. S. Max, submaximal exercise; (○), before treatment; (●), after treatment; *, p < 0.05; **, p < 0.01.

...ed-measures ANOVA, which included the effects of antihypertensive agents and exercise and comparisons among groups. ANOVA was performed on original data even if relative changes are given in the results. Resting and exercise values during, before and after treatment were compared by Student's $t$-test for paired data. Values of $p<0.05$ were considered to indicate statistical significance.

**Results**

**Relationship between Left Ventricular Mass Index (LVMi) and BP Values before Treatment**

Table 2 shows the correlation between LVMi and BP values at rest, during exercise, and during the recovery period after exercise by multiple regression analysis. The stepwise selection (forward conditional) method showed that LVMi was significantly associated with SBP during submaximal exercise and during the recovery period. On the other hand, there was no significant relation between resting BP and LVMi. There was also a significant positive correlation between ventricular mass and the degree of elevation of BP during exercise ($r=0.41$, $p<0.01$).

**Effects of Various Antihypertensive Agents on Hemodynamics during Exercise**

After 4 weeks of antihypertensive treatment, resting SBP was significantly reduced in all groups treated with antihypertensive agents. The effects of β-blockers, α-blockers, and diuretics on BP during exercise are shown in Fig. 1. Metoprolol produced a significant reduction in SBP during exercise; BP did not rise notably with exercise in patients treated with metoprolol. In contrast, systolic BP during exercise was not significantly lower than before the start of treatment in groups treated with doxazosin or trichlormethiazide; SBP at rest and during exercise in these groups was not affected by these drugs. SBP during the exercise recovery period was significantly reduced in all three groups. Figure 2 shows the effects of calcium antagonists and angiotensin converting enzyme (ACE) inhibitors on BP during exercise. Subjects treated with capsules of nifedipine, a short-acting calcium antagonist, showed levels of BP elevation during exercise that were similar to those seen in the pretreatment group, with no
Fig. 2. Effects of nifedipine, amlodipine and temocapril on blood pressure during exercise. All antihypertensive agents reduced resting blood pressure. During exercise, nifedipine did not reduce systolic blood pressure, whereas amlodipine and temocapril did significantly reduce SBP. Results are presented as the means ± SE. S. Max, submaximal exercise; (○), before treatment; (●), after treatment; *, p < 0.05; **, p < 0.01.

Fig. 3. Effects of metoprolol, doxazosin and trichlormethiazide on heart rate during exercise. Metoprolol induced a significant reduction, and doxazosin a significant elevation, in both resting and exercise heart rate. Trichlormethiazide had no significant effect on heart rate during exercise. Results are presented as the means ± SE. S. Max, submaximal exercise; (○), before treatment; (●), after treatment; *, p < 0.05.

Table 3. The Effects of Antihypertensive Drugs on Plasma NE

<table>
<thead>
<tr>
<th></th>
<th>METO</th>
<th>DOXA</th>
<th>TCTZ</th>
<th>NIPE</th>
<th>AMLO</th>
<th>TEMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest (ng/ml)</td>
<td>0.18±0.03</td>
<td>0.20±0.02</td>
<td>0.23±0.03</td>
<td>0.19±0.02</td>
<td>0.22±0.02</td>
<td>0.19±0.02</td>
</tr>
<tr>
<td>Exercise (ng/ml)</td>
<td>0.32±0.04</td>
<td>0.28±0.03</td>
<td>0.38±0.04</td>
<td>0.27±0.03</td>
<td>0.32±0.03</td>
<td>0.38±0.02</td>
</tr>
<tr>
<td>Treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest (ng/ml)</td>
<td>0.20±0.04</td>
<td>0.28±0.06</td>
<td>0.27±0.04</td>
<td>0.19±0.04</td>
<td>0.19±0.04</td>
<td>0.26±0.03</td>
</tr>
<tr>
<td>Exercise (ng/ml)</td>
<td>0.69±0.08</td>
<td>0.40±0.09</td>
<td>0.47±0.08</td>
<td>0.76±0.13</td>
<td>0.30±0.03</td>
<td>0.31±0.03</td>
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</tbody>
</table>

NE, norepinephrine. Data are expressed as mean ± SE.
Fig. 4. Effects of nifedipine, amlodipine and temocapril on heart rate during exercise. Treatment with capsules of nifedipine tended to be associated with elevated resting heart rate, and heart rate during exercise was significantly elevated. The long-acting calcium antagonist amlodipine and the ACE inhibitor temocapril produced no significant changes in heart rate during exercise. Results are presented as the means ± SE. S. Max: submaximal exercise; ○, before treatment; ●, after treatment; *: p < 0.05.

Fig. 5. The effects of various antihypertensives on plasma NE, which was significantly elevated during exercise. The vertical axis shows the degree of increase in exercise plasma NE after drug treatment / the degree of increase before treatment. Exercise-induced elevation of plasma NE was significantly increased in the metoprolol and nifedipine groups. No change was noted in the doxazosin, trichlormethiazide, or amlodipine groups, and the increase in plasma NE was significantly inhibited in the temocapril group. Results are presented as the means ± SE. METO, metoprolol; DOXA, doxazosin; TCTZ, trichlormethiazide; NIFE, nifedipine; AMLO, amlodipine; TEMO, temocapril; *, p < 0.05; **, p < 0.01.

A significant reduction in BP. In contrast, treatment with the long-acting calcium antagonist amlodipine was associated with a significant reduction in SBP during exercise. Treatment with temocapril, an ACE inhibitor, was also associated with a significant reduction in SBP. Figure 3 shows the effects of β-blockers, α-blockers, and diuretics on heart rate during exercise. Metoprolol produced a significant reduction both in resting heart rate and in heart rate during exercise, while doxazosin showed a significant elevation in both resting and exercise heart rate. Trichlormethiazide produced no significant effect on heart rate during exercise. The effects of the calcium antagonists and ACE inhibitors on heart rate during exercise are shown in Fig. 4. Treatment with capsules of the short-acting calcium antagonist nifedipine tended to be associated with elevated resting heart rate, and heart rate during exercise was significantly elevated (before treatment: 116 ± 5 beats/min; after treatment: 128 ± 3 beats/min; p < 0.05). The long-acting calcium antagonist amlodipine and the ACE inhibitor temocapril produced no significant changes in heart rate during exercise.

Figure 5 and Table 3 show the effects of various antihypertensives on plasma NE, which was significantly elevated during exercise. In this diagram, the vertical axis shows the degree of increase in exercise plasma NE after drug treatment minus the degree of increase before treatment. Exercise-induced elevation of plasma NE was significantly increased after treatment with antihypertensives in the METO and NIFE groups (METO: 97%, p < 0.05; NIFE: 177%, p < 0.01). No change was noted in the DOXA TCTZ, or AMLO groups, and the increase in plasma NE was significantly inhibited in the TEMO group (ACE inhibitor) (~48%, p < 0.05).

Discussion

Considerable interest has been focused recently on the correlation between degree of hypertensive LVH and changes in BP during exercise. A recent studies have suggested that, in patients with mild to moderate hypertension, BP values while working (8) are more closely correlated with left ventricular mass than is resting BP. However, Fagard and colleagues (16) have recently reported that exercise blood pres-
sure is no more closely correlated to left ventricular mass than resting BP. Clearly, opinions in this area are not yet in full agreement.

The current goal of antihypertensive treatment is to lower elevated BP in the resting state. During physical exertion or emotional stress, the work of the heart and the load imposed on the vascular bed by the rise in stress-linked BP are substantially increased relative to the resting state. It is desirable, therefore, to protect the cardiovascular system from BP elevations elicited by physical stress. In the present study, we performed an exercise test on 63 patients with essential hypertension, and studied the correlation between our findings and LVMI as determined by echocardiography. We found that LVMI was more closely correlated to BP during exercise than to resting BP, with a significant positive correlation between ventricular mass and the degree of BP elevation during exercise. It thus appears that BP levels and changes in hemodynamics during exercise are a more important predictor of the development and progression of LVH than resting BP. We believe it is important to control both exercise BP and resting BP in order to prevent the development of hypertensive complications.

Next, we studied the effects of antihypertensive agents on BP, heart rate and plasma NE, an indicator of sympathetic nervous activity during exercise. Sustained exercise leads to release of catecholamines from both the terminal neurons and the adrenal gland, and the blood catecholamine levels increase. In this study, we investigated the effects of antihypertensive drugs on the autonomic nervous system during exercise. 1) Of the drugs which inhibit the sympathetic nervous system (β-blockers, α-blockers and diuretics). 2) Among the diuretics and the sympathetic nervous system-inhibiting drugs (β-blockers, α-blockers) studied, the β-blockers, which have no intrinsic sympathomimetic effect, produced significant reductions in BP and heart rate during exercise, while the α-blockers and diuretics did not. As a class, β-blockers interfere with exercise hemodynamics more than other antihypertensive drugs (20). It has been reported that β-blockers decrease heart rate and cardiac index, increase total peripheral resistance, blunt SBP and elevate DBP at all levels of workload (21). The long-term effects of β-blockers on hemodynamics consist of a reduction of systemic resistance concomitant with a normalization of cardiac output. With β-blocker treatment, there is a long-term depression in cardiac output and heart rate with only slight differences between the β1-selective and the nonselective drugs. Although there is a paucity of data concerning the interaction of a previous bout of exercise and antihypertensive therapy on BP, it is noteworthy that β-blockers have been reported to negatively affect the sustained antihypertensive effect of physical training (22). Unlike β-blockers, α1-blockers do not reduce performance during exercise, but on the other hand, β-blockers reduce the exercise-associated rise in systolic pressure, and α1-blockers do not (23). Because doxazosin is less lipid-soluble and has half or less of the affinity for α1-receptors compared to prazosin, it induced a slower and less profound initial fall in BP. We cannot explain the precise mechanism by which doxazosin increased the heart rate at rest and during exercise. Doxazosin demonstrated the basic character of an α-blocker in that it produced a slight degree of reflex sympathetic stimulation in response to vasodilation. The significant increase in heart rate by this agent may have been related to the limited size of the present cohort.

With respect to diuretics, a previous study reported that diuretics did not significantly reduce SBP at maximum exercise, much like the α-blockers and β-blockers studied here (21). However, there is only a limited amount of available data on this subject in hypertensive patients.

When we investigated the effects on hemodynamics during exercise of calcium antagonists and ACE inhibitors, named in WHO/ISH guidelines (24) as drugs of first choice in the treatment of hypertension, we found that short-acting calcium antagonists produced no reduction in BP during exercise and were associated with a significant increase in heart rate. These results differ slightly from those reported earlier (20), but recent reports on patients with myocardial infarction (25) have indicated that short-acting calcium antagonists may be associated with increased mortality, suggesting that treatment with such drugs should be approached cautiously and with consideration for patient pathophysiology during exercise. In contrast, the use of either a long-acting calcium antagonist or an ACE inhibitor was associated with significantly reduced systolic pressure during exercise, and neither drug type affected exercise heart rate.

Both the long-acting calcium antagonist and ACE inhibitor produced a significant reduction in BP without excessive exercise tachycardia. We observed the same results in our previous report, which demonstrated that a new calcium antagonist, azelnidipine, reduced BP during exercise without augmentation of the sympathetic nervous system in essential hypertension by a randomized double-blind placebo-controlled trial (9). In the present study, there was no significant change in the heart rate or plasma NE value by amiodipine treatment either at rest or during exercise, a finding which appears to agree with these previous reports. Previous data provide support for the concept that the concentration of noradrenaline in the circulating plasma provides a sensitive index of the activity of the sympathetic nervous system (26, 27). With acute dynamic exercise, the most striking cardiovascular alteration is an increase in heart rate, which is much greater in human beings than in smaller animals. Changes in heart rate correlate with both cardiac output and V02 (28). The main cause of the rise in heart rate with exercise is sympathetic stimulation. This is demonstrated by the attenuating effects of β-blockade. In the present study, elevation of plasma NE during exercise was more pronounced with short-acting calcium antagonists, indicating enhanced sympathetic nervous activity. Further, in a study by Savonitto et al., the venous plasma concentration of NE increased after short-term administration of a short-term calcium antagonist (29),
suggested a sympathetic counter regulation to the BP lowering.

Temocapril is a novel long-acting ACE inhibitor that is excreted into the bile; temocapril is at least three times as potent as enalapril and has a faster onset of action (30). Although the renin-angiotensin system does not seem to be consistently necessary for BP control in the recumbent state, it becomes important during sitting, standing, and exercise. In the present study, exercise-induced elevation of plasma NE was significantly inhibited during treatment with an ACE inhibitor, temocapril, suggesting that this agent suppressed the sympathetic nervous system. Muijsen et al. similarly reported an absence of reflex tachycardia in the face of a decrease in blood pressure by ACE inhibitors (31). Although no elevation of baroreflex sensitivity was observed in the present study, the absence of reflex tachycardia suggests that the baroreceptor inhibition of autonomic activity was preserved rather than reduced during temocapril therapy, and that baroreflex potentiation might be another possible antihypertensive mechanism of this drug. The effects of temocapril on exercise hemodynamics were similar to those of captopril. If the hemodynamic changes during exercise are mediated by the augmentation of sympathetic activity, ACE inhibitors might produce a fall in BP by inhibition of both angiotensin II formation and the angiotensin-induced increase of sympathetic activity. This hypothesis is supported by our finding that the exercise-induced increase of plasma NE was suppressed by temocapril treatment.

The literature contains few reports on the effects of antihypertensive agents on hemodynamics during exercise (9, 28; 31). In the treatment of hypertensive patients, it is important to select an agent that does not adversely affect exercise hemodynamics. In the present report, we have examined the effects of various antihypertensive agents, widely used as drugs of first choice in the treatment of hypertension, on BP and the sympathetic nervous system during exercise. The results showed that the reductions of resting systolic and diastolic blood pressure were similar among patients administered metoprolol, doxazosin, trichlormethiazide, nifedipine, amlodipine or temocapril. We found that these different types of drugs had varying effects on BP during exercise, suggesting that pathophysiology during exercise should be considered when selecting antihypertensive agents for the treatment of patients who are quite active. In the future, we recommend that antihypertensive treatment include consideration of exercise blood pressure as well as 24-h blood pressure.

References

17. Smith DHG, Neutel JM, Graettinger WF, Myers J,