The Hemodynamics and Hemodynamic Effects of Indenolol in Mild Hypertension

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Summary

For clarifying the onset mechanism of essential hypertension, the hemodynamics in 9 mildly hypertensive men, mean age of 39.8±10.7 (mean±SD), was compared with 7 normotensive men, mean age of 39.8±10.7, by means of exercise echocardiography, and the effects of indenolol (administered 30 mg/day for 7 days orally to both groups) were studied.

The interventricular septum and the left ventricular posterior wall were thickened in the mild hypertensives. No significant differences between the both groups were shown in the cardiac performance at rest and the cardiac index during exercise. The total peripheral vascular resistance was higher in the mild hypertensives than the normotensives during exercise. However, during exercise, the normotensives showed significant increases in the left ventricular end-diastolic dimension (LVDd) and the stroke index (SI); these changes were not significant in the mild hypertensives. After administration of indenolol, the significant increases in LVDd and SI during exercise were observed in the mild hypertensives.

This study suggests that mild hypertensives with cardiac hypertrophy display a diminished Frank-Starling effect during exercise which may be attributed to the decreased left ventricular compliance due to cardiac hypertrophy and elevated afterload. Indenolol improved the Frank-Starling effect, which decreased in the mild hypertensives.

Additional Indexing Words:
Mild hypertension β-blocking agent Indenolol Exercise echocardiography Frank-Starling mechanism
A number of problems are unresolved in essential hypertension. This is especially true with respect to the mechanisms of the onset of hypertension. Hemodynamics and other related factors in mild hypertension have been studied in an attempt to clarify mechanisms of the onset of hypertension. The pathophysiologic condition of increased cardiac output and heart rate, defining feature of the "hyperkinetic circulatory state," have been regarded as early cardiac changes of hypertension.\(^{1,2}\) On the other hand, there have been several reports that the total peripheral vascular resistance is not increased in early hypertension. However, it increases constantly in sustained hypertension.\(^{1-3}\) These findings are based on the observations of hemodynamics of the patients at rest. With advances in echocardiography, it has become possible to accurately and noninvasively observe cardiovascular dynamics during exercise.\(^{4}\) When cardiovascular dynamics in the mildly hypertensive patients at exercise are examined, they are not in the hyperkinetic state.

They display a lowering of the total peripheral vascular resistance during exercise, which does not reach the level of normotensive subjects.\(^{3}\) However, there are few detailed studies of hemodynamics during exercise, and investigations of the influences of antihypertensive agents on hemodynamics are inadequate. The usefulness of \(\beta\)-blockers in antihypertensive treatment has been confirmed recently, and the effects of propranolol and several other agents on hemodynamics at exercise have been evaluated.\(^{3,5}\) However, the results of studies on cardiovascular dynamics are not altogether consistent.\(^{6-8}\)

With the object of clarifying cardiovascular dynamics in mild hypertension and the influence of \(\beta\)-blockers, we have performed (1) a comparative exercise echocardiographic evaluation of age and sex-matched groups of mild hypertensive controls and (2) a study comparing the hemodynamic effects of indenolol,\(^{9}\) a new \(\beta\)-blocker, which was administered orally under identical conditions to both mildly hypertensive subjects and normotensive subjects.

**Materials and Methods**

Nine newly diagnosed and untreated, mildly hypertensive male subjects (Group H) and 7 healthy non-athletic normotensive male subjects (Group N) were studied. Group H subjects had a mean age 39.8±10.7 years (mean ±SD) with diastolic pressure of 90–104 mmHg at rest in the sitting position when examined at our outpatient clinic in accordance with the criteria of the Joint National Committee on Hypertension.\(^{10}\) This group was studied after
admission. Group N subjects had a mean age 39.8±10.7, and were studied in the outpatient clinic (Table I). Those with secondary hypertension, an abnormal electrocardiogram or cardiomegaly in the chest X-ray were excluded from the study. In addition, a submaximal treadmill test was performed in all cases to exclude any patients with coronary artery diseases. From 1 week before the start of observation up to completion of the study, salt intake was restricted to 15 Gm or less per day. Concerning the salt restriction, Group H was given our hospital meal and Group N underwent diet guidance.

**Exercise echocardiography**

The study consisted of recording the baseline blood pressure, electrocardiogram, phonocardiogram and M-mode and two-dimensional echocardiograms after 20 min of rest in the supine position, followed by exercise in the supine position using a multi-stage bicycle ergometer (Model EM-038, Tatebe Seishudo Ltd.). With work load, which started at 25 watts and was increased by 25 watts every 3 min, and at the steady state of 75 watts, the same measurements as before exercise were performed to obtain at-exercise readings. M-mode and two-dimensional echocardiograms were obtained in the third or fourth intercostal space at the left sternal border using a Toshiba SSH-11A echocardiograph with a Honeywell strip-chart recorder at a paper speed of 100 mm/sec, with a 2.24 MHz transducer. Simultaneously, the two-dimensional echocardiogram was recorded on video tape to ascertain that none of the subjects had an asynergy of the left ventricular wall. Systolic and diastolic blood pressures were determined by auscultation.

**Echocardiographic measurements**

Measurements were obtained from M-mode echocardiograms. As shown in Fig. 1, the left ventricular end-diastolic dimension (LVDd), interventricular septal wall thickness (SWT) and left ventricular posterior wall thickness (PWT) were measured on the vertical line drawn at the Q-wave of the electrocardio-
Fig. 1. M-mode echocardiogram from one subject, demonstrating the left ventricular measurements. LVDd = left ventricular end-diastolic dimension; LVDs = left ventricular end-systolic dimension; SWT = interventricular septal wall thickness; PWT = left ventricular posterior wall thickness.

Table II. Methods and Equations Used in the Echocardiographic Measurements

<table>
<thead>
<tr>
<th>Method</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke volume (SV)</td>
<td>SV = LVDd³ - LVDs³</td>
</tr>
<tr>
<td>Stroke index (SI)</td>
<td>SI = SV/BSA</td>
</tr>
<tr>
<td>Cardiac output (CO)</td>
<td>CO = SV·HR</td>
</tr>
<tr>
<td>Cardiac index (CI)</td>
<td>CI = CO/BSA</td>
</tr>
<tr>
<td>Ejection fraction (EF)</td>
<td>EF = (SV/LVDd³)·100</td>
</tr>
<tr>
<td>Mean velocity of circumferential fiber shortening (mVCF)</td>
<td>mVCF = (LVDd - LVDs)/LVDd·ET</td>
</tr>
<tr>
<td>Total peripheral vascular resistance (TPR)</td>
<td>TPR = 1,332·60·mBP/CO = (mBP - (sBP - dBP)/3)/CO</td>
</tr>
</tbody>
</table>

Abbreviations: LVDd = left ventricular end-diastolic dimension; LVDs = left ventricular end-systolic dimension; BSA = body surface area; HR = heart rate; ET = ejection time; mBP = mean blood pressure; sBP = systolic blood pressure; dBP = diastolic blood pressure.

gram. The left ventricular end-systolic dimension (LVDs) was measured at the onset of the aortic component of the second heart sound in the phonocardiogram. The stroke index (SI), cardiac index (CI), mean velocity of circumferential fiber shortening (mVCF), ejection fraction (EF) and total peripheral vascular resistance (TPR) were then calculated (Table II). In addition, the time between the opening of the aortic cusps and the aortic component of the second heart sound and the ejection time (ET) were measured on the M-mode echocardiogram.

Administration of indenolol
After control recordings and measurements, indenolol was administered
orally 30 mg/day for 7 days to all mildly hypertensive and normotensive subjects. Identical recordings and measurements were made on the final day of the administration, with the subjects performing exercise 2 to 4 hr after the final dose.

The indices of cardiac functions before and after exercise in the mildly hypertensive and normotensive subjects were compared before and after the administration of indenolol.

Statistical analysis
The statistical differences between Group N and Group H were tested by one-way analysis of variance. The differences between before and during exercise and between before and after indenolol were analysed by means of two-way analysis of variance of repeated measures. For comparison between each 2 groups non-paired or paired t-values were calculated. Significance refers to a p value less than 0.05.

Results

1. Before administration of indenolol (Table III)
   1) Blood pressures (BP): Systolic blood pressure (sBP), diastolic blood pressure (dBP), mean blood pressure (mBP) [hereafter expressed as sBP/dBP (mBP)] at rest were 135±10/87±10 (100±4) mmHg for the mildly hypertensive subjects and 117±11/73±8 (88±8) mmHg for the normotensive subjects. All of the values were significantly higher in the mildly hypertensive subjects (p<0.01). At exercise, they were 181±16/103±12 (128±10) mmHg for the mildly hypertensive subjects and 162±8/79±9 (107±8) mmHg for the normotensive subjects. Although sBP and mBP were elevated significantly at exercise in both groups, dBP increased significantly only in the mildly hypertensive subjects (p<0.01).
   2) Heart rate (HR): In the mildly hypertensive subjects, the heart rate tended to increase both at rest and at exercise. However, no significant differences were observed.
   3) Ejection time (ET): At rest, the ET for the mildly hypertensive and normotensive subjects were 282±19 msec and 313±26 msec, respectively, but values during exercise were 212±30 msec for the mildly hypertensive subjects and 249±21 msec for the normotensive subjects. The ET for mild hypertensives was significantly shorter in both states (p<0.05).
   4) Interventricular septal wall thickness (SWT), left ventricular posterior wall thickness (PWT): The SWT and PWT for the mildly hypertensive subjects were 10.0±1.0 mm and 8.6±1.2 mm, respectively, while SWT and
Table III. Hemodynamic Parameters at Rest and Exercise

<table>
<thead>
<tr>
<th></th>
<th>sBP (mmHg)</th>
<th>dBP (mmHg)</th>
<th>mBP (mmHg)</th>
<th>HR (bpm)</th>
<th>ET (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest</strong></td>
<td>135±10</td>
<td>87±10</td>
<td>100±4</td>
<td>67±12</td>
<td>282±19</td>
</tr>
<tr>
<td><strong>Mildly hypertensive subjects</strong></td>
<td><strong>181±11</strong></td>
<td><strong>103±12</strong></td>
<td>128±10</td>
<td>120±22</td>
<td>212±30</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td>±16</td>
<td>±12</td>
<td>±10</td>
<td>±22</td>
<td>±30</td>
</tr>
</tbody>
</table>

Values are mean±SD.

* p<0.05: comparison between at rest and during exercise.
** p<0.01: comparison between at rest and during exercise.
† p<0.05: comparison between mildly hypertensive and normotensive subjects.
†† p<0.01: comparison between mildly hypertensive and normotensive subjects.

PWT for the normotensive subjects were 7.1±1.1 mm and 6.4±0.8 mm, respectively. These data suggest a tendency of cardiac hypertrophy in the mildly hypertensive subjects, since both of the thicknesses were greater in this group (p<0.01).

5) Left ventricular end-diastolic dimension (LVDd): The LVDd at rest was 48.3±5.5 mm for the mildly hypertensive subjects and 53.1±4.1 mm for the normotensive subjects, showing no difference between the 2 groups. Although these values increased significantly to 55.3±3.5 mm at exercise in the normotensive subjects (p<0.05), a similar significant expansion at exercise was not observed in the mildly hypertensive subjects, i.e., 49.0±5.4 mm.

6) Left ventricular end-systolic dimension (LVDs): At rest, the LVDs was 30.9±5.0 mm for the mildly hypertensive subjects. This was significantly smaller than 36.4±3.6 mm for the normotensive subjects (p<0.05). On the other hand, the LVDs at exercise was 29.6±5.5 mm for the mildly hypertensive subjects, the same as the at-rest value. However, in the normotensive subjects, it reduced significantly to 34.0±3.2 mm (p<0.05).

7) Stroke index (SI) (Fig. 2): The SI at rest was 51.8±17.1 ml/m² for the mildly hypertensive subjects and 59.6±11.5 ml/m² for the normotensive subjects [no significant difference (n.s.)]. However, exercise increased this index significantly (p<0.01) to 75.3±13.0 ml/m² in the normotensive sub-
HEMODYNAMICS AND INDENOLOL IN MILD HYPERTENSION

during Exercise before Administration of Indenolol

<table>
<thead>
<tr>
<th>LVDd (mm)</th>
<th>LVDs (mm)</th>
<th>SI (ml/m²)</th>
<th>CI (L/min/m²)</th>
<th>mVCF (sec⁻¹)</th>
<th>EF (%)</th>
<th>TPR (dynes·sec·cm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48.3</td>
<td>30.9†</td>
<td>51.8</td>
<td>3.38</td>
<td>1.29†</td>
<td>73.4</td>
<td>1,580</td>
</tr>
<tr>
<td>±5.5</td>
<td>±5.0</td>
<td>±17.1</td>
<td>±1.01</td>
<td>±0.20</td>
<td>±6.4</td>
<td>±565</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>49.0†</td>
<td>29.6</td>
<td>56.3†</td>
<td>6.77</td>
<td>1.92</td>
<td>77.3</td>
<td>992††</td>
</tr>
<tr>
<td>±5.4</td>
<td>±5.5</td>
<td>±16.4</td>
<td>±2.17</td>
<td>±0.47</td>
<td>±7.6</td>
<td>±276</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53.1</td>
<td>36.4</td>
<td>59.6</td>
<td>3.60</td>
<td>1.01</td>
<td>67.4</td>
<td>1,133</td>
</tr>
<tr>
<td>±4.1</td>
<td>±3.6</td>
<td>±11.5</td>
<td>±0.54</td>
<td>±0.15</td>
<td>±5.8</td>
<td>±206</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55.3</td>
<td>34.0</td>
<td>75.3</td>
<td>8.24</td>
<td>1.56</td>
<td>76.3</td>
<td>608</td>
</tr>
<tr>
<td>±3.5</td>
<td>±3.2</td>
<td>±13.0</td>
<td>±0.96</td>
<td>±0.21</td>
<td>±6.1</td>
<td>±92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: sBP = systolic blood pressure; dBP = diastolic blood pressure; mBP = mean blood pressure; HR = heart rate; ET = ejection time; LVDd = left ventricular end-diastolic dimension; LVDs = left ventricular end-systolic dimension; SI = stroke index; CI = cardiac index; mVCF = mean velocity of circumferential fiber shortening; EF = ejection fraction; TPR = total peripheral vascular resistance.

Fig. 2. Stroke index (SI) and the amount of SI change (ΔSI) at rest and during exercise (Ex.) before administration of indenolol. The SI and ΔSI did not significantly increase during exercise in the mildly hypertensive subjects.

jects, while no apparent increase of the index was observed in the mildly hypertensive subjects (56.3 ± 16.4 ml/m²).

8) Cardiac index (CI): The CI at rest was 3.38 ± 1.01 L/min/m² for the mildly hypertensive subjects and 3.60 ± 0.54 L/min/m² for the normotensive
subjects (n.s.). No difference was noted between the 2 groups. At exercise, the CI increased significantly in both groups to 6.77±2.17 L/min/m² and 8.24 ±0.96 L/min/m², respectively, and there was no significant difference between the 2 groups at exercise.

9) Mean velocity of circumferential fiber shortening (mVCF): The mVCF at rest for the mildly hypertensive subjects (1.29±0.20 sec⁻¹) was higher (p<0.01) than for the normotensive subjects (1.01±0.15 sec⁻¹), but this difference disappeared at exercise (1.92±0.47 sec⁻¹ for the mildly hypertensive subjects and 1.56±0.21 sec⁻¹ for the normotensive subjects).

10) Ejection fraction (EF): The EF at rest for the mildly hypertensive subjects was 73.4±6.4% and for the normotensive subjects was 67.4±5.8%. The EF at exercise for the mildly hypertensive and normotensive subjects was 77.3±7.6% and 76.3±6.1%. Thus, there were no significant differences in this parameter between the 2 groups of subjects either at rest or at exercise.

11) Total peripheral vascular resistance (TPR): The TPR at rest was 1,580±565 dynes·sec·cm⁻⁵ for the mildly hypertensive subjects and 1,153 ±206 dynes·sec·cm⁻⁵ for the normotensive subjects (n.s.). This was decreased significantly by exercise in both groups, but the TPR for the mildly hypertensive subjects, 992±276 dynes·sec·cm⁻⁵, was significantly higher (p<0.01) than for the normotensive subjects, 608±92 dynes·sec·cm⁻⁵.

Thus, before indenolol administration, the mildly hypertensive subjects at rest demonstrated increases in SWT and PWT, decreases in LVDs and ET with an increase in mVCF compared to the normotensive subjects. There

<table>
<thead>
<tr>
<th>Table IV. Hemodynamic Parameters at Rest and Exercise</th>
<th>sBP (mmHg)</th>
<th>dBP (mmHg)</th>
<th>mBP (mmHg)</th>
<th>HR (bpm)</th>
<th>ET (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>130†</td>
<td>83</td>
<td>99†</td>
<td>54</td>
<td>300†</td>
</tr>
<tr>
<td>Mildly hypertensive subjects (n=9)</td>
<td>±12</td>
<td>±12</td>
<td>±12</td>
<td>±8</td>
<td>±25</td>
</tr>
<tr>
<td>Exercise</td>
<td>±12</td>
<td>±12</td>
<td>±12</td>
<td>±12</td>
<td>±28</td>
</tr>
<tr>
<td>Normotensive subjects (n=7)</td>
<td>±12</td>
<td>±12</td>
<td>±11</td>
<td>±9</td>
<td>±18</td>
</tr>
<tr>
<td>Exercise</td>
<td>±9</td>
<td>±13</td>
<td>±10</td>
<td>±9</td>
<td>±15</td>
</tr>
</tbody>
</table>

Values are mean±SD.
were no significant differences in HR, LVDd, SI, CI, EF and TPR as compared with the normotensive subjects. However, at exercise, the normotensive subjects showed expansion of LVDd, shortening of LVDs and increased SI. These changes were not prominent in the mildly hypertensive subjects. The ET was shorter in the mildly hypertensive subjects than in normotensives, even at exercise. There were no significant differences observed between the 2 groups in HR, CI, EF and mVCF at exercise. The TPR decreased significantly after exercise in both groups; however, it was still higher in the mildly hypertensive subjects.

2. After administration of indenolol (Table IV)

1) Blood pressures (Fig. 3): Administration of indenolol showed no significant changes in sBP, dBP and mBP at rest or during exercise of the normotensive subjects. On the other hand, while indenolol administration produced no significant changes in sBP, dBP and mBP of the mildly hypertensive subjects at rest, they decreased significantly after administration of indenolol, as compared with the values before administration [sBP from 181±16 to 160±12 mmHg (p<0.01), dBP from 103±12 to 94±10 mmHg (p<0.05) and mBP from 128±10 to 116±9 mmHg (p<0.01)].

2) Heart rate (Fig. 4): The heart rate decreased significantly after administration of indenolol in all instances. The heart rate at rest decreased from 67±12 to 54±8 bpm for the mildly hypertensive subjects and from 63±15 to 51±9 bpm for the normotensive subjects. During exercise the
Fig. 3. Effects of indenolol on blood pressure. After administration of indenolol, systolic (sBP), diastolic (dBP) and mean (mBP) blood pressures during exercise (Ex.) decreased significantly in the mildly hypertensive subjects ($p<0.01$), but remained unchanged in the normotensive subjects.

Fig. 4. Effects of indenolol on heart rate (HR) and ejection time (ET). The HR decreased significantly in both groups of subjects after administration of indenolol ($p<0.01$). The ET was significantly prolonged in only the mildly hypertensive subjects ($p<0.01$).
heart rate changed from $120 \pm 22$ to $99 \pm 12$ bpm for the mildly hypertensive subjects and from $111 \pm 11$ to $97 \pm 9$ bpm for the normotensive subjects ($p < 0.01$).

3) Ejection time (Fig. 4): Administration of indenolol did not change the ET in the normotensive subjects either at rest ($313 \pm 26 \rightarrow 326 \pm 18$ msec) or at exercise ($249 \pm 21 \rightarrow 274 \pm 15$ msec). However, a significantly prolonged ET was observed in the mildly hypertensive subjects at rest ($282 \pm 19 \rightarrow 300 \pm 25$ msec; $p < 0.01$) and during exercise ($212 \pm 30 \rightarrow 273 \pm 28$ msec; $p < 0.01$).

4) Left ventricular end-diastolic dimension (LVDd) (Fig. 5): In the mildly hypertensive subjects, there was no difference in values at rest before and after administration of indenolol. However, while there was no significant increase in this parameter after exercise before administration, it increased significantly after administration, as in the normotensive subjects (at rest $49.2 \pm 3.5$ mm $\rightarrow$ at exercise $52.1 \pm 3.2$ mm; $p < 0.01$).

5) Left ventricular end-systolic dimension (Fig. 5): There was no significant difference between LVDs before and after administration of indenolol in either group at rest or at exercise.

6) Stroke index (Fig. 5): Before administration of indenolol, exercise
Fig. 6. Effects of indenolol on cardiac index (CI), mean velocity of circumferential fiber shortening (mVCF) and ejection fraction (EF) in the mildly hypertensive subjects. All parameters other than mVCF in the mildly hypertensive subjects during exercise (Ex.) remained unchanged after administration of indenolol.

did not significantly increase the SI in the mildly hypertensive subjects. After administration, though, the SI changed significantly from $54.6 \pm 13.9$ ml/m$^2$ at rest to $69.1 \pm 12.6$ ml/m$^2$ at exercise ($p<0.01$).

7) In both the mildly hypertensive subjects and the normotensive subjects, no significant effects of indenolol on the CI, mVCF, EF and TPR were noted at rest or during exercise, with the exception of a lowering of mVCF at exercise in the mildly hypertensive subjects ($1.92 \pm 0.47 \rightarrow 1.54 \pm 0.30$ sec$^{-1}$; $p<0.05$) (Fig. 6).

These data indicate that administration of indenolol does not produce any significant changes in the parameters of the mildly hypertensive subjects at rest, with the exception of a decrease of HR and an extension of ET. However, during exercise, their HR, ET, sBP, dBP and mBP decreased and the LVDd and SI increased significantly as compared with values before administration. The LVDs, CI, EF and TPR did not change significantly. Although the mVCF decreased after administration of indenolol, there was no significant difference in the mVCF during exercise between the 2 groups. In other words, the major changes in the mildly hypertensive subjects after administration of indenolol were a decreased HR, an extension of ET and a lowering of BP during exercise. In addition, the significant increases in LVDd and SI at exercise in the mildly hypertensives, were observed as in the normotensive subjects. These increases were not seen before administration.
Although the mVCF at exercise in the mildly hypertensives was lowered, no change in the CI or EF was noted. Thus, we did not obtain any results which suggest apparent inhibition of the cardiac function by indenolol in either the mildly hypertensives or the normotensives.

**DISCUSSION**

1. Cardiovascular dynamics in mildly hypertensive subjects before administration of indenolol

There are many reports on pathological changes and cardiovascular dynamics of mild or borderline hypertension. Recently, there has been a report showing that cardiac hypertrophy appears in the early stage of borderline hypertension prior to the blood pressure elevation.\(^\text{11}\) Safar et al\(^\text{12}\) reported that a significant increase in the interventricular septal wall thickness / left ventricular posterior wall thickness ratio is observed in borderline hypertension. In the present study, echocardiography showed significant increases in SWT and PWT in the mildly hypertensive subjects. These increases may suggest a tendency of these subjects to develop cardiac hypertrophy.\(^\text{11}\) Although the etiology of cardiac hypertrophy in borderline or mild hypertension is not yet clear, it may be attributed only to the elevation of afterload due to mild elevation of the blood pressure and increased peripheral vascular resistance. Thus, studies including the involvement of the sympathetic nervous system and catecholamines would be required to clarify the mechanism of occurrence of cardiac hypertrophy.

It is a well-known fact that cardiac output increases in early hypertension.\(^\text{11,13}\) However, Weiss et al\(^\text{13}\) measured cardiac output in borderline hypertension twice on different days, and the increased output was observed only in the first measurement. In addition, Julius et al\(^\text{14}\) reported that only 30 to 50% of the patients with borderline hypertension showed increases in cardiac output by two standard deviations or more as compared with the control. Fouad et al\(^\text{15}\) did not observe any specific trend in cardiac output in patients with juvenile hypertension; but the data were distributed widely over the range of 3.86 to 10.3 L/min. In the present study, the hemodynamics of the mildly hypertensive subjects at rest showed a trend of excessive wall motions, such as shortening of LVDs and increase of mVCF, even though SI and CI were not substantially different from those of the normotensive subjects. However, this trend disappeared upon exercise. Thus, no clear 'hyperkinetic state'\(^\text{16}\) was seen in the mildly hypertensive subjects. Accordingly, we cannot draw an unqualified conclusion concerning the difference between our results and those of the past reports, since our subjects
are not definitely limited to 'early hypertension' or young subjects. Nonetheless, as explained earlier, many investigators do not recognize the presence of this pathophysiology. Therefore, disappearance of the 'hyperkinetic state' at exercise is not yet a generally recognized mechanism of the onset of hypertension.

There is a recent report describing a disturbance of the left ventricular diastolic compliance in the early stages of hypertension, when the left ventricular contractility is still maintained at the normal level. In this regard, we have obtained some interesting results in cardiovascular dynamics at exercise. While the dBP at exercise was the same as that at rest in the normotensive subjects, it was elevated significantly in the mildly hypertensive subjects. In addition, the LVDd was increased significantly by a work load in the normotensive subjects, resulting in a significant increase in SI. However, in the mildly hypertensive subjects, no significant increase of either LVDd or SI was produced by the work load. There was no statistically significant difference in HR, and no clear difference seen in CI between the 2 groups. No significant differences were observed between the 2 groups in the mVCF and EF at exercise, which are the indices of left ventricular contractility. The TPR at exercise was significantly higher in the mildly hypertensive subjects, since it reflects mBP and dBP. Thus, in mild hypertension, the at-rest measurements did not clearly show any difference in cardiovascular dynamics compared with the normotensives, but responses of the cardiovascular dynamics at exercise were clearly different from the normotensive subjects. In the mildly hypertensive subjects, the increases in the afterload due to the elevations of the at-exercise dBP and TPR and the responses seen in the LVDd and the SI demonstrate that the Frank-Starling effect is attenuated in the mildly hypertensive subjects. This was possibly due to a decreased left ventricular compliance, resulting from elevation of the afterload and a tendency toward cardiac hypertrophy. There was no CI difference between the 2 groups of subjects and it was thought that the mildly hypertensive subjects maintained the CI by increasing HR. The left ventricular contractility was nearly identical in both groups. Johansen found that the heart rate in WHO Stage I hypertensive subjects at exercise was rather high and that stroke volume was rather low as compared with the normal controls, with the peripheral vascular resistance decreasing less significantly than in the normal controls. The results obtained in the present study do not contradict his findings.

2. Hemodynamic effects of indenolol at rest and during exercise in mildly hypertensive subjects
A number of reports are available on the hemodynamic effects of β-blockers, particularly of propranolol. Reports show that intravenous administration of propranolol\(^{19,20}\) produces cardiac enlargement and lowers left ventricular performances such as cardiac output and ejection fraction. However, there is no consensus on the hemodynamic effects of orally administered propranolol. Crawford et al\(^{6}\) reported that propranolol had practically no direct effect on left ventricular function of normal subjects, while Battler et al\(^{7}\) and Rainwater et al\(^{8}\) indicated that propranolol improved the left ventricular function of patients with coronary artery disease during exercise. On the other hand, Cathcart-Rake et al\(^{21}\) described the effects of this drug as lowering the ejection fraction and increasing the PEP/LVET of normotensive subjects. Thus, the results of studies of the effects of orally administered propranolol on left ventricular function are not unequivocal. There are few reports on cardiovascular dynamics during exercise after the administration of β-blockers in hypertensive patients. Leenen et al\(^{5}\) administered propranolol and atenolol to mildly hypertensive subjects and measured their maximal attained work load. Although they reported that the β-blockers did not decrease the maximal work load, they did not report stroke volume and cardiac output in their study. In the present study, indenolol was administered orally to age and sex-matched mildly hypertensive and normotensive subjects to observe hemodynamic parameters at rest and at a work load of 75 watts.

Indenolol\(^{9}\), 1-(7-indenyloxy)-3-isopropyl aminopropan 2-ol-hydrochloride, is a non-selective β-blocker manufactured in Japan. This drug has been shown to have a stronger β-blocking action than propranolol. However, there are no reports of the effects of this agent on cardiovascular dynamics in hypertensive patients at exercise.

In both mildly hypertensive subjects and normotensive subjects, the blood pressure at rest was not lowered significantly by administration of indenolol. However, blood pressure during exercise decreased significantly in the mildly hypertensive subjects. Heart rate increases were attenuated in both groups of subjects at rest and during exercise. It is noteworthy that no significant increase was observed in LVDd at exercise in the mildly hypertensive subjects before administration of indenolol, but that administration of this drug produced a significant increase in LVDd, which matches results from normotensive subjects before indenolol administration. This resulted in a significant increase in the SI with an increase in the work load. No clear depression of the CI, mVCF or EF, either at rest or during exercise, was observed and the TPR did not change after administration of indenolol. Andersen et al\(^{22}\) reported that atenolol potentiates the Frank-Starling effect.
in healthy men during exercise. The results of the present study suggest that disorders in the Frank-Starling mechanism in the mildly hypertensive subjects during exercise were improved by administration of indenolol. The mechanism for improving the Frank-Starling effect may be that indenolol decreased the HR and increased LVDd, without decreasing left ventricular contractility.

As described above, the comparisons of cardiovascular dynamics of the mildly hypertensive subjects with the normotensive subjects revealed increases in the at-exercise diastolic blood pressure, increases in the afterload due to elevation of the total peripheral vascular resistance, and attenuation of the Frank-Starling effect. This effect appears to be attributable to the tendency toward cardiac hypertrophy, suggesting a decrease in the left ventricular compliance. These findings, however, were not apparent in the subjects at rest. This indicates the necessity to take into consideration the effects on hemodynamics during exercise in selecting a drug for the management of mild hypertension. Indenolol potentiated the Frank-Starling effect and improved the cardiac responses of the mildly hypertensive subjects toward those of the normotensive subjects, suggesting the usefulness of this drug. Further studies are required, though, to determine whether this effect is common to other β-blockers.

**References**

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