Electrocardiographic Changes During Antihypertensive Therapy in the International Prospective Primary Prevention Study in Hypertension

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On Behalf of the ECG Committee of the IPPPSH

SUMMARY In the International Prospective Primary Prevention Study in Hypertension, electrocardiographic changes before and during 3- to 5-year antihypertensive treatment were investigated in a cohort of 5819 men and women aged 40 to 64 years with entry diastolic blood pressures of 100 to 125 mm Hg. They were randomly allocated to treatment regimens that either included or excluded the slow-release β-blocker oxprenolol. Electrocardiograms (ECGs) were assessed using the Minnesota Code and assigned to groups of normal ECGs or ECGs with pressure-related, ischemic, "intermediate," or "other" abnormalities. Antihypertensive treatment was associated with a decrease (mainly in men) of pressure-related and (mainly in women) of intermediate abnormalities. Ischemic abnormalities increased, particularly in men. Inclusion of the β-blocker resulted in a greater reduction in intermediate abnormalities and in a lesser increase in ischemic abnormalities. Better blood pressure control was associated with a lesser increase in ischemic abnormalities and in a regression of pressure-related abnormalities. The presence of ST segment depression and of a complete left bundle branch block in the entry ECG was associated with a significant risk for sudden death and myocardial infarction. Optimal blood pressure control prevents pressure-induced cardiac target organ damage and, hence, heart failure, and may delay the progression of ischemic abnormalities. This tallies with the lower critical cardiac event rate associated with lower blood pressure that was observed in the same study. (Hypertension 9 [Suppl III]: III-69-III-74, 1987)

KEY WORDS • electrocardiography • antihypertensive therapy • primary prevention • Minnesota Code

THE International Prospective Primary Prevention Study in Hypertension (IPPPSH) investigated the incidence of critical cardiac events (sudden death, fatal and nonfatal myocardial infarction) and of stroke in patients with moderate to moderately severe uncomplicated essential hypertension who were on antihypertensive treatment regimens that included the slow-release β-blocker oxprenolol as compared to patients on regimens without the β-blocker. Details of patient selection, trial procedure, and the main results of the IPPPSH were reported previously.1-2 In the IPPPSH, electrocardiograms (ECGs) were recorded as part of the diagnosis for myocardial infarction and to assess cardiac target organ involvement at entry and during the study.

In hypertensive patients, electrocardiographic abnormalities may occur in association with left ventricular hypertrophy3,4 as well as with ischemic heart disease, which prevails in hypertensive patients.3 Since left ventricular hypertrophy reflects the direct effect of the elevated blood pressure on the left ventricle, and ischemic changes may be the consequence of the coronary atherosclerotic process, antihypertensive treatment may influence differently these two patho-
physiological components of hypertensive cardiac involvement and, hence, the associated electrocardiographic abnormalities. This article reports the different effects of 3 to 5 years of antihypertensive treatment on electrocardiographic signs considered to be mainly pressure-related and on those more likely related to myocardial ischemia, which were compared in different sex, blood pressure control, and treatment groups.

Patients and Methods
Patients and Antihypertensive Therapy
The IPPPSH included 6357 patients aged 40 to 64 years, with diastolic blood pressures (Korotkoff V) of 100 to 125 mm Hg but without previous myocardial infarction (seen on clinical examination or ECG), stroke, or angina pectoris. About half of the patients were untreated and the other half were receiving some antihypertensive treatment at entry into the study. About half (3185) of the patients were randomly allocated to receive slow-release oxprenolol (160-320 mg/day) and the remaining 3172 were allocated to receive an identical-looking placebo. To achieve the in-study target diastolic pressure of ≤95 mm Hg, non-\(\beta\)-blocking drugs, mainly diuretics, were added in an open fashion. Mean in-study blood pressure was 144/89 mm Hg for those on the regimen containing the \(\beta\)-blocker and 147/90 mm Hg (\(p<0.001\)) for those on the regimen that did not include the \(\beta\)-blocker. Patients gave their informed consent to participate in the study according to the Declaration of Helsinki, modified by the 29th World Medical Assembly (Tokyo, 1975).

To investigate the effects of long-term antihypertensive treatment on the ECG, the entry and last ECGs of a cohort of 5819 patients (2890 men, 2929 women), who represented 92% of the total IPPPSH population and who were followed for over 3 to 5 years, were taken for analysis. Excluded from this cohort were patients who had a critical cardiac event or a stroke during the study.

Assessment of Electrocardiograms
Twelve-lead ECGs were recorded at the time of each patient's entry into the study and prospectively at yearly intervals thereafter. The ECGs were assessed using the Minnesota Code (MC),\(^6\) with a few modifications to account for abnormalities that may be of importance for delayed intrinsicoid deflection (\(\leq 0.05\) seconds) in ST segment elevation with myocardial injury pattern, and intermediate abnormalities also decreased. In 70% of the patients, although signs of left ventricular hypertrophy and left atrial overload disappeared, the associated ST-T segment alterations and flat to negative T waves that occurred on their own, were grouped as "intermediate" abnormalities (MC 4-2 to 4-5, 5-1 to 5-4). All other codes (conduction defects, arrhythmias) were included into the category designated "other" abnormalities. If no MC designation was applicable, the ECG was defined as normal.

Results
Total Cohort
Table 1 shows the distribution of the entry and last ECGs for the five groups of electrocardiographic characteristics. At entry, slightly less than half of all ECGs were normal. ECGs showing pressure-related abnormalities amounted to 17.5%; of these the majority (77%) demonstrated signs of left ventricular hypertrophy with or without concomitant ST-T changes, a smaller number (22.5%) showed signs of left atrial overload and a few (0.5%) of delayed intrinsicoid deflection. The proportion of entry ECGs with ischemic abnormalities was 3.4%. Intermediate abnormalities were present in 27.5% of all entry ECGs, and approximately half of them showed solitary J point depression with an upslanting ST segment. In the group of other electrocardiographic abnormalities, 81% of the ECGs demonstrated signs of partial right bundle branch block (MC 7-3, 7-5), and the remainder showed first-degree heart block (10%), complete right bundle branch block (7%), or left bundle branch block (2%).

During antihypertensive treatment, the proportion of pressure-related abnormalities decreased. In the majority of patients with changes (63%), the ECG became completely normal. In a smaller number, although signs of left ventricular hypertrophy and left atrial overload disappeared, the associated ST-T changes persisted. The proportion of ECGs demonstrating intermediate abnormalities also decreased. In 70% of the changing ECGs, this decrease was due to the ECG becoming normal. The remainder either showed a worsening of the ST segment depression, and therefore were moved into the category of ischemic abnormalities, or showed additional pressure-related changes. There was an increase of 1.5% in the proportion of ECGs that showed ischemic abnormalities. The increase in the proportion of ECGs with other abnormalities was caused mainly by an increase in ECGs that demonstrated partial right bundle branch block. Overall, this resulted in an increase in the proportion of normal ECGs, with the greatest contribution coming from the normalization of pressure-related electrocardiographic abnormalities.
Electrocardiographic Changes in Relation to Sex and to Randomized Treatment

At entry, pressure-related electrocardiographic abnormalities demonstrating particular signs of left ventricular hypertrophy were more often found in men, whereas intermediate electrocardiographic abnormalities prevailed in women (see Table 1). During antihypertensive treatment there was a greater decrease in the proportion of pressure-related abnormalities, mainly left ventricular hypertrophy, in men. The decrease in the proportion of intermediate abnormalities was greater in women, and the majority of their ECGs (75%) became normal. In men, the decrease in the proportion of intermediate abnormalities was due to only 43% of these ECGs becoming normal, and in a considerable fraction (33%), ST segment depression deteriorated to the extent that by the end of the study the ECGs of these patients appeared in the category of ischemic abnormalities. This accounts in part for the five times greater increase in the proportion of ischemic abnormalities in men to which were added pathological Q waves that had occurred without a clinically recognized myocardial infarction. In men there was also a greater increase in other abnormalities, mainly ECGs demonstrating a partial right bundle branch block. Overall, this resulted in a 2.6% smaller decrease in the proportion of normal ECGs in men compared to the increase of normal ECGs in women.

The inclusion of the β-blocker resulted in a greater decrease in the proportion of intermediate abnormalities and in a smaller increase in ischemic abnormalities. Consequently, the increase in the proportion of normal ECGs doubled with the β-blocker regimen (see Table 1). While at study entry electrocardiographic abnormalities were balanced between the two randomized treatment groups (χ² 3.91; 4 degrees of freedom; p = 0.419) a significant difference was found at the time of the last ECG (χ² 22.3; p < 0.001), the main contribution to this difference coming from the decrease in the proportion of intermediate abnormalities in the face of an increasing proportion of normal ECGs. The smaller increase in ischemic abnormalities with oxprenolol treatment, though showing a clear tendency, does not appear to contribute significantly to this difference. However, there was no difference between the two treatment modalities with respect to the regression of pressure-related abnormalities.

Electrocardiographic Changes in Relation to In-Study Blood Pressure

Table 2 shows the distribution of the entry and last ECGs for the five groups of electrocardiographic characteristics arranged according to the treatment-induced change in diastolic blood pressure (difference between entry and mean in-study diastolic pressure) and according to the blood pressure control achieved (mean in-study diastolic pressure). Starting from a similar distribution at entry, the proportions of electrocardiographic characteristics changed depending on the treatment-induced fall in diastolic blood pressure (Figure 1A). Small falls in pressure were associated with an increase in intermediate abnormalities, a greater increase in ischemic and other abnormalities, and a somewhat smaller decrease in pressure-related abnormalities as well as a decrease in the proportion of normal ECGs. The greater the diastolic fall, the greater was the decrease in the proportion of pressure-related and intermediate abnormalities, the smaller were the increases in the proportions of ischemic and other abnormalities, and, consequently, the greater was the increase in the proportion of normal ECGs. A similar relation to blood pressure was found when mean in-study diastolic pressures were considered (see Figure 1B). Poor blood pressure control was associated with a greater increase in ischemic abnormalities, whereas with good diastolic control this increase was small. On the other hand, the proportions of pressure-related abnormalities decreased even in patients with poor diastolic control; hence, they appeared to be least related to in-study blood pressure control, which tallies with

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**Table 1. Distribution (and Percent) of Entry and Last ECGs in the Five Groups of Electrocardiographic Characteristics According to Randomized Treatment and Gender**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Normal Entry</th>
<th>Normal Last</th>
<th>Pressure-related Entry</th>
<th>Pressure-related Last</th>
<th>Intermediate Entry</th>
<th>Intermediate Last</th>
<th>Ischemia Entry</th>
<th>Ischemia Last</th>
<th>Others Entry</th>
<th>Others Last</th>
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<tr>
<td>Total cohort</td>
<td>(n = 5819)</td>
<td></td>
<td>(n = 5819)</td>
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<td></td>
<td>2606</td>
<td>2917</td>
<td>1021</td>
<td>679</td>
<td>1598</td>
<td>1471</td>
<td>198</td>
<td>267</td>
<td>396</td>
<td>485</td>
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<td></td>
<td>(44.8)</td>
<td>(50.1)</td>
<td>(17.5)</td>
<td>(11.7)</td>
<td>(27.5)</td>
<td>(25.3)</td>
<td>(3.4)</td>
<td>(4.6)</td>
<td>(6.8)</td>
<td>(8.3)</td>
</tr>
<tr>
<td>With β-blocker*</td>
<td>(n = 5924)</td>
<td></td>
<td>(n = 5924)</td>
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<td></td>
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<tr>
<td></td>
<td>1348</td>
<td>1561</td>
<td>507</td>
<td>335</td>
<td>781</td>
<td>683</td>
<td>104</td>
<td>127</td>
<td>202</td>
<td>236</td>
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<tr>
<td></td>
<td>(45.8)</td>
<td>(53.1)</td>
<td>(17.2)</td>
<td>(11.4)</td>
<td>(26.5)</td>
<td>(23.2)</td>
<td>(3.5)</td>
<td>(4.3)</td>
<td>(6.9)</td>
<td>(8.0)</td>
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<tr>
<td>Without β-blocker*</td>
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<td>(n = 2877)</td>
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<td>140</td>
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<tr>
<td></td>
<td>(43.7)</td>
<td>(47.1)</td>
<td>(17.9)</td>
<td>(12.0)</td>
<td>(28.4)</td>
<td>(27.4)</td>
<td>(3.3)</td>
<td>(4.9)</td>
<td>(6.7)</td>
<td>(8.7)</td>
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<tr>
<td>Men</td>
<td>(n = 2890)</td>
<td></td>
<td>(n = 2890)</td>
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<td>618</td>
<td>394</td>
<td>593</td>
<td>584</td>
<td>95</td>
<td>152</td>
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<td>292</td>
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<tr>
<td></td>
<td>(46.7)</td>
<td>(50.8)</td>
<td>(21.4)</td>
<td>(13.6)</td>
<td>(20.5)</td>
<td>(20.2)</td>
<td>(3.3)</td>
<td>(5.3)</td>
<td>(8.1)</td>
<td>(10.1)</td>
</tr>
<tr>
<td>Women</td>
<td>(n = 2929)</td>
<td></td>
<td>(n = 2929)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
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<td>1449</td>
<td>403</td>
<td>285</td>
<td>1005</td>
<td>887</td>
<td>103</td>
<td>115</td>
<td>163</td>
<td>193</td>
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<tr>
<td></td>
<td>(42.8)</td>
<td>(49.5)</td>
<td>(13.8)</td>
<td>(9.7)</td>
<td>(34.3)</td>
<td>(30.3)</td>
<td>(3.5)</td>
<td>(3.9)</td>
<td>(5.6)</td>
<td>(6.6)</td>
</tr>
</tbody>
</table>

All patients were followed up for 3 to 5 years.

*Difference between randomized groups determined by chi-square test: at entry, χ² 3.91 (4 degrees of freedom, p = 0.419); at time of last ECG, χ² 22.3 (p < 0.001).
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Table 2. Distribution (and Percent) of Entry and Last ECGs in the Five Groups of Electrocardiographic Characteristics According to the Treatment-Induced Fall in Diastolic Blood Pressure and According to the Mean In-Study Diastolic Pressure

<table>
<thead>
<tr>
<th>Diastolic pressure (mm Hg)</th>
<th>Normal</th>
<th>Pressure-related</th>
<th>Intermediate</th>
<th>Ischemia</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-induced change*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 (n=217)</td>
<td>94.0 (43.3)</td>
<td>49.0 (22.6)</td>
<td>50.0 (23.0)</td>
<td>9.0 (4.1)</td>
<td>15.0 (6.9)</td>
</tr>
<tr>
<td>&gt;5 to ≤10 (n=838)</td>
<td>404.0 (48.2)</td>
<td>127.0 (15.2)</td>
<td>230.0 (27.4)</td>
<td>25.0 (3.0)</td>
<td>52.0 (6.2)</td>
</tr>
<tr>
<td>&gt;10 to ≤15 (n=1706)</td>
<td>785.0 (46.0)</td>
<td>291.0 (17.1)</td>
<td>461.0 (27.0)</td>
<td>54.0 (3.2)</td>
<td>115.0 (6.7)</td>
</tr>
<tr>
<td>&gt;15 to ≤20 (n=1648)</td>
<td>734.0 (44.5)</td>
<td>272.0 (16.5)</td>
<td>468.0 (28.4)</td>
<td>61.0 (3.7)</td>
<td>113.0 (6.9)</td>
</tr>
<tr>
<td>&gt;20 (n=1410)</td>
<td>589.0 (41.8)</td>
<td>282.0 (20.0)</td>
<td>389.0 (27.6)</td>
<td>49.0 (3.5)</td>
<td>101.0 (7.2)</td>
</tr>
</tbody>
</table>

Mean in-study†

<table>
<thead>
<tr>
<th></th>
<th>Entry</th>
<th>Last</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;100 (n=476)</td>
<td>167.0 (35.1)</td>
<td>134.0</td>
</tr>
<tr>
<td>&gt;95 to ≤100 (n=1052)</td>
<td>438.0 (41.6)</td>
<td>213.0</td>
</tr>
<tr>
<td>&gt;90 to ≤95 (n=2102)</td>
<td>940.0 (44.7)</td>
<td>376.0</td>
</tr>
<tr>
<td>&gt;85 to ≤90 (n=1631)</td>
<td>778.0 (47.7)</td>
<td>227.0</td>
</tr>
<tr>
<td>≤85 (n=558)</td>
<td>283.0 (50.7)</td>
<td>71.0</td>
</tr>
</tbody>
</table>

The cohort of 5819 patients was followed up for 3 to 5 years.

*Difference between entry and mean in-study diastolic pressure.

†Blood pressures achieved.

The observation that already small falls in diastolic pressure were associated with regression of pressure-related abnormalities (see Figure 1A). Patients with poor in-study diastolic pressure control even tended to have a greater decrease in pressure-related abnormalities than did well-controlled patients, which may be due to the fact that poorly controlled patients had more pressure-related abnormalities at entry, thereby possibly providing a greater potential for regression. The relation of pressure to electrocardiographic changes during antihypertensive therapy was similar when analyzed for systolic blood pressure.

Predictive Importance of Electrocardiographic Abnormalities for Critical Cardiac Events

Certain entry electrocardiographic abnormalities were associated with increased risk of suffering a critical cardiac event during the IPPPSH. Relative risks, adjusted for age, sex, smoking, and blood pressure, were 1.76 (p = 0.002) for presence of ST segment depression (≥0.05 mV, MC 4-2 and 4-3) and 3.91 (p = 0.008) for presence of complete left bundle branch block (MC 7-1). None of the other electrocardiographic abnormalities, in particular pressure-related ones, emerged as significant risk factors.

Discussion

In the IPPPSH, slightly more than half of all patients showed at least one MC abnormality in their ECGs at study entry. The dominant features of the ECGs of female patients were minor to moderate repolarization disturbances, whereas pressure-related abnormalities, particularly signs of left ventricular hypertrophy, were seen more often in the ECGs of men. Pressure-related abnormalities occurred more frequently with higher blood pressure, as has been found in other studies.3' 8

Compared with other studies7, 8, 9 that used a similar electrocardiographic assessment, the electrocardiographic features in the IPPPSH can be considered consistent with a population having moderate to moderately severe hypertension without clinical manifestations of coronary artery disease. Since the design of the IPPPSH did not include initial stratification for sex or electrocardiographic abnormalities, analyses of differences between proportions of abnormalities thus would represent subgroup analyses except for differences arising between the two randomized (β-blocker vs non-β-blocker) treatment groups for which overall statistical significance testing was performed (see Table 1).

Antihypertensive treatment was associated with a
decrease mainly in the proportion of pressure-related and, to some extent, of intermediate abnormalities, but with an increase in the proportion of ischemic abnormalities. Disappearance of pressure-related abnormalities independent of the type of treatment occurred even in patients whose blood pressure was not well controlled, indicating that even small falls in pressure may alleviate left ventricular workload and lead to regression of pressure-related abnormalities. Similar degrees of normalization of voltage criteria were observed in the Veterans Administration Study\(^9\) and in the U.S. Public Health Service Hospitals Cooperative Study.\(^9\) Left atrial overload, which was used in the IPPPSH as a pressure-related electrocardiographic feature,\(^11\) regressed like left ventricular hypertrophy during antihypertensive treatment. The lack of a significant predictive power of pressure-related abnormalities for critical cardiac events in the IPPPSH, which is at variance with the results of some studies\(^3\)\(^12\) but in agreement with others,\(^13\) may partly be explained by this marked regression of pressure-related abnormalities.

In contrast to the relationship of blood pressure reduction and pressure-related abnormalities, the proportion of ECGs with signs of myocardial ischemia increased during antihypertensive therapy, and this was more marked in patients with poor blood pressure control. This finding agrees with the poor effect of antihypertensive treatment on the development of pathological Q waves reported in the Veterans Administration Study\(^9\) and with the finding that, despite treatment-induced regression of pressure-related abnormalities, coronary events were not reduced accordingly.\(^14\) The degree of blood pressure control appears to be crucial for delaying the progression of ischemic electrocardiographic abnormalities, but probably it is less so for influencing the regression of pressure-related abnormalities. This may in part explain why antihypertensive therapy, while successfully preventing heart failure, was found not to have a correspondingly
beneficial effect on the incidence of coronary events.\(^1\,\,^3\) The value of ST segment depression in the IPPPSH and of an ischemic electrocardiographic pattern in the Medical Research Council Trial of Mild Hypertension\(^7\) for predicting cardiac events may support this notion. The greater increase in ischemic abnormalities in men in the IPPPSH would thus be compatible with their greater risk for critical cardiac events. The relatively greater improvement of electrocardiographic abnormalities in patients on oxprenolol-containing regimens may be indirectly due to the better blood pressure control. Alternatively, since the actual between-group differences (in terms of mm Hg) were small, this may suggest possible direct effects of the β-blocker on the ECG.\(^1\,\,^8\) However, the finding that the quality of blood pressure control may influence the progression of ischemic abnormalities agrees with the observed lower critical cardiac event rates associated with lower blood pressure in the IPPPSH.\(^2\) The present study thus emphasizes the need for optimal blood pressure control and also demonstrates the usefulness of separating pressure-related from ischemic abnormalities in assessing long-term effects of antihypertensive treatment on the ECG.

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Members of the ECG Committee of the IPPPSH

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