HAEMODYNAMIC CHANGES IN LONG-TERM THERAPY OF ESSENTIAL HYPERTENSION: A COMPARATIVE STUDY OF DIURETICS, α-METHYLDOPA AND CLONIDINE

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SUMMARY

1. The effects of hypotensive therapy with three separate diuretics, methyldopa and clonidine were separately assessed.
2. All the treated groups showed a significant drop in blood pressure.
3. Polythiazide and hydrochlorothiazide each produced a significant fall in total peripheral resistance, whereas chlorthalidone did not.
4. Symptomless hypokalaemia was the only side effect seen with diuretics.
5. Methyldopa and clonidine reduced heart rate and cardiac index, but not total peripheral resistance.
6. The latter drugs also produced dry mouth, lassitude and drowsiness.

Key words: hypertension, diuretics, chlorthalidone, polythiazide, hydrochlorothiazide, α-methyldopa, clonidine, haemodynamics.

It is still an open question whether mild essential hypertension without complications should be treated (Veterans Administration Study Group on Antihypertensive Agents, 1972). However, if it could be demonstrated that long-term therapy with antihypertensives in dosages without side effects could change the disturbed central haemodynamics in a normal direction, then early therapy would at least seem logical.

MATERIALS AND METHODS

The study includes sixty-four males aged 30–59 years, all with previously untreated essential hypertension and no other diseases, all working. The majority were in WHO stage I, a few in stage II. Secondary hypertension was excluded by the usual routine procedures. The material was divided in six groups: I, untreated; II, chlorthalidone (100 mg every second day); III, polythiazide (1 mg every second day); IV, hydrochlorothiazide (50 mg twice daily); V, α-

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methyldopa (500–1500 mg daily, mean 900 mg); and VI, clonidine (275–600 μg daily, mean 383 μg).

The dosages of the last two drugs were adjusted according to side effects and blood pressure response. The age and body surface area for groups I–VI were respectively (mean and SD): 32.9(10.7), 48.0(2.9), 45.7(7.0), 43.3(9.8), 48.2(7.9), 42.6(10.5) years and 1.90(0.15), 1.90(0.07), 1.94(0.11), 1.98(0.19) and 1.97(0.09) m². The mean casual blood pressures before the study started were respectively 160/101, 179/117, 176/117, 180/113, 176/115 and 183/116 mmHg. The untreated group (n = 7) includes mostly younger patients with slight hypertension at rest and during exercise. The treated groups were not matched, but compared well with respect to age, body surface area, casual blood pressure and habitual physical activity.

Informed consent was obtained from all subjects. The patients were studied during strictly standardized conditions at rest supine, and sitting, and during cycling in steady-state exercise at 300, 600 and 900 kpm/min.

Oxygen consumption (Douglas bag and micro-Scholander), intra-arterial pressure (polyethylene catheter in the brachial artery), heart rate (ECG) and cardiac output (Cardiogreen) were measured in duplicate in each situation. The methods have been described in detail by Lund-Johansen (1967). All studies were made in ambulatory out-patients. After 1 year the haemodynamic study was repeated.

The difference between the results at first and second study was tested by Student's t-test (P<0.05 regarded as significant).

**RESULTS**

**Untreated group**

There were no significant changes in casual blood pressure or haemodynamic parameters either at rest or during exercise. At rest, however, there was a slight drop in mean arterial pressure (MAP) and a tendency to a drop in cardiac index (CI) and increase in total peripheral resistance index (TPRI). The mean values at rest sitting at the first and second study being: 115–111 mmHg, 3.39–2.97 l min⁻¹ m⁻² and 2777–3079 dyn s cm⁻² m⁻². During 900 kpm/min exercise the mean values at the first and second study were practically identical, 136–135 mmHg, 10.4–10.2 l min⁻¹ m⁻² and 1081–1082 dyn s cm⁻² m⁻².

**Treated groups**

In all treated groups there was a significant drop in casual blood pressure, the mean reductions in groups II–VI being: 40/20, 32/20, 39/18, 30/15 and 31/17 mmHg.

At the first haemodynamic study all treated subjects presented as the cardinal haemodynamic disturbance an increased TPRI at rest and during exercise. The TPRI was not uniformly influenced by long-term therapy and the mechanism behind the pressure reduction differed in the various groups (Table 1). Space permits presentation of only the most important findings. Details from groups I–V have been published by Lund-Johansen (1970, 1972).

**Group II (chlorthalidone).** The pressure reduction during rest and exercise was associated with a significant drop in CI, with no significant decrease in TPRI. The CI reduction was due to a decrease in stroke index (SI), heart rate (HR) being unchanged. Oxygen consumption (VO₂) showed no significant changes. Individual results showed that only two of nine subjects achieved at least a 10% reduction in TPRI at rest, but none also during exercise.
<table>
<thead>
<tr>
<th>Patient group</th>
<th>n</th>
<th>MAP  (mmHg)</th>
<th>CI (l min⁻¹ m⁻²)</th>
<th>TPRI  (beats/min)</th>
<th>HR  (beats/min)</th>
<th>MAP  (mmHg)</th>
<th>CI (l min⁻¹ m⁻²)</th>
<th>TPRI  (beats/min)</th>
<th>HR  (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rest sitting</td>
<td>Work (600 km/min)</td>
<td></td>
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<td></td>
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<td>Mean ± SD</td>
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<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>II. Chlorthalidone</td>
<td>9</td>
<td>135 ± 15</td>
<td>2.88 ± 0.4</td>
<td>3808 ± 724</td>
<td>70 ± 12</td>
<td>165 ± 22</td>
<td>8.37 ± 0.7</td>
<td>1582 ± 240</td>
<td>125 ± 16</td>
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<tr>
<td></td>
<td></td>
<td>-21 ± 4</td>
<td>-17 ± 6</td>
<td>-3 ± 0.3</td>
<td>0 ± 0.0</td>
<td>-19 ± 2</td>
<td>-20 ± 0.0</td>
<td>± 3 ± 0.0</td>
<td>± 2 ± 0.0</td>
</tr>
<tr>
<td>III. Polythiazide</td>
<td>7</td>
<td>129 ± 14</td>
<td>2.94 ± 0.5</td>
<td>3580 ± 641</td>
<td>73 ± 12</td>
<td>150 ± 15</td>
<td>7.32 ± 1.0</td>
<td>1647 ± 381</td>
<td>131 ± 19</td>
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<td></td>
<td></td>
<td>-15 ± 0.5</td>
<td>-10 ± 2</td>
<td>-6 ± 0.5</td>
<td>2 ± 0.1</td>
<td>-13 ± 1.0</td>
<td>0 ± 0.2</td>
<td>-1 ± 0.1</td>
<td>-1 ± 0.1</td>
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<tr>
<td>IV. Hydrochlorothiazide</td>
<td>15</td>
<td>131 ± 13</td>
<td>2.90 ± 0.4</td>
<td>3657 ± 487</td>
<td>74 ± 9</td>
<td>151 ± 19</td>
<td>7.52 ± 0.8</td>
<td>1638 ± 295</td>
<td>133 ± 13</td>
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<td></td>
<td></td>
<td>-18 ± 0.5</td>
<td>-5 ± 0.9</td>
<td>-14 ± 0.6</td>
<td>0 ± 0.1</td>
<td>-16 ± 1.0</td>
<td>-2 ± 0.1</td>
<td>-15 ± 1.0</td>
<td>-15 ± 1.0</td>
</tr>
<tr>
<td>V. a-Methyldopa</td>
<td>13</td>
<td>126 ± 12</td>
<td>2.95 ± 0.5</td>
<td>3517 ± 607</td>
<td>76 ± 12</td>
<td>143 ± 17</td>
<td>7.61 ± 0.9</td>
<td>1519 ± 200</td>
<td>127 ± 14</td>
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<td></td>
<td></td>
<td>-9 ± 0.4</td>
<td>-15 ± 0.7</td>
<td>-9 ± 0.3</td>
<td>-9 ± 0.2</td>
<td>-11 ± 0.9</td>
<td>-9 ± 0.1</td>
<td>-2 ± 0.1</td>
<td>-2 ± 0.1</td>
</tr>
<tr>
<td>VI. Clonidine</td>
<td>13</td>
<td>133 ± 12</td>
<td>2.87 ± 0.4</td>
<td>3741 ± 392</td>
<td>73 ± 10</td>
<td>150 ± 13</td>
<td>7.19 ± 0.6</td>
<td>1673 ± 217</td>
<td>128 ± 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-13 ± 0.4</td>
<td>-12 ± 0.5</td>
<td>-2 ± 0.1</td>
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<td>-9 ± 0.6</td>
<td>-5 ± 0.2</td>
<td>-5 ± 0.2</td>
<td>-2 ± 0.2</td>
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</tbody>
</table>

TPRI and HR are expressed as dyn s cm⁻⁵ m⁻².
**Groups III and IV (polythiazide and hydrochlorothiazide).** The pressure reduction at rest was associated with an insignificant drop in CI while TPRI was reduced, significantly so in the hydrochlorothiazide group. HR and $V_{O_2}$ showed no significant changes. During exercise the TPRI was significantly reduced in both groups, the CI being practically unchanged with no changes in HR. Individual results showed that of the twenty-two thiazide-treated subjects thirteen got a 10% reduction or more of TPRI at rest and eleven did so both at rest and during exercise.

**Group V (α-methyldopa).** The pressure reduction at rest was associated with a significant drop in CI mainly due to a significant reduction in HR. $V_{O_2}$ tended to be decreased, but not significantly. TPRI showed no significant changes, and at rest sitting it was higher in ten of thirteen. During moderate exercise the CI was still significantly lower than before therapy, with no significant reduction in TPRI. During severe exercise (900 kpm/min) the MAP was reduced only 7% and the changes in TPRI, CI and HR were insignificant. Individual results showed that no subjects achieved a 10% reduction in TPRI both at rest and during two exercise loads.

**Group VI (clonidine).** The mechanisms behind the pressure reduction showed a more varied picture. At rest, the CI was reduced in eleven of thirteen, both supine and sitting, the mean reduction being significant. The reduction in CI was due to a significant decrease in HR whereas SI was unchanged. $V_{O_2}$ was reduced in eleven of thirteen, mean reduction being 16.2 ml min$^{-1}$ m$^{-2}$ or 10% and significant. TPRI showed inconsistent changes. During moderate exercise TPRI was usually reduced, but not significantly. Individual results showed that only four of thirteen obtained a 10% reduction in TPRI at rest and only three of thirteen both at rest and during exercise.

During severe exercise (900 kpm/min) the effect on blood pressure was small, the mean reduction of MAP only 2%.

**DISCUSSION**

The present study indicates that the haemodynamic changes obtained after 1 year of antihypertensive therapy are not independent of the drug. The results in the thiazide groups at rest confirm results by Conway & Lauwers (1960). In addition it is shown that the same changes in TPRI are also present during exercise. It is surprising that the same reduction in TPRI was not obtained by chlorthalidone.

The changes obtained during rest with α-methyldopa and clonidine are rather similar. Both drugs mainly reduced the blood pressure by reduction in HR and CI, without significant changes in TPRI. Haemodynamic studies of combined long-term therapy with these drugs and diuretics (Reubi, Vorburger & Bütikofer, 1970; Sannerstedt, Schröder & Werkö, 1972) have shown conflicting results.

Symptomless hypokalaemia was the only side effect with diuretics, whereas drowsiness, lack of energy and dry mouth were frequent in groups V and VI and sometimes prohibited increase in dosage. The haemodynamic changes together with lack of subjective side effects seem to make the thiazide diuretics usually more suitable for therapy of mild and moderate established essential hypertension than the drugs interfering with the sympathetic nervous system like α-methyldopa and clonidine.
REFERENCES


