STUDIES ON THE MECHANISM OF ALDOSTERONE-INDUCED HYPERTENSION IN MAN

A. DISTLER, H. J. JUST AND TH. PHILIPP

First and Second Department of Internal Medicine, University Hospital, Mainz, Germany

(Received 21 June 1973)

SUMMARY

1. Haemodynamic studies were performed in six patients with hypertension, hyperaldosteronism and low plasma renin (five patients with a solitary adrenocortical adenoma, one patient with bilateral adrenocortical nodular hyperplasia), and in ten normotensive control subjects.

2. Studies in the chronic phase of hypertension uniformly showed elevated total peripheral resistance while cardiac output was not increased.

3. In four patients haemodynamics were studied in the early phase of hypertension following a normotensive period induced by spironolactone. Under these latter conditions the raised blood pressure was associated with increased cardiac output whereas total peripheral resistance was normal. It is suggested that the haemodynamic pattern observed during the phase of the renewed elevation of blood pressure is similar to that at the onset of aldosterone-induced hypertension.

4. Serial measurements in two patients revealed that the haemodynamic characteristics were dependent on the phase of hypertension: during the chronic phase total peripheral resistance was increased whereas cardiac output was not. The new rise in blood pressure following discontinuation of spironolactone therapy was associated with increased cardiac output while total peripheral resistance was normal.

5. Although limited, the findings suggest that the initial step in the development of aldosterone-induced hypertension is a rise in cardiac output. This may be an important factor for the final elevation of total peripheral resistance.

Key words: aldosterone-induced hypertension, changes in haemodynamics, spironolactone, plasma volume, extracellular fluid volume.

The mechanism of aldosterone-induced hypertension is still unknown. In the chronic stage of primary aldosteronism hypertension has been shown to be the consequence of elevated total

Correspondence: Professor A. Distler, 1. Medizinische Universitätsklinik, Langenbeckstrasse 1, Mainz, Germany.
peripheral resistance (Frohlich, Tarazi & Dustan, 1969; Marsen, Dissmann, Oelkers, Lohmann, Molzahn & Gotzen, 1971). Haemodynamic data in the early phase of blood pressure elevation which might provide some information on the pathogenesis of hypertension in primary aldosteronism have not yet been published. The reason for the lack of information on the early phase of hypertension in primary aldosteronism derives probably from the difficulty in detecting this stage clinically. We have therefore attempted to gain insight into the early phase of aldosterone-induced hypertension by an indirect approach: patients with hypertension, aldosteronism and low plasma renin were studied before, during and after normalization of blood pressure by treatment with spironolactone. Spironolactone normalizes blood pressure in patients with primary aldosteronism caused by a solitary adrenal adenoma (Spark & Melby, 1968; Brown, Davies, Lever, Peart & Robertson, 1965) as well as in patients with aldosteronism due to bilateral nodular adrenocortical hyperplasia (Brown, Davies, Ferris, Fraser, Haywood, Lever & Robertson, 1972). After cessation of spironolactone therapy blood pressure rises again. The assumption would seem to be justified that haemodynamics under these latter conditions are comparable to those of the early stage of aldosterone-induced hypertension.

Table 1. Clinical and laboratory data in the patients studied. The observations were made after antihypertensive drug therapy had been withdrawn for at least 11 days (see the text).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Blood pressure (mmHg)</th>
<th>Serum potassium (mmol/l)</th>
<th>Total blood volume (ml/kg)</th>
<th>Plasma volume (ml/kg)</th>
<th>Aldosterone secretion rate (μg/24 h)</th>
<th>Plasma renin concentration (ng h⁻¹ ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>42</td>
<td>181/117</td>
<td>3.19</td>
<td>63.0</td>
<td>40.6</td>
<td>943</td>
<td>Recumbent: 1.7, After 3 h upright posture: 2.5</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>40</td>
<td>183/119</td>
<td>2.95</td>
<td>55.1</td>
<td>35.8</td>
<td>786</td>
<td>Recumbent: 1.6, After 3 h upright posture: 2.9</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>47</td>
<td>169/98</td>
<td>2.90</td>
<td>64.9</td>
<td>43.7</td>
<td>1351</td>
<td>Recumbent: 2.5, After 3 h upright posture: 5.4</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>50</td>
<td>164/88</td>
<td>2.95</td>
<td>58.4</td>
<td>39.1</td>
<td>384</td>
<td>Recumbent: 0.8, After 3 h upright posture: 0.8</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>30</td>
<td>162/104</td>
<td>3.05</td>
<td>68.9</td>
<td>45.0</td>
<td>942</td>
<td>Recumbent: 2.5, After 3 h upright posture: 2.7</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>48</td>
<td>176/101</td>
<td>3.11</td>
<td>63.7</td>
<td>40.9</td>
<td>864</td>
<td>Recumbent: 0.8, After 3 h upright posture: 0.8</td>
</tr>
</tbody>
</table>

(1) Mean values
(2) ⁵¹Cr-labelled erythrocytes.
(3) ¹³¹I-labelled human serum albumin.

**PATIENTS AND METHODS**

Informed consent was obtained from all subjects participating in the study.

Clinical and laboratory data of the patients studied are listed in Table 1. In five patients a solitary adrenocortical adenoma was found at operation; one patient (no. 2) showed bilateral nodular adrenocortical hyperplasia. Aldosteronism due to adrenocortical hyperplasia is possibly an entity distinct from true primary aldosteronism (Distler, Barth, Roscher, Vecsei,
Dhom & Wolff, 1969; Baer, Sommers, Krakoff, Newton & Laragh, 1970). However, since spironolactone normalized blood pressure completely (Fig. 1) hypertension in patient 2 was considered aldosterone induced, as in the cases with classic primary aldosteronism. The patients were studied under ward conditions while on a diet of 100–120 mmol of sodium and 60–80 mmol of potassium/day. Antihypertensive drug therapy had been discontinued in patient 1 3 months prior to the study; patient 2 had received 1 g of α-methyl dopa and 0.75 mg of reserpine/day up to 11 days prior to the study. Patient 3 had taken 100 mg of spironolactone/day up to the 16th day before the study. This low dosage had not influenced the blood pressure significantly. On another occasion, however, 400 mg of spironolactone had been given to this patient with complete normalization of blood pressure. Patients 4, 5 and 6 were treated with 400 mg of spironolactone daily (see below).

Haemodynamic studies were carried out in the supine position in the morning following a 12 h period of rest. An early morning snack was allowed 2–3 h prior to the study. Central venous and arterial pressures were measured in the brachial artery with Statham pressure transducers. Mean pressures were obtained through electrical integration. Cardiac output was determined by indicator-dilution technique using Cardiogreen. Electrocardiogram and pressures were continuously recorded on a multichannel direct-writing instrument (Hellige Multiscriptor EK 21). Cardiac index (CI), stroke volume index (SVI) and total peripheral resistance (TPR) were calculated according to standard formulae. Haemodynamic measurements were begun 30–40 min after the catheters and needles had been inserted. All measurements were done in duplicate and averaged. For comparison, haemodynamic measurements were done in ten normotensive healthy volunteers not receiving therapy, between 16 and 57 years of age, under identical conditions to those under which the patients were studied.

Aldosterone secretion rate was estimated by an isotope-dilution technique (Lommer, Distler, Philipp & Wolff, 1972). Blood samples for determination of plasma renin concentration were drawn in the morning with the patient supine after 12 h bedrest and after a 3 h orthostatic period during which slow ambulation was allowed. Plasma renin concentration was measured according to the micro-method of Boucher, Ménard & Genest (1967) by incubating the patient’s plasma with a substrate prepared from sheep plasma by ammonium sulphate precipitation (Boucher et al., 1967). The concentration of renin is expressed in terms of ng of angiotensin produced/h of incubation per ml. For estimation of blood volume a radio-isotope-dilution technique either with $^{131}$I-labelled human serum albumin or with $^{51}$Cr-labelled erythrocytes was used. Large vessel haematocrit was corrected for its difference from total-body haematocrit and a correction factor was used for plasma trapping:

$$TBV = \frac{100 - HT}{100 - 0.89 \times HT} \times BV_m$$

where $TBV =$ total blood volume; $HT =$ large-vessel haematocrit; 0.89 = ratio of total-body haematocrit to large-vessel haematocrit (0.91) minus correction factor for trapped plasma (0.02) and $BV_m =$ blood volume measured.

Plasma volume (PV) was calculated according to the formula:

$$PV = TBV \times \frac{100 - 0.89 \times HT}{100}$$
For assessment of extracellular fluid volume the distribution space of $^{51}$Cr-labelled EDTA (Kunkel, Oberhausen & Kirsch, 1969) was determined. For determination of exchangeable sodium ($Na_e$) $1\mu$Ci of $^{22}$Na was injected intravenously and total-body radioactivity was measured in a whole-body counter following a 48 h equilibration period. In addition, specific radioactivity of serum Na was determined. $Na_e$ was calculated from the ratio of total-body radioactivity still present after 48 h to the specific radioactivity of serum Na after 48 h equilibration.

RESULTS

The results of the haemodynamic studies are summarized in Table 2.

TPR was uniformly elevated in those patients whose blood pressure had not been normalized by previous spironolactone therapy (patients 1–3). SVI and CI were normal. By contrast, in those subjects who were studied shortly after previous normalization of blood pressure (patients 4 and 5) SVI and CI were increased while TPR was normal. Haemodynamics in patient 6, who was studied 48 days after withdrawal of spironolactone, were similar to those of the patients studied during the chronic phase of hypertension (patients 1–3). Heart rate was normal or slow throughout.

### Table 2. Haemodynamic measurements. Patient 4 was studied 19 days, patient 5 20 days and patient 6 48 days after cessation of spironolactone therapy (400 mg/day). Patients 1–3 had no high-dose spironolactone pretreatment (see the text). The normal values of haemodynamic indices were obtained from ten normotensive healthy volunteers.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Normal values (extreme ranges)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>167</td>
<td>165</td>
<td>140</td>
<td>118</td>
<td>130</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>78</td>
<td>78</td>
<td>65</td>
<td>72</td>
<td>67</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Cardiac index (l/min per m$^2$)</td>
<td>3.19</td>
<td>3.33</td>
<td>2.33</td>
<td>4.74</td>
<td>4.59</td>
<td>1.82</td>
<td>2.3–4.5</td>
</tr>
<tr>
<td>Stroke volume index (ml/beat per m$^2$)</td>
<td>40.9</td>
<td>42.7</td>
<td>35.8</td>
<td>65.9</td>
<td>68.5</td>
<td>35.8</td>
<td>35.8–60</td>
</tr>
<tr>
<td>Total peripheral resistance (dyne s cm$^{-5}$)</td>
<td>2381</td>
<td>2012</td>
<td>2724</td>
<td>1126</td>
<td>1109</td>
<td>2800</td>
<td>900–1500</td>
</tr>
</tbody>
</table>

Patient 2 was studied in the chronic stage of hypertension as well as during and shortly after spironolactone therapy (Fig. 1). Under spironolactone treatment blood pressure was completely normal as were CI, SVI and TPR. At 10 days after cessation of spironolactone therapy a new rise in arterial pressure could be demonstrated which was caused by an increase in SVI and in CI. TPR and heart rate were even lower than during spironolactone therapy. The rise in SVI was accompanied by an increase in body weight, plasma volume, extracellular fluid volume and in $Na_e$ (Fig. 1).
Mechanism of aldosterone-induced hypertension

Patient 6 was first studied 48 days after normalization of blood pressure by spironolactone therapy. Repeat studies were carried out under renewed spironolactone administration as well as shortly after (Table 3). Although ambulatory blood pressure readings had been normal,
A. Distler, H. J. Just and Th. Philipp
direct measurement of mean arterial pressure and of TPR revealed slightly elevated values
during spironolactone treatment. At 18 days after cessation of spironolactone therapy blood
pressure had increased again. At that time the raised blood pressure was mainly the result of a
rise in SVI and CI whereas TPR was even lower than during spironolactone therapy. Heart
rate was slow under the different conditions studied. Body weight was 79.5 kg at the first
study, 79.0 kg at the time of the study under spironolactone therapy and 80.7 kg 18 days after
cessation of treatment.

**Table 3.** Haemodynamic measurements in a patient with primary aldosteronism (patient 6) 48 days after
cessation of spironolactone therapy, during renewed spironolactone therapy and 18 days after withdrawal
of spironolactone

<table>
<thead>
<tr>
<th></th>
<th>At 48 days after cessation of</th>
<th>At 4 weeks after start of</th>
<th>At 18 days after cessation of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>spironolactone therapy (400 mg/day)</td>
<td>renewed spironolactone therapy (400 mg/day)</td>
<td>spironolactone therapy</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>123</td>
<td>112</td>
<td>127</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>51</td>
<td>53</td>
<td>55</td>
</tr>
<tr>
<td>Cardiac index (l/min per m²)</td>
<td>1.82</td>
<td>2.66</td>
<td>3.50</td>
</tr>
<tr>
<td>Stroke volume index (ml/beat per m²)</td>
<td>35.7</td>
<td>50.3</td>
<td>64.3</td>
</tr>
<tr>
<td>Total peripheral resistance (dyn s cm⁻⁵)</td>
<td>2800</td>
<td>1800</td>
<td>1596</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Although in some respects our observations are limited, a fairly consistent pattern was ap-
parent. In the chronic phase of aldosterone-induced hypertension (patients 1–3) TPR was found
to be elevated. This is in agreement with previous reports on haemodynamics in primary
aldosteronism (Frohlich et al., 1969; Marsen et al., 1971). Stroke volume and cardiac output
were normal. Similar values were found in patient 6, who was first studied 48 days after
previous normalization of blood pressure with spironolactone (Table 3).

A different haemodynamic state was observed in those patients whose blood pressure had
completely normalized under spironolactone and who were studied shortly after withdrawal
of the drug (patients 4 and 5). In these subjects the rise in blood pressure following cessation
of spironolactone therapy resulted from an increase in cardiac output while TPR was normal
(Table 2). The increase in cardiac output resulted from augmented stroke volume; heart rate
was normal in both cases. These latter findings suggested that the new rise in blood pressure
following termination of spironolactone therapy was caused by an increase in cardiac output
while in the chronic stage hypertension was maintained by an elevated TPR. This assumption
was supported by repeated studies before, during and at different time-intervals after cessation
of spironolactone treatment (Fig. 1; Table 3).

It remains doubtful whether the maximal increase in stroke volume after cessation of spir-
onolactone therapy was documented. Since no patient was studied earlier than 10 days after
treatment had ended, the possibility has to be taken into consideration that stroke volume
may have been higher within the first days after withdrawal of spironolactone.
Mechanism of aldosterone-induced hypertension

The increase in stroke volume observed after cessation of spironolactone therapy may be explained as follows: aldosterone excess produces a positive salt and water balance after spironolactone treatment has ended. This was manifested by an increase in weight, in exchangeable sodium, in extracellular fluid volume and in plasma volume (Fig. 1). Increased circulating blood volume enhances venous return and thereby augments cardiac filling pressure and cardiac performance (Borst & Borst-de Geus, 1963). A direct positive inotropic effect of aldosterone (Tanz, 1962) has also to be taken into account. Our studies, however, do not clarify this point.

It appears likely that the effects of aldosterone excess after cessation of spironolactone therapy are similar in principle to those at the onset of aldosterone overproduction. The results obtained shortly after withdrawal of spironolactone therefore suggest that in the early phase of aldosterone-induced hypertension stroke volume and cardiac output are likewise increased while TPR is still normal.

Haemodynamic changes similar to those we have found in aldosterone-induced hypertension have been described in other forms of salt- and water-dependent hypertension. Coleman & Guyton (1969) demonstrated in dogs that hypertension can be induced by administration of iso-osmotic saline after partial nephrectomy. In this type of experimental hypertension stroke volume and cardiac output are increased in the early phase while elevated TPR accounts for the raised blood pressure later on. In nephrectomized patients, while on inadequate dialysis, hypertension develops likewise due to augmented cardiac output, but then TPR rises while cardiac output returns to normal (Bower & Coleman, 1969).

Uncertainty remains regarding the mechanism underlying the rise in TPR. It has been suggested that the initial rise in cardiac output elicits a secondary autoregulatory response in the tissues to increase TPR (Freis, 1960; Ledingham & Cohen, 1964; Conway, 1966; Coleman & Guyton, 1969; Guyton, Coleman, Bower & Granger, 1970). Autoregulatory responses, however, are known to occur within seconds, while the rise in TPR in our patients, as well as in other forms of salt- and water-dependent hypertension, requires days. Resetting of baroreceptors, normally observed a few days after chronic elevation of blood pressure (McCubbin, Green & Page, 1956), may be an important factor. This would result in increased sympathetic tone which might account for the increase in TPR. There is no evidence, however, that this mechanism might be operative. Sympathetic tone has been described as diminished rather than increased in aldosterone-induced hypertension (Biglieri & McIlroy, 1966; Distler, Barth, Liebau, Vecsei & Wolff, 1970). Another possible explanation for the rise in TPR would be an increased content in the blood vessel walls of water and salt as has been described in various kinds of experimental hypertension (Tobian & Binion, 1952; Tobian, Olson & Chesley, 1969). The excess could act mechanically by engorging the vessel walls.

Because of the small number of observations in our study no firm conclusions can be drawn. Although limited, our findings suggest, however, that the initial step in aldosterone-induced hypertension is a rise in cardiac output. This may be an important factor for the final elevation of TPR.

ACKNOWLEDGMENTS

We should like to thank Professor Lommer for estimations of aldosterone secretion rates; Professor Fischer's department for blood-volume determinations; Dr W. Stahlhofen and Dr Werner for estimation of exchangeable sodium; and Professor Kümmerle for surgical collaboration. This work was supported by the Deutsche Forschungsgemeinschaft (SFB 36).
REFERENCES


