Abnormalities of Renal Function and Circulatory Reflexes in Primary Aldosteronism

By Edward G. Biglieri, M.D., and Malcolm B. McIlroy, M.D.

In patients with autonomic insufficiency, rapid intravenous infusion of an isotonic solution of sodium chloride results in abnormally rapid renal excretion of both sodium and water. An identical renal response to intravenous infusion of saline solution was obtained in a preliminary study of two patients with primary aldosteronism. In subsequent investigations of hyperaldosteronism of renal and adrenal origin, determinations of arterial pressure during Valsalva's maneuver showed an absence of hypertensive "overshoot" after release of intrathoracic pressure in the group with primary aldosteronism. These observations led us to undertake a more detailed investigation of the renal response to salt loading and the circulatory reflex reactivity of the patients with adrenal adenomas. The results of studies carried out before and after surgical removal of the tumor and of additional preoperative studies in three patients before and after potassium repletion are described in this report.

Clinical Data

The study group consisted of nine patients with primary aldosteronism, eight of whom have been described in detail previously. The pertinent clinical and laboratory data are summarized in table 1. The criteria for diagnosis were the presence of hypertension, hypokalemic alkalosis, and increased urinary excretion of aldosterone. Hypokalemia was present in all patients; two patients had a long history of weakness and potassium depletion. One patient was normovolemic; in the other eight, total blood volume ranged from 10 to 40 per cent above "predicted" normal volumes calculated on the basis of height and weight. Significant nocturia was a symptom of all patients. In all cases, the abnormalities disappeared or became less severe after surgical removal of an adrenocortical adenoma. A decrease in blood pressure was a consistent finding after the operation, although five of the nine patients remained slightly hypertensive.

Methods

Renal studies were carried out on five of the nine patients 4 to 8 weeks preoperatively and 6 to 10 weeks postoperatively. Circulatory reflex reactivity was tested in six of the patients at approximately the same intervals. In additional preoperative studies in two cases, renal function and circulatory reflex tests were performed before and after the addition of potassium chloride, 8 to 12 Gm. daily, to the diet for 1 week. In the ninth patient, circulatory reflex tests were carried out before and after administration of spironolactone, 1 Gm. daily, for 3 days.

All hypertensive medications were discontinued 3 or more weeks before the patients were studied; four of the group had never been treated for hypertension. To avoid the effect of variations in salt intake, studies were carried out after the patient had received a diet containing 110 mEq. of sodium chloride daily for at least 1 week.

The renal response to salt loading was studied after the patient had fasted overnight. After control specimens of urine had been collected via catheter, 3 liters of sodium chloride solution were infused at a rate of 50 ml. per minute for 60 minutes, as described previously. Glomerular filtration rates were established by inulin clearance. Urinary sodium levels were determined by internal standard flame photometry.

Circulatory reflex reactivity was studied by measuring the response of arterial pressure and pulse rate during a number of test conditions, according to the technic of Sharpey-Schafer. Systemic arterial pressure was recorded continuously by means of a catheter inserted into a brachial artery and connected to a strain-gauge held at the levels of the sternal angle. Pulse rate was determined from the arterial pressure tracing. Measurements of arterial pressure and pulse rate...
### Table 1

Clinical and Laboratory Data in Nine Patients with Primary Aldosteronism

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex, age (yr.)</th>
<th>State*</th>
<th>Serum electrolytes</th>
<th>Blood pressure (mm Hg)</th>
<th>Urinary aldosterone (μg/24 hr.)</th>
<th>Total blood volume (L.)</th>
<th>Insulin clearance Control</th>
<th>Insulin Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>B</td>
<td>150 1.9 95.0 36.0</td>
<td>178/116</td>
<td>30</td>
<td>4.65</td>
<td>90 132</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>B</td>
<td>138 4.5 103.0 29.0</td>
<td>160/100</td>
<td>3</td>
<td>3.95</td>
<td>73 85</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>B</td>
<td>138 4.3 104.7 24.5</td>
<td>174/110</td>
<td>38</td>
<td>4.2</td>
<td>131 152</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>B</td>
<td>149 4.2 92.8 30.1</td>
<td>220/140</td>
<td>100</td>
<td>3.32</td>
<td>90 104</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>B</td>
<td>146 3.2 95.5 34.3</td>
<td>168/96</td>
<td>55</td>
<td>3.72</td>
<td>65 132</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>B</td>
<td>136 4.9 98.6 27.6</td>
<td>145/90</td>
<td>56</td>
<td>4.59</td>
<td>68 84</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>B</td>
<td>147 2.6 94.4 39.8</td>
<td>170/100</td>
<td>60</td>
<td>4.30</td>
<td>60 120</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>B</td>
<td>142 4.9 99.5 29.1</td>
<td>210/120</td>
<td>28</td>
<td>4.65</td>
<td>72 82</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>B</td>
<td>139 5.2 102.0 27.4</td>
<td>160/90</td>
<td>15</td>
<td>3.72</td>
<td>58 70</td>
<td></td>
</tr>
</tbody>
</table>

*B, before operation or potassium repletion; A, after operation; K, after potassium repletion.
were made during a standard test procedure in the following sequence: (1) the Valsalva maneuver, with mouth pressure held at 40 mm. Hg for 10 seconds, while the patient was standing; (2) alternate 30-second periods of squatting and standing; (3) the Valsalva maneuver, as described, while the patient was lying down; (4) mental arithmetic for 30- to 60-second periods, during which the patient was successively asked to subtract either 7 or 9 from a number between 90 and 100; attempts were made to hurry the answers; (5) a “cold pressor test,” consisting of immersing one of the patient’s hands in ice-cold water for 1 minute; (6) inhalation of amyl nitrite (four sniffs from a freshly opened ampule); (7) continuous infusion of norepinephrine, in amounts that were increased every 2 minutes until systolic or diastolic pressure had risen 20 mm. Hg or more above the control value.

Control measurements were made while the patient was recumbent and resting. Since the results of the test procedures vary in normal subjects of different ages, each patient served as his own control.

Results
Renal Responses to Saline Infusions

Before and after operation. The results of infusion of isotonic saline solution in the five patients tested are shown in figure 1 and table 1. Preoperatively, the infusions resulted in prompt diuresis and natriuresis and an increase in glomerular filtration rate averaging 52 per cent above control values. Urinary excretion of sodium ranged from 2,500 to 4,500 μEq. per minute and urinary flow from 25 to 40 ml. per minute. These changes reached a maximum during the last 10 to 15 minutes of the infusion period.

After the operation, a slight decrease in control inulin values was noted in four of the five patients. The postoperative infusions of saline solution were followed by minimal increases in urinary flow and sodium excretion. The average increase in glomerular filtration rate was only 17 per cent above control values.

Before and after potassium replacement. In preoperative studies on two patients before and after dietary addition of potassium, the results were similar to those obtained after the operation. In both patients, the abnormal renal response to saline infusions was corrected by administration of potassium chloride (fig. 2).

![Figure 1](http://circ.ahajournals.org/)

**Figure 1**

Response to intravenous infusion of isotonic sodium chloride solution in five patients with primary aldosteronism before and after surgical removal of an adrenal adenoma.
PRIMARY ALDOSTERONISM

Figure 2

Response to intravenous infusion of isotonic sodium chloride preoperatively in two patients with primary aldosteronism after dietary potassium repletion.

Circulatory Reflex Reactivity

Before and after operation. The results of tests before and after removal of an adrenal adenoma are shown in figures 3 and 4 and table 2. Preoperatively, impairment of circulatory reflex reactivity was demonstrable in all cases. The most marked abnormalities were shown by the two patients with hypokalemia and weakness of long duration (cases 4 and 7, table 1). The responses obtained in the postoperative studies showed a return to more normal reflex reactivity. In two cases, tests repeated 2 months after the operation showed no further changes.

The representative responses to Valsalva's maneuver in various positions in three of the six patients tested is shown in figure 3. Preoperatively, the hypertensive overshoot in arterial pressure and the reflex bradycardia seen normally after release of intrapulmonary pressure was minimal (four cases) or absent. Both systolic and pulse pressures decreased during the maneuver. Since the stimulus to the baroreceptor mechanism is greater during standing than during recumbency, the fall in systolic and pulse pressures was greater when the patient was standing than when he was lying down. Postoperatively, the overshoot after Valsalva's maneuver approached normal (fig. 3).

Changes in posture. In the five patients tested, preoperative arterial pressure tracings

Figure 3

Representative response to the Valsalva maneuver in three patients with primary aldosteronism before and after surgical removal of an adrenal adenoma.
During alternate periods of squatting and standing (fig. 4) showed no evidence of a reflex response to the rise in pressure on squatting. Postoperatively, the tracings showed bradycardia on squatting and tachycardia on standing, as is seen in normal subjects.9

The average systolic and diastolic pressures and pulse rate in the five patients during recumbency (control) and standing are compared in table 2. As shown, the blood pressure did not return to normal levels, either before or after the operation, while the patients were standing. Preoperatively, the average systolic and diastolic pressures during standing were less by 27 and 9 mm. Hg, respectively, than the control values, and the pulse rate was increased an average of 11 beats per minute. Postoperatively, the reflex responses to standing were more normal. The average pulse rate during standing was increased by 24 beats per minute, although the average systolic pressure was only 14 mm. Hg less than the control value and diastolic pressure rose an average of 5 mm. Hg.

Other tests. The response of the five patients to all other tests also indicated impairment of circulatory reflex reactivity preoperatively and small but definite increases in reactivity postoperatively (table 2). Before the operation both arterial pressure and pulse rate rose during mental arithmetic and the cold pressor test. Because of the fall in blood pressure after removal of the adrenal adenoma, the application of these stimuli in postoperative tests resulted in relatively greater rises in pressure. During inhalation of amyl nitrite, blood pressure decreased and heart rate in-
creased preoperatively. Postoperatively, the decrease in blood pressure was less than before the operation; however, the increase in heart rate was greater. Both before and after the operation, infusion of norepinephrine at a rate of 9 \( \mu \text{g} \) per minute was required to effect a rise of 20 mm. Hg or more in blood pressure and a decrease in pulse rate. Postoperatively, infusion of the same amount of norepinephrine at the same rate resulted in a greater increase in arterial pressure and a greater decrease in pulse rate.

After potassium repletion. The results of circulatory reflex tests carried out preoperatively on three patients after administration of potassium or spironolactone were similar to those obtained postoperatively. In all three, circulatory reflex responses showed a return to near normal reactivity. The response of the blood pressure and pulse rate during the standing Valsalva maneuver in the patient treated with spironolactone is illustrated in figure 5. As shown, hypertensive overshoot and bradycardia occurred only after potassium repletion. The results of other tests of circulatory reflex reactivity before and after potassium repletion are shown in table 3.

![Figure 5](http://circ.ahajournals.org/)

**Figure 5**

Response to the Valsalva maneuver in a preoperative test on a patient with primary aldosteronism after potassium repletion by administration of spironolactone.

**Discussion**

The absence of hypertensive overshoot after the Valsalva maneuver and the abnormal responses to changes in posture provided definite evidence of impairment of circulatory reflex activity in the patients with primary aldosteronism. In the four cases in which both renal function and circulatory reflexes were

| Table 3 |

**Results of Circulatory Reflex Studies in Three Patients with Primary Aldosteronism before and after Potassium Replacement**

<table>
<thead>
<tr>
<th>Test*</th>
<th>Mean blood pressure (mm. Hg)</th>
<th>Pulse rate (beats/min.)</th>
<th>Mean blood pressure (mm. Hg)</th>
<th>Pulse rate (beats/min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before replacement</td>
<td></td>
<td>After replacement</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>208</td>
<td>110</td>
<td>82</td>
<td>193</td>
</tr>
<tr>
<td>Standing</td>
<td>190</td>
<td>108</td>
<td>94</td>
<td>182</td>
</tr>
<tr>
<td>Difference</td>
<td>-18</td>
<td>-2</td>
<td>+12</td>
<td>-11</td>
</tr>
<tr>
<td>Control</td>
<td>195</td>
<td>105</td>
<td>78</td>
<td>195</td>
</tr>
<tr>
<td>Mental arithmetic</td>
<td>205</td>
<td>112</td>
<td>82</td>
<td>213</td>
</tr>
<tr>
<td>Difference</td>
<td>+10</td>
<td>+7</td>
<td>+4</td>
<td>+18</td>
</tr>
<tr>
<td>Control</td>
<td>195</td>
<td>102</td>
<td>76</td>
<td>190</td>
</tr>
<tr>
<td>Cold pressor test</td>
<td>223</td>
<td>122</td>
<td>84</td>
<td>221</td>
</tr>
<tr>
<td>Difference</td>
<td>+28</td>
<td>+20</td>
<td>+8</td>
<td>+31</td>
</tr>
<tr>
<td>Control</td>
<td>200</td>
<td>108</td>
<td>81</td>
<td>193</td>
</tr>
<tr>
<td>Amyl nitrite inhalation</td>
<td>128</td>
<td>58</td>
<td>103</td>
<td>131</td>
</tr>
<tr>
<td>Difference</td>
<td>-72</td>
<td>-50</td>
<td>+22</td>
<td>-62</td>
</tr>
<tr>
<td>Control</td>
<td>200</td>
<td>105</td>
<td>72</td>
<td>192</td>
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<tr>
<td>Norepinephrine infusion†</td>
<td>222</td>
<td>118</td>
<td>67</td>
<td>233</td>
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<tr>
<td>Difference</td>
<td>+22</td>
<td>+13</td>
<td>-5</td>
<td>+41</td>
</tr>
</tbody>
</table>

*Control values were obtained while patients were recumbent and quiet.
†At a rate of 9 \( \mu \text{g} \) per minute.

_Circulation, Volume XXXIII, January 1966_
studied, the results indicated a temporal relationship; the responses to salt loading and tests of reflex reactivity returned to normal or near normal at about the same time after the operation. Repetition of the reflex tests in two cases 2 months later showed no further changes. In all cases nocturia also disappeared shortly after the operation, suggesting that this symptom might be related in some way to the abnormalities of renal function and reflex reactivity.

The relationship of both the reflex and renal abnormalities to the hypertensive state is not clear. Several clinical and experimental investigations have been concerned with circulatory reflex activity in hypertension. In patients with essential hypertension, the response to the cold pressor test is abnormally great.\(^\text{10}\) In hypertensive rats, the reflexes involving the aortic and carotid baroreceptors are normal.\(^\text{11}\) A normal response to the Valsalva maneuver was reported in two patients with severe hypertension of renal origin and secondary hyperaldosteronism;\(^\text{4}\) one of these patients had hypokalemia, as well as hyperaldosteronism and hypertension, all of which were present in our patients preoperatively.

In patients with essential hypertension, intravenous infusion of saline solution is followed by increased excretion of sodium chloride but no change in glomerular filtration rate.\(^\text{12}\) Ortuizár and associates,\(^\text{13}\) however, reported a decrease in the excretion of infused saline after administration of ganglion-blocking agents in hypertensive patients and in one patient with primary aldosteronism. In our patients, postoperative studies showed limited excretion of salt loads, similar to that found in normal subjects, yet two of the five patients tested were still hypertensive at the time. In preoperative tests on our patients, the rapid excretion of sodium chloride after infusion of saline solution appeared to be related, at least in part, to increases in glomerular filtration rate and filtered load of sodium, as is seen characteristically in patients with autonomic insufficiency.\(^\text{1}\) This lability of glomerular filtration rate and prompt excretion of infused sodium chloride solutions does not occur in normal subjects. According to Gill, Mason, and Bartter,\(^\text{14}\) however, normal subjects treated with ganglion-blocking agents to abolish the hypertensive overshoot following the Valsalva maneuver rapidly excrete such salt loads.

Circulatory reflex responses are also affected by ganglion-blocking agents, as well as by other drugs such as reserpine, chlorothiazide, monoamine oxidase inhibitors, and certain tranquilizers.\(^\text{15}, \text{16}\) The effect of drugs would not account for the abnormal responses in our patients, however, since all antihypertensive medications were withdrawn at least 3 weeks before the studies; in addition, four patients had never been treated.

The impairment of circulatory reflex function in the patients with primary aldosteronism was not so severe as that found in tabes dorsalis,\(^\text{7}\) diabetes mellitus,\(^\text{17}\) or idiopathic postural hypotension.\(^\text{18}\) None of the patients had symptoms of autonomic insufficiency, with the possible exception of nocturia, and in no case did blood pressure fall to normal levels with change in posture to the standing position. The failure of postural changes to produce noticeable variations in blood pressure might be related to hypervolemia, which was present in eight of the nine patients.

In an attempt to localize the site of the reflex abnormalities in our patients, a number of tests were used to assess circulatory reflex function. Both the response to central nervous stimuli, such as mental arithmetic\(^\text{7}\) and local cold,\(^\text{19}\) and the response of the aortic and carotid baroreceptors during the Valsalva maneuver and postural changes were tested. The generalized depression of response to both types of test indicate that in patients with primary aldosteronism the lesion does not lie in the afferent pathways, as it does in tabes dorsalis and diabetes mellitus.\(^\text{7}, \text{17}\)

Interpretation of the results in our patients, however, is complicated by the fall in blood pressure that occurred in all cases after removal of the adrenal adenoma. If the increase or decrease in pressure and pulse rate during each test (tables 2 and 3) were expressed as percentage changes rather than as absolute
changes in millimeters of mercury, the responses to mental arithmetic, the cold pressor test, and infusion of norepinephrine would appear greater in magnitude and the responses to postural changes and inhalation of amyl nitrite would appear smaller in magnitude. Expression of the results in this fashion, however, would not greatly alter their significance. In addition, the normal range of variability of circulatory function is not well defined. In three of the six patients tested, the abnormal responses became apparent only when the results of the preoperative and postoperative studies were compared (table 2).

The most marked abnormalities in circulatory reflex responses were in the two patients who had a long history of weakness and potassium depletion. To our knowledge, impairment of circulatory reflexes has not been observed in association with weakness and prostration, although both are symptoms of potassium depletion.\(^{20}\) The results obtained in three cases after potassium repletion also suggest that hypokalemia plays an important part in the production of both renal and circulatory reflex abnormalities. Conflicting data, however, were obtained in a study of two normal subjects after administration of large doses of salt-retaining hormones for 21 days.\(^{8}\) This treatment resulted in considerable hypervolemia, and the response to the Valsalva maneuver became "square wave"\(^{21}\) in type; no circulatory reflex abnormalities could be demonstrated, however, and the renal response to sodium chloride infusions remained normal. Similar results were obtained after potassium depletion had been produced in one of the subjects by infusion of mannitol. The inability to produce renal and reflex abnormalities in these subjects may have been attributable to the failure to induce hypotension and the mild degree and short duration of potassium depletion. In their studies of potassium-deficient rats, Friedman, Freed, and Rosenman\(^{22}\) found impaired peripheral vascular reactivity, which they attributed to a functional defect in the peripheral arterioles occasioned by potassium deficit. The reversible abnormal responses to all tests of circulatory reflex reactivity in our patients suggest a less reactive vascular system and less effective cardio-accelerator impulses in patients with aldosterone-secreting tumors.

It remains difficult to link the abnormalities of the autonomic nervous system with the observed renal changes. The rapid excretion of sodium chloride loads is not specific to the hypertensive state associated with primary aldosteronism, but the mechanism may be different from that in hypertension from other causes. The increase in glomerular filtration rate was a constant finding in the patients studied. Restoration of more normal circulatory reflex responses after potassium replacement preoperatively in three patients was associated with failure to increase sodium excretion during rapid infusion of sodium chloride, supporting the concept that some relationship between these phenomena may exist. Both chronic potassium depletion and hypertension appear to be necessary to effect the observed results. The nature of the relationship between the autonomic nervous system and renal function in primary aldosteronism, however, remains obscure.

Summary

The renal response to intravenous administration of isotonic saline solution and circulatory reflex reactivity was studied in nine patients with primary aldosteronism before and after surgical removal of an adrenal adenoma. In preoperative tests, infusion of saline was followed by abnormally rapid renal excretion of sodium and water, such as occurs in patients with autonomic insufficiency. Circulatory reflex function was also abnormal in all patients; the most severe impairment was shown by two patients with hypokalemia and weakness of long duration. Postoperatively, both renal and circulatory reflex responses returned to normal or near normal. In preoperative tests on three patients, potassium repletion effect a similar correction of both renal and circulatory reflex abnormalities. The cause of these abnormalities in patients with primary aldosteronism is not known. Potassium depletion may be a factor, al-
though a general disturbance of autonomic cardiovascular function cannot be excluded.

Acknowledgment

The authors are indebted to Mary Anne Herron for technical assistance, to Mrs. Hisaye Mochizuki for dietary management, and to Professor Peter H. Forsham, Director of the Metabolic Research Unit, University of California School of Medicine, San Francisco, for his continued interest and encouragement.

References

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Circulation. 1966;33:78-86
doi: 10.1161/01.CIR.33.1.78

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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