Antidiuretic Action of the Urine of Patients in Cardiac Failure

By Bernard A. Bercu, M.D., Stanley N. Rokaw, M.D., and Edward Massie, M.D.

Stimulated by the increasing interest in the operation of antidiuretic principles and the recent development of new concepts of the mechanism of heart failure, this investigation was planned to study antidiuretic effects of the urine of patients with heart failure. It is noteworthy that an antidiuretic effect was induced in hydrated dogs by the intravenous injection of concentrated dialyzed urine of 12 of 15 patients with congestive heart failure. No such effect was exerted by urine from normal controls. Additional studies indicated that the antidiuresis could not be attributed to a substance with the characteristics of commercial Pitressin.

Increasing interest in the operation of antidiuretic principles in the normal and diseased organism has been stimulated by the recent writings of various investigators. Verney studied the production of acute antidiuresis in animals by noxious stimuli and by hypertonic intracarotid injections. He showed that liberation of posterior pituitary antidiuretic hormone is determined by the osmotic pressure of the arterial plasma. Robinson and Farr investigated the antidiuretic effects of urine from patients with acute nephritis, the nephrotic syndrome, and Cushing's syndrome, as well as other conditions. By using the rat assay method of Burn, they found an antidiuretic substance in the urine of these patients and correlated this with the presence of clinical edema. Ralli and co-workers found the presence of such a urinary factor in patients with cirrhosis, and Teel and Reid concerned themselves with its occurrence in eclampsia and pre-eclampsia. Others studied the finding of antidiuretic principles in the urine in acute hepatitis. Since the conventional explanation for the mechanism of cardiac failure has been challenged by many workers, the important report of Warren and Stead concerning their finding of diminution of renal flow and salt clearance in this condition inevitably produced widespread interest in and stimulated further investigation of all the possible etiologic factors. The concept of the kidney as a "key organ" in initiating the chain of events leading to the manifestations of cardiac failure is most intriguing, but the complexities governing water balance have to some extent interfered with adequate evaluation of this concept. It was thought important therefore, to investigate the presence of antidiuretic principles in the urine of normal individuals and of patients with congestive heart failure.

Procedure

Two normal mature female dogs weighing 15.8 Kg. and 12.2 Kg., respectively, were maintained in metabolism cages on daily horsemeat (2 pounds each), Purina chow, and water ad libitum. Perineotomy had been performed and healed before the experimental period to enable access to the urethra for indwelling catheters. The dogs were trained to spend long periods suspended in a canvas sling and evidenced no emotional disturbance at the procedures of hydration, intravenous injection, or catheter manipulation. The dogs were hydrated at the start of each experiment with tap water (35 cc. per Kg. of body weight introduced by stomach tube). The resultant urine output was collected directly into volumetric containers and measured at approximately four minute intervals. In preliminary experiments, in attempting to secure prolonged high level urine flows (3 to 4 cc. per minute), we had learned that a lag of thirty to fifty minutes might be expected between the time of ingestion of a given drink and the time of appearance of a diuresis increase, and that a falling off in the rate of flow from peak values after a single hydrating drink began between ninety and one hundred twenty minutes after ingestion. In addition it was found that smaller added drinks (1½ per cent of body weight), spaced in

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accordance with these observations, provided sustained diuresis at desired levels without causing regurgitation by the animals. When needed, such subsequent drinks of tap water were administered directly to the dogs without disturbance or removal from the sling.

Commercial Pitressin* (20 pressor units per cc.) was used as the bio-assay standard. This was freshly prepared during each experiment by dilution with physiologic (0.9%) saline to a concentration of 0.2 milliunits per cc. Intravenous administration of this substance produced antidiuretic effects in direct proportion to the dose given. Doses of 0.05 to 0.1 milliunits were sufficient to produce a significant drop in urine output when given to dogs in water diuresis. A graphic representation of this effect is seen in figure 1, where are shown the curve of diuresis of a normal dog (15.8 Kg.) in response to

the hydrating drink, and the curve of response when injections of Pitressin solution were given.

The test material was obtained by preparing urine of patients and of normal controls, collected over known periods (usually six to twelve hours) after the method of Ralli and associates. Tohoal as a preservative and sufficient 3% acetic acid to produce a pH between 6.0 and 6.5 were added. The entire sample was then evaporated by fan at room temperature within a twenty-four hour period to volumes between 80 and 100 cc. This was then dialyzed with agitation, for periods of six to twenty-four hours in casing containers against cold running tap water. The final volume was determined and after filtration through filter paper, a portion equivalent to a fifteen-minute urine output period was used as the test dose. This was usually between 1.5 and 4.0 cc. This test dose was given intravenously following recovery of urine flow to diuretic levels

from a preceding Pitressin dose. In some experiments (not shown in the figures), further injections of Pitressin were also given following the test injection, for evaluation of the reactivity of the animal to another known quantity of antidiuretic substance. No evidence was noted of untoward reaction, dyspnea, collapse, excitement, or other state which might be expected to influence urine production.

Urine specimens studied were secured from patients with chronic congestive failure and peripheral edema. Those with definite kidney diseases or independent liver diseases were excluded. Some patients had no preceding treatment with digitalis or mercurial diuretics; some had had digitalization but still presented definite evidence of decompensation; and others had had both therapeutic measures. Urine specimens from normal individuals were collected over measured intervals under normal conditions of hydration. In addition, Pitressin was added to some normal specimens which were then prepared in the usual manner.

RESULTS

In no instance did injection of physiologic saline or of urine from normal subjects produce an antidiuretic effect in dogs which had previously responded to Pitressin. Normal urine dialyzed after the addition of Pitressin would produce an antidiuretic effect only if large amounts (10 milliunits per cc.) of the drug had been added. No antidiuretic effect occurred after dialysis when the added Pitressin concentration was only 0.6 milliunit per cc. In figure 1 are shown the effects on the diuresis curve of fresh Pitressin, dialyzed normal urine and normal urine dialyzed after Pitressin addition (10 milliunits per cc.). It will be noted that both fresh and dialyzed Pitressin produced a fall in urine output of approximately equal amounts. Normal urine had no antidiuretic effect.

In table 1 are summarized the results obtained from the injection of urine from cardiac failure patients and the pertinent clinical data. A total of 15 patients were studied. The diagnoses included 7 of arteriosclerotic heart disease (ASHD), 5 of rheumatic heart disease (RHD), 5 of hypertensive heart disease (Hyp. H. D.), and 2 instances of cor pulmonale (Cor. Pulm.). One additional patient had cardiac failure of undetermined etiology. Five of the patients had multiple cardiac diagnoses.

Positive antidiuretic effects were obtained in

* Pitressin—Parke Davis Co.
† Visking $133—‘Nojax’ casing.
12 cases, while no antidiuretic effects were noted in the urines of 3 patients, as can be seen in table 1. An estimate, proportional to the "area" of oliguria induced, of the antidiuretic potency (in terms of milliliters of pitressin activity) contained in fifteen minutes of urine output from these patients, is shown in the last column of table 1. Figure 2 presents the effect on the diuresis curve of fresh Pitressin and the typical effects of positive urines from cases 8 and 12. In figure 3 can be seen the graded effects of increasing doses of positive urine from case 6. In each instance, a definite and prolonged antidiuretic effect was obtained.

**Discussion**

The results of this study established the occurrence of antidiuretic factors in the urine excreted by patients in congestive failure. The identification of the source of these factors in the body, and assessment of the roles played in the genesis of failure remain problems for future attention. Review of the reports of Verney, Pickford, deBodo, and others supports the idea of a posterior pituitary origin for such antidiuretic factors, while the research of Heinbecker and White, Walker, and others introduces the possibility of other mechanisms of water control. Shorr and others

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**TABLE 1.—Patients with Congestive Failure—Clinical Data and Antidiuretic Effect of Urine**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>B.P.</th>
<th>V.P.*</th>
<th>C.T.</th>
<th>Edema</th>
<th>Liver</th>
<th>Prior Therapy</th>
<th>Urine Effect</th>
<th>Equivalence of Pitressin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>M</td>
<td>RHD, Hyp.</td>
<td>170/105</td>
<td>190</td>
<td>30</td>
<td>1+</td>
<td>6 cm</td>
<td>None</td>
<td>pos.</td>
<td>0.4 m.u.</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>M</td>
<td>ASHD</td>
<td>120/80</td>
<td>195</td>
<td>33</td>
<td>3+</td>
<td>3</td>
<td>None</td>
<td>pos.</td>
<td>0.1 m.u.</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>F</td>
<td>Hyp. ASHD</td>
<td>170/120</td>
<td>—</td>
<td>—</td>
<td>3+</td>
<td>6+</td>
<td>Digit.</td>
<td>pos.</td>
<td>0.4 m.u.</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>M</td>
<td>Cor. Pul.</td>
<td>140/70</td>
<td>300</td>
<td>30</td>
<td>4+</td>
<td>6+</td>
<td>None</td>
<td>pos.</td>
<td>0.2 m.u.</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>F</td>
<td>ASHD</td>
<td>120/80</td>
<td>230</td>
<td>23</td>
<td>3+</td>
<td>4</td>
<td>Digit.</td>
<td>neg.</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>F</td>
<td>RHD</td>
<td>130/80</td>
<td>—</td>
<td>—</td>
<td>3+</td>
<td>6+</td>
<td>Digit.</td>
<td>pos.</td>
<td>0.1 m.u.</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>M</td>
<td>ASHD Hyp.</td>
<td>160/100</td>
<td>—</td>
<td>—</td>
<td>3+</td>
<td>4</td>
<td>Digit.</td>
<td>pos.</td>
<td>0.3 m.u.</td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>M</td>
<td>RHD</td>
<td>130/85</td>
<td>—</td>
<td>35</td>
<td>2+</td>
<td>7</td>
<td>None</td>
<td>pos.</td>
<td>0.5 m.u.</td>
</tr>
<tr>
<td>9</td>
<td>59</td>
<td>M</td>
<td>ASHD Cor. Pul.</td>
<td>115/80</td>
<td>—</td>
<td>—</td>
<td>4+</td>
<td>4</td>
<td>Digit.</td>
<td>neg.</td>
<td>—</td>
</tr>
<tr>
<td>10</td>
<td>72</td>
<td>M</td>
<td>ASHD</td>
<td>130/60</td>
<td>210</td>
<td>40</td>
<td>2+</td>
<td>4</td>
<td>Digit.</td>
<td>pos.</td>
<td>0.3 m.u.</td>
</tr>
<tr>
<td>11</td>
<td>48</td>
<td>M</td>
<td>? etiol.</td>
<td>115/95</td>
<td>270</td>
<td>50</td>
<td>3+</td>
<td>6+</td>
<td>Digit. NH4CL</td>
<td>pos.</td>
<td>0.6 m.u.</td>
</tr>
<tr>
<td>12</td>
<td>49</td>
<td>F</td>
<td>Hyp.</td>
<td>200/125</td>
<td>—</td>
<td>—</td>
<td>4+</td>
<td>6</td>
<td>Digit.</td>
<td>pos.</td>
<td>1.4 m.u.</td>
</tr>
<tr>
<td>13</td>
<td>70</td>
<td>M</td>
<td>Hyp. ASHD</td>
<td>180/125</td>
<td>270</td>
<td>—</td>
<td>4+</td>
<td>6</td>
<td>None</td>
<td>neg.</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>39</td>
<td>F</td>
<td>RHD</td>
<td>116/78</td>
<td>—</td>
<td>30</td>
<td>4+</td>
<td>7+</td>
<td>Digit. Mercur.</td>
<td>pos.</td>
<td>0.4 m.u.</td>
</tr>
<tr>
<td>15</td>
<td>16</td>
<td>F</td>
<td>RHD</td>
<td>105/80</td>
<td>—</td>
<td>—</td>
<td>4+</td>
<td>3</td>
<td>Digit. Mercur.</td>
<td>pos.</td>
<td>1.5 m.u.</td>
</tr>
</tbody>
</table>

* Venous pressure in mm. saline
† Circulation time in seconds, arm to tongue (Decholin)
‡ Ascites present
m.u. signifies milliunits

**Fig. 2.** The antidiuretic effect of fresh Pitressin (A), and prepared urine from case 8 (B) and case 12 (C). Dog weight, 15.8 Kg.

**Fig. 3.** The antidiuretic effect of increasing amounts of urine injected. 1.6 cc. given (C) produced about twice the effect of 0.8 cc. (B). Dog weight, 15.8 Kg.
have given evidence of one such source in the liver.

We cannot identify the effective substance in "cardiac failure" urine as a posterior pituitary principle. Previous investigators\(^2\) with Pitressin had reported that it dialyzed through membranes of the type used, the residual solution having decreased potency. We can report similar experience with commercial Pitressin. Figure 4 depicts our results with injections of Pitressin, freshly diluted and following dialysis. When dialyzed, an increase in the concentration of 100 times or more was necessary to produce the threshold responses obtainable with 0.1 milliunits of nondialyzed Pitressin. The substance contained in cardiac failure urine, however, apparently lost no potency through the preparation and dialyization process, nor did filtration remove the active principles. Although these methods of preparation of urine have been recently challenged,\(^3\) it would appear that the effective substance is not identical with commercial Pitressin.

The question of the role of these substances in the development of cardiac failure is even more difficult to clarify. Many observers have indicated that in cases of congestive failure, there is a disturbance of the normal metabolism of electrolytes and water leading to sodium retention and ensuing increased fluid volume.\(^7\)\(^,\)\(^8\)\(^,\)\(^9\)\(^,\)\(^20\)\(^,\)\(^21\) Investigation of the effect of cardiac failure urine containing antidiuretic substances on sodium excretion by the test animal is contemplated.

The evidence presented here strongly indicates the occurrence of an antidiuretic substance or substances in the urine of some patients with cardiac failure, which may be important in the retention of fluid in this condition. To the list of clinical syndromes in which antidiuretic substances have previously been reported, namely cirrhosis,\(^3\) acute hepatitis,\(^20\) nephrotic edema,\(^2\) acute hemorrhagic nephritis,\(^2\) eclampsia and other toxemias of pregnancy,\(^4\) Cushing’s syndrome,\(^2\) premenstrual edema,\(^2\) dehydration,\(^12\) and hypertension,\(^33\) congestive failure may well be added.

**Summary**

1. An antidiuretic effect was induced in hydrated dogs by the intravenous injection of concentrated dialyzed urine of 12 of 15 patients with congestive heart failure. No such effect was exerted by urine of normal controls.

2. Evidence was obtained that the antidiuresis could not be attributed to a substance with the characteristics of commercial Pitressin.

**Acknowledgments**

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