Relation of the Renin-Angiotensin-Aldosterone System to Clinical State in Congestive Heart Failure

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SUMMARY The status of the renin-angiotensin-aldosterone system (RAAS) in congestive heart failure (CHF) varies in many reports, in part because of the heterogeneity of the clinical status of the patients studied. To relate the RAAS to clinical state, we studied 23 patients with severe CHF (New York Heart Association functional classes III-IV): five had recent onset of severe pump failure with pulmonary edema (group 1), nine had recent cardiac decompensation superimposed on chronic CHF (group 2) and nine had chronic stable CHF (group 3). The severity of cardiac dysfunction in patients in group 3 was comparable to that in the other two groups (cardiac index, 1.6 ± 0.2 l/min/m²; ejection fraction, 19.3 ± 3%). Pulmonary wedge pressure was similar in all groups (29 ± 3, 28 ± 2 and 29 ± 5 mm Hg). Groups 1 and 2 had reduced mean blood pressure (71 ± 4 and 79 ± 4 mm Hg), increased plasma renin activity (PRA) (65 ± 12 and 29 ± 4 ng A 1/ml/hour), plasma aldosterone (117 ± 19 and 59 ± 11 ng/dl) and serum creatinine (2.5 ± 0.5 and 3.0 ± 0.3 mg/dl). Serum sodium concentration was reduced only in group 2 (131 ± 2 mEq/l). These variables were normal in group 3. PRA and mean systemic blood pressure were inversely correlated in all patients (r = -0.48, p < 0.05), as were PRA and serum sodium concentration in patients in groups 2 and 3 (r = -0.51, p < 0.05). In four patients in group 2 who were followed longitudinally, PRA fell from 13.5 ± 1.3 to 3.9 ± 1.0 ng/ml/hour, plasma angiotensin II level from 177 ± 76 to 25 ± 11 pg/ml as their CHF was stabilized. In nine patients with an acute, apparently uncomplicated myocardial infarction, PRA was normal (5.0 ± 2.1 ng/ml/hour). The RAAS is markedly activated during decompensated cardiac failure but returns to normal with stabilization, even though evidence for severe cardiac dysfunction persists. A major stimulus for the activation of the RAAS in acute decompensation appears to be a decrease in systemic blood pressure associated with a decrease in cardiac output.

Among the homeostatic mechanisms activated when the heart fails as a pump, an increase in peripheral vascular resistance and expansion of the extracellular fluid volume secondary to salt and water retention are prominent. The contribution of the renin-angiotensin-aldosterone system (RAAS) to these two responses, and thus the pathogenesis of the clinical syndrome, is not known. Elevations in plasma renin activity (PRA) and aldosterone concentration in subjects with congestive heart failure have not been consistently observed.1-9 The severity of congestive heart failure ranges from early mild congestive failure to chronic compensated failure and to acute severe decompensation. Most studies have not defined the clinical status of the patients or have ignored the potential for compensation. Recent experimental studies in conscious animals with cardiac failure have suggested that the RAAS is activated early, during the acute phase after induction of low cardiac output.10-13 During the chronic compensated state of experimental heart failure, PRA and plasma aldosterone concentration (PAC) decrease toward normal as the extracellular fluid volume expands.10, 13 Thus, the discrepancies in the state of the RAAS in the clinical literature may in part be due to a lack of clear definition of the clinical status of the patients studied. To assess this possibility, we studied the activity of the RAAS in three well-defined groups of patients with severe congestive heart failure: those with acute severe decompensated cardiac failure, those with chronic failure with recent decompensation, and those with chronic stable congestive failure. PRA and PAC were determined in 23 such patients, four of whom were studied longitudinally during decompensation and as they achieved the chronic stable state.

Materials and Methods

We studied 23 patients (21 males and two females) who were admitted to the Intensive Care Unit or the medical wards of the Peter Bent Brigham Hospital. The patients were 32-74 years old (mean 58 years). The etiology of cardiac failure included ischemic heart disease in 11 patients (four with recent myocardial infarction), nonischemic cardiomyopathy in 10 patients, acute myocarditis in one patient and acute rupture of chordae tendineae in one patient (table 1). The patients were arbitrarily divided into three groups: five who had severe uncompensated pump failure of recent onset (less than 1 week) with pulmonary edema but no peripheral edema (group 1), nine who had recent progressive cardiac decompensation (less than 1 week) superimposed on a history of chronic failure (greater than 1 year) with peripheral edema or ascites (group 2), and nine who had chronic, stable, advanced heart failure (greater than 1 year) and were ambulatory (group 3). None of these patients had a history of hypertension or intrinsic renal disease. The mean serum creatinine level on admission was 1.7 mg/dl,
and urinary sediment was normal in all, as were renal contour and size in six patients who had plain abdominal radiography.

All patients in groups 1 and 2 had suffered recent severe cardiac decompensation (with or without a history of chronic congestive heart failure) that necessitated emergency admission for cardiovascular monitoring (including the placement of Swan-Ganz catheters) and therapy. Because of the severity of their illness, all patients in these two groups were bedridden; salt and water intake were restricted to minimal i.v. replacement of about 1.1 of 5% dextrose in half-normal saline daily.

Group 3 consisted of patients with chronic severe congestive failure (mean New York Heart Association functional class = 3.8) who were admitted to the medical wards for further evaluation and therapy. All patients had variable degrees of peripheral edema and were receiving digitalis and diuretics. Cardiac function was evaluated in these patients by left- or right-heart catheterization, radionuclide ventriculography and cardiac echocardiography. They were placed on a 1-g sodium diet.

PRA and angiotensin II levels were determined in two additional groups. In four of the patients with chronic congestive heart failure, studies were performed during an acute decompensation and again when they were stable in the chronic compensated state. Because acute myocardial ischemia complicated the course of many of the patients in groups 1 and 2, we also examined the PRA of nine patients selected at random from among patients with an uncomplicated acute myocardial infarction.

The protocol was approved by the Human Subjects Committee of the Peter Bent Brigham Hospital and the Harvard Medical School. The patients and their

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### Table 1. Clinical and Hemodynamic Profile of the Study Patients

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>NYHA class</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Pulmonary capillary wedge pressure (mm Hg)</th>
<th>Cardiac index (l/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>M</td>
<td>CAD</td>
<td>IV</td>
<td>67</td>
<td>18</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>M</td>
<td>Acute rupture chordae</td>
<td>IV</td>
<td>68</td>
<td>35</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>M</td>
<td>CAD</td>
<td>IV</td>
<td>67</td>
<td>28</td>
<td>1.75</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>M</td>
<td>CAD</td>
<td>IV</td>
<td>67</td>
<td>30</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>F</td>
<td>CAD</td>
<td>IV</td>
<td>85</td>
<td>32</td>
<td>1.6</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>71 ± 4</td>
<td>29 ± 3</td>
<td>1.68 ± 0.08</td>
</tr>
</tbody>
</table>

| Group 2 | | | | | | | |
| 6  | 63          | M   | Cardiomyopathy             | IV         | 57                          | 20                                        | —                        |
| 7  | 67          | M   | Myocarditis                | IV         | 92                          | 28                                        | —                        |
| 8  | 58          | M   | Cardiomyopathy             | IV         | 73                          | 32                                        | —                        |
| 9  | 52          | M   | CAD                        | IV         | 75                          | 27                                        | —                        |
| 10 | 74          | M   | CAD                        | IV         | 93                          | 35                                        | —                        |
| 11 | 37          | M   | Cardiomyopathy             | IV         | 78                          | 35                                        | 1.6                      |
| 12 | 67          | M   | Cardiomyopathy             | IV         | 87                          | 16                                        | 1.72                     |
| 13 | 60          | M   | CAD                        | IV         | 80                          | 30                                        | 2.0                      |
| 14 | 67          | M   | Cardiomyopathy             | IV         | 80                          | 30                                        | 1.6                      |
| Mean ± SEM |           |     |                            |            | 79 ± 4                      | 28 ± 2                                    | 1.73 ± 0.1              |

| Group 3 | | | | | | | |
| 15 | 67          | M   | Cardiomyopathy             | IV         | 92                          | 32                                        | 1.4                      |
| 16 | 56          | M   | Cardiomyopathy             | IV         | 90                          | 40                                        | 2.0                      |
| 17 | 66          | M   | Cardiomyopathy             | IV         | 88                          | 28                                        | 1.3                      |
| 18 | 36          | M   | CAD                        | III        | 103                         | —                                         | —                        |
| 19 | 69          | M   | Cardiomyopathy             | III        | 80                          | —                                         | —                        |
| 20 | 65          | M   | CAD                        | IV         | 79                          | —                                         | —                        |
| 21 | 56          | F   | CAD                        | IV         | 81                          | —                                         | —                        |
| 22 | 32          | M   | Cardiomyopathy             | IV         | 96                          | 16                                        | 1.9                      |
| 23 | 58          | M   | CAD                        | IV         | 84                          | —                                         | —                        |
| Mean ± SEM |           |     |                            |            | 88 ± 3                      | 29 ± 5                                    | 1.65 ± 0.2              |

Abbreviations: NYHA = New York Heart Association; CAD = coronary artery disease.
families were informed of the purpose and the potential adverse effects of the study, and the subjects gave written consent.

Blood was drawn for measurement of PRA and PAC within 72 hours of admission. Samples were obtained between 8:00 a.m. and 10:00 a.m. with the patient in the recumbent position. PRA, PAC and angiotensin II concentration were determined by radioimmunoassay techniques previously described.14, 18 The mean PRA measured in 42 normal recumbent subjects on a low-sodium intake was 3.5 ng A/1/ml/hour (upper limit of normal, 7.5 ng A/1/ml/hour).18

The mean PAC measured in 19 subjects on low-sodium diet was 25.6 ± 3.6 ng/100 ml (upper limit of normal, 56 ng/100 ml).17 Similarly, the normal range for plasma angiotensin II level on low-salt diet was 15-50 pg/ml. Serum and urinary sodium, potassium and creatinine were determined by standard autoanalyzer techniques.

The results are reported as mean with standard error of the mean as the index of dispersion. Statistical analysis was performed using the t test, the Mann-Whitney U test, or analysis of correlation and regression.

**Results**

The corresponding values of systemic arterial pressure, pulmonary capillary wedge and PRA of the three groups are summarized in figure 1. The mean systolic blood pressures in groups 1, 2 and 3 were 71 ± 5, 78 ± 6 and 88 ± 8 mm Hg, respectively. Patients in all three groups had evidence of severe impairment of left ventricular function — the pulmonary capillary wedge pressures as determined by Swan Ganz catheter were 29 ± 3, 28 ± 2 and 29 ± 5 mm Hg, respectively, and the cardiac indexes by thermodilution technique were 1.68 ± 0.8, 1.73 ± 0.09, 1.7 ± 0.18 1/min/m², respectively. All patients in group 3 also had noninvasive evaluation of cardiac function, including radionuclide ventriculography and cardiac echocardiography. The mean left ventricular ejection fraction (by radionuclide ventriculography and left-heart catheterization) was 19 ± 3%, and the mean left ventricular end-diastolic diameter by echocardiography was 7.1 ± 0.4 cm.

PRA was elevated in all patients from groups 1 and 2, ranging from 14.6-97.0 ng A/1/ml/hour. The mean PRA of group 1 was 65 ± 12 ng A/1/ml/hour and that of group 2 was 29 ± 4 ng A/1/ml/hour. A parallel increase in PAC was observed in groups 1 and 2 (117 ± 19 and 59 ± 11 ng/dl, respectively). In contrast, the mean PRA in group 3 was within the normal range (3.3 ± 0.5 ng A/1/ml/hour) and mean PAC was 11.3 ± 3.5 ng/dl. Because all patients had a similar degree of cardiac impairment (cardiac index and pulmonary wedge pressure), no correlation could be found between PRA and cardiac hemodynamics. However, a significant inverse correlation was observed between systemic blood pressure and PRA (r = -0.48, p < 0.05). As expected, PAC levels paralleled the PRA in these patients (r = 0.65, p < 0.01).

Sequential determinations of PRA and angiotensin II levels were performed in four patients who were followed from the decompensated to the chronic stable state. The mean PRA decreased from 13.5 ± 1.3 to 3.9 ± 1.0 ng A/1/ml/hour while plasma angiotensin II level decreased from 177 ± 76 to 25 ± 11 pg/ml (fig. 2).

PRA was normal (5.0 ± 2.1 ng A/1/ml/hour) in the nine patients with an uncomplicated acute myocardial infarction.

The cardiac and renal status remained relatively stable in patients from group 3 throughout the hospitalization. During a 9-month follow-up, seven of nine patients were still alive. However, most patients in groups 1 and 2 did poorly — four of five patients in group 1 and five of nine patients in group 2 died from intractable cardiac failure during the hospitalization. Associated with the progressive cardiac deterioration, they also developed variable degrees of azotemia — the blood urea nitrogen increased from the admission level of 28 ± 7 to 60 ± 13 and 73 ± 11 mg/dl and serum creatinine increased from 1.7 ± 0.2 to 2.5 ± 0.5 and 3.0 ± 0.3 mg/dl in groups 1 and 2, respectively, at the time the PRA was determined. PRA correlated...
The role of the RAAS in congestive heart failure is controversial. Levels of plasma renin and aldosterone in patients with cardiac failure have been variously reported as high, normal or even low. Some investigators have found abnormally high levels of PRA and plasma angiotensin II levels and/or aldosterone in many patients; others have found the levels to be quite variable. The occurrence of abnormalities ranges from infrequent to occasional. The variability in renin and aldosterone levels has been attributed to the failure in many studies to control dietary sodium and potassium intake or diuretic administration or the influence of posture. However, even when dietary sodium intake was carefully controlled and the response of the renin and aldosterone levels to diuretics was assessed, there was still considerable variability. Chonko et al. found elevated plasma aldosterone levels despite sodium loading, whereas Sanders et al. found no correlation between sodium balance and aldosterone excretion. With diuretic administration, Nicholls et al. observed that plasma aldosterone decreased to unmeasurable levels, whereas Brown et al. found a variable response in PRA to diuretic therapy.

One of the important factors not described carefully in these studies was the clinical condition of the patients examined. Indeed, investigators rarely group patients by the severity or acuteness of cardiac failure. Recent work using animal models of congestive heart failure, where the severity of cardiac failure was graded and sequential studies were performed as compensatory mechanisms came into play, has increased our understanding of the evolution of this process. The RAAS was activated to a striking degree early with acute heart failure and was essential for maintenance of blood pressure as converting-enzyme inhibition induced immediate hypotension. Then, extracellular fluid volume expansion occurred, resulting in restoration of blood pressure and return of plasma renin and aldosterone levels to normal. With expansion of extracellular fluid volume in the chronic phase of experimental congestive heart failure, converting-enzyme inhibition reduced arterial blood pressure little or not at all. Such compensation was possible even with moderately severe lesions. However, profound cardiac failure resulted in persistent hypotension, elevation of PRA and PAC and continued sensitivity of blood pressure to converting-enzyme inhibition.

In this study, patients at different stages of severe congestive heart failure, potentially comparable to the phases identified in the animal model, were selected for assessment. Groups 1 and 2 consisted of 14 patients who presented with severe unrelenting cardiac failure of recent onset. All these patients were relatively hypotensive and had elevated pulmonary wedge pressure. PRA and PAC were markedly increased in these patients, consistent with the findings of experimental acute heart failure in animals. Of these patients, group 1 (patients without peripheral
The presence of peripheral edema in group 2 was indicative of right ventricular failure with extracellular fluid volume expansion, a more prolonged interval and at least a partial circulatory response to the heart failure and hypotension. The markedly elevated PRA in group 1 was consistent with the absence of clinical signs of secondary extracellular fluid volume expansion in response to the severe cardiac failure. All nine patients with chronic severe congestive heart failure (group 3) had normal PRA and aldosterone levels on a low-salt diet despite documented persistently low cardiac output, ejection fraction and high pulmonary wedge pressures comparable to the levels seen in groups 1 and 2. These findings are in agreement with those observed during the chronic compensated phase of experimental cardiac failure. This hypothesis was further confirmed when sequential measurements were performed in four patients who were followed from the decompensated to the chronic compensated state. Both PRA and angiotensin II levels were elevated during the former but returned to normal when measured during the latter state. Thus, severe clinical heart failure, either progressing relentlessly or suddenly aggravated, with inadequate circulatory compensation, appears to be associated with marked activation of the RAAS. The activity of the RAAS returns to normal as cardiac failure stabilizes and circulatory compensation occurs.

A major stimulus for the increase in renin release during acute cardiac failure appears to be arterial hypotension secondary to decreased cardiac output. This mechanism appears to be operative here...
as evidenced by the inverse correlation between mean blood pressure and PRA. Other possible mechanisms include alterations in the state of cardiopulmonary receptors or macula densa sodium concentration. In patients with cardiac failure associated with ischemic heart disease, especially those with recent myocardial infarction, neurosympathetic stimulation secondary to ischemia is a possible stimulus for renin secretion. In this study, however, the mean PRA was normal in patients with acute myocardial infarction without cardiac failure. In addition, in patients who had chronic congestive heart failure with or without superimposed recent decompensation, the development of hyponatremia might be a further stimulus for increased PRA.\textsuperscript{18-20} Indeed, there was a significant inverse relationship between serum sodium concentration and the PRA in these patients. As sodium and water retention occur, the resultant expansion of extracellular fluid volume restores blood pressure to normal and suppresses renin release. Thus, the PRA and aldosterone levels return to normal.

A potential deficiency of this study is the lack of data on metabolic balance in these patients. This was not possible because of the severity of their illness. However, because we based our normal values on those obtained from subjects on a low-sodium diet, the elevated PRA and aldosterone levels in groups 1 and 2 are undoubtedly significant.

Because of the possible role of the RAAS in the pathogenesis of congestive heart failure, the effect of converting-enzyme inhibition (by teprotide or captopril) have been recently studied in patients with advanced heart failure.\textsuperscript{21-24} Improvement of cardiac function associated with a decrease in systemic vascular resistance was observed over a wide range of PRA. Curtiss et al.\textsuperscript{21} and Dzau et al.\textsuperscript{22} observed a positive correlation between the decrease in systemic vascular resistance and the pretreatment PRA, but other investigators did not.\textsuperscript{25, 24} This discrepancy may be related to the complex mechanisms of action of the converting-enzyme inhibitors. However, it appears that patients with very elevated PRA (e.g., group 1 patients in the present study) may be highly sensitive to these agents and, therefore, captopril must be administered, with great caution to these patients.\textsuperscript{21, 22} However, captopril may be particularly effective in patients such as those in group 2, especially when their course is complicated by the development of secondary azotemia.\textsuperscript{22}

The secondary rise in serum creatinine and blood urea nitrogen associated with progressive cardiac deterioration in the patients from groups 1 and 2 may well reflect reduced renal perfusion pressure, sympathetic vasoconstriction, and angiotensin-induced renal vasoconstriction. As part of the compensating cardiovascular response to pump failure, intense peripheral vasoconstriction occurs in most vascular beds including the renal circulation.\textsuperscript{28-33} Thus, reduction in renal blood flow may be partially the result of renal arteriolar vasoconstriction, potentially resulting from increased sympathetic tone or activation of the renin-angiotensin system.\textsuperscript{28} With the significant reduction in renal blood flow, glomerular filtration rate decreases and azotemia develops. The role of angiotensin in the pathogenesis of azotemia was suggested by the finding of a significant correlation between serum creatinine and PRA in this study and by our recent observation that azotemia in patients with cardiac failure improved with captopril therapy.\textsuperscript{22} Brown et al.\textsuperscript{2} observed a similar positive correlation between plasma renin concentration and blood urea nitrogen in 79 patients with congestive heart failure. This correlation may simply reflect a relationship between renin release and altered intrarenal distribution of blood flow resulting from low cardiac output.

Finally, hyponatremia in group 2 patients was most likely a result of inappropriate antiuretic hormone secretion and decreased glomerular filtration rate accompanying the prolonged severe cardiac failure.\textsuperscript{34} The suddenness of cardiac deterioration in group 1 patients probably did not allow sufficient time for hyponatremia to develop; nor, however, was hyponatremia observed in patients with chronic but stable heart failure and relatively normal renal function (group 3).

In conclusion, the state of activation of the RAAS in congestive heart failure depends in part on the clinical status of the patients studied. During severe decompensated left ventricular failure before the development of extracellular fluid volume expansion and restoration of systemic blood pressure, PRA and aldosterone levels are markedly elevated. With stabilization of cardiac failure and extracellular fluid volume expansion, PRA and aldosterone levels return to normal. Azotemia was observed in association with the activation of the RAAS in severe congestive heart failure, suggesting a causal relationship. Finally, in patients with chronic congestive heart failure, hyponatremia was associated with recent decompensation and a high renin state.

Acknowledgment

We are grateful to Dr. A. Clifford Barger for inspiration, suggestions and support.

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Relation of the renin-angiotensin-aldosterone system to clinical state in congestive heart failure.
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Circulation. 1981;63:645-651
doi: 10.1161/01.CIR.63.3.645

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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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