Increased Plasma Arginine Vasopressin Levels in Patients With Congestive Heart Failure

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The antidiuretic hormone arginine vasopressin could contribute to both the vasoconstriction and impaired water handling frequently found in patients with congestive heart failure. In order to determine basal levels for vasopressin in this condition, plasma vasopressin was measured by radioimmunoassay in a group of 31 patients with advanced congestive heart failure. At the same time, plasma norepinephrine, plasma renin activity and numerous hemodynamic variables were also measured. In a subgroup of patients, the response of vasopressin to hemodynamic changes induced by nitroprusside infusion and to inhibition of the renin-angiotensin system with captopril was studied. The basal vasopressin levels in the patients were compared with those obtained from 51 comparably aged normal subjects. The mean vasopressin level (± standard error of the mean) in the patients was 9.5 ± 0.89 pg/ml as compared with 4.7 ± 0.66 (probability [p] < 0.001) in the normal subjects. Serum sodium was 137 ± 0.56 mEq/liter. The vasopressin level did not correlate with any hemodynamic variable and was increased to the same degree in patients with both low and normal cardiac index. The vasopressin level failed to correlate with serum sodium, and was similarly increased in patients with low and normal serum sodium. There was no correlation of vasopressin and plasma norepinephrine, but vasopressin did correlate modestly with plasma renin activity (r = 0.53, p < 0.02). Acute hemodynamic changes induced by nitroprusside did not influence vasopressin levels, nor did comparable changes accompanied by inhibition of the renin-angiotensin system with captopril.

Thus, vasopressin levels measured under steady state conditions are usually increased in patients with congestive heart failure. The increase is not dependent on reduced cardiac index. There appears to be an abnormality in the relation between vasopressin and serum sodium in some persons and vasopressin does not respond to acute hemodynamic changes with or without the inhibition of the renin-angiotensin system. The mechanisms causing increased vasopressin levels and their biologic importance in congestive heart failure remain to be defined.

Vasoconstrictor mechanisms frequently are activated in patients with congestive heart failure. Both increased sympathetic tone and increased activity of the renin-angiotensin system have been demonstrated in this condition (1–3). Neither the stimulus that activates these systems nor the physiologic significance of this activation is yet apparent.

Vasoconstriction may begin as part of a compensatory response to impaired cardiac function, but it may also contribute to the pathophysiology of congestive heart failure by inappropriately increasing vascular impedance and promoting excessive salt and water retention (4).

The antidiuretic hormone, arginine vasopressin, is a powerful endogenous vasoconstrictor (5–8) which has been little studied in patients with congestive heart failure, in part because of the unavailability of reliable assay techniques until the last several years. A previous report using a bioassay (9) has suggested that vasopressin levels may sometimes be abnormal in this condition. This report, together with the observation of the higher levels of other vasoconstrictor substances in congestive heart failure and the known propensity of patients with congestive heart failure to become hyponatremic, led us to measure vasopressin levels in patients with congestive heart failure using a sensitive and specific radioimmunoassay for this hormone (10). The de-
vealopment of selective blockers of the vascular and renal effects of vasopressin gives additional impetus to the study of this hormone in disease states because it may become possible to modify its effects if abnormalities are demonstrated (5, 8, 11). This paper reports our initial findings in 31 patients with heart failure and demonstrates that vasopressin levels, like those of plasma norepinephrine and renin activity, are increased in patients with this condition.

**Methods**

**Patient selection.** Thirty-one patients with clear evidence of congestive heart failure on the basis of typical history and physical findings formed the basic study population. All had supporting noninvasive evidence for the syndrome including an enlarged heart on chest X-ray examination and either depressed fractional shortening by M-mode echocardiography or a depressed ejection fraction by radionuclide scan. There were 29 men and 2 women, and the mean age was 55 years. The cause of the heart failure was either primary or ischemic cardiomyopathy. No patient with hypertension requiring treatment was included and no patient was studied within 3 months of myocardial infarction. All patients were taking diuretic drugs and most were taking digitalis and vasodilating drugs as well.

**Protocol.** After giving informed consent, patients were admitted to a clinical research unit. Baseline blood samples for hematologic and blood chemistry studies were obtained. All diuretic and vasodilating drugs were then withheld for at least 48 hours. Administration of digitalis and arrhythmic drugs was continued if the patient was taking such medication. One or two daily morning supine plasma samples for vasopressin were obtained in some patients while they were not receiving diuretic and vasodilating drugs. During the observation period, patients were maintained on a low salt diet (500 mg to 2 g, depending on clinical assessment of the severity of disease).

The night before planned invasive study, serum electrolytes were rechecked. If clinical status and electrolytes were stable, the patient was taken at 8 a.m. the next day to a special procedure room where a Swan-Ganz thermodilution catheter and an arterial cannula were inserted using percutaneous technique. After a 30 to 60 minute rest period following catheter insertion, measurements were made of heart rate, blood pressure, right atrial pressure, pulmonary artery and capillary wedge pressures and cardiac output. These measurements were repeated 15 minutes later and if the two sets of values differed by 10% or less, they were averaged and accepted as basal. At this time, blood was drawn for measuring vasopressin, plasma norepinephrine, plasma renin activity and in most patients, electrolytes. The results of these determinations were used to compute the mean values for each variable and substance measured and in the analysis of their interrelations.

**Control group.** Blood from 51 normal volunteer subjects (mean age 46 years) was obtained by venipuncture after 30 minutes of supine rest in the morning after an overnight fast similar to that observed by the patients. All subjects were on a normal diet and were clinically free of heart disease or hypertension.

**Nitroprusside and captopril studies.** In patients with heart failure, we also wished to examine the acute effects of alterations in nonosmotic variables known to influence the control of vasopressin release. We were particularly interested in the possibility that angiotensin II, a known short-term (12), but perhaps not long-term (13) regulator of vasopressin levels, might be playing a role in sustaining vasopressin levels in this condition if they were increased. Therefore, we studied the effects of hemodynamic changes produced by sodium nitroprusside infusion and by the administration of the angiotensin-converting enzyme inhibitor, captopril, in 11 patients in this series by measuring the response of vasopressin during peak hemodynamic effects. The nitroprusside was given first at 10 µg/min and increased every 10 minutes until left ventricular filling pressure was reduced by approximately 30% unless systolic pressure less than 90 mm Hg occurred earlier. At the peak hemodynamic response, generally 60 to 75 minutes after the start of the infusion, vasopressin levels were measured. After the infusion was stopped and hemodynamic variables returned to control values, blood was obtained for a recontrol measurement of vasopressin and 25 mg of captopril was then given. Hemodynamic measurements were made every 15 minutes after ingestion of the drug and blood was sampled for vasopressin. The sample obtained at peak hemodynamic response, which varied from 45 to 75 minutes after drug ingestion, was compared with the recontrol value.

**Assay techniques.** All blood samples were immediately centrifuged with the plasma removed and frozen at −4°C. Vasopressin was analyzed by a sensitive and specific radioimmunoassay (10) with an intra-assay coefficient of variation less than 4% and an ability to detect changes in vasopressin as small as 0.2 pg/ml. Plasma norepinephrine was analyzed radioenzymatically with the Cat-a-kit (Upjohn Pharmaceuticals) and plasma renin activity was determined with the radioimmunoassay for the generation of angiotensin I (14). Both of these assays have coefficients of variation less than 8% in our laboratory.

**Statistical analysis.** Results of vasopressin levels in patients and normal subjects were compared using the unpaired t test. Stability of the daily vasopressin measurements in the subpopulation of patients studied was assessed by one way analysis of variance. Correlation coefficients were calculated by the usual methods. Responses to nitroprusside and captopril were analyzed with the paired t test.
Results

Hemodynamics. The hemodynamic data (mean ± standard error of the mean) from patients at the time of study were as follows: heart rate, 81 ± 1.9 beats/min; mean arterial pressure, 82 ± 1.1 mm Hg; right atrial pressure, 11 ± 1.5 mm Hg; left ventricular filling pressure, 26 ± 0.80 mm Hg (estimated from the pulmonary capillary wedge or if not obtainable the pulmonary artery diastolic pressure); cardiac index, 2.2 ± 0.07 liters/min per m² and systemic vascular resistance, 1,512 ± 58 dynes·s·cm⁻⁵. As a group then, these patients had relatively advanced disease on the basis of hemodynamic measurements.

Plasma vasopressin (Table 1). Plasma vasopressin was increased in these patients, with the mean level of 9.5 ± 0.89 pg/ml differing from normal at a high level of statistical significance. The values for plasma norepinephrine and plasma renin activity were also substantially elevated. Serum sodium in the patients averaged 137 ± 0.60 mEq/liter.

Fifteen patients had determinations of vasopressin on 1 or 2 additional days while not taking medication and awaiting hemodynamic study. The range of differences between vasopressin values for the multiple day determinations was 0 to 4.2 pg/ml with an average change of 12.9%. Differences among multiple day values were not significant by analysis of variance. Multiple analyses for plasma norepinephrine and plasma renin activity were not done in this study, but have previously been shown to be stable under similar circumstances (2).

Vasopressin levels did not correlate with any hemodynamic variable or with serum sodium. They also did not correlate with plasma norepinephrine but did correlate moderately and significantly with plasma renin activity (Fig. 1).

Correlation of vasopressin levels and hemodynamic values. The possibility that hemodynamic factors were a determinant of vasopressin levels in the basal state was further explored by classifying patients on the basis of cardiac index (< or ≥ 2.5 liters/min per m²). No difference was observed in vasopressin between groups (Table 2). No subgroup analysis was carried out with blood pressure as it was normal in all subjects, or with cardiac filling pressures because they were increased in all (in the case of left ventricular filling pressure) or nearly all (in the case of right atrial pressure) subjects.

Correlation with serum sodium. To further explore the relation between vasopressin and serum sodium, we classified patients on the basis of eunatremia or hyponatremia (defined as sodium < 135 mEq/liter). The results of the

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Table 1. Values for Plasma Vasopressin, Norepinephrine and Renin Activity in Patients With Congestive Heart Failure and Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients With Congestive Heart Failure</th>
<th>Normal Subjects</th>
</tr>
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<tbody>
<tr>
<td>Vasopressin (pg/ml)</td>
<td>9.5 ± 0.89</td>
<td>4.7 ± 0.66*</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>599 ± 64</td>
<td>196 ± 23†</td>
</tr>
<tr>
<td>Renin activity (ng/ml per h)</td>
<td>11 ± 2.2</td>
<td>1.9 ± 0.27†</td>
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</table>

* = p < 0.001; † = p < 0.01.

Values are expressed as mean values ± standard error of the mean.

There are 31 patients with congestive heart failure for each variable. In the normal group, 51 subjects had vasopressin measurements; 11 of these had plasma norepinephrine and plasma renin activity measured as well.

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Table 2. Classification of Patients by Cardiac Index

<table>
<thead>
<tr>
<th>Group I (n = 22)</th>
<th>Group II (n = 9)</th>
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<tbody>
<tr>
<td>Cardiac index (liters/min per m²)</td>
<td>1.9 ± 0.06</td>
</tr>
<tr>
<td>Vasopressin (pg/ml)</td>
<td>9.6 ± 1.0</td>
</tr>
</tbody>
</table>

Patients are classified according to normal (≥ 2.5 liters/min per m²) or low < 2.5 liters/min per m² cardiac index. Differences in vasopressin are not significant. Values are expressed as mean values ± standard error of the mean.
Effect of nitroprusside and captopril. Nitroprusside and captopril both induced significant hemodynamic changes. Mean arterial pressure decreased with both drugs (80 ± 2.0 to 70 ± 2.0 mm Hg with nitroprusside, 84 ± 1.9 to 72 ± 2.7 mm Hg with captopril) as did right atrial pressure (9.6 ± 1.9 to 5.0 ± 1.3 mm Hg and 13 ± 1.9 to 8 ± 1.7 mm Hg, respectively), left ventricular filling pressure (26 ± 2.1 to 17 ± 2.3 mm Hg and 28 ± 19 to 22 ± 2.0 mm Hg, respectively) and systemic vascular resistance (4,877 ± 108 to 1,036 ± 59 dynes·s·cm⁻¹, and 1,595 ± 106 to 1,218 ± 88 dynes·s·cm⁻¹, respectively). Cardiac index increased from 2.1 ± 0.15 to 2.7 ± 0.16 liters/min per m² with nitroprusside and from 2.1 ± 0.22 to 2.4 ± 0.19 liters/min per m² with captopril. Vasopressin, however, did not change significantly with either intervention (Table 4).

### Discussion

**Plasma vasopressin in congestive heart failure.** These data demonstrate that plasma vasopressin levels obtained in a steady clinical state and free for at least 48 hours of the effects of diuretic and vasodilating drugs are usually increased in patients with congestive heart failure. Further, these levels are quite stable if measured on a daily basis under similar conditions. The increase and stability of vasopressin levels parallel the increase and stability we have previously observed with plasma norepinephrine and plasma renin activity when measured under similar circumstances (2).

This demonstration of increased vasopressin levels by radioimmunoassay confirms the findings previously reported by Yamane (9) (using a bioassay) of increased vasopressin in some patients with congestive heart failure and bears out our preliminary observations reported previously (4), although the vasopressin levels in that pilot study of only a few subjects were slightly higher. Yamane (9) did not fully characterize his patient population from a hemodynamic standpoint and did not mention medication that patients may have been taking at the time of study. Nonetheless, the levels of vasopressin in Yamane’s patients with “combined right and left heart failure” were similar to those in our patients assuming a conversion of microunits to picograms of 0.38 μU/pg.

**Correlation with hemodynamic variables.** Vasopressin did not correlate with any hemodynamic variable in our series of patients. This result differs in one respect from the study of Yamane (9) in which a positive correlation existed between vasopressin and right atrial pressure. The explanation for the discrepancy may reside in the fact that nearly all of our patients had high right-sided pressures, whereas Yamane studied a large group with normal right-sided pressures. In this case, because of a wider range of values for both vasopressin and right atrial pressure, a significant correlation may have emerged. However, because we do not know the status of treatment in Yamane’s patients, we make this conclusion with caution, noting that several patients in our series had elevated right atrial pressure and normal vasopressin levels.

**Vasopressin and regulation of peripheral vascular resistance.** Whether plasma vasopressin in the range found in our patients plays a role in the regulation of the peripheral vascular resistance cannot as yet be commented on with certainty. There was no correlation of vasopressin with calculated systemic vascular resistance; however, simple correlation techniques may not be adequate to reveal what may be a highly complex relation between neuroendocrine activity and vascular control. For example, although plasma renin activity at rest usually does not correlate with systemic vascular resistance, the improvement induced by angiotensin-converting enzyme inhibition frequently correlates well with plasma renin activity (15), suggesting (although converting-enzyme inhibitors may also have other effects) that increased activity of the renin-angiotensin system does have pathophysiologic importance in patients with heart failure.

It is also important to note that vasopressin levels in the moderately increased range have definite vasoactive effects in dogs, in terms of both the overall vascular resistance (6) and the distribution of regional cardiac output (7). Vasopressin in the moderately increased range also has an important role in blood pressure maintenance in dehydrated rats (8). Finally, because patients with congestive heart fail-

### Table 3. Classification of Patients by Serum Sodium

<table>
<thead>
<tr>
<th>Sodium (mEq/liter)</th>
<th>Hyponatremia Group 2 (n = 7)</th>
<th>Eunatremia Group 2 (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasopressin (pg/ml)</td>
<td>132 ± 1.2</td>
<td>139 ± 0.56</td>
</tr>
<tr>
<td>9.4 ± 2.2</td>
<td>9.8 ± 1.0</td>
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</tbody>
</table>

Patients are classified according to normal (≥135 mEq/liter) or low (<135 mEq/liter) serum sodium level. Differences in vasopressin are not significant. Values are expressed as mean values ± standard error of the mean.

### Table 4. Response of Vasopressin to Nitroprusside and Captopril

<table>
<thead>
<tr>
<th>Vasopressin Level (pg/ml)</th>
<th>Control Study</th>
<th>Peak Effect</th>
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</thead>
<tbody>
<tr>
<td>Nitroprusside</td>
<td>12.8 ± 1.7</td>
<td>11.4 ± 0.70</td>
</tr>
<tr>
<td>Captopril</td>
<td>11.4 ± 0.9</td>
<td>11.9 ± 1.2</td>
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</table>

Vasopressin was measured during the peak effect of each intervention. Differences are not significant. Values are expressed as mean values ± standard error of the mean.
ure have abnormal baroreflexes (16), it is worth noting that
due to an apparently specific interaction between vasopres-
sin and the sinoaortic baroreflex, the vascular effects of
vasopressin may be exaggerated when this reflex malfunction-
s or is removed (6). Thus, data will be needed either
on the effects of inhibiting the pressor actions of vasopressin
or on the vascular sensitivity to vasopressin in patients with
heart failure before we know what, if any, role vasopressin
plays in the regulation of the peripheral resistance in this
condition.

Relation of vasopressin to serum sodium and water
balance. The nature of the relation between vasopressin
and disturbed water balance in congestive heart failure is
also not clear. We did not find a correlation between vaso-
pressin and serum sodium in this group of patients, and
vasopressin levels were the same whether patients had low
or normal sodium (Table 3). There is, therefore, a failure
of vasopressin to suppress in the face of hyponatremia in
some patients with congestive heart failure (as noted also
by Szatolowicz et al. [17]). However, it is questionable whether
nonsuppressed vasopressin itself actually induces hypona-
tremia in most patients, as most of our patients had normal
sodium despite increased vasopressin levels. It is possible
that in some patients, incompletely suppressed vasopressin
along with other factors, such as impaired distal delivery
of sodium and perhaps increased water intake due to the
dipsogenic effects of increased angiotensin II, may combine
to cause a low serum sodium level (18, 19). Serial studies
of osmolar changes and vasopressin levels in heart failure
will be needed to clarify these issues.

Mechanisms of increased vasopressin in congestive
heart failure. Although the mechanism leading to in-
creased vasopressin levels in these patients is not apparent
from this initial descriptive study, some possibilities may
be considered. First, we should exclude the possibility that
the increase is an artifact due to effects of drugs or the
protocol itself. All patients had been withdrawn from di-
uretic and vasodilator therapy for at least 48 hours to min-
imize drug effects and were clinically stable when studied.
Residual effects of the diuretic drugs cannot be completely
excluded, but grossly elevated cardiac filling pressures strongly
militate against the possibility of excessive diuresis leading
to nonosmotic stimulation of vasopressin secretion. Diets
were different in the patients and normal subjects because
of the necessity of maintaining patients on low sodium diets
while not taking diuretic medication, but low sodium diets
do not independently stimulate vasopressin release unless
water is restricted (20). They may, however, stimulate renin
which indirectly, by way of angiotensin II, could stimulate
vasopressin (12). In fact, there was a correlation of vaso-
pressin and plasma renin activity (Fig. 1). The lack of an
acute effect of captopril on the vasopressin level, however,
does not support the possibility that high angiotensin II
levels were maintaining the vasopressin level. Furthermore,
the fact that vasopressin also failed to change in response
to similar hemodynamic changes induced by nitroprusside
suggests that the lack of response to inhibition of the genesis
of angiotensin II was not due to offsetting factors working
to increase vasopressin, such as a decrease in mean arterial
pressure. Therefore, it seems unlikely that the protocol diet
influenced the results of the vasopressin determinations,
either directly or indirectly, and it is more likely that both
plasma renin activity and vasopressin are responding to a
similar stimulus in congestive heart failure rather than di-
rectly affecting one another.

Most patients were taking digitalis and some were taking
antiarrythmic drugs. Experimental studies suggest that dig-
italis, by sensitizing cardiac receptors that influence vaso-
pressin secretion and sympathetic nervous system activity
(21), might actually promote a decrease in plasma vaso-
pressin for any given level of receptor stimulation. No data
are available on the effects of antiarrhythmic drugs.

It is also unlikely that the increase in vasopressin was
due to a nonspecific stress reaction during the procedure.
A rest period was observed after catheterization, patients
were comfortable and at ease at this point of the study and,
most importantly, the determinations made simply by veni-
puncture on noncatheterization days were not significantly
different from those on the day of catheterization in the
patients having multiple determinations. We therefore doubt
that the increase in vasopressin is artifactual more likely it
is a characteristic of the heart failure state as studied here.

Increased vasopressin levels could arise either from in-
creased secretion of hormone or from decreased clearance
of hormone secreted at a normal rate. The circulatory half-
life of vasopressin is approximately 6 minutes (although
estimates vary) and the hormone is cleared by both hepatic
and renal mechanisms (22). As our patients did not exhibit
decompensated liver disease or renal failure, it is unlikely
that clearance is the major factor although it was not spe-
cifically studied here. Rather, abnormalities in either or both
the osmotic control networks for vasopressin release seem
more likely to be involved. The lack of correlation between
serum sodium and vasopressin in these patients suggests a
possible disruption of the normal osmotic regulatory mech-
anism. This disruption could be primary or secondary to
abnormalities in the nonosmotic control pathways. Both
cardiopulmonary receptors and sinoaortic baroreceptors in-
fluence vasopressin secretion nonosmotically (23, 24) and
function of both may be abnormal in congestive heart failure
(16, 25).

The lack of response of vasopressin to acute decreases
in both cardiac filling pressure and mean arterial pressure
(Table 4) may indicate that these reflexes are unimportant
modulators of vasopressin release in patients with conges-
tive heart failure. In addition, the observation in the current
study that vasopressin levels under basal conditions are not
confined to patients with hypotension (all of our subjects
298x458}
being normotensive) or low cardiac index (Table 2) considerably diminishes the likelihood that these factors play a role in the maintenance of increased vasopressin in the chronic state as has been speculated elsewhere (17).

In summary, we have shown that vasopressin levels determined by radioimmunoassay are usually increased in patients with congestive heart failure studied under circumstances approximating the basal state. It seems unlikely that this higher level is due to the concomitant heightened activity of the renin-angiotensin system or to hypotension or reduced cardiac output. There may be an abnormality in the osmotic regulation of vasopressin in this condition because low serum sodium may coexist with higher vasopressin levels; conversely, increased vasopressin levels do not always result in hyponatremia. The precise nature of the derangements in both nonosmotic and osmotic control that may lead to increased vasopressin in heart failure, as well as the biologic importance of the increase, remains to be discovered.

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References