Impaired Response of Plasma Vasopressin to Orthostatic Stress in Patients With Congestive Heart Failure

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Arginine vasopressin, a potent vasoconstrictor and regulator of body water, is frequently increased in the plasma of patients with congestive heart failure. Other neurohumoral control networks, such as the sympathetic nervous system and the renin-angiotensin system, also demonstrate increased activity in congestive heart failure, but fail to respond normally to physiologic stress, such as orthostatic tilt. To assess the response of plasma vasopressin to orthostasis in heart failure, vasopressin was measured before and at 10 and 45 minutes during passive upright tilt in 15 patients with congestive heart failure and their response was compared with that in 9 normal control subjects. Arginine vasopressin was measured by radioimmunoassay. In the normal subjects, plasma arginine vasopressin was 5.3 ± 2.3 pg/ml at control, was unchanged at 10 minutes, but significantly increased to 7.0 ± 2.5 pg/ml at 45 minutes (p < 0.05). In contrast, patients with congestive heart failure showed no significant changes in arginine vasopressin levels from the control levels of 11.6 ± 5.5 pg/ml. Both plasma norepinephrine and renin activity increased in the normal subjects, but failed to increase from higher baselines in patients with congestive heart failure.

Thus, plasma arginine vasopressin, like plasma norepinephrine and renin activity, does not increase in response to upright tilt in patients with congestive heart failure. The explanation is not evident but could involve either abnormalities in reflex control of plasma vasopressin in congestive heart failure or in clearance of the hormone during orthostasis.

Previous studies from our laboratory (1–3) demonstrated that activities of neurohumoral control networks, such as the sympathetic nervous system and the renin-angiotensin system, often are increased in patients with congestive heart failure and that these systems often function abnormally in response to stimuli such as orthostatic tilt and dynamic exercise. In more recent investigations (4), we found that circulating levels of arginine vasopressin, a potent vasoconstrictor and regulator of body water balance, also increase in patients with congestive heart failure. Because plasma arginine vasopressin, like plasma norepinephrine and renin activity, increases with orthostasis in normal individuals (5–7), we undertook this study to investigate the response of arginine vasopressin to this stimulus in patients with congestive heart failure.

Methods

Study patients. Two groups of patients were studied: 9 normal control subjects without evidence of heart failure or hypertension and 15 patients with congestive heart failure. The normal control subjects were all men and ranged in age from 37 to 72 years (mean 46). The 15 patients had clear evidence of congestive heart failure on the basis of typical findings on history and physical examination. The cause in each case was either ischemic or primary cardiomyopathy. Fourteen of the patients were men and the group ranged in age from 42 to 65 years (mean 53). All individuals were in clinically stable condition at the time they were studied and all were studied after being admitted to a clinical research unit where all diuretic and vasodilating drugs were withheld for at least 48 hours to preclude measuring drug effects. The patients were maintained on a low sodium diet during the time they were without medication. Electrolytes were checked throughout the observation period and were within

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normal limits at the time of study. Serum sodium content averaged $137 \pm 2.1$ mEq/liter and although osmolality was not measured, no patient had more than minor increases in blood urea nitrogen and glucose.

Protocol. On the morning of the study, the patients reported to a special procedures room where Swan-Ganz catheters and arterial cannulas were placed by percutaneous technique. Direct measurements of mean arterial pressure, cardiac filling pressures and cardiac output by thermodilution were available, while heart rate was taken from an electrocardiogram. At least 30 minutes after catheterization, blood was sampled for vasopressin, as well as norepinephrine and renin activity. The patients were then tilted upright on a tilt table to 65° for 45 minutes. Hemodynamic measurements were made at 10 and 45 minutes during which times blood was resampled for vasopressin. Norepinephrine level was redetermined at 10 minutes and plasma renin activity at 45 minutes. Osmolality was not determined, because it previously had been reported (5) not to change during this duration and type of tilt protocol.

The normal subjects underwent an identical tilting protocol; however, hemodynamic measurements were confined to heart rate from an electrocardiogram and blood pressure as determined by standard cuff techniques.

Assays. All blood samples were collected into chilled tubes and centrifuged immediately at 4°C. Plasma was removed and frozen at −20°C for later analysis. Vasopressin levels were determined by a sensitive and specific radioimmunoassay with a coefficient of variation under 4% (8). Norepinephrine and plasma renin activity were determined by radioenzymatic assay (Cat-a-Kit, Upjohn Corporation) and radioimmunoassay (9), respectively. Both assays have coefficients of variation under 8% in our laboratory.

Results were analyzed by an analysis of variance for multiple measures on the same elements in the case of heart rate, blood pressure and arginine vasopressin determinations. Norepinephrine and plasma renin activity, for which only two measurements were made, were analyzed by a paired t test.

Results

Hemodynamics. Table 1 contains the response of heart rate and arterial pressure to tilt in the two groups. Both variables increased in the normal subjects, whereas neither variable changed in patients with congestive heart failure. These patients did, however, show decreases in right atrial pressure ($11 \pm 6.6$ to $6.3 \pm 7$ mm Hg, probability $[p] < 0.001$) and pulmonary capillary wedge pressure ($25 \pm 6.3$ to $18 \pm 11$ mm Hg, $p < 0.05$). Cardiac index ($2.1 \pm 0.67$ ml/min per m$^2$) did not change significantly in the patients with heart failure, but systemic vascular resistance increased ($1,573 \pm 527$ to $1,758 \pm 522$ dynes⋅s⋅cm$^{-5}$, $p < 0.05$).

Plasma arginine vasopressin. Figure 1 displays the response of plasma arginine vasopressin to the tilting protocol in normal subjects and Figure 2 displays the response in patients with congestive heart failure. There was a small but significant increase in plasma arginine vasopressin in the normal subjects at 45 minutes (from $5.3 \pm 2.3$ to $7.0 \pm 2.5$ pg/ml), although the 10 minute value was not changed. In patients with congestive heart failure, the control level of $11.6$ pg/ml did not change at either 10 or 45 minutes. Plasma norepinephrine also increased in the normal subjects ($195 \pm 75$ to $350 \pm 120$ pg/ml, $p < 0.01$), as did plasma renin activity ($1.9 \pm 0.09$ to $4.5 \pm 3.4$ ng/ml per h, $p < 0.02$). The patients with congestive heart failure had higher rest levels (plasma norepinephrine $634 \pm 432$ pg/ml and plasma renin activity $16 \pm 13$ ng/ml per h) that did not change during orthostatic tilt.

Discussion

The data from this study demonstrate that plasma arginine vasopressin levels, elevated in patients with congestive heart failure, fail to increase in response to upright tilt. In this respect, arginine vasopressin resembles plasma norepinephrine and renin activity, which also tend not to increase with tilt in patients with congestive heart failure. If a large group of patients with heart failure is studied, however, heterogeneity in response of plasma renin activity and norepinephrine becomes apparent (3), and therefore it is still possible that if a larger experience were obtained, subgroups of patients might be found in whom arginine vasopressin does increase.

Abnormalities in reflex control of arginine vasopressin. The explanation for the abnormal response of arginine vasopressin to tilt in patients with congestive heart failure is unclear, particularly because the mechanism of the increase in normal subjects is also not well understood. The increase in arginine vasopressin levels seen in normal subjects in our study was less than that previously reported (5) by investigators using a bioassay for arginine vasopressin.

<table>
<thead>
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<th>Table 1. Heart Rate and Blood Pressure Response to Upright Tilt</th>
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<tr>
<td>Study Group</td>
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<td>Normal subjects (n = 9)</td>
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<td>Heart rate (beats/min)</td>
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<td>Patients with congestive heart failure (n = 15)</td>
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<td>Heart rate (beats/min)</td>
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*p < 0.005 compared with control. Values are ± 1 standard deviation.
measurements, but was similar to their findings in that an increase in arginine vasopressin was seen only after 45 minutes of orthostasis. The magnitude of response seen in our study was, however, nearly identical to that found in two earlier studies (6,7) in which arginine vasopressin levels were measured by radioimmunoassay (assuming the usual conversion of µU/ml to pg/ml of 0.38 µU/pg). In those studies the increase in arginine vasopressin levels was also apparent only after 45 minutes of tilt.

Previous investigators attributed the increase in arginine vasopressin levels during tilt to "unloading" of low pressure cardiopulmonary baroreceptors by the presumed decrease in central venous pressure during this procedure. This assumption was based on the prevailing concept derived from many dog studies that modest changes in intracardiac pressure do influence arginine vasopressin levels. However, in a careful study (10) of the effects of selectively unloading cardiopulmonary and sinoaortic baroreceptors in normal subjects using lower body negative pressure, we found that decreases in cardiopulmonary receptor tone alone did not stimulate vasopressin. Unless hypotension occurred, arginine vasopressin also failed to increase in response to modest unloading of the sinoaortic baroreceptor. These observations, plus the fact that vasopressin did not increase immediately after tilting, may cast doubt on a reflex-based mechanism for the increase; however, it is still possible that the increase

**Figure 1.** Response of plasma arginine vasopressin (AVP) to 10 (a) and 45 (b) minutes of upright tilt in normal subjects. The 45 minute value is significantly (p < 0.05) different from control (c).

**Figure 2.** Response of plasma arginine vasopressin (AVP) to 10 (a) and 45 (b) minutes of upright tilt in patients with congestive heart failure. Differences are not significant.
in arginine vasopressin with tilt in normal subjects could be a result of more prolonged unloading of either or both of these receptor groups. If so, then reflex control of arginine vasopressin in patients with congestive heart failure may be abnormal. Supporting this possibility are the observations that sinoaortic baroreceptor function may be abnormal in congestive heart failure in human beings (11), whereas cardiopulmonary baroreceptor function may be abnormal in animals with this condition (12). However, it is unlikely that nonosmotic signals were simply overridden by an osmotic stimulus during tilt, because serum sodium was normal at the outset and, as previously noted, osmolality does not change during a brief orthostatic stress (5).

Abnormal response to changes in clearance of hormone. Another explanation for the failure of arginine vasopressin to increase during tilt in patients with congestive heart failure may involve abnormalities in the clearance of the hormone with the assumption of the upright posture. Both the liver and the kidney are responsible for the metabolism of arginine vasopressin (13). Few data are available concerning the regional blood flow response to orthostasis in patients with congestive heart failure, but we have reported (14) that hepatic vascular resistance does not increase during tilt as it does with normal individuals, and Lilly et al. (15) reported that renal blood flow does not decrease in at least some patients with congestive heart failure during orthostasis. It is possible, therefore, that the absence of dynamic changes in blood flow to these organs during tilt could explain the lack of change in plasma arginine vasopressin if decreased clearance were the mechanism responsible for the increase in vasopressin in normal subjects.

Implications. The biologic importance of the absence of change in vasopressin during tilt in congestive heart failure is unclear. Vasopressin levels in the physiologic range can affect both the total and regional vascular resistance in animals (16,17). We do not yet know whether levels in the range in our study have actual circulatory effects in patients with congestive heart failure. Theoretically, however, the absence of change in vasopressin during tilt, together with that of sympathetic nervous system activity and renin, could explain, in part, the abnormal regional blood flow response to orthostasis in this condition (14,15) if the normal increase in forearm, hepatic and renal vascular resistance during orthostasis depends on an increase in the activity of any of these neurohumoral controllers.

In summary, this study has shown that the response of vasopressin to orthostatic tilt, like that of plasma norepinephrine and plasma renin activity, is blunted in patients with congestive heart failure. Mechanisms could involve either abnormalities in reflex control of arginine vasopressin or abnormalities in clearance of the hormone during this maneuver. These observations add to the picture of generalized disturbances in important neurohumoral control mechanisms of the peripheral circulation both at rest and with stress in patients with congestive heart failure.

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