Short-term Hemodynamic Effects of Vasopressin V₁-Receptor Inhibition in Chronic Right-Sided Congestive Heart Failure

Charles K. Stone, MD, Chang-seng Liang, MD, PhD, Naoaki Imai, MD, Susumu Sakamoto, MD, Celia D. Sladek, PhD, and William B. Hood Jr., MD

Arginine vasopressin is elevated in congestive heart failure. To determine the effect of arginine vasopressin upon systemic hemodynamics and regional blood flows, we administered the specific inhibitor of the vascular action of vasopressin [1-(β-mercaptop-β,β-cyclopentamethylenepropionic acid),2-(O-methyl-tyrosine)-arginine vasopressin [d(CH₃)₂Tyr(Me)AVP] to 15 dogs with chronic right-heart failure produced by tricuspid avulsion and progressive pulmonary artery constriction. The animals exhibited increased plasma arginine vasopressin and norepinephrine levels. Vasopressin inhibition increased cardiac output and left ventricular dP/dt and dP/dt/P, and it decreased total peripheral vascular resistance, whereas mean aortic pressure did not change significantly. Simultaneously, blood flow increased to skeletal muscle, kidneys, skin, and right and left ventricular myocardium. Plasma catecholamines also increased. Pretreatment with propranolol and prazosin abolished the increases in cardiac output and left ventricular function produced by vasopressin inhibition. Pretreatment also led to a decrease in mean aortic pressure after vasopressor inhibition. In contrast, administration of d(CH₃)₂Tyr(Me)AVP to 11 sham-operated animals or administration of normal saline to nine sham-operated and eight heart-failure dogs was without effect either in the absence or in the presence of adrenergic receptor blockade. Thus, arginine vasopressin participates in the control of the circulation in right-sided congestive heart failure, with both a direct constrictor action on blood vessels and an indirect action by inhibition of the sympathetic nervous system. (Circulation 1988; 78: 1251–1259)

Arginine vasopressin (AVP) is a vasoactive neurohypophysial hormone.1–3 It exerts a potent vasconstrictor effect on isolated vascular smooth muscle through a direct action on the AVP V₁-receptor.4 However, in the intact animal, this effect is less obvious because AVP also sensitizes the arterial baroreflex,5 resulting in a decrease in sympathetic tone that, in turn, offsets the elevation in blood pressure produced by the direct vasoconstrictor action of AVP.6 The latter effect probably is mediated by an action of AVP on the area postrema.6

The role of AVP as a pressor hormone has been shown in fluid deprivation in which administration of a specific inhibitor of the vascular action of vasopressin decreases blood pressure.7 AVP is also tonically elevated in congestive heart failure,8–10 but the vascular response to AVP V₁-receptor inhibition has been inconsistent. Nicod et al11 found that AVP inhibition produced no significant systemic hemodynamic changes in patients with heart failure with moderately elevated AVP, but AVP might be important in maintaining arterial pressure in patients with very high plasma AVP levels. Creager et al12 found in patients with congestive heart failure that, unlike angiotensin converting enzyme inhibitors, the AVP V₁-receptor inhibitor produced no significant changes in blood pressure although some patients showed a decline in systemic vascular resistance, suggesting effective peripheral vasodilatation. More recently, Rieger et al13 found that the AVP V₁-receptor inhibitor did produce a statistically significant de-
crease in arterial blood pressure in rats with right ventricular failure produced by pulmonary artery stenosis. This decrease, however, was smaller than that produced by an angiotensin converting enzyme inhibitor, as it was in patients with congestive heart failure. Riegger et al also found that plasma AVP was increased in right ventricular failure, indicating that the vasopressin system is activated in congestive heart failure, regardless of which ventricle is affected. These studies further indicate that AVP may play a role in modulating vasomotor tone in congestive heart failure.

However, little information is available regarding the effects of AVP inhibition on cardiac function and regional circulations or the interactions between the sympathetic nervous system and the elevated levels of AVP in congestive heart failure. The purpose of the present study was to evaluate the effects of AVP upon systemic hemodynamics and regional circulations in congestive heart failure. We administered [1-(β-mercapto-β,β-cyclopentamethylenepropionic acid),2-(O-methyl)-tyrosine]-arginine vasopressin [d(CH2)5Tyr(Me)AVP], a specific AVP V1-receptor inhibitor, to dogs with chronic right-sided congestive heart failure. The results were compared with those in sham-operated dogs. In addition, to determine the role of the sympathetic nervous system on the responses to AVP inhibition, we administered the AVP V1-receptor inhibitor to heart-failure dogs after they had been pretreated with α- and β-adrenergic receptor blocking agents.

Materials and Methods

Surgical Preparation of Animals

Adult healthy mongrel dogs, weighing 19.5–31.0 kg, underwent a two-step surgical preparation by a modified method of Barger et al. Animals were anesthetized with intravenous sodium pentobarbital (25 mg/kg) and ventilated with room air by a Harvard respirator (Harvard Apparatus, South Natick, Massachusetts). In the first procedure, an aseptic right thoracotomy was performed, and the tricuspid valve was avulsed by a right atriotomy. A Tygon catheter (i.d., 1.02 mm; Norton, Akron, Ohio) was placed in the right atrium. Two weeks later, also with aseptic techniques, a left thoracotomy was performed, and a pulmonary artery hydraulic occluder (R.E. Jones, Silver Spring, Maryland) was placed. At that time, Tygon catheters were placed in the main pulmonary artery, left atrium, and aorta, and a Konigsberg micromanometer (Konigsberg Instruments, Pasadena, California) was inserted into the left ventricle at the apex. All catheters were exteriorized at the nape. The study was approved by the University of Rochester Committee on Animal Resources, Rochester, New York, and conformed to the guiding principles of the American Physiological Society in the care and use of animals.

After 2 weeks of recuperation, the dogs underwent weekly progressive inflation of the pulmonary occluders. Sham-operated dogs underwent two surgical procedures without tricuspid valve avulsion or inflation of the pulmonary artery occluder. Stable right-sided congestive heart failure developed in 6–8 weeks and was characterized by ascites, tachycardia, and elevation in right atrial pressure.

Measurements and Protocols

Dogs were trained to lie quietly in a lateral decubitus position. The previously implanted catheters were attached to Statham P23Db transducers (Statham Instruments, Oxnard, California) with recordings made on an eight-channel Brush 480 recorder (Gould, Cleveland, Ohio). For each hemodynamic measurement, aortic pressure, left and right atrial pressures, and left ventricular pressure were recorded. The peak rate of rise of left ventricular pressure (dP/dt) was obtained by an electronic differentiator. The ratio of left ventricular dP/dt at a developed pressure of 50 mm Hg occurring during isovolumic systole and the developed pressure (dP/dt/P) was measured as an index of isometric state because it is relatively unaffected by changes in ventricular afterload. Cardiac output was determined by injecting indocyanine green (CardioGreen; Hynson, Westcott & Dunning, Baltimore, Maryland) into the pulmonary artery and measuring the arterial dye concentrations with a Gilford Model 140 cardiac output system (Gilford Instrument Laboratories, Oberlin, Ohio). Total peripheral vascular resistance was calculated with the conventional formula.

Regional organ blood flows were measured by a radioactive microsphere technique of NEN-TRAC microspheres (New England Nuclear, Boston, Massachusetts) at a specific activity of 10 mCi/g, 15 ± 3 μm in diameter and labeled with either 141Ce, 51Cr, 113Sn, 109Ru, 95Nb, or 46Sc were used. Approximately 1 million microspheres were injected into the left atrium for each flow determination. Organ blood flows were calculated by an arterial reference sample method. Organ vascular resistances were calculated by dividing the difference between mean aortic pressure and mean right atrial pressure by organ blood flow.

Blood samples were taken for measuring plasma AVP and catecholamines. AVP was measured by radioimmunoassay with antiserum generously provided by Drs. Jacques A. Durr and Marshall D. Lindheimer, University of Chicago, Chicago, Illinois. The antibody is highly specific for AVP and has negligible cross-reactivity with oxytocin (0.001%). However, because the antiserum cross-reacts with the AVP inhibitor, no samples were taken for AVP measurements after administration of d(CH2)5Tyr(Me)AVP. Plasma was extracted before assay by the acetone-ether procedure of Robertson et al. Recovery from extraction was determined for each set of samples and averaged.
72±15% (mean±SD). Values were corrected for percent recovery during extraction. Catecholamines were determined by a radioenzymatic assay with Cat-A-Kit reagents (Amersham, Arlington Heights, Illinois).

Right-heart failure and sham-operated dogs were each divided into three groups, groups 1–3 and groups 4–6, respectively, according to the following experimental protocols. The first two protocols consisted of a control period of 20 minutes followed by intravenous infusion of either d(CH₂)₅Tyr(Me)AVP (25 μg/kg, Bachem, Torrance, California) (groups 1 and 4) or 10 ml normal saline (groups 2 and 5) during 1 minute. d(CH₂)₅Tyr (Me)AVP was dissolved in 10 ml normal saline. The third protocol (groups 3 and 6) differed from the first one only in that it also included treatment with intravenous propranolol (1.25 mg/kg) and prazosin (0.2-mg/kg bolus followed by a 2-μg/kg/min infusion) beginning 20 minutes before the control period. The effectiveness of prazosin and propranolol in producing α- and β-receptor blockade was determined by comparing the pressor and chronotropic responses to serial injections of methoxamine and isoproterenol obtained before the drug pretreatment and at the end of the experiments.

Systemic hemodynamics were measured in triplicate during the control period, along with the measurements of baseline regional blood flows and plasma AVP and catecholamines. Systemic hemodynamic measurements were repeated at 5-minute intervals for 40 minutes after the administration of d(CH₂)₅Tyr(Me)AVP or normal saline. Regional blood flows were again measured at 30 minutes after d(CH₂)₅Tyr(Me)AVP or saline administration, whereas plasma catecholamines were repeated at 20 and 40 minutes after drug administration. Effective AVP inhibition was verified in each animal by abolition of the pressor response to exogenous AVP (40 mIU/kg, Sigma Chemical, St. Louis, Missouri) administered at the end of the experiment.

After the experiment, animals were killed by lethal doses of intravenous pentobarbital sodium. Brains, hearts, livers, stomachs, skin, small and large intestines, spleens, kidneys, quadriiceps muscles, and adrenal glands were removed, and radioactivity was counted with a Packard gamma spectrometer with a Model 9012 multichannel analyzer (Packard Instrument, Downers Grove, Illinois). Flows of the spleen, stomach, small intestine, and large intestine were summed to form the splanchnic flow.

Statistical Analysis

Results are expressed as mean±SEM. The experimental data were analyzed by two-way analysis of variance for repeated measures in independent groups. The significance of differences between the serial experimental values and the control was determined by Dunnett’s test. The significance of a difference between two means was determined by Student’s t test. A p value of less than 0.05 was considered statistically significant.

Results

Baseline Hemodynamic and Neurohumoral Characteristics

Table 1 shows the baseline hemodynamics in right-heart failure and sham-operated dogs. Compared with sham-operated dogs (groups 4 and 5, n=20), the heart-failure dogs (groups 1 and 2, n=23) were notable for an increase in heart rate and right atrial pressure and a decrease in cardiac output and left ventricular dP/dt and dP/dt/P. However, neither left atrial pressure nor mean aortic pressure differed between the heart-failure and sham-operated dogs.

Heart-failure dogs had a greater body weight (26.7±0.6 kg) than sham-operated dogs (23.9±0.6 kg, t=3.14, df=41, p<0.01). Plasma AVP and norepinephrine also were elevated in right-heart failure. The heart-failure dogs exhibited a fourfold increase in plasma AVP at baseline (20±2 pg/ml) compared with the sham-operated animals (5±1 pg/ml, t=5.40, df=41, p<0.01). The corresponding plasma norepinephrine was 0.60±0.05 and 0.25±0.03 ng/ml in the heart-failure and sham-operated dogs, respectively (t=6.00, df=41, p<0.01). Baseline plasma epinephrine values also tended to be higher in heart-failure dogs (0.19±0.03 ng/ml) than in sham-operated dogs (0.14±0.02 ng/ml), but the difference between the two groups was not statistically significant.

Hemodynamic Responses to Arginine Vasopressin Inhibition

Effective AVP V₁-receptor inhibition was produced by d(CH₂)₅Tyr(Me)AVP. In animals without the AVP inhibitor, intravenous administration of AVP (40 mIU) increased mean aortic pressure by 35±5 mm Hg. Similar administration of AVP had minimal effect on mean aortic pressure (2.2±0.3 mm Hg). TABLE 1. Baseline Hemodynamics in Right-Sided Congestive Heart-Failure and Sham-Operated Normal Dogs

<table>
<thead>
<tr>
<th></th>
<th>Congestive heart failure dogs (n=23)</th>
<th>Sham-operated normal dogs (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>142±4*</td>
<td>96±5</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>99±2</td>
<td>104±2</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>17.7±0.9*</td>
<td>3.4±0.5</td>
</tr>
<tr>
<td>Left atrial pressure (mm Hg)</td>
<td>7.1±0.7</td>
<td>6.2±0.4</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>3.55±0.14*</td>
<td>4.52±0.24</td>
</tr>
<tr>
<td>LV dP/dt (100' mm Hg/sec)</td>
<td>2.58±0.14*</td>
<td>3.24±0.19</td>
</tr>
<tr>
<td>LV dP/dt/P (sec⁻¹)</td>
<td>38±1*</td>
<td>44±1</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
LV, left ventricular.
*Values that differ from the sham-operated dogs at p<0.05, as determined by Student’s t test for unpaired data.
mm Hg) 40 minutes after the administration of d(CH₂)₅Tyr(Me)AVP. The difference in the pressor response between the two groups was statistically significant at p<0.001.

Figure 1 shows the acute hemodynamic effects of AVP V₁-receptor inhibition in heart failure. d(CH₂)₅Tyr(Me)AVP caused a significant increase in cardiac output and left ventricular dP/dt and dP/dt/P and a decrease in total peripheral vascular resistance in group 1 (n = 15, 27 ± 1 kg). The changes reached a steady state between 20 and 40 minutes after drug administration and were not associated with alterations in heart rate, mean aortic pressure, right atrial pressure (from 17.3 ± 1.4 to 17.5 ± 1.5 mm Hg), or left atrial pressure (from 7.5 ± 0.9 to 7.2 ± 0.6 mm Hg). AVP inhibition also caused increases in plasma norepinephrine and epinephrine (Table 2). In contrast, administration of normal saline (group 2, n = 8, 27 ± 1 kg) produced no significant changes in any of the hemodynamic or neurohumoral variables measured (Figure 1).

Heart rate, mean aortic pressure, cardiac output, total peripheral vascular resistance, right and left atrial pressures, and left ventricular dP/dt and dP/dt/P did not change significantly in sham-operated dogs after either d(CH₂)₅Tyr(Me)AVP (group 4, n = 11, 24 ± 1 kg) or normal saline administration (group 5, n = 9, 24 ± 1 kg) (Table 3). Also, AVP inhibition did not increase plasma norepinephrine or epinephrine in the sham-operated dogs (Table 2). Because the plateau effects of AVP inhibition occurred in group 1 between 20 and 40 minutes after the drug administration, hemodynamic values obtained between 20 and 40 minutes after drug administration in groups 4 and 5 were averaged and compared with the baseline values in Table 3.

Effects of Arginine Vasopressin Inhibition After α- and β-Receptor Blockade

Blockade of α- and β-adrenergic receptors was produced by prazosin and propranolol pretreatment. The dose of isoproterenol needed to increase heart rate 25 beats/min was increased by the drug pretreatment from 0.03 ± 0.01 to 0.43 ± 0.14 µg/kg (t = 2.92, df = 8, p<0.05) in sham-operated dogs and from 0.20 ± 0.04 to 1.23 ± 0.25 µg/kg (t = 4.72, df = 5, p<0.01) in heart-failure dogs. The pressor response to 0.1 mg/kg of methoxamine was reduced by the pretreatment from 31.8 ± 2.7 to 6.7 ± 0.8 mm Hg (t = 10.40, df = 8, p<0.001) in sham-operated dogs and from 22.0 ± 2.7 to 5.7 ± 1.3 mm Hg (t = 5.60, df = 5, p<0.01) in heart-failure dogs.

Significant hemodynamic changes were produced by prazosin and propranolol. Mean aortic pressure, cardiac output, and left ventricular dP/dt were lower in both heart-failure dogs (group 3, n = 6, 24 ± 1 kg)

Table 2. Effects of Arginine Vasopressin Inhibition on Plasma Catecholamines in Right-Sided Congestive Heart-Failure and Sham-Operated Normal Dogs

<table>
<thead>
<tr>
<th>Time</th>
<th>Congestive heart-failure dogs (n = 15)</th>
<th>Sham-operated normal dogs (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Norepinephrine (ng/ml)</td>
<td>Epinephrine (ng/ml)</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.59 ± 0.06*</td>
<td>0.21 ± 0.04</td>
</tr>
<tr>
<td>20 min</td>
<td>0.83 ± 0.09**</td>
<td>0.30 ± 0.04**</td>
</tr>
<tr>
<td>40 min</td>
<td>0.94 ± 0.13**</td>
<td>0.46 ± 0.08**</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* Values that differ from the sham-operated dogs at p<0.05; † values that differ from the baseline at p<0.05.
TABLE 3. Systemic Hemodynamic Response to d(CH2)3Tyr(Me)AVP* and Normal Saline in Sham-Operated Normal Dogs

<table>
<thead>
<tr>
<th></th>
<th>Group 4 (n=11)</th>
<th>Group 5 (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>d(CH2)3Tyr(Me)AVP</td>
<td>Saline</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>97 ± 5</td>
<td>96 ± 8</td>
</tr>
<tr>
<td>Mean aortic pressure</td>
<td>103 ± 3</td>
<td>104 ± 3</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV dP/dt (10^8 mm Hg/sec)</td>
<td>3.29 ± 0.25</td>
<td>3.28 ± 0.30</td>
</tr>
<tr>
<td>LV dP/dt/P (sec⁻¹)</td>
<td>43 ± 1</td>
<td>44 ± 1</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>4.28 ± 0.34</td>
<td>4.82 ± 0.35</td>
</tr>
<tr>
<td>Right atrial pressure</td>
<td>4.9 ± 0.4</td>
<td>3.9 ± 0.6</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial pressure</td>
<td>6.9 ± 0.6</td>
<td>5.6 ± 0.6</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total vascular resistance (10^9 dynes·sec·cm⁻³)</td>
<td>1.96 ± 0.13</td>
<td>1.75 ± 0.13</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

* d(CH2)3Tyr(Me)AVP, 1-(β-mercapto-β,β-cyclopentamethylenepropionic acid), 2-(O-methyl)-tyrosine-arginine vasopressin; LV, left ventricular.

No significant changes occurred in any of these variables in sham-operated dogs after d(CH2)3Tyr(Me)AVP or normal saline administration.

and sham-operated (group 6, n = 9, 23 ± 1 kg) dogs after prazosin and propranolol pretreatment when compared with animals without the drug pretreatment. Adrenergic receptor blockade also reduced heart rate and left ventricular dP/dt/P in heart-failure dogs but not in sham-operated dogs. Figure 2 shows that baseline values of heart rate, cardiac output, and left ventricular dP/dt and dP/dt/P were significantly lower in the heart-failure dogs after adrenergic receptor blockade (group 3) than the similarly pretreated sham-operated animals (group 6). Figure 2 further shows that d(CH2)3Tyr(Me)AVP produced no statistically significant hemodynamic changes in sham-operated dogs after they had been pretreated with prazosin and propranolol. In contrast, in heart-failure dogs with adrenergic receptor blockade, mean aortic pressure and total peripheral vascular resistance decreased significantly after AVP V1-receptor inhibition. Cardiac output increased slightly after AVP inhibition, but there were no statistically significant increases in heart rate and left ventricular dP/dt and dP/dt/P. AVP inhibition also had no effect on either left atrial pressure (from 5.0 ± 0.6 to 5.0 ± 0.7 mm Hg) or right atrial pressure (from 16.3 ± 2.3 to 16.4 ± 2.1 mm Hg) in the heart-failure dogs.

Pretreatment with prazosin and propranolol had no significant effects on baseline values of plasma AVP or plasma catecholamines. Plasma AVP was 17 ± 4 pg/ml before and 20 ± 4 pg/ml after drug pretreatment in heart-failure dogs; the difference was statistically insignificant (t = 1.60). The corresponding values in the sham-operated dogs were 6.7 ± 1.5 and 6.3 ± 1.5 pg/ml, respectively. Baseline plasma norepinephrine and epinephrine were 0.57 ± 0.08 and 0.18 ± 0.05 ng/ml, respectively, in the heart-failure dogs and were 0.22 ± 0.05 and 0.09 ± 0.03 ng/ml.

FIGURE 2. Plots of changes in heart rate, mean aortic pressure, cardiac output, total peripheral vascular resistance, and left ventricular dP/dt and dP/dt/P after intravenous administration of 1-(β-mercapto-β,β-cyclopentamethylenepropionic acid), 2-(O-methyl)-tyrosine-arginine vasopressin in six right-sided congestive heart failure and nine sham-operated dogs after they had been pretreated with prazosin and propranolol. Bars denote SEM. Asterisks indicate values that differ from the baseline values (time 0) at p < 0.05 by analysis of variance and Dunnett's test. LV, left ventricular.
respectively, in the sham-operated dogs. These values did not differ statistically from those obtained in dogs without adrenergic receptor blockade.

**Regional Blood-Flow Responses to Arginine Vasopressin Inhibition**

Table 4 shows the organ blood flows before and after AVP inhibition in right-sided congestive heart-failure (group 1) and sham-operated (group 4) dogs. Heart failure was associated with a lower baseline blood flow to kidneys, skin, adrenal glands, stomachs, small intestines, and spleens, and a higher blood flow to right and left ventricular myocardium. Total splanchnic blood flow was lower in heart-failure dogs. There were, however, no differences between the two groups in blood flows to quadriceps muscles, brains, livers, and large intestines at baseline.

Table 4 also shows that blood flow increased to right and left ventricular muscles, kidneys, quadriceps muscles, skin, and livers after d(CH2)5Tyr(Me)AVP administration. Simultaneously, vascular resistance significantly decreased in right ventricular muscle (from 0.49 ± 0.06 to 0.39 ± 0.07 mm Hg/ml/100 g/min), left ventricular muscle (from 0.48 ± 0.03 to 0.39 ± 0.04 mm Hg/ml/100 g/min), quadriceps muscle (from 25 ± 3 to 18 ± 2 mm Hg/ml/100 g/min), skin (from 28 ± 6 to 21 ± 5 mm Hg/ml/100 g/min), and liver (from 2.5 ± 0.4 to 2.1 ± 0.4 mm Hg/ml/100 g/min). Other organ blood flows and vascular resistances were not significantly affected by AVP inhibition.

AVP inhibition had no effects on regional blood flows (Table 4) or vascular resistances in sham-operated dogs. Administration of normal saline also produced no significant changes in the regional circulations in heart-failure (group 2) and sham-operated (group 5) dogs.

Effects of AVP inhibition on the regional circulations of the prazosin and propranolol-pretreated heart-failure dogs (group 3) are shown in Table 5. Unlike the animals without adrenergic receptor blockade (group 1), group 3 animals did not respond to d(CH2)5Tyr(Me)AVP with an increase in blood flow in any of the organs measured. Renal blood flow actually decreased. However, organ vascular resistance was decreased significantly by AVP inhibition in right and left ventricular muscle, skin, brain, small intestine, spleen, and total splanchnic bed. Vascular resistance did not change significantly in kidneys, quadriceps muscles, adrenal glands, and livers after AVP inhibition. AVP inhibition did not result in any significant changes in either organ blood flow or vascular resistance in sham-operated dogs after prazosin and propranolol pretreatment (group 6).

**Discussion**

Our present study shows that plasma AVP and norepinephrine were increased in right-sided congestive heart-failure dogs, analogous to patients with congestive heart failure.8-10 Our dogs exhibited an increase in body weight, ascites, and tachycardia, and hemodynamic measurements confirmed the presence of increased right atrial pressure and reduced cardiac output. A depressed right ventricular contractile function has been demonstrated in vitro with an isolated trabecular muscle preparation (C.K. Stone, S. Sakamoto, T-HM. Fan, and C-s. Liang, unpublished data). Mean aortic pressure, however, was maintained. This preparation for chronic heart failure has been studied extensively by us16,24-26 and
other investigators. These animals show many hemodynamic, neurohumoral, and biochemical changes like those of congestive left heart-failure in humans.

Left ventricular function also appeared to be depressed in right heart-failure animals as demonstrated by the diminished left ventricular dP/dt and dP/dt/P. In addition, the left ventricle has been shown to have a subnormal inotropic response to β-agonist stimulation. This decrease in left ventricular β-adrenergic responsiveness is not associated with a reduction of β-adrenoceptor density but probably is caused by a defect in the coupling mechanism between the adrenergic β-receptor and adenylate cyclase. The mechanism by which this postreceptor change occurs has not been fully elucidated. Also, it is not known whether the defect in the β-adrenoceptor–coupled adenylate cyclase system is responsible for the reduced resting left ventricular systolic function.

Earlier studies have shown that acute release of AVP such as occurs during hemorrhage, fluid deprivation, and acute hypoxia plays a role in the maintenance of blood pressure. However, the effect of chronically elevated AVP on blood pressure is well less elucidated. Long-term infusions of AVP have been shown to increase arterial pressure. This change, however, does not occur if fluid retention is prevented by rigorously controlling total body fluid volume. Hall et al. have shown that the initial pressor response to AVP wanes after 4–5 days despite continuous infusions and that the tendency for arterial pressure to return to normal after several days of continuous AVP infusion is prevented when renal artery pressure is not allowed to increase. These findings indicate that long-term elevations of plasma AVP may not cause sustained hypertension when plasma volume is allowed to contract by pressure diuresis.

Our present study showed that AVP inhibition by d(CH₃)₂Tyr(Me)AVP produced a decrease in total peripheral vascular resistance and an increase in cardiac output in heart-failure dogs without adrenergic receptor blockade. The rise in cardiac output was associated with increases in left ventricular dP/dt and dP/dt/P and plasma norepinephrine, but neither right atrial nor left atrial pressure changed significantly. Mean aortic pressure did not change significantly after AVP inhibition in the heart-failure dogs. However, after pretreatment with prazosin and propranolol, AVP inhibition caused a prompt decrease in mean aortic pressure and a reduction in total peripheral vascular resistance and vascular resistances in cutaneous, coronary, and splanchnic circulations. The findings indicate that the sympathetic nervous system was stimulated by AVP V₁-receptor blockade, with increased left ventricular contractile performance and cardiac output. Our findings that adrenergic receptor blockade attenuated the increase in cardiac output and abolished the increases in left ventricular dP/dt and dP/dt/P produced by d(CH₃)₂Tyr(Me)AVP are consistent with the adrenergically mediated cardiac responses. The small residual increase in cardiac output probably was secondary to the decrease in ventricular afterload. Thus, sympathetic stimulation probably occurs to offset the vasodilator effect of AVP V₁-receptor inhibition and prevents arterial pressure from decreasing. Our results suggest that AVP plays a role in maintaining vasomotor tone during its long-term elevations and contributes to the maintenance of arterial pressure in chronic heart failure when body-fluid volume is expanded.

Our findings that the right-heart failure animals responded to d(CH₃)₂Tyr(Me)AVP with a reduction

### Table 5. Changes in Organ Flow and Vascular Resistance after Arginine Vasopressin Inhibition in Right-Sided Congestive Heart-Failure Dogs After Prazosin and Propranolol Pretreatment

<table>
<thead>
<tr>
<th>Blood flow (ml/100 g/min)</th>
<th>Vascular resistance (mm Hg/mg/100 g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Inhibition</strong></td>
</tr>
<tr>
<td>Right ventricle</td>
<td>141 ± 9</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>127 ± 17</td>
</tr>
<tr>
<td>Kidneys</td>
<td>328 ± 31</td>
</tr>
<tr>
<td>Quadriceps muscle</td>
<td>5.7 ± 1.0</td>
</tr>
<tr>
<td>Skin</td>
<td>2.8 ± 0.5</td>
</tr>
<tr>
<td>Brain</td>
<td>80 ± 5</td>
</tr>
<tr>
<td>Adrenal glands</td>
<td>131 ± 32</td>
</tr>
<tr>
<td>Liver (hepatic artery)</td>
<td>62 ± 13</td>
</tr>
<tr>
<td>Stomach</td>
<td>25 ± 5</td>
</tr>
<tr>
<td>Small intestine</td>
<td>33 ± 8</td>
</tr>
<tr>
<td>Large intestine</td>
<td>47 ± 7</td>
</tr>
<tr>
<td>Spleen</td>
<td>90 ± 29</td>
</tr>
<tr>
<td>Splanchnic beds</td>
<td>40 ± 6</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. *Values that differ from the baseline at p<0.05.
in total peripheral vascular resistance and no significant change in mean arterial pressure are qualitatively similar to those reported in studies of patients with left-sided congestive heart failure.\textsuperscript{11,12} However, because left atrial pressure was not elevated in our animals with right-heart failure, the cardiac responses to the afterload reduction induced by d(CH\textsubscript{2})\textsubscript{5}Tyr(Me)AVP could be quantitatively different from those in left-heart failure.

AVP inhibition caused increases to blood flow to, and concomitant reductions in vascular resistance in, the skin, myocardium, skeletal muscle, kidneys, and liver in heart failure. Because the increase in myocardial blood flow was associated with increased cardiac work and left ventricular contractile function, the coronary vasodilation produced by AVP inhibition probably was caused, at least in part, by the increase in myocardial oxygen demand. Other mechanisms, however, might also be operative because coronary vascular resistance also decreased after AVP inhibition in dogs with adrenergic receptor blockade, despite an attenuated cardiac output response and no change in left ventricular dP/dt and dP/dt/P. Reductions in cutaneous and coronary vascular resistances also occur after administration of an AVP inhibitor in dogs with long-term plasma AVP elevation produced by 48 hours of intravenous AVP infusions.\textsuperscript{35} An increase in cutaneous blood flow also occurs after AVP inhibition in patients with congestive heart failure with high plasma AVP levels.\textsuperscript{11} These decreases in organ vascular resistances after AVP inhibition may be caused by either removal of the vasopressin-mediated vasoconstrictor or reflexly induced vasodilation resulting from the increase in cardiac output.

Our results further show that when the increase in cardiac output was attenuated markedly by the combined α- and β-receptor blockade, vascular resistance decreased after AVP inhibition only in the skin, myocardium, brain, and splanchnic beds. These findings indicate that AVP probably exerted a direct vasoconstrictor action on the cutaneous, coronary, cerebral, and splanchnic circulations. In contrast, the reductions in renal, hepatic, and skeletal muscle vascular resistances, which occurred after AVP inhibition only in animals not pretreated with adrenergic receptor–blocking agents, probably were caused by the reflexly mediated vasodilation. Furthermore, because splanchnic vascular resistance decreased after AVP inhibition only in dogs with adrenergic receptor blockade, a sympathetically mediated vasoconstriction probably occurred in the splanchnic circulation in the untreated animals to offset the splanchnic vasodilation produced directly by AVP inhibition.

The mechanism by which d(CH\textsubscript{2})\textsubscript{5}Tyr(Me)AVP causes sympathetic stimulation has not been fully elucidated. AVP is known to cause sensitization of arterial baroreflexes by an action on the area postrema,\textsuperscript{6,36} and subsequent withdrawal of the sympathetic nervous activity.\textsuperscript{37} That AVP acts centrally to diminish sympathetic outflow also has been reported to occur during vagal cold block in conscious dogs.\textsuperscript{38} Inhibition of this action of AVP by d(CH\textsubscript{2})\textsubscript{5}Tyr(Me)AVP enhances the sympathetic activity, as evidenced by the increase in plasma norepinephrine in our present experiments.

In conclusion, plasma AVP was elevated in right-sided congestive heart failure. Administration of the AVP inhibitor d(CH\textsubscript{2})\textsubscript{5}Tyr(Me)AVP was associated with an increase in cardiac output and improvement in left ventricular function and a decrease in total peripheral vascular resistance. Mean aortic pressure did not change significantly. The changes in left ventricular function were mediated by the sympathetic nervous system. Additionally, in dogs pretreated with adrenergic receptor blockers, AVP inhibition caused a decrease in mean aortic pressure. Total peripheral vascular resistance also decreased, along with reductions in vascular resistances in the skin, brain, myocardium and splanchnic beds. The results are consistent with AVP promoting vasoconstriction on a long-term basis, especially in the cutaneous, coronary, cerebral, and splanchnic circulations, and possibly inhibiting the sympathetic nervous system in congestive heart failure.

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KEY WORDS • systemic hemodynamics • regional blood flows • sympathetic nervous system • vasopressin inhibitor
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