Cardiac output distribution during vasopressin infusion or dehydration in conscious dogs

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LIARD, J. F., O. DÉRIAZ, P. SCHELLING, AND M. THIBONNIER. *Cardiac output distribution during vasopressin infusion or dehydration in conscious dogs.* Am. J. Physiol. 243 (Heart Circ. Physiol. 12): H663–H669, 1982.—To better understand the role of arginine vasopressin in cardiovascular regulation, we measured in unanesthetized dogs regional blood flows with radioactive microspheres before and during 1-h vasopressin infusions that increased the vasopressin concentration of plasma by 11 ± 0.6 pg/ml. Cardiac output measured by an electromagnetic flowmeter decreased by 13%. Blood flows to the skeletal muscle and skin, the areas most affected, decreased by 30.8 and 34.3%, respectively. In the same group of dogs a period of 48-h water restriction increased plasma vasopressin by 6.9 ± 1.3 pg/ml and reduced cardiac output by 14.4%. Skeletal muscle blood flow decreased by 32.8%, a pattern strikingly similar to that following vasopressin infusion. Obvious differences between vasopressin infusion and dehydration were also noted, in particular in the skin and splanchnic areas. However, the possibility that vasopressin contributed to the cardiovascular adjustments to dehydration must be considered. The use of an antagonist of the vascular effects of vasopressin, [1-deaminopenicillamine, 2-(*O*-methyl)tyrosine]arginine-vasopressin {[dPTyr(Me)]AVP}, did not permit us to clarify this issue, because this analogue given alone exerted pronounced systemic and regional cardiovascular effects that resembled those of vasopressin.

antidiuretic hormone; hemodynamics; microspheres

WE RECENTLY REPORTED that small increases in plasma concentration of vasopressin such as those associated with osmotic stimuli are followed by hemodynamic effects, notably a decrease in cardiac output and an increase in total peripheral resistance (18). This finding suggested that antidiuretic hormone might play a role in cardiovascular control, a concept that has received increasing support during the past few years as discussed by Cowley (4), Johnston et al. (12), and Liard (16). Inasmuch as moderately increased plasma levels of vasopressin reduce cardiac output, it would be of interest to determine which vascular beds experience decreases in perfusion and how much the reduction of each regional blood flow contributes to the global fall in systemic blood flow. Furthermore, identification of vascular beds more sensitive to the effects of vasopressin than others should provide some clues about the physiological meaning of the vasoconstrictive action of the hormone and about its impact in cardiovascular regulation in situations of increased endogenous release.

A number of previous studies that looked at the distribution of cardiac output during vasopressin administration have been reviewed by Saameli (21), Nakano (19), and Cowley (4). However, they do not provide adequate answers to the questions raised, because one or several of the following remarks apply to all these experiments. First, the vasopressin infusion rates used often increased plasma levels above 30 pg/ml, a limit rarely exceeded in the day-to-day operation of the normal mammalian organism. Second, a reliable measurement of plasma vasopressin concentration was usually not performed. Third, in many studies anesthetized preparations were used with varying degree of surgical trauma, which led to high endogenous levels of vasopressin. Finally, there was no quantitative assessment of the contribution of each organ to the overall decrease in cardiac output, and the effect of an increase in mean arterial pressure complicated the interpretation of regional vascular resistance changes in many instances.

The present study was performed in unanesthetized dogs at plasma vasopressin levels below 20 pg/ml, as measured by a sensitive radioimmunoassay, and with simultaneous measurement of cardiac output and regional blood flows. The increased levels of vasopressin resulted either from intravenous infusion of the substance or from stimulation of its endogenous release by dehydration.

METHODS

Animal Preparation

A total of 25 male mongrel dogs were included in these studies (body wt on *day 0*, 19.6 ± 0.7 kg). The dogs were operated on under pentobarbital anesthesia (30 mg/kg, supplemented as necessary) and in sterile conditions. Catheters were inserted into the aorta and the inferior vena cava through the iliac vessels for arterial pressure measurement, blood sampling, and intravenous infusions. Through a thoracotomy at the fourth intercostal space, an electromagnetic flow transducer was placed around the ascending aorta for cardiac output measurement (without coronary blood flow), and a catheter was inserted into the left atrium for microsphere injections. All cables and catheters were exteriorized on the back of the animals, and at least 1 wk of recovery from surgery was allowed.

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Measurement of Systemic Hemodynamics and Regional Blood Flows

All measurements were performed in the awake animals as previously described (15, 18). Mean and pulsatile arterial pressure, cardiac output (computed from integration of the aortic flow signal), and heart rate were continuously recorded on a multichannel paper oscillograph. Intermittent measurements of left atrial pressure were also performed. Experiments were conducted when the dogs were trained to lie quietly in the recording pen for several hours.

Regional blood flows were determined with radioactive microspheres using techniques described and discussed in detail elsewhere (15). Briefly, 1.0–1.5 × 10^6 NEN-TRAC microspheres, 15-μm in diameter, were flushed into the left atrial catheter over 20 s through an injector vial while a reference arterial sample was collected at a precisely measured rate. Approximately 15 ml of blood were removed for each measurement. Three isotopes were used at different times in each dog: ^{46}Sc, ^{113}Sn, and ^{153}Gd. After the animals were killed, organs and tissues were cut into small pieces and counted, allowing determination of the blood flow corresponding to each isotope. Extensive tissue sampling was performed, and most of the organs were counted in toto (15). The results of regional blood flow measurements were rejected if one of the following criteria was not met. First, in each dog the sum of all regional blood flows measured with each isotope was divided by the cardiac output measured at the time of the microsphere injection with the electromagnetic flowmeter; if one or both ratios obtained at the second and third injections differed from that calculated at the first injection by more than 15%, they were rejected. Second, hemodynamic values at the time of microsphere injection had to be representative of basal values prevailing during the 15 min before injection. Seventeen out of a total of 50 experimental values were rejected on the basis of these two criteria.

Other Measurements

Blood samples were taken from the aortic catheter. Hematocrit was measured by microcentrifugation, plasma vasopressin concentration by a radioimmunoassay (24), and plasma renin concentration by radioimmunoassay of angiotensin I formed following incubation with excess angiotensinogen. Sodium and potassium concentrations were measured by flame photometry in plasma, urine, and ashed food dissolved in 0.1 N HCl. Osmolality was obtained by freezing-point depression osmometry in plasma and urine. A total of 20 ml of blood was removed for these measurements.

Experimental Protocols

The dogs were kept in metabolic cages for several days before the experimental period; their urine was collected and the amount of drinking water was measured. The food was given in constant quantity, by forced feeding if necessary. The diet contained about 80 meq/kg of sodium and 15 meq/kg of potassium, although the latter was more variable. Sodium chloride (156 mmol) was added each day to the food to increase the effect of water restriction on plasma osmolality. The amount of water ingested in the food was approximately 600 ml/day and remained constant throughout the experiment.

On the morning of *day 0* the animals were brought to the recording pen and, after 1 h of continuous monitoring of hemodynamic variables, received a 1-h infusion of one of the three solutions indicated in Table 1. Before and at the end of this infusion regional blood flows were obtained by the first and second microsphere injections. Also blood samples were taken for plasma vasopressin, renin, and electrolyte concentration, as well as for hematocrit and osmolality. The dogs were returned to the metabolic cages and were either allowed or denied drinking water. After 48 h, on *day 2*, a third microsphere injection was performed after a 1-h monitoring of hemodynamic data and, in one instance, after a new 1-h infusion. Table 1 summarizes the experimental maneuvers performed in the three groups of dogs studied. The measurements made before the infusion on *day 0* served as controls in each group for the value measured during infusion on *day 0*, as well as for the value obtained on *day 2*. Dogs of *group 2* served as a time control group for the values obtained during infusion on *day 0*, and dogs of *group 3* served as a time control group for the values obtained on *day 2*.

All infusions were given intravenously at a rate of 0.2 ml/min. Arginine vasopressin was supplied by Ferring. The vasopressin analogue, [1-deaminopenicillamine, 2-(*O*-methyl)tyrosine]arginine-vasopressin, {[dPTyr(Me)]-AVP} was kindly supplied by Prof. Maurice Manning, Toledo, OH (3). The ability of this substance to antagonize the cardiovascular effects of vasopressin was tested

TABLE 1. *Experimental conditions for dogs of groups 1–3 at time of microsphere injections*

Group	Total No.	1st Microsphere Inj (*day 0*)	2nd Microsphere Inj (*day 0*)	3rd Microsphere Inj (*day 2*)
1	11	Before infusion of arginine vasopressin 217 pg·kg^{-1}·min^{-1} (n = 7)	During infusion of arginine vasopressin 217 pg·kg^{-1}·min^{-1} (n = 5)	After 48 h water restriction (n = 5)
2	8	Before infusion of isotonic saline (n = 6)	During infusion of isotonic saline (n = 5)	After 48 h water restriction and during infusion of [dPTyr(Me)]-AVP 20 ng·kg^{-1}·min^{-1} (n = 6)
3	6	Before infusion of [dPTyr(Me)]-AVP 20 ng·kg^{-1}·min^{-1} (n = 6)	During infusion of [dPTyr(Me)]-AVP 20 ng·kg^{-1}·min^{-1} (n = 6)	After 48 h control period (n = 6)

Nos. in parentheses indicate no. of experiments accepted for regional blood flows.

in five dogs 2 days after completion of the experiments. Bolus injections of vasopressin were given intravenously at 30-min intervals; then [dPTyr(Me)]AVP was infused at 20 ng·kg^{-1}·min^{-1}, and vasopressin injections were repeated starting 30 min after the beginning of the infusion of the antagonist while mean arterial pressure, heart rate, and cardiac output were continuously monitored. Peak changes in each variable were calculated for each dose.

Statistical Analysis

Results are given as means ± SE. Most of them are presented as changes from the control value obtained before the infusion on *day 0*. The statistical significance of these changes was assessed by a paired *t* test. Differences were considered significant for $P < 0.05$. Linear regressions were calculated with the least-squares method.

RESULTS

Control Values

The values obtained in the three groups of dogs on *day 0* before the infusion, or, for the balance studies, during the 2 days preceding *day 0*, have been combined because analysis of variance indicated that they did not differ significantly. The only exception was the urinary excretion of potassium, which was higher in *group 3* due to a higher content of potassium in the food.

Humoral parameters and balance studies. For the 25 dogs studied on *day 0* before the infusion, plasma vasopressin concentration was 2.34 ± 0.35 pg/ml, plasma renin 0.97 ± 0.32 ng ANG I·ml^{-1}·h^{-1}, plasma osmolality 294.8 ± 0.9 mosmol/kg, plasma sodium 144.6 ± 0.6 meq/l, plasma potassium 3.71 ± 0.06 meq/l, and hematocrit 37.3 ± 1.1%.

During the two days preceding *day 0*, the average daily intake of drinking water was 680 ± 54 ml and the daily urinary volume 870 ± 51 ml. Urinary osmolality was 1,079 ± 46.5 mosmol/kg. The daily urinary excretion of sodium was 203 ± 13 meq for a sodium intake of 220 meq.

Systemic hemodynamics. At the time of the first microsphere injection, mean arterial pressure was 97.6 ± 3.2 mmHg ($n = 19$), cardiac output (electromagnetic flowmeter) 2,448 ± 110 ml/min, heart rate 83.7 ± 3.0 beats/min, and left atrial pressure 2.1 ± 0.5 mmHg. The ratio of mean arterial pressure and cardiac output (defined as total peripheral resistance) was 41.0 ± 1.9 mmHg·min·l^{-1}.

Regional blood flows. Table 2 gives control values for those organs and tissues that represent a sizable portion of cardiac output. The splanchnic area (liver, gastrointestinal tract, spleen, pancreas, and abdominal fat) represents 27.8 ± 1.3% of the total of all regional blood flows (817.4 ± 37.6 ml/min). Because the flow to various bones and muscles was not homogeneous, we have not indicated values per unit weight for these tissues.

TABLE 2. *Control regional blood flows in 19 conscious dogs*

Organ	Blood Flow		
	ml/min	ml·100 g^{-1}·min^{-1}	% Cardiac output (sum of all regional blood flows)
Skeletal muscle	792.7 ± 77.9		25.94 ± 1.96
Heart	113.9 ± 6.0		3.84 ± 0.17
Left	88.0 ± 4.5	80.9 ± 4.8	
Right	25.9 ± 2.0	53.7 ± 3.1	
Kidney	440.0 ± 34.9	417.5 ± 22.1	14.61 ± 0.76
Liver	207.5 ± 28.5	33.6 ± 4.0	6.95 ± 0.98
Gastrointestinal tract	359.6 ± 19.8		12.30 ± 0.81
Esophagus	5.8 ± 0.6	12.6 ± 1.7	
Stomach	87.6 ± 7.4	72.1 ± 4.5	
Duodenum	18.4 ± 1.8	60.5 ± 5.4	
Small intestine	189.1 ± 11.1	72.6 ± 4.4	
Colon	58.7 ± 5.6	77.6 ± 5.9	
Spleen	131.6 ± 12.4	178.9 ± 17.9	4.88 ± 0.51
Pancreas	67.6 ± 9.5	183.9 ± 20.8	2.28 ± 0.30
Abdominal fat	51.1 ± 3.8	15.3 ± 1.6	1.74 ± 0.13
Lungs*	123.2 ± 14.0	40.4 ± 4.4	4.07 ± 0.43
Brain	64.5 ± 3.1	68.1 ± 3.3	2.24 ± 0.16
Skin	302.1 ± 30.5	11.2 ± 0.9	10.04 ± 0.89
Bone	334.7 ± 19.5		11.39 ± 0.65

Values are means ± SE. * Bronchial + shunt blood flow.

Vasopressin Infusion (Group 1 on Day 0)

Humoral changes. Plasma vasopressin concentration increased by 11.0 ± 0.6 pg/ml ($n = 11$). Plasma renin concentration did not change significantly (−0.1 ± 0.1 ng ANG I·ml^{-1}·h^{-1}) nor did plasma sodium and potassium concentrations or osmolality. In the dogs receiving an infusion of isotonic saline (*group 2* on *day 0*, $n = 8$), plasma vasopressin remained unchanged (+0.4 ± 0.2 pg/ml) as did all the other variables apart from plasma renin, which increased significantly by 0.5 ± 0.2 ng ANG I·ml^{-1}·h^{-1}.

Systemic hemodynamics. Mean arterial pressure (MAP) remained unchanged (ΔMAP = +1.6 ± 4.7 mmHg), but cardiac output (CO) fell by 325 ± 91 ml/min (13%) and total peripheral resistance increased by 7.4 ± 1.8 mmHg·min·l^{-1}. In the group receiving isotonic saline there were no changes in any of these variables (ΔMAP = +1.8 ± 2.2 mmHg, ΔCO = +9.2 ± 39.7 ml/min).

Regional blood flows. None of the changes in regional blood flows measured in the group receiving an isotonic saline infusion differed significantly from zero. On the contrary, in the animals receiving vasopressin a number of changes were noted that are summarized in Fig. 1. The regional blood flows have been divided into eight groups for the purpose of simplification. Significant decreases were observed in skeletal muscle (−258 ± 91 ml/min or 30.8%), myocardium (−21.1 ± 7.5 ml/min or 16.6%), brain (−6.4 ± 1.5 ml/min or 9.4%), and skin (−84.8 ± 3.1 ml/min or 34.3%). The changes in the control group for these organs and tissues were 9.6% in skeletal muscle, −2.3% in myocardium, −5.0% in the brain, and −14.3% in the skin. By far the largest contribution to the overall decrease in cardiac output after vasopressin infusion was the fall in skeletal muscle blood flow. The fraction of cardiac output was significantly reduced in the skeletal muscle and in the skin. During vasopressin infusion, skeletal muscle blood flow represented 19.7 ± 1.0% of cardiac output vs. 25.9 ± 2.0% in controls, and skin blood flow 5.7 ± 0.5% vs. 10.0 ± 0.9% in controls.

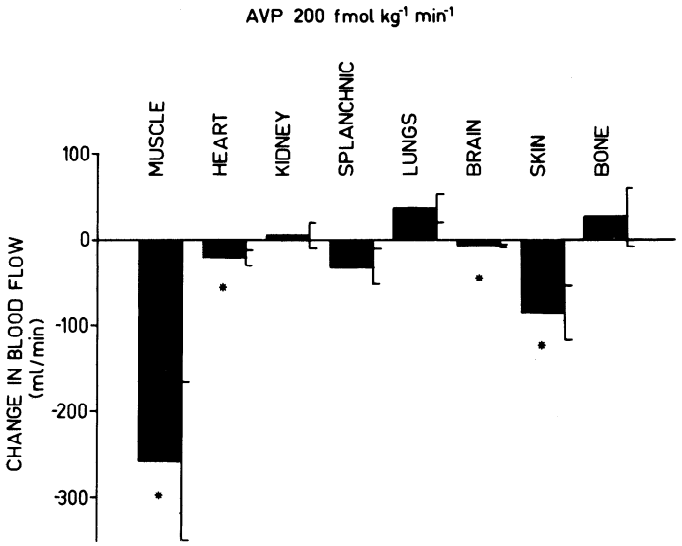

FIG. 1. Changes in regional blood flows induced by a 1-h infusion of arginine vasopressin, 217 pg·kg^{-1}·min^{-1}, in 5 conscious dogs. * Significant change from value before infusion.

Although the splanchnic area as a whole did not show a significant decrease in blood flow, some areas did, such as the esophagus (−3.2 ± 0.3 ml·100 g^{-1}·min^{-1} or 27%), the duodenum and the small intestine (−9.0 ± 3.1 ml·100 g^{-1}·min^{-1} or 12%), the colon (−19.1 ± 7.8 ml·100 g^{-1}·min^{-1} or 24.2%), the pancreas (−40.8 ± 15.1 ml·100 g^{-1}·min^{-1} or 24.6%), and the abdominal fat (−3.0 ± 1.0 ml·100 g^{-1}·min^{-1} or 24.8%). The changes in the control group were −1.2% in the gastrointestinal tract, −12.0% in the pancreas, and −8.4% in the abdominal fat. Among the 18 groups of muscles that were weighed and sampled separately, the largest relative decreases during vasopressin infusion took place in the muscles of the hip, abdominal wall, diaphragm, intercostal muscles, muscles of the shoulder, cranial brachial muscles, and muscles of the crus and hindpaw. Other territories that showed a decreased blood flow in response to vasopressin infusions were the aortic wall (15% fall from a control value of 13.8 ± 1.3 ml·100 g^{-1}·min^{-1}), the thyroid gland (28.1% decrease from a control value of 420.4 ± 108.3 ml·100 g^{-1}·min^{-1}), the mandibular gland (23.4% fall from a control value of 33.7 ± 6.2 ml·100 g^{-1}·min^{-1}), and the pericardium (30.3% decrease from a control value of 31.5 ± 4.8 ml·100 g^{-1}·min^{-1}). No significant changes were noted in the adrenals, the gallbladder, the prostate, the bladder, the testicles, the eyes, and the trachea.

Since arterial pressure did not change in these experiments, a decrease in blood flow indicates a fall in vascular conductance of a similar magnitude, neglecting possible modifications of venous pressure.

Water Restriction for 48 h (Groups 1 and 2 on Day 2)

Humoral changes and balance studies. The dogs belonging to *group 1* and to *group 2* (before infusion of [dPTyr(Me)]AVP were all subjected to 48-h water restriction. Therefore, their results have been combined.

Compared with the average value for 2 days preceding the period of water restriction, the dogs decreased their urinary volume on the 2nd day of water restriction by 351.7 ± 93.4 ml. On the contrary, the dogs in *group 3* did not change their urinary volume significantly (+41.7 ± 118.4 ml), nor did they modify the amount of water they drank. Sodium and potassium excretion did not change significantly throughout the experiment whether the dogs underwent water restriction or not.

Table 3 summarizes the humoral consequences of 48-h water restriction. They include an increased plasma and urinary osmolality and an increased plasma vasopressin concentration.

Systemic hemodynamics. In the dogs of *group 1* subjected to water restriction mean arterial pressure at the time of the third microsphere injection was similar to its control value (−2.8 ± 2.1 mmHg), but cardiac output was lower by 334 ± 123 ml/min (or 14.4%) and heart rate by 13.2 ± 5.9 beats/min. Left atrial pressure decreased by 2.2 ± 0.3 mmHg. Total peripheral resistance increased by 6.2 ± 4.2 mmHg·min·l^{-1}, which was not significant. In the dogs of *group 3* on *day 2* mean arterial pressure was unchanged (−1.2 ± 2.5 mmHg), but cardiac output decreased significantly by 112.7 ± 40 ml/min and left atrial pressure by 0.4 ± 0.15 mmHg.

Regional blood flows. In the dogs of *group 3* on *day 2* (controls) the changes measured after 48 h were not significantly different from zero and were all within ±12% of the control value with the exception of the lungs (−61.2 ± 22 ml/min or 46.7%) and the skin (−56.4 ± 17.8 ml/min or 19.2%). We have no explanation for these significant changes in the control group. They might represent a consequence of repeated microspheres injections.

Figure 2 summarizes the changes observed after 48-h water restriction alone (dogs of *group 1*). Significant decreases were measured in the skeletal muscle (−254 ± 92 ml/min or 32.8%), the myocardium (−24 ± 10 ml/min or 20.8%), and in some portions of the splanchnic area (liver, −38 ± 15.6 ml/min or 25.4%). On the other hand, and contrary to what had been observed with vasopressin infusion, the gastrointestinal tract showed an overall increase by 63.9 ± 22.7 ml/min or 23.9%, the largest portion of which took place in the small intestine. There was no tendency for pancreatic blood flow to decrease (+15.5 ± 17.1 ml/min). Another striking difference between vasopressin infusion and 48-h water restric-

TABLE 3. *Changes in various parameters induced by a 48-h period of water restriction or of normal water intake in dogs*

	Water Restriction (*groups 1-2, n* = 19)	Normal Water Intake (*group 3, n* = 6)
Urinary osmolality, mosmol/kg	+636.6*	−94.9
	±51.5	±65.9
Plasma AVP, pg/ml	+6.9*	+1.2
	±1.3	±0.9
Plasma renin, ng ANG I·ml^{-1}·h^{-1}	+1.0*	+0.4
	±0.2	±0.2
Plasma osmolality, mosmol/kg	+11.8*	+0.7
	±2.3	±2.0
Plasma sodium, meq/l	+4.2*	+0.1
	±0.9	±0.8

Values are means ± SE. * Significantly different from zero.

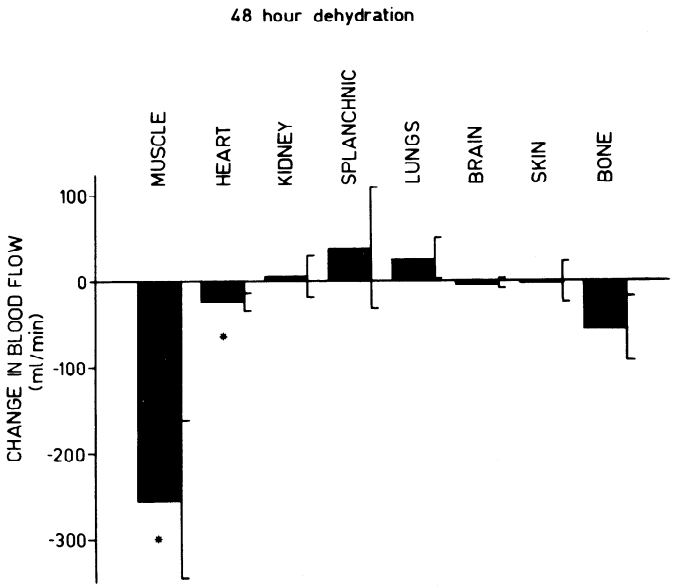

FIG. 2. Changes in regional blood flows induced by a 48-h period of water restriction in 5 conscious dogs. * Significant change from value before dehydration.

tion was the behavior of skin blood flow, which did not change in the latter instance (−0.9 ± 23.6 ml/min). In the brain there was a pronounced variability in the response to dehydration (−5.2 ± 5.8 ml/min, NS). We measured a significant reduction of the flow to the thyroid gland (18.4%) and to the gallbladder (22.8%) but no significant changes in the flow to the aorta, mandibular gland, pericardium, adrenals, prostate, bladder, testicles, eyes, or trachea. The blood flow to some bones was decreased, the only significant change being observed in the ribs (−22.6 ± 5.8 ml/min or 28.7%). For the skeletal muscle blood flow, the most conspicuous decreases took place in the muscles of the thoracic wall, the abdominal wall, the epaxial spinal muscles, the intercostal muscles, and the muscles of the shoulder.

Regional blood flows were also studied during infusion of the vasopressin analogue [dPTyr(Me)]AVP administered in dogs deprived of water for 48 h (*group 2*), in an attempt to determine whether some of the changes observed in dehydrated animals could be attributed to increased vasopressin levels. However, hemodynamic measurements showed that cardiac output fell even more after administration of the antagonist than with water restriction alone. Regional blood flow measurements indicated that pronounced vasoconstrictor effects took place in several areas, including the gastrointestinal tract, pancreas, abdominal fat, skin, and skeletal muscle. This suggested that the analogue might have effects of its own, which prompted the study of the hemodynamic consequences of infusion of [dPTyr(Me)]AVP.

Infusion of [dPTyr(Me)]AVP (Group 3 on Day 0)

Humoral changes. Plasma vasopressin concentration could not be measured following infusion of [dPTyr-(Me)]AVP at 20 ng·kg^{-1}·min^{-1} because the analogue exhibited pronounced cross-reactivity in the radioimmunoassay. Plasma renin activity decreased slightly but significantly by 0.16 ± 0.05 ng ANG I·ml^{-1}·h^{-1}, and hematocrit fell by 2.8 ± 0.8 hematocrit units. Plasma electrolytes and osmolality did not change significantly.

Systemic hemodynamics. Mean arterial pressure did not change significantly (+1.8 ± 2.1 mmHg), but cardiac output showed a marked fall by 689 ± 77 ml/min (or 31.1%) and heart rate decreased by 16.8 ± 4.2 beats/min. Total peripheral resistance increased by 23.3 ± 5.1 mmHg·min·l^{-1}. The rate of infusion of the analogue was increased to 200 ng·kg^{-1}·min^{-1} for a short time after microsphere injection and blood sampling. Still, there was no significant increase in mean arterial pressure. In the five dogs that served to evaluate the extent of vasopressin blockade, the analogue infused at 20 ng·kg^{-1}·min^{-1} did not affect the slope of the dose-response curve to vasopressin but shifted the curve to the right. To obtain a 10-mmHg increase in mean arterial pressure, the dose of vasopressin necessary was 7.3 times greater with the antagonist.

Regional blood flows. Significant falls in flow were observed in skeletal muscle (−394.1 ± 150.6 ml/min or 53.7%), myocardium (−29 ± 9.2 ml/min or 24.8%), splanchnic area (−241.7 ± 50 ml/min or 27.6%), skin (−207.0 ± 32.4 ml/min or 70.4%), and bone (−78.7 ± 21.7 ml/min or 23.6%). In the splanchnic region, prominent changes took place in all parts of the gastrointestinal tract, including the stomach (55.3% reduction), the pancreas (77.6% reduction), and the abdominal fat (64.7% decrease). Other organs showing pronounced decreases in flow were the aorta (42.4%), thyroid gland (55.7%), mandibular gland (54%), pericardium (57.4%), bladder (34.3%), and trachea (59.8%).

DISCUSSION

The results obtained in this study confirmed that arginine vasopressin infusions that increase its plasma concentration by less than 20 pg/ml lower cardiac output (18). They further demonstrated that under these circumstances blood flow to the skeletal muscle and to the skin was reduced proportionately more than cardiac output, as were flows to the pancreas, the abdominal and pericardial fat, and the thyroid gland. In the gastrointestinal tract, the myocardium, and the brain, relative blood flow reduction was similar to that of cardiac output, whereas some organs showed no decrease in blood flow at all, in particular the kidney. The reliability and limitations of the microsphere method for the study of regional circulations have been extensively discussed (8, 9). Our results thus indicate that resistance vessels in some areas, particularly the muscle and skin, are very sensitive to the constrictive effects of vasopressin. This conclusion was reached before by several investigators using larger amounts of vasopressin. Ericsson (6) found in anesthetized dogs that lysin vasopressin infused at a rate of 0.75 mU·kg^{-1}·min^{-1} decreased blood flow to some muscles, to the gastrointestinal tract, and to the pancreas but not to the brain, the heart, or the hindlimb musculature. Schmid et al. (22), also using anesthetized dogs, indicated that the sensitivity to vasopressin appeared highest in skeletal muscle, smaller in the mesentery, and even smaller in the kidney. Hoffman (11) reported that arginine vasopressin infused into unanesthetized rats at 0.5

$mU \cdot kg^{-1} \cdot min^{-1}$, a rate five times higher than that used in our study, produced the greatest increase in vascular resistance of muscle and skin tissues. Our results extend these previous observations and show that increases of plasma vasopressin levels that are within the range of response to osmotic stimuli are sufficient to selectively constrict muscle, skin, and other vascular beds. Since the fall in myocardial blood flow was of the same order as the decrease in cardiac output, it may be more the consequence of a decrease in cardiac work than of a specific coronary vasoconstriction. Indeed, the resistance changes measured in a given area reflect not only direct vasoconstrictive effects of vasopressin, but also interaction with other factors controlling arteriolar diameter.

We have previously suggested that low infusion rates of vasopressin might lower cardiac output by an effect on the central nervous system (17, 18). Such an effect would result in underperfusion of all organs and tissues of the body, were it not for differential vasoconstriction. Decreased perfusion in the skin and skeletal muscle is certainly not as detrimental as in some other territories, which indirectly supports the suggestion that vasopressin might play a role in the control of arterial pressure in hemorrhage (5, 14, 20, 23).

Strong vasoconstrictive effects of vasopressin in some areas might suggest that this hormone plays there a role based on its vascular action. Thus, marked reductions of skin blood flow could have implications for thermoregulation. However, Forsling et al. (7) have shown that plasma vasopressin levels increase at high temperatures. Also, an impact on carbohydrate metabolism could result from the prominent effect of vasopressin on pancreatic and fat blood flow.

Reduction of blood flow to a given area does not necessarily imply a high sensitivity of its blood vessels to vasopressin but may reflect an effect of vasopressin on the metabolism of the tissue. Another possibility that may account for differential vascular effects of a vasoactive agent is an inhomogeneous distribution of reflex withdrawal of sympathetic tone, as discussed by Heyndrickx et al. (10). In the case of vasopressin, this appears very unlikely because we found a pronounced vasoconstriction in the muscular bed, which is one of the main targets of the reflex control of the circulation by the baroreceptor feedback loop (13).

Since vasopressin affected some regional circulations at low plasma concentrations, we tested the possibility that it might contribute to the cardiovascular adjustments in dehydration. We noted several similarities between the effects of water restriction for 48 h and vasopressin infusion, in particular a decrease in cardiac output and in heart rate, as well as a marked reduction in skeletal muscle blood flow which represented by far the largest contribution to the overall decrease in cardiac output in both instances. Although this parallelism is no proof that skeletal muscle blood flow reduction in dehydration was caused by vasopressin, it is compatible with such a possibility. However, several additional factors certainly contribute to the systemic and peripheral hemodynamic picture in dehydration, such as increased plasma osmolality, sodium concentration, renin activity (which was only modestly elevated however), presumably enhanced sympathetic tone and reduced blood volume. These other factors could account for some of the differences that were observed in dehydrated dogs compared with animals receiving vasopressin infusions, despite increases in plasma vasopressin concentration of a similar magnitude. Alternatively, local or systemic control mechanisms might counteract the acute vasoactive properties of vasopressin when its plasma concentration remains durably increased, as was the case in dehydration.

In an attempt to demonstrate the participation of vasopressin in the hemodynamic consequences of dehydration, we administered an antagonist of the pressor effects of vasopressin, [dPTyr(Me)]AVP. A similar approach has been used before (1, 2). The results of our experiments with this antagonist in dehydrated dogs could not be interpreted, because they reflected cardiovascular effects of the antagonist itself instead of those of blockade of endogenous vasopressin. Indeed, [dPTyr(Me)]AVP given alone decreased cardiac output and heart rate markedly, with little or no effect on mean arterial pressure. Furthermore, it reduced several regional blood flows with a pattern that resembled that of vasopressin itself. These results suggest that [dPTyr(Me)]AVP acts as a partial agonist in the conscious dog. In other experimental conditions and species, no vascular agonistic activity was detected when using this compound (1, 3), a result which was confirmed by Dr. Karl Hofbauer (Ciba-Geigy, Basle), who tested the preparation we used in anesthetized Brattleboro rats homozygous for diabetes insipidus and could detect no agonistic activity from measurements of arterial pressure and mesenteric and renal blood flow. Whether the cardiovascular effects of [dPTyr(Me)]AVP found in our study reflect interaction of this substance with vascular receptors or not, they emphasize the need for caution in interpreting the results obtained with these newly synthesized antagonists of vasopressin.

In conclusion, we have observed that vasopressin exerted pronounced effects on some regional circulations at concentrations that are commonly associated with osmotic stimuli. It appears therefore likely that the vascular effects of vasopressin are of importance in the regulation of peripheral circulations and that it should be considered as a possible factor in the mechanisms responsible for changes in cardiac output distribution that are associated with various conditions known to modify the plasma concentration of vasopressin.

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