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Hemodynamics in Experimental Hypernatremic Dehydration with Special Reference to Individual Organ Blood Flow in Shock and after Rehydration

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Summary

Shock after hypernatremic dehydration in the mini-pig is characterized by low cardiac output but little reduction of arterial blood pressure. Maintenance of pressure is due to extensive arteriolar vasoconstriction in the splanchnic and renal vascular bed, as calculated from their markedly diminished blood flow. The expected preservation of flow to vital organs did occur in the brain and the adrenals, but not in the heart. Sufficient oxygen was probably provided by the elevated hematocrit.

After 24 h, intravenous fluid therapy produced adequate rehydration as seen from the correction of azotemia, metabolic acidosis, and hypernatremia; only serum creatinine remained elevated. Although cardiac output increased, it did not reach the initial value. Blood flow to most organs was back to normal, but gastrointestinal and particularly renal blood flow remained diminished.

Although diagnosis and treatment of hypernatremic dehydration in infancy follows established guidelines (10, 18), proper management of this disease remains a challenge for the clinician. Assessment of the circulatory state still represents a major problem because these infants are often in a state of pre-shock or shock. Little is known about the hemodynamic consequences of the perfusion of vital organs and the effect of treatment. We therefore developed an animal model where hemodynamic changes and particularly cardiac output, its distribution and individual organ blood flow could be investigated.

METHODS

In 20 young 2-month-old mini-pigs, weighing 3.0 kg (2.6–3.66), polyvinyl catheters were inserted into the right femoral vessels; through a left-sided thoracotomy a thin polyethylene PP 30 catheter was introduced into the left atrium via the left atrial appendage. The operation was performed under halothane/O_2 anesthesia with the animal intubated and ventilated. The atrial catheter went through a subcutaneous dorsal tunnel and the femoral catheters were fixed at the groin in order that the catheters could be manipulated in the unrestrained awake animal. Operation time was on average 240 min. After 3 days of recovery, measurements of blood chemistry and hemodynamics were performed. Sodium, potassium, and calcium were measured with flame photometry; chloride was determined amperometrically. Glucose was measured with the oxidase reaction, creatinine with the Jaffé's reaction, and urea with the urease digestion-method. Osmolarity was determined by the freezing point depression. Arterial blood gases were measured on an Acid-Base-O_2 Microanalyzer, model 939, AVL AG, Schaffhausen, Switzerland, and adjusted to the animals body temperature, which was measured continuously with a rectal probe. Cardiac output was calculated with the dye dilution method using cardiogreen on a Waters XC-Densitometer. Pressure measurements were done with a Statham P 23 Dc transducer and a Honeywell 2106 Visicorder. Distribution of cardiac output was measured with the left atrial injection of radioactive microspheres ([^{46}Sc], [^{85}Sr], [^{51}Cr], [^{141}Ce], and [^{125}I]) (9, 15, 17).

In five animals, spheres with a diameter of 50 μ and in 15 animals spheres with a diameter of 15 μ were used and each injection averaged 37,670 for the 50- and 351,000 for the 15-μ spheres. Studies on the use of microspheres in the mini-pig showed no difference in extraction for 50- or 15-μ spheres for all major organs (11).

The relatively small number of injected 50-μ spheres limited the accuracy of flow determination in the adrenal and partly in pancreas, liver artery, and spleen because 400 microspheres are required for a $\pm 10\%$ accuracy and this number could not always be reached (1). This problem was, however, compensated for by an adequate number of animals.

The gamma activity of the dissected animals was counted on

a Packard 5986 counter with a model 9012 pulse height analyzer, according to previously described methods (9, 11, 17).

Dehydration. After the initial measurements (Time "A") hypernatremic dehydration and metabolic acidosis were produced in 12 animals (experimental group), weight 3.05 (2.6–3.66) kg by feeding 8 ml of a 1 M NaCl + 8 ml 1 M NH_4Cl solution per kg body weight, 4–6 times via gastric tube until dehydration from osmotic diuresis caused cardiac output to fall to 50% of its initial value. The time interval from initial measurements ("A") to this point of circulatory failure ("B") was on average 45 h 30 min (39 h–55 h 30 min).

The reduction of body weight during this period was 23% (19–27) of the initial value. Because these animals were starved, we assessed weight loss in a series of six animals with a zero calorie diet and free water for the time interval of the experiment. Weight loss of 8.2–10.1%, average 9%, of the initial value after 48 h was found, and we therefore considered the weight loss from dehydration alone to be on an average, 23 − 9 = 14%. This value correlated well with the fluid balance obtained in a number of animals.

Rehydration. The fluid deficit was calculated from the weight loss between A − B and corrected for the starving group, *i.e.*, 140 ml/kg of weight A corresponding to 195 ml/kg of weight B. A maintenance requirement of 85 $ml \cdot kg^{-1} \cdot 24\ h^{-1}$ was added that resulted in a total of 280 ml/kg weight B. This amount of fluid was divided in a 3-h intravenous rehydration period with 60 ml/kg (time B − C) and a 21-h period with the remaining fluid, on average 220 ml/kg (time C − D). The solutions were 2.5% glucose + 42 mM/liter NaCl + 42 mM/liter $NaHCO_3$ and 3.35% glucose + 28 mM/liter $NaHCO_3$ + 28 mM/liter KCl, respectively. In a control group of eight animals, weighing 2.65–3.66 kg, mean 3.0 kg, without dehydration and with normal food intake, the measurements were done within similar time intervals, namely A − B, 46 h; B − C, 3 h; and C − D, 21 h.

The statistical analysis of the results was done by forming the differences between initial values and shock, as well the differences between initial values and the 3 and 24 h rehydration; these differences in the experimental group were compared with those obtained for the same time intervals in the control group by using the non-parametric U-test of Wilcoxon, Mann and Whitney (19).

In addition, all values from the control animals were compared with each other at the different time intervals and with initial values from the experimental group. There was no difference using the U-test, as described, and therefore the values of the control animals are not presented.

RESULTS

Initial values at control state are referred to as time A, shock as time B, rehydration at 3 h as C, and after 24 h as time D. The results are shown in Tables 1–5. Clinically, the animals were irritable and lethargic at the time of dehydration; only one of the 12 had convulsions. They were all oliguric, the skin was dry and cold with markedly reduced turgor. In the course of rehydration they appeared unchanged at C, but were more alert and lively at D where all had increasing diuresis. The skin showed normal turgor but was still cold and pale.

The highly significant rise of serum Na, Cl, urea, creatinine, osmolarity, and the severe metabolic acidosis at the state of dehydration (B) were only slightly corrected by 3 h of fluid administration (C), but reached normal values after the 24-h rehydration period (D). Glucose was elevated at B and already normal at C, whereas at D the only persisting abnormal value was a high creatinine, all other values being back to normal.

The basic hemodynamic changes at B were those of an elevated heart rate, low cardiac output and stroke volume, but high total peripheral arterial resistance and thus maintained arterial pressure. The distribution of cardiac output showed increased fractions to brain and adrenals and a reduction of the pancreatic and portal fraction; all other percentages were unchanged. Blood flow to most organs was therefore diminished to the same extent as was cardiac output. Maintained flow, however, was found in the brain and the adrenals, and also in arterial blood flow to the liver. At C, all these flow values remained unaffected, but at D, the following changes were observed: stroke volume and cardiac output were still slightly but significantly reduced, and total peripheral arterial resistance elevated, the kidney fraction also remained diminished, and an increase was seen for splenic and cutaneous fractions. Flow to most organs continued to be reduced, especially to the gastrointestinal tract and to the kidneys. A tendency towards normalization was evident whereas brain, adrenals, skin, and the spleen had a normal blood flow at this time.

DISCUSSION

Experimental hypernatremia produced by exogenous salt poisoning was associated with osmotic diuresis. Subsequent hypernatremic dehydration caused metabolic acidosis, azotemia, and circulatory disturbances. These biochemical changes match severe human hypernatremic dehydration, and clinical similarities such as lethargy and irritability were also observed. Dehydration of 10% of body weight is considered severe (18) with circulatory failure occurring very frequently. In the hyperosmolar variety of dehydration, however, the shift of intracellular water into the extracellular space and hence into the vascular compartment is considered to be the reason why a more severe fluid loss, up to 20% of body weight, has to occur before signs of shock appear in hypernatremic dehydration (12). In our animals we observed important hemodynamic alterations with an average loss of 14% of body weight. These changes consisted mainly of low cardiac output whereas arterial pressure was maintained. It is possible that bedside diagnosis of shock, which relies mainly on blood pressure measurements, could miss this pattern of circulatory failure.

Hematocrit increased from an average of 33–41% as a consequence of fluid loss from the circulation. It is possible that this hematocrit elevation contributed to the decrease of organ perfusion because viscosity increases linearly with hematocrit, although the slope of this curvilinear relation becomes steep only after a hematocrit value of 50% is reached (6, 14). We therefore assume that the increase in hematocrit was of minor importance for most organs. The special situation of the heart with regard to an increased hematocrit is discussed later.

This type of shock, with lowered cardiac output, elevated peripheral arterial resistance, and thus preserved arterial pressure is observed when there is powerful stimulation of the sympathoadrenergic system with subsequent vasoconstriction in the majority of vascular beds (3). A further contribution to such a widespread arteriolar vasoconstriction could arise from the fact that hyperosmolarity and the consequent release of vasopressin triggers vasoconstriction. Elevated blood osmolarity and low blood volume potentiate vasopressin secretion in the rat (4), and it was shown in the dog that the severe vasoconstriction of the mesenteric vascular bed in hemorrhagic shock was absent or attenuated in animals where vasopressin deficiency was produced (5). In fact, in our experiments at B there was an elevated resistance mostly in the splanchnic and renal bed which together reduced their total flow from 257 to 112 ml/min and contributed accordingly to the elevated total peripheral resistance.

Preservation of flow to vital organs from redistribution of a reduced cardiac output (7) was seen in our experiments in the brain and adrenals but coronary flow fell proportionally to cardiac output, and was thus not favoured as described in other shock situations. The increase in hematocrit from 33 to 41% augments O_2-transport capacity of the blood and reduces myocardial flow. The simultaneous small increase in viscosity could be an additional factor (6). Furthermore, coronary arterial constriction was observed in dogs as a result of lowering arterial

Table 1. *Serum electrolytes and arterial blood gases*[1]

	Time periods			
	A	B	C	D
Sodium (mmole/liter)	143[2] (140–147)	166*** (156–175)	160*** (151–174)	143 (133–151)
Potassium (mmole/liter)	4.0 (3.4–4.7)	4.0 (3.5–5.0)	3.4 (2.9–3.7)	3.8 (3.2–4.3)
Calcium (mmole/liter)	2.66 (2.37–2.77)	2.85 (2.33–3.15)	2.52 (1.45–2.66)	2.45 (2.25–2.70)
Chloride (mmole/liter)	100 (94.5–109.5)	145*** (114–149)	132*** (115–140)	104 (98–126)
Glucose (mmole/liter)	5.8 (4.44–6.65)	12.8*** (9.08–28.5)	7.2 (2.66–30.6)	4.9 (3.0–9.19)
Urea (mmole/liter)	2.37 (1.38–5.76)	20.7*** (7.75–35.3)	17.00*** (6.44–36.2)	3.50 (0.68–17.4)
Creatinine (μmole/liter)	51.4 (34.0–62.8)	90.1*** (61.0–248.0)	82.5*** (54.0–257)	62.9* (41.0–191)
Osmolarity (mosmole/liter)	285 (265–300)	370*** (305–410)	343*** (305–365)	285 (246–320)
pH	7.41 (7.39–7.48)	7.19*** (6.91–7.29)	7.28*** (7.14–7.36)	7.45 (7.28–7.50)
P_{CO_2} (mmHg)	38.2 (32.0–43.0)	24.5*** (19.5–28.0)	27** (18.2–27.0)	33 (20.5–39.1)
Bicarbonate (mmole/liter)	23.6 (18.6–27.5)	8.0*** (4.5–12.2)	11.5*** (6.4–15.6)	21.1 (13.2–26.2)
P_{O_2} (mmHg)	90.2 (81.0–(120.0)	102.4 (88.0–(131.0)	96.8 (81.0–114.0)	89.9 (74.0–111.0)

[1] $n = 12$.
[2] Median values (full range).
[3] Significant at *5% level; **1% level; and ***0.1% level.

Table 2. *General hemodynamic data and hematocrit*[1]

	Time periods			
	A	B	C	D
Arterial pressure (mmHg)				
Systolic	134 (124–159)	138 (105–188)	135 (107–160)	134 (103–187)
Diastolic	73 (64–93)	61 (46–87)	69 (58–94)	81 (52–110)
Mean	98 (87–118)	88 (67–114)	93 (73–117)	103 (74–139)
Heart rate	145 (100–200)	170* (120–190)	145 (112–230)	115 (100–170)
Cardiac output (ml/min)	551 (264–1094)	272*** (154–618)	339*** (251–675)	492* (187–778)
Stroke volume (ml)	4.68 (1.65–6.89)	1.61*** (0.91–4.98)	2.44*** (0.91–5.62)	4.03* (1.1–7.57)
Total peripheral arterial resistance (units)	0.164 (0.095–0.446)	0.336*** (0.133–0.558)	0.273** (0.146–0.390)	0.197* (0.141–0.540)
Hematocrit (%)	33 (26–41)	41** (35–56)	33 (27–51)	29 (25–45)

[1] See footnotes in Table 1.

P_{CO_2} (2), and finally, the diminished venous return from hypovolemic rehydration could reduce preload and thus myocardial oxygen requirements. The combined effect of these factors may explain a fall in coronary flow, even in the presence of an increased heart rate and a maintained systolic peak pressure.

Fluid replacement for 3 h did not restore hematocrit or the electrolytes, and also the hemodynamic alterations were virtually the same as at B. After 24 h, however, we observed normalization of hematocrit, blood gases, and serum electrolytes, but the circulation was still abnormal in many respects. Although cardiac output was steadily increasing during treatment, its value at D was still 10% below control. Reduced venous return from persisting dehydration was probably not the cause because hematocrit and serum solutes were normal. In those animals where central venous pressure could be recorded, its values were not elevated. It is, however, conceivable that a myocardial depressant factor, which was possibly contributing to the low cardiac output throughout, was operative at this stage. This substance is thought to be released from the ischemic pancreas (13), and in fact, pancreatic flow in our experiments was still reduced to about 60% at D. Apart from the pancreas there were other vascular beds that showed markedly reduced flow at D, namely the

Table 3. *Fractions of cardiac output (%)*[1]

	Time periods			
	A	B	C	D
Heart	3.69 (2.72–4.52)	3.44 (3.08–6.11)	3.36 (2.20–7.77)	3.62 (2.46–5.50)
Brain	4.67 (3.38–5.98)	6.79*** (3.95–10.05)	7.59** (4.18–16.09)	5.68 (3.44–9.60)
Gastrointestinal tract	15.7 (9.31–25.5)	12.9 (5.05–16.6)	14.4 (8.17–19.6)	15.8 (8.44–22.9)
Pancreas	1.59 (0.63–2.87)	0.745* (0.50–1.09)	0.988** (0.533–1.55)	1.37 (0.991–1.92)
Spleen	3.76 (1.92–8.13)	1.56 (0.30–5.23)	4.91 (0.63–11.03)	9.04* (2.24–14.5)
Portal[2]	22.0 (12.7–35.0)	14.8* (5.85–22.9)	20.1 (9.34–27.2)	24.5 (14.9–34.4)
Liver, arterial	1.30 (0.60–18.4)	6.60 (3.10–10.6)	5.26 (1.92–9.58)	2.12 (0.352–7.92)
Liver, total[3]	27.0 (19.6–36.1)	23.0 (9.85–29.6)	25.7* (18.9–32.6)	27.8 (17.1–36.9)
Kidneys	19.1 (11.3–25.5)	21.7 (10.0–34.3)	15.2 (9.3–24.8)	12.8* (6.69–19.5)
Adrenals	0.167 (0.07–0.283)	0.310** (0.182–0.489)	0.157 (0.148–0.362)	0.260 (0.088–0.587)
Skin	2.74 (1.53–4.40)	3.80 (2.01–8.71)	5.40 (3.70–6.90)	4.82* (2.64–7.26)

[1] See footnotes in table 1.
[2] Sum of fractions to GI tract, pancreas, and spleen.
[3] Sum of portal and liver arterial fractions.

Table 4. *Organ blood flow (ml/min)*[1]

	Time periods			
	A	B	C	D
Heart	19.1 (10.2–48.8)	11.4** (7.48–20.2)	13.5** (5.39–23.0)	16.8* (8.03–33.3)
Brain	29.7 (11.7–49.8)	19.6 (10.8–38.4)	22.3 (17.5–50.0)	26.6 (14.5–58.1)
Gastrointestinal tract	102 (36.2–246)	34.9** (14.7–99.5)	54.8*** (17.4–95.7)	65.0** (28.7–140)
Pancreas	10.1 (3.38–20.1)	2.25* (0.952–6.72)	3.61*** (1.14–9.25)	6.14** (1.65–11.34)
Spleen	21.8 (8.87–88.9)	4.35** (0.871–31.3)	16.3* (1.34–65.9)	45.1 (4.18–62.4)
Portal[2]	134.9 (51.8–342)	40.1** (17.0–137)	73.2** (19.9–162)	121* (48.6–213)
Liver, arterial	11.4 (2.5–94.0)	17.9 (8.5–41.9)	14.9 (6.10–50.9)	9.26 (1.65–47.9)
Liver, total[2]	153.7 (54.4–353)	60.3*** (28.7–174)	92.4*** (40.3–207)	134.7 (55.0–231)
Kidneys	103 (65.3–195.5)	52.0*** (29.2–132.1)	59.0*** (23.0–132.3)	61.7** (24.6–118)
Adrenals	0.922 (0.467–1.64)	1.01 (0.465–1.94)	0.976 (0.497–1.71)	0.715 (0.432–1.74)
Skin	17.2 (10.9–27.4)	11.6* (3.09–42.9)	18.6 (8.39–36.3)	20.4 (8.99–55.0)

[1] See footnotes in Table 1.
[2] See footnotes in Table 3.

gastrointestinal tract and the kidneys. This phenomenon was also observed in hemorrhagic shock, where retransfusion of the total amount of blood withdrawn did not lower the high renal and mesenteric resistances after 8–24 h and where neurohumoral vasoconstrictor activity was thought to persist (3, 20).

The reduced flow to the kidneys appears to be due to preglomerular vascular constriction, which in turn can lower glomerular capillary pressure below the level necessary to sustain glomerular filtration (16), and the markedly elevated urea and creatinine show severe renal impairment. Consistent with a still reduced renal blood flow at D was the increased serum creatinine; the urine/plasma concentration ratio of urea and creatinine in five animals showed average values of 52 for urea and 83 for creatinine, which suggests continuing functional renal impairment. The hepatic artery did not participate in the mesenteric vasoconstriction and maintained its contribution to total liver

Table 5. *Resistance*[1] *(units; arterial mean pressure/flow)*

	Time periods			
	A	B	C	D
Heart	4.74 (2.35–11.5)	8.97** (4.02–12.0)	7.23** (4.30–13.5)	5.67* (3.97–12.6)
Brain	3.31 (2.37–10.1)	4.06 (2.08–9.35)	3.85 (1.74–5.37)	3.44 (2.27–6.97)
Gastrointestinal tract	0.994 (0.377–3.26)	2.42** (0.803–7.75)	1.79*** (1.03–4.77)	1.72** (0.906–3.48)
Pancreas	10.3 (5.30–34.9)	43.2*** (12.6–90.3)	26.8*** (10.3–73.1)	13.6* (9.66–61.2)
Spleen	4.82 (1.17–10.1)	20.1*** (2.56–130)	5.65 (1.44–61.8)	2.48 (1.33–24.2)
Liver, arterial	9.22 (0.925–47.3)	5.35 (2.12–9.79)	5.68 (1.94–14.3)	11.3 (2.75–54.0)
Kidneys	0.951 (0.475–0.941)	1.56** (0.756–3.91)	1.65* (0.718–3.60)	1.57** (0.940–5.64)
Adrenals	111 (53.0–223)	85.5 (51.5–214)	108 (55.4–181)	137 (75.9–241)
Skin	5.80 (3.40–10.2)	8.20* (2.05–27.8)	4.60 (2.72–9.89)	4.63 (2.31–11.2)

[1] See footnotes in Table 1.

flow in the presence of a markedly reduced portal venous return. Local metabolites from the portal circuit may have prevented hepatic arterial constriction (8). Perhaps an autoregulatory mechanism also restored splenic flow at D whereas all other splanchnic organs were still under vasoconstrictor influences. The overall result was an almost normal total liver flow at D.

Because 50-μ microspheres were used in only five of 20 animals, a separate analysis of total skin blood flow was not meaningful, and our pooled results express predominantly nutritional flow. We nevertheless found a reduced cutaneous flow at B, whereas at C, when vasoconstriction was still severe in the rest of the body, skin flow was already restored. Clinically, the animal's skin was never doughy as seen in infants with hypernatremic dehydration.

If conclusions can be drawn from such an animal model to human pathophysiology, the following clinical implications would arise. Even if normal blood pressure is measured in hyperosmolar dehydration, profound hemodynamic disturbances can already be present, and bedside measurements of cardiac output would be the only means of detecting them. Rehydration following established therapeutic guidelines does not lead to full hemodynamic recovery after 24 h: renal flow reduction is no longer the direct result of dehydration, *i.e.*, of volume depletion, but induced by lasting vascular constrictor activity which causes impaired renal function. Further studies will show whether continuing rehydration alone will normalize the circulation during the following days or whether adding vasoactive substances, such as renal vasodilators, *e.g.* dopamine, would be preferable, particularly because too vigorous an initial rehydration may lead to water intoxication and its neurologic complications.

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Age-Dependent Depressor Effect of L-Dopa in Dogs with Inhibition of Extracerebral Dopa Decarboxylase

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SUMMARY

The results of this study demonstrate that a carbidopa-L-dopa combination has a greater depressor effect in puppies than in adult dogs. These effects are believed to be due to the action of a metabolite of L-dopa within the CNS. These data should alert clinicians to the possibility that CNS cardiovascular control centers, which utilize catecholamines as neuromediators, may be more responsive to pharmacological stimulation in the young than in the adult.

ABBREVIATIONS

CNS, central nervous system
PRA, plasma renin activity

INTRODUCTION

Carbidopa is an inhibitor of dopa decarboxylase which does not cross the blood-brain barrier (2). Pretreatment with carbidopa followed by L-dopa administration is associated with reductions in arterial pressure, heart rate (1, 8) and sympathetic nerve activity (5, 9). These effects are believed to be due to the action of a metabolite(s) of L-dopa within the CNS. L-dopa has no effect on arterial pressure in animals pretreated with agents which inhibit both cerebral and extracerebral dopa decarboxylase activity (4, 8). This study was done to determine if the depressor effect of a carbidopa-L-dopa combination was age-dependent.

METHODS

Ten male mongrel dogs were obtained for the studies from Animal Care Service of Colorado State University. Four of the dogs were pups between 7 - 9 wks of age, and 6 were mature dogs (>6 months of age). Feed and water were withheld from the animals for 4 h before the studies.

The dogs were anesthetized with sodium pentobartibal (30 mg/kg I.V.) with supplementary doses as required. A vascular occluder was placed around the abdominal aorta just cranial to the renal arteries, through either a left flank incision (mature dogs) or a mid-line incision (pups). Cannulae were placed in the right brachial artery, right femoral artery, and right femoral vein. Systemic arterial pressure above the vascular occluder was recorded from the brachial artery cannula and aortic pressure below the clamp was recorded from the femoral artery cannula. Pressures were recorded using Statham strain gauge transducers and a Model 7 Grass polygraph. The femoral vein cannula was used to infuse drugs and obtain blood samples.

Thirty min after the surgery was completed, the occluder was used to compress the aorta so that aortic pressure below the occluder was 60% of the initial value. The 60% value was chosen as a level below the predicted drop of arterial pressure in the mature dogs following administration of carbidopa and L-dopa. Thus, aortic pressure distal to the occluder was to be maintained constant after carbidopa-L-dopa treatment by releasing the occluder. The maintenance of a constant aortic pressure at this level was to prevent large variations in renal arterial pressure and subsequent changes in renin release due to variations in renal arterial pressure. This procedure was an attempt to maintain the activity of the renin-angiotensin system at a relatively constant level. The predicted depressor effect of the drugs was based on previous studies by Blair et al. (3).

Thirty min after aortic pressure had been reduced, carbidopa (MK-486, L-alpha-hydrogino-alpha-methyldopa; Merck, Sharp & Dohme, West Point, PA) was given intravenously at a dosage of 20 mg/kg. The carbidopa was dissolved in 1.0 ml of one N HCl per 100 mg of drug and then diluted with 9 ml of 0.9% saline just before infusion. The infusion was over a period of 2 - 3 min. Thirty-five minutes after the carbidopa was administered, L-dopa (L-3-4 dihydroxyphenyl-alanine; Sigma Chemical, St. Louis, MO) was given intravenously at a dose of 40 mg/kg. L-dopa was dissolved, diluted, and infused similarly to carbidopa. Within 20 min after the administration of the L-dopa, arterial pressure had fallen in all animals. The occluder was adjusted, as arterial pressure decreased, in an attempt to maintain a constant aortic pressure below the occluder constant for the remainder of the recording period, which continued for 90 min post-L-dopa administration.

Blood samples for the determination of PRA were taken just before the reduction in aortic pressure, just before carbidopa and L-dopa administration, and 20, 40, 60, and 90 min after the administration of L-dopa. Samples were taken into a syringe with immediate transfer to a chilled tube containing EDTA. Warm 0.9% saline was infused to replace the volume of blood removed. Plasma was stored at -20 deg C until assayed for PRA. PRA was determined with a radioimmunoassay for angiotensin I, as previously described (10).

Paired t-tests were used for comparison of data from the same animals before and after L-dopa injections. Analyses of variance were used for comparison of data from the same age group taken at different times post-L-dopa and for comparison between age groups. P values of < 0.05 were considered statistically significant.

RESULTS

Twenty min after the injection of L-dopa, with prior carbidopa treatment, both mature dogs and puppies had decreases in brachial blood pressure ($P < 0.05$; Table I). At this time, arterial pressure in all puppies had decreased below the value for femoral blood pressure before the injection, and the vascular occluder on the aorta was completely released in all puppies. No significant change in brachial AP occurred in dogs or pups between 20 - 90 min post-L-dopa injection. At 20 min post-L-dopa, brachial AP in puppies was 44% of the value for the period just before L-dopa injection (Table I). At this time, the brachial AP value for mature dogs was 69% of the value before L-dopa (Table I), and the difference in % brachial AP between pups and dogs was significant ($P < 0.05$).

Both pups and mature dogs had significant decreases in heart rate by 20 min post-L-dopa (Table I). Heart rate for puppies at this time was 73% of that before L-dopa, while in dogs it was 83% (Table I). This difference between age groups approached statistical significance ($P = 0.07$).

PRA was not significantly changed in mature dogs or pups at any time after either the carbidopa or L-dopa injection (Table I). The value shown for PRA 60 min post-L-dopa for pups is speciously low because a value was not available for one pup who had a relatively high PRA at the other sampling times.

DISCUSSION

The results of this study demonstrate that a carbidopa-L-dopa combination has a greater depressor effect in puppies than in adult dogs. The results suggest that the greater depressor effect in neonates is associated with a greater reduction in heart rate. Several different mechanisms exist which could produce the greater depressor and bradycardial effects in neonates. These include: (1) an increased rate in the generation of L-dopa metabolites within the CNS, (2) an increased sensitivity to the metabolites of L-dopa within the CNS, or (3) an increased gain of the control systems at some point between the cells stimulated by the L-dopa metabolites and the effector organs. These data do not discriminate between these possibilities.

The first possibility seems unlikely due to previous studies on developmental changes in CNS L-dopa and catecholamine metabolism. In neonatal rats pretreated with an inhibitor of peripheral dopa decarboxylase, the concentration of norepinephrine within the brain one h after peripheral administration of L-dopa is less than similarly treated 3-wk old rats or mature pregnant rats (7). Dopamine levels were similar in the brains of these three groups of rats. Thus, the generation of catecholamine within the brains of immature animals treated with L-dopa and an inhibitor of peripheral decarboxylase is equal to or less than similarly treated mature animals.

PRA was not affected by the carbidopa-L-dopa combination in either puppies or adult dogs. This indicates that the depressor effects of the drug in this experimental setting was not associated with any reduction in activity of this vasoconstrictor system. The reasons for the discrepancy between these results and other similar studies where carbidopa-L-dopa combinations reduced PRA in adult dogs (3) is unknown. However, the basal PRA in the adult animals in this study was higher than in the referenced study.

These data should alert clinicians to the possibility that CNS cardiovascular control centers, which utilize catecholamines as neuromediators, may be more responsive to pharmacological stimulation in the young than in adults. Clonidine, an alpha$_2$ agonist and centrally active antihypertensive, is an agent whose depressor effects are believed to be due in part to stimulation of CNS cardiovascular control centers. Clonidine is not currently recommended for use in children by the manufacturer, but recommended doses for children have been reported (6).

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I. Effect of carbidopa-L-dopa on mean blood pressure (AP), heart rate and plasma renin activity (PRA) in puppies and mature dogs.[1]

	Age	After reduction	After carbidopa	+20	+40	+60	+90
AP brachial mmHg	Dog	138 ± 8	145 ± 8	100 ± 11[2]	104 ± 11	114 ± 12	121 ± 12
	Pup	104 ± 7	100 ± 12	44 ± 8[2]	50 ± 10	51 ± 12	55 ± 12
AP femoral mmHg	Dog	75 ± 3	75 ± 3	71 ± 3	75 ± 3	76 ± 3	76 ± 3
	Pup	63 ± 2	63 ± 3	45 ± 7[2]	47 ± 8	46 ± 8	50 ± 8
Heart rate per min	Dog	150 ± 13	141 ± 13	116 ± 9[2]	115 ± 9	115 ± 11	119 ± 12
	Pup	147 ± 9	130 ± 6	94 ± 6[2]	88 ± 6	92 ± 7	89 ± 7
PRA ng angio I ml^{-1} hr^{-1}	Dog	15.15 ± 2.43[3]	17.38 ± 3.30	17.64 ± 3.12	16.14 ± 3.24	15.21 ± 1.65	15.67 ± 0.41
	Pup	15.39 ± 6.02	15.44 ± 4.72	15.85 ± 4.01	16.65 ± 5.18[4]	8.01 ± 2.97[4]	12.81 ± 5.15
% AP brachial[5]	Dog	------	100%	69 ± 6	71 ± 5	77 ± 4	82 ± 4
	Pup	------	100%	44 ± 3[6]	49 ± 5	50 ± 6	54 ± 5
% HR[5]	Dog	------	100%	83 ± 2	82 ± 2	82 ± 2	85 ± 2
	Pup	------	100%	73 ± 5	68 ± 6	72 ± 8	69 ± 8

1 Periods are: after pressure reduction before carbidopa, after carbidopa but before L-dopa and 20, 40, 60 and 90 min after L-dopa. Values are mean ± S.E. for 6 mature dogs and 4 pups except as noted.
2 Level of significance as compared to after carbidopa value, $P < 0.05$.
3 n = 5.
4 n = 3.
5 Value for period before L-dopa injection but after carbidopa considered to be 100%.
6 Level of significance for comparison between age groups, $P < 0.05$.

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