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Research Article

FACTORS CONCERNED IN THE CIRCULATORY FAILURE OF ADRENAL INSUFFICIENCY

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An increase in the packed cell volume of the blood is a typical finding in the crisis of adrenal insufficiency. Swingle, Vars and Parkins (1), by direct and indirect (dye method) measurements of blood and plasma volumes, demonstrated that a reduced plasma volume was the main cause of the increase in the relative volume of red cells. In a series of papers, Swingle and his coworkers (2, 3, 4, 5) postulated the importance of impairment of capillary tone and consequent increase in capillary permeability to protein as an independent factor in the causation of reduced plasma volume and of circulatory failure in crisis.

On the other hand, Loeb (6, 7) and Harrop (8, 9) focused their attention on the changes in the elimination of sodium and potassium by the kidneys and on the changes in electrolyte content of the blood and their logical consequences upon the body fluids. A net loss of sodium could cause a depletion of the plasma volume either by carrying away an equivalent volume of extracellular fluid or simultaneously causing a shift of water from the extracellular to the intracellular compartment because of the reduction in effective osmotic pressure of the extracellular fluid. A net retention of potassium might be expected to have a similar net effect, namely, a shift of fluid from the extracellular to the intracellular compartments. According to Harrison and Darrow (10), "Shifts in body fluids do not play a deciding role in the genesis of symptoms following adrenalectomy in the rat." Others, however, have found that slight hydration of muscle does occur in the rat (10) and in the dog (11, 12, 13) in adrenal insufficiency, being more pronounced in the latter animal.

If the plasma volume were diminished as a result of any or all of these aberrations in the regulation of electrolytes, it should be accompanied by a decrease in the interstitial fluid (extracellular tissue fluid). And, indeed, since interstitial fluid is considered to be a labile reservoir for the plasma volume, one might even expect a greater relative change in the interstitial volume than in the plasma volume. On the other hand, if decreased capillary tone and increased capillary permeability to protein were the only important factors in the reduction of plasma volume, the volume of interstitial fluid should show a concomitant increase. If both electrolytes and capillary factors were important and independent consequences of adrenal insufficiency, the changes in interstitial fluid might well be very variable. The interstitial fluid volume might sometimes increase and sometimes decrease. If the permeability of capillaries to protein increased as a result of changes in electrolytes, *e.g.* a change in ratio of sodium to potassium, a decrease in the interstitial fluid volume should be the rule, but it might be very variable in extent. A study of interstitial fluid volumes in adrenal insufficiency produced under different circumstances might thus throw some light on the relative importance of the various factors which have been postulated. So far, the only study of the interstitial fluid of the body as a whole in adrenal insufficiency is that of Harrop (9) on one adrenalectomized dog, which showed a striking decrease, supporting the importance of the electrolyte changes in the production of crisis.

In the present study, we have measured the plasma volume by the blue dye T 1824 and the interstitial fluid by sulfocyanate in adrenalectomized dogs during adequate maintenance with hormone and during crisis after deprivation of hormone. We have also watched for evidence of still another factor in the circulatory failure of crisis, namely, impairment of the function of the heart. Cleghorn and his coworkers have stressed the importance of cardiac failure in adrenal insufficiency in cats, in dogs, and in patients with Addison's disease (14, 15). It may occur in the absence of hemoconcentration or changes in the electrolyte pattern of the blood and quite apart from

over-treatment with desoxycorticosterone, as reported by Ferrebee *et al.* (16). Loeb (17), too, has reported cardiac failure in patients apparently not over-treated and McGavack (18) has drawn attention to the small size of the heart in Addision's disease.

A preliminary account of these experiments has been reported previously in abstract form (19).

METHODS

The following series of experiments were conducted:

Series 1. Seven adrenalectomized dogs were studied while adequately maintained with cortin (1 ml. twice daily) on a diet containing approximately 2.0 per cent NaCl. The studies were repeated on the same dogs during crisis after deprivation of cortin.

Series 2. Three of these dogs, after recovery from the experiments of Series 1, were maintained on a low salt diet (about 1.0 per cent NaCl) and larger amounts of cortical extract (4 ml. twice daily) and the studies repeated and again repeated during crisis after deprivation of hormone.

Series 3. Two dogs were maintained on cortin (2 ml. twice daily) and desoxycorticosterone acetate (1.25 mgm. once daily) with low salt diet and the same studies repeated before and during crisis after deprivation of both substances.

Plasma volumes and available fluid volumes were measured by the method of Gregersen and Stewart (20), modified for use with the Evelyn photoelectric colorimeter. Available fluid volume is defined as the volume in which sulfocyanate would be dissolved in the same concentration as in the plasma. Available fluid $(A) = Q/S$, where Q = quantity of sulfocyanate injected and S its concentration in serum. This volume includes plasma volume and approximately half the red cell volume, in addition to some volume corresponding roughly to the volume of extracellular tissue fluids. The latter hypothetical entity we have called the Interstitial Volume (I.V.). It is calculated by the formula $\text{I.V.} = 0.95(A\text{-}P - .5C)$, where P = plasma volume and C = erythrocyte volume. No particular significance is attached in this paper to the absolute value of the Interstitial Volume as defined above. In spite of some disagreement (21, 22) as to the meaning of the apparent volume of distribution of sulfocyanate in the body, it is generally conceded that changes in its magnitude represent changes in a fluid compartment of the body in which many electrolytes diffuse rather freely. Determinations were done during the period of maintenance and after the development of severe adrenal insufficiency when loss of appetite, vomiting, weakness, or bradycardia had developed. All animals were restored by energetic therapy after the determinations in insufficiency and were used again. Blood was drawn from the jugular vein in an oiled syringe and delivered under oil. Urine was analyzed for chloride in daily specimens, for sodium in 2-day samples. The analytical methods were: sodium [Butler and Tuthill (23)], potassium [Shohl and Bennett (24)], chloride [modified Volhard Harvey (25)], non-protein nitrogen [Folin and Dennis (26)]. Packed cell volume determinations were made on heparinized blood spun to a constant volume at 3,000 r.p.m. No calculation was made for plasma trapped between the cells.

RESULTS

The observations on all 3 series of experiments are shown in Table I. Table II gives the averages of the principal findings in each series. The average plasma volume in Series I during maintenance agrees well with the average value for normal dogs (48 ml. per kgm.) (27).

In Series II the average plasma volume during

TABLE I

Series I (cortin + extra NaCl)

Dog no.	Body wt.	Packed cell volume	Cardiac rate	Plasma volume	Interstitial volume	Serum Na	Serum K
	kgm.	*per cent*		*ml.*	*ml.*	*meq. per l.*	*meq. per l.*
1. A	16.60	33.0	110	715	3,910	143	5.20
B	16.30	42.0	52	550	3,820	130	8.90
2. A	8.50	30.0	100	500	2,310	142	5.90
B	8.15	39.0	40	381	2,230	133	8.00
3. A	10.75	32.0	108	459	2,400	140	6.40
B	10.24	39.0	110	325	1,910	132	7.40
4. A	11.20	45.0	110	610	2,630	137	4.65
B	10.60	49.0	52	394	2,410	128	8.90
5. A	16.56	48.0	120	623	2,880	141	5.40
B	15.45	55.0	66	393	2,780	127	7.90
7. A	11.50	46.0	110	550	2,288	140	5.60
B	11.04	57.6	46	377	2,150	125	
8. A	10.90	38.0	112	585	2,781	151	5.40
B	9.70	52.0	122	373	2,252	122	7.10
Series II (cortin only)							
1. A	17.10	35.5	116	610	3,630	142	5.60
B	17.00	42.0	125	537	3,120		8.20
2. A	8.60	36.0	112	452	1,787	144	5.40
B	8.33	45.0	40	326	1,710		9.40
4. A	11.60	39.0	130	580	2,460	138	5.60
B	11.46	43.0	48	491	2,380		8.40
Series III (cortin plus desoxycorticosterone)							
2. A	8.90	29.0	85	635	2,440	156	
B	8.40	51.0	44	373	1,431	139	
6. A	10.10	33.0		552	2,342	146	
B	9.60	44.0	55	300	2,290	123	

A—Control. B—Crisis.

TABLE II

Averages

	Plasma volumes		Interstitial volumes		Decrease in absolute volumes	
	Control	Crisis	Control	Crisis	P.V.	I.V.
	ml. per kgm.	*ml. per kgm.*	*ml. per kgm.*	*ml. per kgm.*	*per cent*	
Series I	48.3	35.3	227	218	30.9	9.0
Series II	46.1	37.9	211	202	22.8	7.2
Series III	63.0	37.8	253	200	43.5	21.8

maintenance was slightly lower, while in Series III it was distinctly higher than the average for normal dogs. In crisis the plasma volume was invariably reduced. Expressed as ml. per kgm. of body weight in crisis, the average plasma volume in all 3 series is strikingly similar.

Interstitial fluid volumes (I.V.) in Series I and II were within normal limits during maintenance but higher than average for the 2 dogs receiving desoxycorticosterone (Series III). In all cases the interstitial volume was reduced in crisis but much less in relation to its original value than was the plasma volume. In some cases there was no reduction in the I.V. relative to body weight, although a small absolute decrease had occurred.

In all but 3 experiments, bradycardia developed during crisis.

In the dogs on the high salt diet, crisis occurred 11 to 13 days after stopping cortin. The dogs on low salt diets went into crisis on the third to the fifth day after stopping cortin.

Sodium and potassium levels in the serum showed the usual alterations. The total urinary excretion of electrolytes and water was followed in several animals, but control of total intake and output was hardly rigorous enough to allow us to draw definite conclusions as to the relative importance of electrolyte and water loss versus fluid redistribution within the body as contributory factors to the reduction of extracellular fluid. In the animals maintained without added salt, the increased excretion of sodium chloride and water was sufficiently great to account for most of the reduction in extracellular fluid.

In the dogs on the diet with extra sodium chloride a net loss of sodium and chloride was not obvious from the primary findings but might have occurred. On these animals, however, one striking observation was made which appears to have escaped notice heretofore. After deprivation of cortin, the intake of water and output of urine increased markedly, as if in the absence of cortin there was some hindrance to the excretion of urine with a high concentration of salt.

TABLE III

Water intake and urinary volumes and electrolytes on constant diet

A. 2.0 per cent NaCl diet—Average daily amounts for 7 days before, and 7 days after withdrawal of cortin.

Dog. no.	Water intake	Urine output	Sodium output	Chloride output
	ml.	*ml.*	*meq.*	*meq.*
1. before	718	420	62	62
after	823	513	76	70
2. before	603	243	40	42
after	757	441	47	45
3. before	525	241	53	54
after	553	299	56	52
4. before	738	348	73	73
after	969	475	74	72

B. 1.0 per cent NaCl diet—Average daily amounts for 3 days before and after withdrawal of cortin.

2. before	384	147	7	8
after	281	237	35	28
6. before	820	450	11	18
after	443	273	30	33

DISCUSSION

The observation that interstitial fluid volumes are reduced in crisis, together with the well known fact which has been confirmed in these experiments that a high salt diet delays the onset of crisis, may be taken as evidence of the importance of electrolyte disturbances as a contributory factor in the production of crisis. Since, however, changes in the interstitial volume are variable and often slight, our results must be regarded as giving some support to Swingle's hypothesis of increased capillary permeability to protein.

In another communication we plan to present data which show that there is a considerable loss of protein, especially albumin, from the circulating plasma during the development of adrenal insufficiency. This loss must have been slow, for the concentration-time curves of the blue dye used in the determinations of blood volume did not de-

cline more rapidly in crisis than in control experiments. Our experiments contribute no evidence on the question of whether the capillary changes may be due to changes in the ratio of sodium and potassium in the plasma or are a manifestation of some effect of cortin quite independent of actions on sodium and potassium, either as to their renal excretion or distribution between intracellular or extracellular fluids.

If the average decrease in plasma volume in crisis is only about 30 per cent and the decrease in total blood volume much less (17 per cent according to our calculations), then we are forced to the conclusion that the circulatory failure of crisis must be due to something more than diminished blood volume. The extra factor may well be cardiac damage, as evidenced by the frequent occurrence of bradycardia. Dogs with intact adrenals will stand bleeding which reduces their blood volume by 45 per cent (28, 30). More recently blood volume measurements have been made by the dye method on humans in shock from burns and hemorrhage (29, 31). The reductions in blood volume compatible with recovery seem to be considerably greater than we have found in dogs in crisis. Cardiac failure would be a factor which would enhance the gravity of a modest decline in blood volume.

Evidence regarding the shift of fluid from extracellular to intracellular spaces is provided in these experiments only by changes in body weight of the animals. The loss in body weight in the 12 experiments averaged 500 grams. The estimated loss of plasma and interstitial fluid averaged 440 grams. In the 12 hours prior to crisis the animals usually ate and drank nothing. During that time the net loss of weight in the form of exhaled H_2O and CO_2 (less O_2 retained) might have amounted to 200 grams. If the decrease in extracellular fluid all represented urinary (and fecal) loss, the total weight loss should have been 640 grams. It seems permissible to postulate an average shift of about 140 grams of extracellular fluid into the intracellular space.

CONCLUSIONS

Our data on the whole support the hypothesis that in the crisis of adrenal insufficiency, loss of interstitial fluid contributes significantly to a decrease in plasma volume but does not account for all of it. Loss of protein from the plasma may also be a factor in reducing the plasma volume.

The reduction in circulating plasma volume seems insufficient to account for the circulatory failure in crisis. Cardiac failure and possibly loss of capillary tonus may contribute to the circulatory failure.

The loss of interstitial fluid seems to be mostly by renal excretion but some shift to intracellular spaces may also occur.

SUMMARY

1. In 12 experiments on 8 dogs, plasma volumes measured by the dye method in the crisis of adrenal insufficiency were about 30 per cent below normal on the average, while the total blood volume calculated from the plasma volume was only about 17 per cent below normal.

2. Interstitial fluid volumes measured by the sulfocyanate method in crisis were always reduced, but relatively much less than the plasma volumes, *viz.* about 5 per cent on the average with much variation.

3. The decrease in plasma volume may be attributed to at least 2 factors: (*a*) loss of total extracellular fluid as a result of loss of sodium and retention of potassium; (*b*) reduction in plasma proteins and consequent loss of plasma to the extravascular spaces.

4. Cardiac failure as evidenced by a high incidence of bradycardia is a more important factor in crisis than is usually recognized. It may be responsible, together with decreased capillary tone, for the severe circulatory failure associated with the apparently moderate decrease in blood volume.

5. In those experiments in which crisis after deprivation of cortin was delayed by a high salt diet, there was evidence suggesting inability of the kidneys to produce urine of high salt content.

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