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Research Article

THE EFFECT OF ANOXIC ANOXIA ON THE HUMAN KIDNEY [1]

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Congestive heart failure is associated with reduction of renal blood flow and retention of salt and water. The possibility has been raised that these changes may result from the concomitant renal anoxia (1, 2). The present studies are concerned with the effect of anoxia on the human kidney under situations of normal cardiovascular dynamics.

METHODS

In subjects with normal cardiovascular and respiratory systems, an arterial blood oxygen tension of approximately 50 mm. Hg was induced by the inhalation of 14 per cent oxygen. This concentration of oxygen was selected in order to induce a maximum degree of anoxia compatible with minimal changes in cardiovascular and respiratory dynamics (3). Observations of discrete renal functions were then made in these subjects and compared with renal functions while breathing room air. Observations were also conducted on emphysematous individuals who had arterial blood oxygen tensions of approximately 50 mm. Hg while breathing room air and observations were repeated while breathing 100 per cent oxygen. In the latter cases, periods while breathing room air were considered to be anoxic periods and periods while breathing 100 per cent oxygen were considered control periods. In all cases, 20 to 45 minutes were allowed for equilibration following a change of oxygen concentration in respired air.

Glomerular filtration rate was measured as the inulin clearance and renal plasma flow as p-aminohippurate clearance, following the principles outlined by Smith (4). An intravenous infusion of saline containing inulin and sodium p-aminohippurate was administered at a rate of 3 ml./min. subsequent to an appropriate priming dose. Urine was collected in periods of 15 to 30 minutes through an indwelling multi-eyed catheter. At the end of each period the bladder was rinsed with distilled water. Urine samples for measurement of pH were collected and kept under oil. At the mid-point of each urine collection period, blood was drawn anaerobically from the femoral

artery through an indwelling needle. Heparin was used as an anticoagulant. The renal data in the tables represent the means of three collection periods.

Since the inulin and p-aminohippurate were administered in an infusion, the addition of a small amount of normal saline to the circulating volume (500 ml. over 3 hours) might be responsible for the observed changes in electrolyte excretion. To obviate this factor, the time relationship of the control to anoxic periods was varied. In CH, LS, LB, MH, and MS, the control periods preceded the anoxic periods. In KN, DV, and NG, the control periods followed the anoxic periods. MS was . further studied to follow his return to the control levels.

Inulin was measured in urine and plasma by Harrison's modification (5) of Alving's method (6). p-Aminohippurate was measured in diluted urine and trichloracetic acid filtrates of plasma by the Bratton-Marshall reaction (7). Sodium and potassium were determined with an internal standard flame photometer (8). Chloride was determined according to Wilson and Ball (9); phosphorus according to Fiske and SubbaRow (10); ammonia according to Summerson's modification of the Van Slyke and Cullen procedure (11); pH with a Leeds and Northrup pH meter; urinary protein was determined by the micro-Kjeldahl technique using a trichloracetic acid precipitation.

Expired air was collected in a Tissot spirometer which recorded respiratory rate and volume. The mouth piece and nose clip were kept on the subject throughout the procedure except for a few minutes rest prior to a change in oxygen concentration in the inspired air. Arterial blood oxygen and carbon dioxide contents were determined by the method of Van Slyke and Neill (12), and tensions by the direct method of Riley (13). Respiratory gases were analyzed in a Haldane-Henderson apparatus and micro-Scholander gas analyzer (14).

The pulse rate and brachio-arterial blood pressure were recorded at five-minute intervals throughout any particular procedure. Mean arterial blood pressure levels were calculated by adding a third of the systolic and diastolic difference to the diastolic pressure.

With a view to minimizing the problem of anxiety, prior to the day of experiment the subjects were catheterized and were acclimated to breathing through a Tissot spirometer. The subject was not informed of changes in oxygen concentration during the experiment and gave no indication of having noticed the change.

OBSERVATIONS

There were slight alterations in respiration and circulation during inhalation of 14 and 100 per cent oxygen (Table I). The changes in respiration were all within the error of measurement. The average pulse rate did not change significantly in four observations while it rose 8 to 14 beats during anoxia in the other five. The average mean blood pressure during the anoxic periods was not different from that of the control except in one instance when it rose 13 mm. Hg during anoxia.

Renal plasma flow did not decrease during the anoxic periods. On the contrary, there was a tendency for it to increase. In observations in individuals with normal pulmonary function, three comparisons exhibited no appreciable change in renal plasma flow and four increased 13 to 20 per cent. In the two subjects with pulmonary emphysema, the administration of 100 per cent oxygen induced a fall in renal plasma flow; considering periods of breathing room air as the anoxic periods there was an increase in renal plasma flow of 29 per cent in each subject during anoxia. The filtration rate did not change appreciably during anoxia in four observations, increased 9 to 23 per cent in four, and decreased 19 per cent in one.

The interpretation of p-aminohippurate clearance as a measure of renal plasma flow is based on its almost complete extraction by the kidney. Under normal situations this extraction is at a maximum. A decrease in p-aminohippurate clear-

ance during anoxia would be difficult to interpret in terms of renal plasma flow if the anoxia altered its extraction. However, the observed clearances increased and a change in this direction can be interpreted as an increase in effective renal plasma flow.

In the five comparisons where a change in pulse rate did occur, those which evidenced the greatest change in pulse rate did not have the greatest change in renal plasma flow. Since it has been observed that the increase in cardiac output which occurs during inhalation of anoxic gas mixtures results from an increase in pulse rate rather than stroke volume (15, 16), the observed changes in renal plasma flow are not considered to reflect changes in cardiac output.

There was an invariable and frequently marked increase in the rate of sodium and chloride excretion during anoxia (Table II). Sodium increased from a mean excretion of 162 μEq./min. to 256 μEq./min. Chloride increased from a mean excretion of 161 μEq./min. to 245 μEq./min. The urine flow tended to increase during anoxia presumably in consequence of the increased concentration of sodium and chloride in the urine. The magnitude of change in salt and water excretion exhibited little if any correlation with the magnitude of change in filtration rate or renal plasma flow.

Other electrolyte changes which occurred during anoxia were not as marked as those of sodium and

TABLE I

Effect of anoxia on respiratory, cardio-vascular, and renal dynamics

Subject	Pulmonary disease	Arterial blood oxygen tension		Respiratory minute volume			Pulse rate*			Mean arterial blood pressure*			Inulin clearance†			p-Aminohippurate clearance†		
		Control	Anoxia	Control	Anoxia	Change	Control	Anoxia	Change	Control	Anoxia	Change	Control	Anoxia	Change	Control	Anoxia	Change
		mm. Hg	mm. Hg	Lits/ min.	Lits/ min.	Lits/ min.	Beats /min.	Beats /min.	Beats/ min.	mm. Hg	mm. Hg	mm. Hg	ml./ min.	ml./ min.	per cent	ml./ min.	ml./ min.	per cent
CH‡	None	97.6	54.3	4.7	5.3	+0.6	79	82	+ 3	89	88	− 1	95	90	− 5.3	394	389	− 1.3
LS‡	None	99.8	50.1	8.1	7.3	−0.8	82	84	+ 2	106	103	− 3	111	121	+ 9.0	601	682	+13.5
LB‡	None	97.0	61.4	7.4	8.7	+1.3	59	62	+ 3	95	96	+ 1	101	82	−18.8	613	546	− 2.8
MH‡	None	96.9	49.0	7.3	8.9	+1.6	67	75	+ 8	100	101	+ 1	92	92	0	382	434	+13.6
MS‡	None	95.0	51.0	8.3	8.0	−0.3	77	77	0	116	129	+13	72	84	+16.7	347	356	+ 2.6
MS§	None	98.5	51.0	7.6	8.0	+0.4	63	77	+14	125	129	+ 4	76	84	+10.5	316	356	+12.6
KN§	None	93.3	54.3	8.6	9.3	+0.7	72	80	+ 8	102	101	− 1	111	117	+ 5.4	402	483	+20.1
DV§	Emphysema	105%‖	57.5	8.3	8.4	+0.1	91	98	+ 7	94	90	− 4	105	129	+22.8	371	480	+29.4
NG§	Emphysema	108%‖	46.1	9.4	9.9	+0.5	82	94	+12	89	86	− 3	107	114	+ 6.5	276	356	+29.0

* Mean of consecutive five-minute observations.
† Mean of three observation periods, uncorrected to surface area.
‡ Control periods preceded anoxic periods.
§ Anoxic periods preceded control periods.
‖ Per cent hemoglobin saturation while breathing 100 per cent oxygen. Per cent saturation used in this instance because the measurement of tension by Riley's method is inaccurate at tensions over 110 mm. Hg. The values appear greater than 100 per cent because of the oxygen dissolved in the plasma.

TABLE II

Effect of anoxia on renal excretion of electrolytes

All values represent the mean of three consecutive periods

Subject	Sodium			Chloride			Urine flow			Potassium			Phosphorus			Ammonia			pH		
	Control	Anoxia	Change	Control	Anoxia	Change	Control	Anoxia	Change	Control	Anoxia	Change	Control	Anoxia	Change	Control	Anoxia	Change	Control	Anoxia	Change
	μEq/min.	μEq/min.	μEq/min.	μEq/min.	μEq/min.	μEq/min.	ml./min.	ml./min.	ml./min.	μEq/min.	μEq/min.	μEq/min.	μM/min.	μM/min.	μM/min.	μEq/min.	μEq/min.	μEq/min.	units	units	units
CH*	346	397	+51	299	388	+89	2.35	2.01	-0.34	72	81	+9	27.8	74.0	+46.2	11.5	4.3	-7.2	7.6	7.3	-0.3
LS*	216	278	+62	206	241	+35	5.18	4.17	-1.01	64	58	-6	4.6	10.0	+5.4	24.0	22.9	-1.1	6.8	7.0	+0.2
LB*	92	186	+94	70	176	+106	0.50	0.84	+0.34	50	56	+6	18.9	23.6	+4.7	18.0	22.0	+4.0	5.2	5.3	+0.1
MH*	141	338	+197	202	286	+84	2.04	2.43	+0.39	109	76	-33	15.4	21.2	+5.8	15.8	7.1	-8.7	6.4	7.0	+0.6
MS*	152	243	+91	131	241	+110	0.81	1.24	+0.43	60	80	+20	24.4	35.6	+11.2	7.2	5.8	-1.4	6.4	7.0	+0.6
MS†	132	243	+111	118	241	+123	0.60	1.24	+0.64	43	80	+37	40.2	35.6	-4.6	6.6	5.8	-0.8	5.3	7.0	+1.7
KN†	191	234	+43	182	217	+35	0.95	4.45	+3.50	47	67	+20	11.2	8.8	-2.4	20.4	18.6	-1.8	6.3	7.1	+0.8
DV†	90	163	+73	112	136	+24	0.67	1.17	+0.50	36	76	+40	6.3	3.9	-2.4	31.5	12.0	-9.5	6.0	7.6	+1.6
NG†	95	222	+127	132	282	+150	1.08	3.07	+1.99	38	91	+53	19.9	23.2	+3.3	33.7	27.4	-6.3	4.6	5.0	+0.4
Mean	162	256	+94	161	245	+84	1.57	2.29	+0.72	58	74	+16	18.7	26.2	+7.5	17.6	14.0	-3.6	6.1	6.7	+0.6

* Control periods preceded anoxic periods.
† Control periods followed anoxic periods.

chloride. Urinary pH shifted to higher values in all observations except one but this subject had a control value of pH 7.6. Ammonia production decreased in all but one observation. Potassium excretion increased in all but two observations. Proteinuria did not develop during anoxic periods.

The phosphorus excretion usually increased as the experiment progressed irrespective of changes in blood oxygen tension.

DISCUSSION

A lowered arterial blood oxygen tension in subjects with normal cardiovascular function induced a marked increase in the renal excretion of sodium and chloride. In no instance did renal plasma flow decrease during anoxia. It would appear, therefore, that anoxic anoxia per se is not the cause of the retention of salt and water nor in the reduction of renal plasma flow observed in congestive heart failure.

If arterial blood oxygen tension is lowered in normal subjects, renal plasma flow and sodium and chloride excretion increase. If arterial oxygen tension is raised in anoxic emphysematous subjects, renal plasma flow and the excretion of sodium and chloride decrease.

The duration of anoxia was only one to two hours in the normal individuals in the investigation, but the emphysematous individuals had maintained a status of anoxic anoxia over a period of years. It is of interest that even in the latter subjects the effect of chronic anoxic anoxia on the kidney was readily altered.

The effect of lowering arterial blood oxygen tension beyond 50 mm. Hg was not investigated as complicating changes in cardiovascular and pulmonary dynamics were likely to be introduced. It is to be noted that in congestive heart failure and in disease states associated with arterial oxygen unsaturation, oxygen tensions seldom fall below 50 mm. Hg.

In the normal subjects during anoxia, oxygen tension in inspired air was 106 mm. Hg. McDonald and Kelley (17) investigated renal plasma flow and filtration rate in dogs at simulated altitudes where oxygen tensions in inspired air were 79.4 and 61.6 mm. Hg. They found renal plasma flow to increase at higher altitudes, observations which are in accord with those reported here.

The increase in urine flow in these studies confirms previous work in the rat (18), dog (19), and man (20) where polyuria has been observed at higher altitudes. Burrill *et al.* (21) reported a rise in the excretion of sodium and chloride during one hour exposures of adult males to simulated altitudes of 18,000 feet. Interestingly enough, they observed a compensatory retention of these ions following the exposure so that the 24 hour excretion was not altered.

The normal dog excretes excessive amounts of sodium and chloride when exposed to 10.5 per cent oxygen for 24 hours whereas the adrenalectomized animal fails to do so (22). Thorn (23) found rats treated with adrenal cortical extract survived longer at higher altitudes than untreated animals. These facts suggest the possibility that the changes in sodium and chloride observed in the present study may be in some way related to altered adrenal metabolism at low oxygen tensions. The behavior of potassium did not, however, conform to this hypothesis.

SUMMARY

Renal plasma flow in man did not decrease under situations of anoxia where arterial oxygen tension was lowered to about 50 mm. Hg. The most pronounced effect of lowered oxygen tension on renal tissue was the increased excretion of sodium and chloride. Anoxic anoxia alone, therefore, does not appear to be the cause of the reduction of renal plasma flow nor the retention of salt and water observed in congestive heart failure.

ACKNOWLEDGMENTS

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