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Comparison of Creatinine and Inulin Clearance in the Dog During Hypoxia.* (19880)

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The creatinine/inulin clearance ratio has been reported by Shannon to be 0.99 in unanesthetized dogs(1,2). This agreement was found to be maintained during anesthesia (chloralose), but discrepancies began to appear in the isolated perfused dog kidney probably subjected to varying degrees of anoxia at low urine volumes where the ratio averaged 0.86(3). The desire to gain assurance that the creatinine clearance remained an index of glomerular filtration rate during hypoxic conditions in the dog prompted the present investigation in which this clearance was compared to the accepted standard of reference, the inulin clearance.

Methods. Pentobarbitalized animals were used in these experiments. Arterial blood pressure was recorded with a mercury manometer by direct cannulation of a femoral artery, and the trachea was cannulated for connection to a Douglas bag. Urine was collected by direct catheterization of the ureters. Substances to be analyzed for clearance were infused at a constant rate by a motor driven syringe. A moderate diuresis was instituted by infusion of Ringer's solution prior and during the experiment. *Hypoxia* was produced by inhalation of an 8% oxygen, 92% nitrogen mixture. In animals which tolerated the procedure well, alternate stages of low oxygen mixture and room air were observed, with a pair of urine collection periods of ten minutes duration at each stage, for a total of five stages (Table I). In some animals difficulties were encountered as the result of continued breathing of the low oxygen mixture (fall in blood pressure, respiratory paralysis) so that experiments were of briefer duration. Although inhalation of 8% oxygen produced the lowest level of blood oxygen content compatible with survival, in two experiments the kidney was subjected to an even greater degree of hypoxia by a technic of perfusion of the kidney *in situ* with venous blood while the animal breathed 8% oxygen. This was done with the aid of a pump previously described (4), which took blood from the right ventricle through a cannula introduced via the external jugular vein and delivered it into the renal artery at pressure kept at arterial pressure levels by proper adjustment of the stroke volume of the pump. An experiment of this type appears in Table II. *Blood oxygen* content was determined by the method of Van Slyke and Neill(5) in samples taken mid-way in each stage of the experiment. Since these were single determinations they cannot be taken as average values for oxygen content, but serve only as a relative index of the degree

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TABLE I. A Representative Experiment Showing Effects of Inhalation of 8% Oxygen-92% Nitrogen Mixture on the Creatinine and Inulin Clearance. (20 kg female. Values are for one kidney only.)

Period	Blood O_2,* vol/%	MABP,† mm Hg	Urine vol, ml/min	Creatinine P, mg/%	Creatinine U, mg/%	Creatinine UV/P, ml/min	Inulin P, mg/%	Inulin U, mg/%	Inulin UV/P, ml/min	C_{CR}/C_{IN}
A. Room air										
1	14.1	122	1.30	11.3	240	27.6	23.3	500	27.9	.99
2		121	1.60	12.6	210	26.8	23.6	397	27	.99
B. 8% oxygen										
3	9.6	122	1.60	14	233	26.8	23.6	394	26.7	1
4		121	1.42	13.8	268	27.6	23	457	28.2	.98
C. Room air										
5	13.9	123	1.44	14.8	296	28.9	25	467	26.9	1.07
6		121	1.42	15.3	307	28.4	26.6	475	25.4	1.12
D. 8% oxygen										
7	10.4	120	1.44	16.5	305	26.6	27.4	469	24.6	1.08
8		115	1.25	17	364	26.8	27.1	543	25	1.07
E. Room air										
9	14.7	121	1.27	17.8	374	26.8	27.6	542	24.9	1.07
10		125	1.33	18.3	369	26.8	28	529	25.1	1.06

* Blood O_2 content is given as that combined with hemoglobin. The rather low values noted during periods in which room air was inhaled are attributed to the effects of anesthesia on respiration and to reduction of red cell hematocrit (to 37%) resulting from hemodilution by Ringer's infusion.

† Mean arterial blood pressure was typically briefly elevated immediately after instituting 8% oxygen inhalation. It tended to subside by the time urine collection was started.

TABLE II. A Representative Experiment in Which Perfusion of the Kidney with Venous Blood Was Carried on While Breathing 8% Oxygen. (13.2 kg male. Values for one kidney only.)

Period	Blood O_2, vol/%	MABP, mm Hg	Urine vol, ml/min	Creatinine P, mg/%	Creatinine U, mg/%	Creatinine UV/P, ml/min	Inulin P, mg/%	Inulin U, mg/%	Inulin UV/P, ml/min	C_{CR}/C_{IN}
A. Room air										
1	14.1	129	2.15	11.6	124	23	19.2	229	25.6	.90
2		132	2.27	11.7	131	25.5	19.9	221	25.3	1.01
B. 8% oxygen										
3	5.5	134	1.32	11.9	212	23.5	20.4	350	22.7	1.03
4		135	1.05	12.2	281	24.3	19.7	485	25.9	.94
C. 8% oxygen + venous perfusion										
5	2.1	133	1.32	13.2	158	15.8	20.5	278	17.9	.88
6		134	1.60	14.1	94	10.6	21.7	176	12.9	.82
D. Room air										
7	14.6	133	4.10	16	89	22.8	24.4	141	23.7	.96
8		134	4.13	16.7	93	23	24	140	24.1	.95

of saturation. Carotid artery blood was usually analyzed, but when the pump was used the sample was drawn from a stopcock in the renal perfusion circuit, supplied either by carotid or venous blood. *Chemical methods* for the clearance determinations employed the alkaline picrate method for determination of creatinine in urine and sodium tungstate filtrates of the plasma. The modified Seliwanoff reaction of Higashi and Peters(6) was employed for the inulin determination.

Results. Results were obtained from six animals. The creatinine/inulin clearance ratio averaged 1.01 (S.D., ± 0.066) in 28 clearance periods in which the animals were breathing room air. This compares with an average of 0.97 (S.D., ± 0.06) found by Higashi and Peters(6) employing the same inulin method, and a ratio of 0.99 (S.D., ± 0.048) found by Shannon using another inulin method(2).

During hypoxia produced by inhalation of 8% oxygen this correspondence was well maintained, as shown in the representative

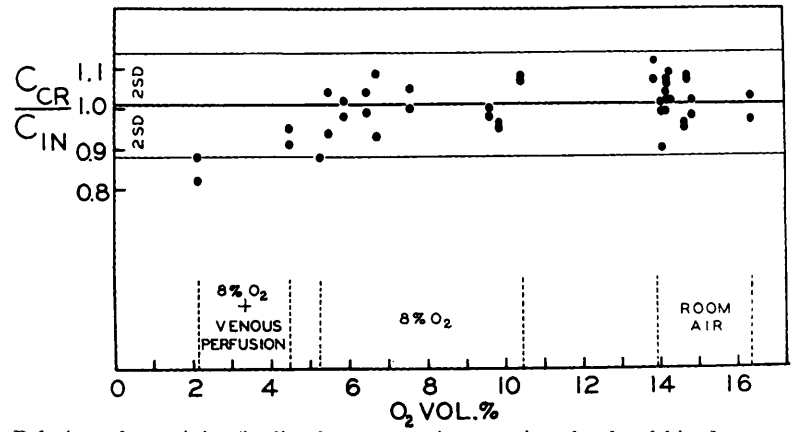

FIG. 1. Relation of creatinine/inulin clearance ratio to various levels of blood oxygen content. The mean ratio and $\pm$ 2 S.D. are based on a total of 28 clearance observations while breathing room air. During 8 clearance periods blood O_2 content was not measured; hence only 20 control values appear in the figure.

experiment. A total of 17 observations fell within the limits of ± 2 S.D. from the mean of the control in a range of oxygen content of 5.5 to 10.4 vol. %.

In two experiments in which perfusion of the kidney with venous blood was superimposed on a generalized hypoxia created by inhalation of 8% oxygen, a slight reduction in the ratio appeared. This can be noted in Table II. In these experiments there was a tendency for the absolute clearance values to be reduced. At the low value of 2.1 vol. % the ratio declined to 0.82, the lowest observed ratio in these experiments. However, in the other experiment with oxygen content of 4.46 vol. % ratios were 0.91 and 0.95.

Discussion. The present investigation gives assurance that the clearance of creatinine can be used as a valid index of glomerular filtration rate during hypoxia with oxygen content of the blood as low as 5.5 vol. % continued for periods as long as 30 minutes. Below this level of oxygen, the tendency was noted for the creatinine clearance to be diminished relative to the inulin clearance. This may have been the result of back diffusion of creatinine through the tubular epithelium by mechanisms discussed by Shannon(3). The possibility is not excluded that both substances may back-diffuse during the most severe hypoxic states, with creatinine diffusing more rapidly than inulin. However, this was not believed to be the case in the present experiments in which 8% oxygen was inhaled because the absolute clearance values were well maintained, as illustrated in the experiments of Tables I and II.

Summary. The creatinine/inulin clearance ratio remains close to unity during hypoxia in anesthetized dogs with blood oxygen content as low as 5.5 vol. % resulting from inhalation of an 8% oxygen mixture. Supported by the fact that absolute clearance values do not decrease, it is concluded that the creatinine clearance remains an adequate measure of glomerular filtration rate under these conditions.

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