

# Progress in Renal Investigation

## *Anatomy and Physiology of Intrarenal Oxygen Tension: Preliminary Study of the Effects of Anesthetics*

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MEASUREMENTS of the partial pressure of oxygen (oxygen tension,  $P_{O_2}$ ) in the urinary tract were first attempted more than a century ago. The idea continued to be of interest to investigators for various reasons but, owing to the limitation of the methods employed, did not produce significant advances for many decades. A review by Campbell<sup>1</sup> and the major contribution of Sarre<sup>2</sup> stimulated contemporary investigation of the urinary oxygen tension ( $P_{U_{O_2}}$ ). The introduction of polarographic methods of measurement created a new interest which led to the development of the membrane-covered Clark electrode and its modifications. Pappenheimer and his group firmly established the methodology and the physiological significance of the study of urinary oxygen tension.<sup>3</sup> The results of these studies formed a major part of the evidence for their "plasma-skimming, cell-separation theory" of the renal circulation.<sup>4</sup> Later, Rahn and his associates proposed a "countercurrent gas diffusion system" in the renal medulla to explain the low  $P_{U_{O_2}}$ .<sup>5</sup> Levy and Imperial were able to confirm this concept by a different approach using densitometer tracings of oxygenated blood and labeled red cells.<sup>6</sup> They also demonstrated that countercurrent shunting of oxygen is not confined to the medulla but also occurs in the entire cortex. Finally, using polarographic microtechniques, a progressive centripetal decline of the renal parenchymal  $P_{O_2}$  was demonstrated independently by Aukland and Krogh<sup>7</sup> in the dog and

by us in man.<sup>8</sup> These findings were substantiated by others.<sup>9</sup>

In previous work we have attempted to explore the clinical implications of these methods under physiological and pathological conditions. The following summary of the basic findings in regard to the urinary oxygen tension is presented in order to relate them to the present discussion.<sup>8, 10</sup>

(1)  $P_{U_{O_2}}$  changes with the state of hydration: antidiuresis is associated with a low urinary  $P_{O_2}$ , whereas diuresis is accompanied by a high  $P_{U_{O_2}}$ .

(2) Inhalation of oxygen results in a steady, characteristic rise to a plateau, followed by a more rapid exponential return to the baseline, when breathing of air is resumed. If standard procedures and steady-state conditions are attained, reproducible and well defined  $P_{U_{O_2}}$ -time curves are obtained. We have recently described such records in normal subjects and in patients with renal disease.<sup>11</sup> Typical deviations from the normal pattern are consistently observed in chronic pyelonephritis, acute and chronic hydronephrosis, carcinoma of the kidney, renal arterial stenosis, and arteriolar nephrosclerosis.

(3) Cardiocirculatory decompensation (congestive heart failure, shock, arrhythmias) and respiratory failure (emphysema, pulmonary fibrosis, status asthmaticus) are associated with extremely low values for  $P_{U_{O_2}}$ .

(4) Administration of cyclopropane anesthesia results in a low urinary oxygen tension which remains unchanged for 3 to 4 hours postoperatively, whereas halothane and methoxyflurane are followed by normal or slightly elevated values.

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(5) Administration of norepinephrine to hypotensive patients increases blood pressure and urinary output but simultaneously lowers the  $P_{UO_2}$ . Ganglionic blocking agents on the other hand, if given to normotensive or hypertensive subjects, reduce blood pressure and urine flow but raise  $P_{UO_2}$ . Physical and emotional stress markedly lower the  $P_{UO_2}$ .

From these data a number of conclusions applicable to our present study were derived.<sup>8, 10, 11</sup> The significance of  $P_{UO_2}$  in the renal pelvis was defined as follows:

(1) This represents the  $P_{UO_2}$  existing in the loops of Henle and collecting ducts of the inner medulla; there it equilibrates with the oxygen tension of interstitial tissue and the medullary water and electrolyte pool.

(2) The latter oxygen tension reflects the oxygen tension of renal medullary blood which in turn indicates the magnitude of blood flow in the vasa recta. Therefore  $P_{UO_2}$  is an expression of renal medullary perfusion and the records obtained during  $O_2$  inhalation may be considered as an indicator-dilution technique of blood flow measurement.

(3) The medullary circulation influences and, to a degree, controls dilution and concentration of urine in the papillae, since the vasa recta are components of the countercurrent exchange and multiplier system. On the other hand the countercurrent mechanism influences the oxygen tension of medullary interstitial tissue which is a function both, of blood flow and countercurrent activity.

(4) Medullary perfusion represents a small fraction of the total renal blood flow and cannot be evaluated by estimates of the latter. Medullary blood flow does not participate in the autoregulatory mechanism of the cortical circulation but displays large fluctuations in volume of flow due to diuretic or antidiuretic stimuli in the normal subject. In systemic and renal disease, alterations in medullary blood flow appear to be due to sympatho-adrenal vasoconstriction or organic vascular alteration.

Throughout our investigations of the urinary oxygen tension we felt the need to complement these findings with direct measurements of the renal parenchymal and vascular  $P_{O_2}$ . Therefore these measurements were applied whenever the opportunity arose. At present, an adequate number of observations

and an improved methodology permit a preliminary presentation of the findings. Accordingly, it is the purpose of this study to test the conclusions derived from urinary findings and to map out intrarenal  $O_2$  distribution upon a background of functional, microcirculatory and metabolic alterations.

### Methods

Fifteen patients undergoing nephrectomy or renal exploration for various diseases of the kidney were the subjects of this investigation. In twelve, advanced renal pathology was present. In three patients requiring exploration for renal neoplasms, solitary renal cysts were found, associated with essentially normal function of the affected kidney. The present report is concerned mainly with the latter group.

A Beckman oxygen microelectrode combined with a Model 160 physiological gas analyzer was used for measurements of tissue oxygen tension. Physical principles, technical details and general methodology of this polarographic technique have been previously published.<sup>8, 12</sup> The instrument requires rigid calibration and temperature control. Nevertheless, it proved suitable for application in the operating room and at the bedside. The following improvements have been effected: (1) Puncture sites were chosen on the lateral curvature of the kidney from the upper to the lower pole. (2) The electrode tip was advanced approximately 1.5 mm. for each consecutive reading until it reached the pelvis. (3) A Sanborn dual channel d.c. amplifier-recorder gave permanent records. (4) Recalibration in sterile water at a known  $P_{O_2}$  and temperature was performed between probings. (5) Heparin was added to the calibration solution to minimize clotting at the needle tip. (6) During determinations, pressure or torsion of the electrode was avoided. (7) Attempts were made to achieve comparable "steady-state" conditions in regard to respiration, circulation, composition of the blood and anesthesia. (8) Depth of anesthesia was monitored by electroencephalography to establish equivalent levels of central nervous system depression.

The two men and one woman studied ranged in age from 38 to 50 years and in body weight from 65 to 72 kg. They were free of respiratory and cardiovascular disease.

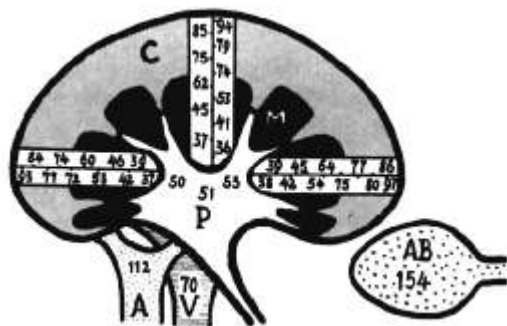


FIG. 1. Intrarenal oxygen distribution under halothane-nitrous oxide anesthesia plus 21 per cent oxygen. Note progressive decline of tissue oxygen tension in the corticomedullary axis. The  $P_{O_2}$  of pelvic urine reflects the midmedullary tissue oxygen tension. Arterial (A), renal venous (V) and inspiratory (AB = anesthesia bag) oxygen tensions are shown.

History, physical examination, laboratory data and roentgenograms were within normal limits except for signs and symptoms of space-occupying lesions of the kidney.

Preanesthetic medication consisted of 75 mg. meperidine and 0.5 mg. atropine sulfate injected intramuscularly 45 minutes before induction of anesthesia. Induction was accomplished with an injection of a 1 per cent solution of thiopental sodium until the lid reflex disappeared. Succinylcholine chloride, 30 mg., was injected for endotracheal intubation followed by maintenance with halothane or cyclopropane. The former was vaporized by means of a Fluotec vaporizer placed outside of the anesthetic circuit. In each instance an Ohio Heidbrink Series 2000 Kinet-o-Meter was used in combination with an Ohio 300 D/O Ventilator. Respiratory minute volume was monitored with a Monaghan Ventilation Meter in order to provide moderate alveolar hyperventilation. Arterial carbon dioxide tensions were determined 5 minutes before the renal parenchymal probings with a Beckman Model 160 physiological gas analyzer and a Severinghaus electrode. Lead 2 of the electrocardiogram and the electroencephalogram (paramedian fronto-occipital lead) were monitored on a Sanborn 762 Dual Oscilloscope and intermittently recorded on the corresponding Sanborn instrument. The EEG level was evaluated according to the classifications of Brechner, Walter and Dillon.<sup>13</sup> With halothane a

frequency of 10 to 15 cycles per second and an amplitude of 100 to 150 microvolts were considered characteristic of light surgical anesthesia. With cyclopropane an equivalent anesthetic level was assumed with the appearance of 4 to 8 cycles per second and 100–200 microvolt waves. These levels corresponding to Guedel's plane 1 were established shortly after induction and maintained throughout the procedure. Dimethyltubocurarine was employed for muscular relaxation. Mechanical ventilation was supplemented by a deep manual inflation of the lungs every 3 minutes. Blood pressure and pulse were maintained within the normal range by blood replacement, postural measures and adjustments of the anesthetic concentration. Renal parenchymal  $P_{O_2}$  determinations were started from 56 to 62 minutes after induction of anesthesia. Esophageal temperature was monitored continuously by means of a Model 44 A Yellow Springs telethermometer.

The following combinations of anesthetic agents and oxygen concentrations were employed in a semiclosed system with a total gas flow of 4 liters per minute: (1) 1.5–2 per cent halothane, 21 per cent oxygen and 77 per cent nitrous oxide; (2) 1.5–2 per cent halothane, 60 per cent oxygen and 38 per cent nitrous oxide; (3) 15 per cent cyclopropane and 85 per cent oxygen. The exact  $O_2$  concentration at the time of probing was ascertained by  $P_{O_2}$  determinations in arterial blood and the gas mixture of the anesthesia bag.

## Results

*Patient 1 (1.5–2 per cent halothane, 77 per cent nitrous oxide, 21 per cent oxygen).* A progressive decline of the parenchymal oxygen tension from the subcapsular layer to the tip of the papilla was encountered at all puncture sites, as the electrode was advanced in the corticomedullary axis. This finding represents a spatial arrangement best described as a concentric stratification of the renal parenchyma in regard to oxygen tension (fig. 1). The largest fall between two single readings was observed after passing the cortico-medullary border zone. The rate of decline then decreased, terminating in the papilla with the lowest value for each probing. The  $P_{O_2}$  gradi-

ent from papilla to the outer cortex amounted to 60 mm. of mercury. Readings from the three separate probings were almost identical, representing the smallest degree of variation encountered in this study ( $\pm 1.5$  per cent).

Arterial oxygen tension averaged 112 mm. of mercury, corresponding to a hemoglobin saturation of 97.8 per cent when measured intravascularly and 115 mm. of mercury or 98 per cent saturation *in vitro*. The  $P_{O_2}$  of renal venous blood was 68 mm. of mercury, 92.5 per cent saturation, *in vivo*, and 71 mm. of mercury, 93.2 per cent saturation, *in vitro*. Arterial carbon dioxide tension averaged 32 mm. of mercury. The patient's preoperative hemoglobin averaged 14.8 g./100 ml. (3 determinations) and the hematocrit 45 per cent. The arteriovenous difference in oxygen content was calculated as 1.2 ml. per 100 ml. of renal blood. The oxygen tension in the pelvic urine ranged from 51 to 53 mm. of mercury or approximately 20 mm. of mercury lower than that in the renal vein.

Parenchymal  $P_{O_2}$  findings plotted against the distance of the electrode tip from the renal pelvis provide a curve of the declining oxygen tension from the cortex to the papilla. Two parabolic curves could be fitted readily to the  $P_{O_2}$ -distance plot, a short curve to the cortical and a longer one to the medullary zone (fig. 2). While a more complex mathematical formula-

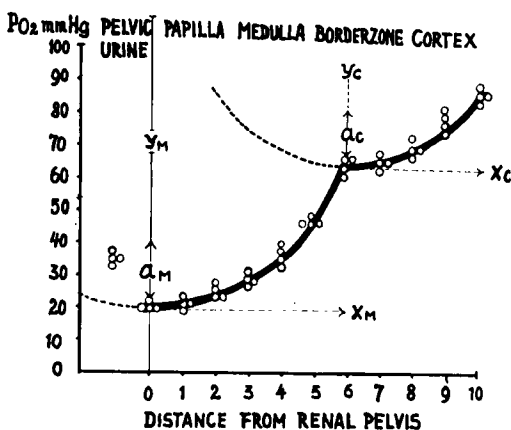


FIG. 2. Example of parabolic fittings to  $P_{O_2}$ -distance plot. The results of four separate probings in the same kidney were entered at each distance.  $y_c$ ,  $x_c$ , and  $a_c$  are the coordinates and focal distance of the cortical, and  $y_m$ ,  $x_m$ ,  $a_m$  those of the medullary parabola. Dotted sectors complete parabolic curves.

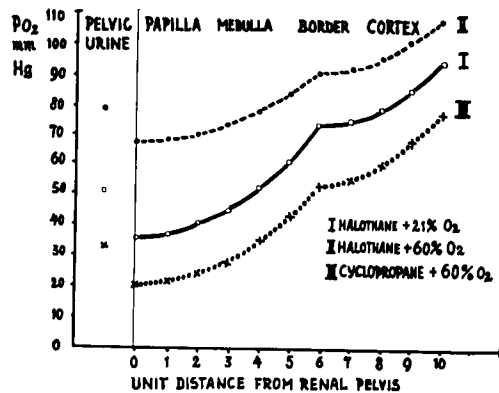


FIG. 3. Parabolic fittings to the cortical and medullary  $P_{O_2}$ -distance plot of three normal kidneys. Anesthetic agents and inspired oxygen concentration as indicated (for details see text).

tion might be considered, the parabola combines adequate representation with simple mathematical treatment. It offered a useful model to describe intrarenal oxygen distribution (fig. 3I).

*Patient 2* (1.5–2 per cent halothane, 38 per cent nitrous oxide, 60 per cent oxygen). The previously described centripetal decline of the parenchymal oxygen tension was again observed at each of four puncture sites. However, the  $P_{O_2}$  was elevated throughout and the rate of decline appeared less marked at succeeding layers. The elevation was most pronounced in the inner medulla and less obvious in the cortex (fig. 4). The total  $P_{O_2}$  gradient from the subcapsular cortex to the tip of the papilla, therefore, amounted to only 40 mm. of mercury. The results from four probings showed a mean deviation of  $\pm 3.5$  per cent.

Arterial and renal venous oxygen tensions averaged 370 and 99 mm. of mercury, respectively, corresponding to a hemoglobin saturation of 100 and 97 per cent, respectively. Considering the oxygen dissolved in the plasma and the hemoglobin concentration of 15.0 g./100 ml., an arteriovenous oxygen difference of 1.4 ml. was calculated. With a high inspiratory oxygen concentration, therefore, renal  $O_2$  requirements were met by the physically dissolved oxygen in the plasma while the venous blood remained saturated.

Arterial carbon dioxide tension averaged 28 mm. of mercury. Pelvic urine showed a  $P_{O_2}$  of 78 mm. of mercury which again ranged 20

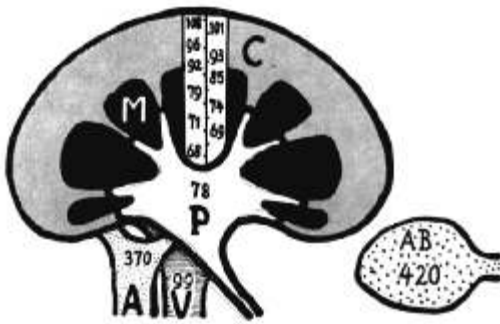


FIG. 4. Intrarenal oxygen distribution under halothane-nitrous oxide anesthesia plus 60 per cent oxygen. Each parenchymal  $P_{O_2}$  entry represents the mean value from four separate probings. The oxygen tension of pelvic urine (P), arterial (A) and renal venous blood (V) and inspired gas mixture (AB) are indicated (for details see text).

mm. of mercury below that of renal venous blood, but correlated well with parenchymal readings from the midmedulla.

The  $P_{O_2}$ -distance plot again could be fitted with a cortical and medullary parabola, showing a smooth transition in the border zone. In contrast to the previous case the parabolic model presented a flat appearance, especially in the medulla (fig. 3 II).

*Patient 3 (10 per cent cyclopropane, 28 per cent nitrogen, 62 per cent oxygen).* Although anesthesia was maintained with 15 per cent cyclopropane in oxygen, the  $P_{O_2}$  in the reservoir bag corresponded to only 62 per cent oxygen. Arterial oxygen tensions confirmed the lower figure. The discrepancy was attributed to dilution with ambient air, because tracheal suction had to be performed repeatedly. The above concentrations, as calculated from the known composition of the inspired gas before dilution and the observed difference in  $O_2$  concentration, were present when the renal  $P_{O_2}$  was measured.

The typical pattern of a decreasing parenchymal  $P_{O_2}$  in the corticomedullary axis was confirmed. In contrast to the second patient (halothane and a comparable oxygen concentration) the values during cyclopropane anesthesia were lower throughout the kidney, even below those of the first subject who received only 21 per cent  $O_2$ . The difference was most pronounced in the juxtamedullary zone and the entire medulla. The total  $P_{O_2}$  decline during one probing approximated 60 mm. of

mercury. Corresponding findings from two separate runs showed a mean deviation of  $\pm 2$  per cent (fig. 5).

The renal vascular oxygen tensions *in vivo* and *in vitro* were as follows: arterial  $P_{O_2}$  388 and 400 mm. of mercury, 100 per cent saturation; venous  $P_{O_2}$  67 and 65 mm. of mercury, 91.2 to 92 per cent saturation. Considering a hemoglobin concentration of 14.0 g., a hematocrit of 42 per cent and the oxygen dissolved in plasma, an arteriovenous difference in oxygen content of 2.7 ml. per 100 ml. of blood was calculated.

The arterial carbon dioxide tension at the time of probing averaged 30 mm. of mercury. In the pelvic urine a  $P_{O_2}$  of 33 mm. of mercury was found, ranging more than 30 mm. of mercury below that of renal venous blood. The urinary oxygen tension again approximated the parenchymal findings in the midmedulla.

The  $P_{O_2}$ -distance plot further corroborated the suitability of a parabolic model for the cortical and medullary distribution (fig. 3 III).

## Discussion

*Intrarenal Oxygen Distribution and Renal Function.* It is generally accepted that oxygen tension of tissues and blood are in equilibration at an end-capillary site. Therefore availability of oxygen to tissues is proportional to the regional blood flow and inversely proportional to the local oxygen consumption, the latter reflecting varying degrees of functional activity. Furthermore, studies of viscera other

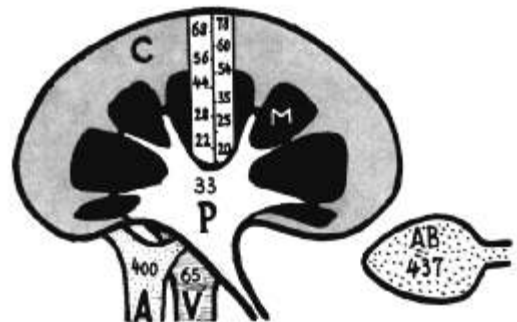


FIG. 5. Intrarenal oxygen distribution under cyclopropane anesthesia plus 62 per cent oxygen. Each parenchymal recording represents the mean  $P_{O_2}$  of two separate probings. For methodological details in regard to arterial (A), renal venous (V), pelvic urinary (P) and inspiratory (AB) oxygen tension see text.

than the kidneys suggest an uniform oxygen distribution throughout a given anatomical component, even though the  $P_{O_2}$  may vary among different parts of the organ. Obviously, the greater blood-tissue gradient of  $P_{O_2}$  on the arterial side of the capillary is compensated for by hemodynamic and biochemical changes as the blood advances through the capillary, thus providing uniform release of oxygen.

As we have shown, renal parenchyma represents an unique exception to this rule: neither in the cortex nor in the medulla does uniform distribution exist. The pattern of concentric, corticomedullary stratification, therefore, calls for an explanation, perhaps based on the countercurrent theory of urinary concentration and dilution in the medulla.<sup>14</sup> This theory, first proposed about 20 years ago, has been substantiated ingeniously by renal physiologists within the past decade.<sup>15</sup> Micropuncture studies at different levels of the nephron established a gradual increase of osmolality in the interstitial pool from the outer medulla toward the papilla, where it exceeds by many times that of extracellular fluid. Stop-flow techniques and micro-measurements of tubular potentials contributed further evidence.

The theory postulates that the hairpin-like arrangement of the loops of Henle and collecting ducts form the anatomical basis for the countercurrent multiplier and exchange mechanism. The vasa recta, also hairpin-like structures, and the interstitial water and electrolyte pool complete the countercurrent system. The close proximity of the several ascending and descending components permits partial equilibration of an osmotic gradient between a single element and the rest of the system. Therefore, in the outer medulla, "highly diffusible material" such as oxygen is cross-shunted from the descending channels through the interstitial pool into the ascending components, thus lowering intraluminal oxygen supply to the inner medulla. Similarly, water leaves the descending components by filtration and enters the ascending element at the same level, without flowing through the inner medulla. On the other hand, "less diffusible substances" such as sodium and urea are carried through to the papilla by mass flow. Due to the continuous water loss in the outer zone these solutes are highly concentrated when

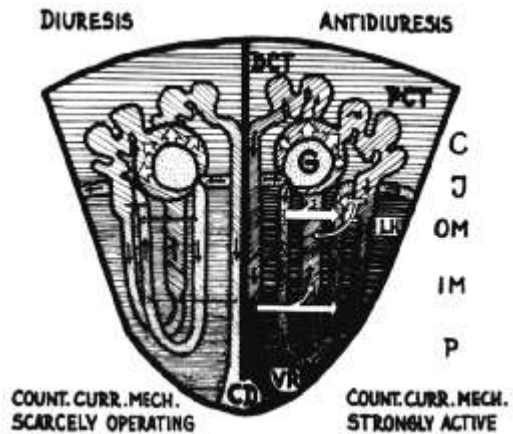


FIG. 6. Countercurrent diffusion of oxygen in the renal medulla during diuresis and antidiuresis. The white arrows indicate magnitude, direction and location of transparenchymal oxygen shunts. The black arrows show direction of intraluminal flow of tubular urine and vasa recta blood. The degree of shading expresses the decreasing availability of oxygen in the corticomedullary axis. G = glomerulus, DCT = distal convoluted tubules, PCT = proximal convoluted tubules, LH = loops of Henle, VR = vasa recta, CD = collecting ducts.

entering the ascending limbs. Therefore an osmotic gradient is established causing outward diffusion, recirculation and trapping in the inner medulla. Sodium remaining in the loop after passive exchange, enters the zone of active sodium reabsorption. The "sodium pump" is the driving force of the countercurrent multiplier mechanism which, in combination with the described diffusion shunts, causes a gradual build-up of osmolality toward the papilla. The magnitude of this osmotic force determines the amount of water reabsorbed from the collecting ducts and therefore the concentration of the urine excreted (fig. 6). While changes in permeability of the collecting ducts in response to antidiuretic hormone have been recognized for some time, only in recent years has the role of medullary blood flow attracted attention.<sup>16</sup> Our urinary  $P_{O_2}$  studies contribute evidence in support of this mechanism.

Obviously, removal of solutes from, or addition to the interstitial water and electrolyte pool is only possible by means of the two drainage systems of the area: the tubular and vascular channels. Since under physiological conditions glomerular filtration remains con-

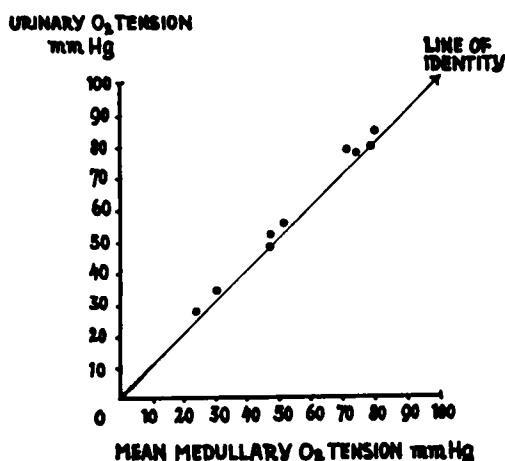


FIG. 7. The urinary oxygen tension in the segmental calyx from nine individual probings of three normal kidneys is plotted against the corresponding mean medullary oxygen tension. The plottings approximate the line of identity throughout the range of distribution.

stant, medullary blood flow must be responsible for changes in osmolality in the medulla. Increased perfusion will serve to wash solutes out of the pool, reduce the osmotic gradient toward the collecting ducts and initiate a diuresis. On the other hand, a low medullary blood flow favors uptake of osmotically active substances, increases water reabsorption from the ducts and therefore causes antidiuresis.\* In renal or systemic disease and under the influence of various drugs, glomerular filtration also varies and the volume and composition of the tubular urine entering the medulla will, in addition to the perfusion, change the interstitial solute concentration.

In normal renal physiology, therefore, the degree of countercurrent activity appears to be controlled by a perfusion-limited wash-out process. There is evidence that oxygen and water are handled in a somewhat similar way by the countercurrent mechanism. Representing what has been termed "highly diffusible material"<sup>16</sup> these substances are readily cross-shunted in the border zone. In view of the different physical characteristics of water and

\* Wash-in of solutes occurs whenever reabsorption from the loops exceeds removal by either blood or urine, leaving the medulla. Vice versa, solutes are washed out when the rate of removal exceeds that of reabsorption.<sup>17</sup>

oxygen, "diffusibility" *per se* does not seem to be the governing factor. Instead, as a common denominator a biological similarity is suggested: both substances have a great "affinity" for medullary venous blood which constantly removes them from the interstitial pool, thus maintaining a steep countercurrent gradient. For oxygen this is due to the reduced hemoglobin and, for water, to the high colloid-osmotic pressure of ascending capillary blood. Therefore, with due caution, the oxygen distribution may reflect distribution of water and serves as a crude model of the concentration process.

Our data on medullary oxygen distribution provide strong evidence in support of the countercurrent theory. Since, to a lesser degree, a similar decline in  $P_{O_2}$  was observed in the cortex, the possibility of a cortical countercurrent mechanism as demonstrated by Levy and Imperial<sup>6</sup> is confirmed. These authors suggested as the anatomical substrate, the short loops of Henle which are the cortical counterparts of the longer elements in the juxtamedullary nephrons, and the peritubular capillaries which form a dense network.

The effects of various anesthetic agents on renal blood flow, glomerular filtration rate and electrolyte excretion have been well studied.<sup>17</sup> A stereotyped response was commonly reported which suggested some uniform changes associated with the state of anesthesia.<sup>18</sup> In contrast to these findings, derived from cortical parameters, the effects of cyclopropane and halothane on the inner medullary  $P_{O_2}$  differ significantly. Despite a high and equal concentration of oxygen in the inspired gas and comparable arterial values of  $P_{O_2}$ , cyclopropane is associated with a papillary  $P_{O_2}$  of 19 mm. of mercury as compared to 68 mm. of mercury during halothane anesthesia. Comparison of the  $P_{O_2}$ -distance curves from patients 2 and 3 shows a low and steep course in the latter, suggestive of preglomerular vasoconstriction and a high degree of oxygen shunting in the outer medulla. It would appear that the medullary circulation, being "perfusion-limited" in contrast to the abundant blood flow in the cortex, operates within a narrow margin of safety. Conceivably, in adverse circumstances, cyclopropane might con-

tribute to production of prolonged hypoxemia of the lower nephron.

*Intrarenal Oxygen Distribution and Urinary Oxygen Tension.* Factors determining the oxygen tension of the urine and their relationship to the  $P_{O_2}$  of renal parenchyma have been largely a matter of speculation. In recent years it has been widely accepted that the  $P_{U_{O_2}}$  in some way reflects intrarenal conditions. A more accurate definition, however, appears crucial for a meaningful interpretation of urinary findings. For this purpose a total of nine complete probings terminating in the renal pelvis were used in three normal kidneys. In order to plot the pelvic  $P_{U_{O_2}}$  of each separate run against the corresponding parenchymal oxygen tension, it became necessary to determine the mean cortical and medullary  $P_{O_2}$ .

The parabolic model permits the following estimates: In any curvilinear equation the mean ordinate ( $\bar{y} = \text{mean } P_{O_2}$ ) equals the area below the curve ( $A_0^x$ ) from the abscissa ( $x$ ) to zero divided by  $x$ . Therefore:

$$\bar{y} = \frac{\int_0^x kx^2 dx}{x} = \frac{kx^3}{3x} = \frac{kx^2}{3} = \frac{y}{3} \quad (1)$$

where  $y$  represents the maximal  $P_{O_2}$  difference within the cortex or medulla from border to border and  $x$  equals total distance.

When the mean medullary  $P_{O_2}$  was plotted against the corresponding calyceal  $P_{U_{O_2}}$ , a close correlation between the two parameters was found. No relation could be discerned between the mean cortical and the segmental  $P_{U_{O_2}}$ . As shown in figure 7 the plottings closely approximate the line of identity throughout the range of distribution. Of the nine segmental  $P_{U_{O_2}}$  values, two are identical to the mean medullary oxygen tension, seven are slightly higher and none lower. The minor differences are indicative of slightly incomplete equilibration between urine and papillary parenchyma. In our experiments and for most practical purposes this deviation is negligible but may assume significance during maximal diuresis and certain pathological conditions. Therefore in the normal human kidney, within physiological limits, the  $P_{U_{O_2}}$  equals the mean tissue oxygen tension of the medulla. This holds true for both anesthetics studied as well as for different concentrations of oxygen in the inspired gas.

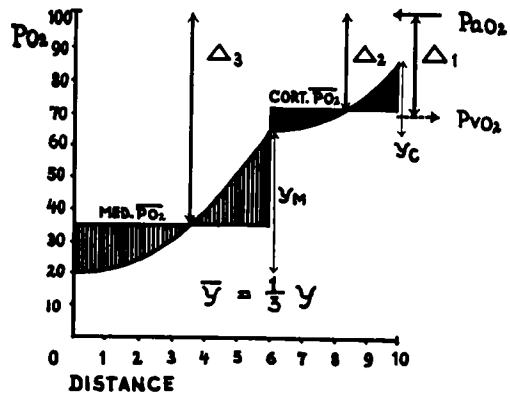


FIG. 8. Mean cortical and medullary oxygen tension as calculated from the parabolic model (equations, see text). At  $\bar{y}$  (mean  $P_{O_2}$ ) the shaded area above the parabola equals the one below it in cortex and medulla.  $\Delta_1$  represent the arterio-venous  $P_{O_2}$  difference,  $\Delta_2$  the mean arterio-end-capillary  $P_{O_2}$  difference in the cortex and  $\Delta_3$  the mean arterio-end-capillary  $P_{O_2}$  difference in the medulla.

*Parenchymal O<sub>2</sub> Tension and Distribution of Intrarenal Blood Flow.* Estimates of mean oxygen tensions in the cortex and medulla seem to eliminate the effects of the countercurrent mechanism on intrarenal O<sub>2</sub> distribution. The mean value expresses the balance between the countercurrent-induced excess of oxygen in the border zone and a corresponding absence in the papilla. Thus the factors determining parenchymal  $P_{O_2}$  may be reduced to blood flow and oxygen consumption as in an ordinary capillary bed: this implies attainment of equilibrium between the  $P_{O_2}$  of tissue and end-capillary blood throughout the region and permits application of the Fick principle for determination of blood flow (fig. 8). In these studies, oxygen saturation, capacity and content of arterial, venous and end-capillary blood were determined from the vascular and mean parenchymal  $P_{O_2}$ , the oxygen dissociation curve, the large vessel hemoglobin concentration and the plasma oxygen, in the usual way. There is a growing body of evidence that the difference between renal and large vessel hematocrit on the one hand and the hematocrit of cortical and medullary tissue on the other is considerably less than formerly assumed.<sup>17, 19</sup> From these data a cortical/large vessel hematocrit ratio of 0.8 and a corresponding medullary figure of 0.6 appear to be justified. Therefore the above estimates



TABLE 1. Intrarenal Blood Flow Distribution in Normal Kidneys

Influence of Anesthetic Agent and Inspired O <sub>2</sub> Concentration	77% Nitrous Oxide + 1.5-2% Halothane + 21% Oxygen	38% Nitrous Oxide + 1.5-2% Halothane + 60% Oxygen	28% Nitrogen (Air Dilution) + 10% Cyclopropane + 62% Oxygen
Medullary blood flow Percentage of total blood flow	4.8	4.5	3
Cortical blood flow Percentage of total blood flow	95.2	95.5	97
Total renal blood flow Percentage of normal in unanesthetized subject	100	100	60

Medullary and cortical distributions are expressed in percentage of the total renal blood flow. The figures are based on mean values from multiple probings (calculations described in text). The total blood flow of normal unanesthetized subjects represents average of data in recent literature.

based on the large vessel hematocrit were corrected according to the calculated values for parenchymal end-capillary content of oxygen.

With these estimates the medullary blood flow ( $\dot{Q}_M$ ) can be expressed as a fraction of the total renal blood flow ( $\dot{Q}_{Tot}$ ):

$$\frac{\dot{Q}_M}{\dot{Q}_{Tot}} = \frac{100 \dot{V}_{O_{2M}} (C_{aO_2} - C'_{vO_2})}{(C_{aO_2} - C'_{cO_{2M}}) 100 \dot{V}_{O_{2Tot}}} \quad (2)$$

where  $\dot{V}_{O_{2M}}$  and  $\dot{V}_{O_{2Tot}}$  represent the oxygen consumption in the medulla and whole kidney,  $C_{aO_2} - C'_{cO_{2M}}$  the arterio-ende-capillary oxygen difference of medullary blood and  $C_{aO_2} - C'_{vO_2}$  the arterio-venous oxygen difference. Similarly, the cortical blood flow ( $\dot{Q}_C$ ) can be expressed as a fraction of the total renal blood flow. Since the absolute values for oxygen consumption were not known, the equation was rearranged to yield fractions ( $F$ ) of  $\dot{V}_{O_2}$ , while the total blood flow and oxygen uptake were designated as unity:

$$F_{\dot{Q}_M} + F_{\dot{Q}_C} = 1 \quad (3)$$

$$F\dot{V}_{O_{2M}} + F\dot{V}_{O_{2C}} = 1 \quad (4)$$

The fraction of medullary oxygen consumption was termed  $x$ , the complementary cortical figure ( $1 - x$ ), both incorporated in equations (2) and the corresponding formula for cortical blood flow. By adding the two resulting expressions according to (3) the equation could be solved for  $x$  as follows:

$$\frac{x(C_{aO_2} - C'_{vO_2})}{C_{aO_2} - C'_{cO_{2M}}} + \frac{(1-x)(C_{aO_2} - C'_{vO_2})}{C_{aO_2} - C'_{cO_{2C}}} = 1 \quad (5)$$

Finally, the medullary and cortical share of the total oxygen consumption were interpolated into equation (2) to determine the fraction or percentage of medullary and cortical blood flow in relation to total flow.

Results of these calculations are presented in table 1. Since these figures are based on the mean parenchymal oxygen tension, they represent the mean cortical and medullary blood flow. The area which is most representative of our estimates is defined by  $x(\bar{y})$ , i.e., the distance corresponding to the mean  $P_{O_2}$  in both structures: this is located on the corticomedullary axis about 1 mm. peripherally to the midpoint in cortex and medulla.

Methodologically the "mean medullary blood flow" closely approximates the "inner medullary flow" determined by several investigators. Our findings of a mean medullary blood flow of 4.5-4.8 per cent of the total renal blood flow in halothane anesthesia are in good agreement with a number of recent estimates in dogs under pentobarbital anesthesia, obtained with a variety of methods. Kramer *et al.* employing photoelectric measurements of mean circulatory transit times in the cortex and medulla, calculated figures ranging from 11 per cent in the outer medulla to 0.9 per cent in the papilla.<sup>17</sup> Thornburn and his associates studied the distribution of radioactive krypton in unanesthetized and moderately dehydrated dogs permitting estimates of 6 per cent in the outer medulla and 0.6 per cent in the papilla.<sup>20</sup> Extrapolation of our figures by means of the parabolic model would indicate a range from

14 per cent in the outer medulla to 4.5 per cent in the inner medulla, and to less than 1 per cent in the papilla.

*Oxygen Distribution and Metabolism During Anesthesia.* It is generally accepted that total blood flow to one kidney in normal man approximates 600 ml. per minute. Equally well established is an average kidney weight of 150 g. There is less agreement on the renal arteriovenous oxygen difference of unanesthetized man. Nevertheless, the variations reported are mainly attributable to differences in methods, and a number of recent studies using renal vein catheterization have arrived at nearly identical figures.<sup>22</sup> An arteriovenous oxygen difference of 2.0 to 2.3 ml. appears well documented for healthy subjects. Accordingly, the calculated  $O_2$  consumption should be close to 12 ml. per minute for one kidney.

In comparison, our findings in halothane anesthesia show an arteriovenous oxygen difference considerably smaller than the lowest of the quoted reports. This observation can be attributed either to an elevated blood flow or a decreased oxygen consumption. The first possibility may be discarded, since halothane in the concentration employed consistently lowers cardiac output,<sup>21</sup> though it is realized that cardiac output and renal blood flow do not necessarily change in the same direction. However, a decrease in cardiac output would produce either hypotension or reflex elevation of the peripheral resistance, associated in both cases with activation of renal autoregulatory mechanisms. As has been shown repeatedly, maintenance of the pre-existing blood flow would be the optimal response in either event, while a moderate decrease might occur but never an increase.<sup>17</sup> It may therefore be concluded that halothane depresses renal metabolism to approximately 60 per cent of normal. There is evidence that halothane in contrast to most other anesthetic agents reduces the total body oxygen consumption.<sup>18</sup> Such metabolic depression may be a manifestation of selectivity in certain tissues such as the myocardium and the brain.

During cyclopropane anesthesia the arteriovenous oxygen difference was larger than the largest value reported in unanesthetized subjects. In contrast to halothane, this observation can be explained entirely by circulatory

changes, that is, a reduction of the total renal blood flow to approximately 60 per cent of normal. On the other hand, an elevated oxygen consumption, as has been claimed for cyclopropane,<sup>16</sup> may contribute to the higher rate of  $O_2$  extraction. Even if we consider the latter possibility as pertinent to the cortex, it would not appear to apply to the medulla. According to our estimates of  $O_2$  uptake per gram of tissue in the medulla it is only one third of the cortical  $O_2$  consumption. This rather carries the implication that a low perfusion rate activates the anaerobic metabolic pathway of medullary tissue.

### Summary and Conclusions

We have previously reported reproducible changes of the urinary oxygen tension in normal and diseased kidneys under a variety of conditions. Evidence for the circulatory nature of these observations was presented and the conclusion advanced that urinary oxygen tension may indicate the changing conditions in the medulla. To test this hypothesis and to promote understanding of intrarenal hemodynamics the present study was undertaken. The oxygen tension of the renal parenchyma was measured *in vivo* by a polarographic micro-technique in 15 patients undergoing renal exploration or nephrectomy. The present report is mainly concerned with the effects of anesthesia in 3 subjects free of systemic and renal disease. A progressive decline in  $P_{O_2}$  was consistently observed in the corticomedullary axis, causing a concentrational stratification of the entire organ in regard to oxygen tension. This finding was considered strong evidence for the countercurrent theory of renal function. A mathematical model for renal parenchymal oxygen distribution was presented which permits calculation of intrarenal distribution of blood flow and regional metabolism. The mean medullary blood flow amounted to 4 per cent of the total renal blood flow;  $O_2$  consumption per gram of tissue was considerably lower in the medulla than in the cortex; urinary oxygen tension was found to equal the mean medullary oxygen tension.

Halothane anesthesia was associated with a high parenchymal and urinary  $P_{O_2}$ , normal renal and medullary blood flow, and a fairly high  $O_2$  consumption in the medulla. In con-

trast, cyclopropane lowered the  $P_{UO_2}$  of the parenchyma and urine and reduced the total and the medullary blood flow. At the same time the oxygen consumption in the medulla decreased.

From these data the following conclusions were derived: (1) Renal parenchymal oxygen tension depends upon regional blood flow, local consumption of oxygen and activity of the countercurrent mechanism. (2) The latter is not only confined to the medulla but is operative in the cortex. (3) Urinary oxygen tension equals the mean medullary  $P_{O_2}$  regardless of the inspired oxygen concentration or the anesthetic agent. (4) A standard procedure for continuous or serial  $P_{O_2}$  determination in the urine appears suitable for the study of medullary perfusion and countercurrent activity. (5) This procedure may be more sensitive than other tests in determining the effects of anesthetic agents.

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