

COURSE CODE:	VBP 201
COURSE TITLE:	Blood, Cardiovascular, Renal and Respiratory Physiology
NUMBER OF UNITS:	3 Units
COURSE DURATION:	Three hours per week

COURSE DETAILS:

Course Coordinator:	Dr. Eyitayo Solomon Ajibola, D.V.M, M.Sc.
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Office Location:	Dept of Veterinary Physiology/ Pharmacology, COLVET, UNAAB
Other Lecturers:	Dr. O.E Adeleye

COURSE CONTENT:

Functions of the respiratory system, mechanism of respiration and gas exchange in the lungs. Properties and regulation of respiratory gases and buffers in the blood. Composition and functions of blood. Production, function and break down of blood cells. Electrical and mechanical function of the heart, Electrocardiogram and Arrhythmias. Hemodynamics, , Coronary circulation, Cerebral circulation and Splanchnic circulation. The role of the kidney in water and electrolyte homeostasis. Glomerular and tubular function. Kidney function assessment, micturition reflex and diuretics.

COURSE REQUIREMENTS:

This is a compulsory course for all Pre-clinical Veterinary Medical Students. In view of this students are expected to participate in all the course activities and have a minimum of 75% attendance to be able to write the final examination.

READING LIST:

1. James G. Cunningham and Bradley G. Klein. Textbook of Veterinary physiology, 4thedition. Saunders Elsevier, Missouri, 2007.
2. Duke' Physiology of domestic Animals 10TH ed. Cornell University Press, London. 1984

LECTURE NOTES

RENAL PHYSIOLOGY

Excretory and Endocrine functions of the kidney

The kidneys are the main excretory organs which eliminate in the urine, most metabolites primarily those containing nitrogen such as ammonia, urea and creatinine.

The production and excretion of urine is termed **diuresis**. Therefore the major function of the kidney involves the elimination of degradable by products, toxic substance, excess water, salt and some drugs from the body.

The kidney also maintains homeostasis by participating in the water-salt metabolism (eliminates excess salt & water) and also through osmoregulation. Hence, together with other mechanisms the kidney maintains the acid base balance of the body by modifying the rate of secretion of acid or alkaline phosphate when the blood becomes acidic or alkaline.

The kidney also mediates the synthesis of a number of compounds and also eliminates these compound e.g. Hippuric acid which is a product of glycolic acid and benzoic acid and ammonia which is a product of deamination of amino acid.

The kidney also functions in the secretion of the organic acids and bases including K^+ and H^+ . They are also involved in lipid – protein, carbohydrate metabolism such as arginine metabolism, gluconeogenesis and peptide hydrolysis.

The kidneys are also a source of hormones e.g. Angiotensin II, D – hormones, prostaglandins and Erythropoietin. Erythropoietin, synthesized in the kidney, stimulates the production of red blood cells in the bone marrow and thus, regulates the oxygen carrying capacity of the blood.

Therefore the kidney maintains relative homeostasis by regulating the osmotic pressure, acid – base balance, synthesis, secretion and excretion of metabolic by products.

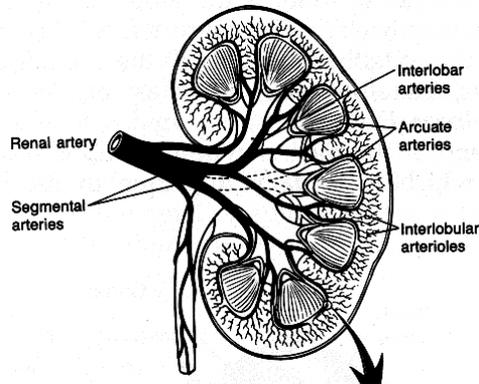


Diagram of the inner portions of the kidney

Summary of the functions of the kidney

- Conservation of water, fixed cations, glucose and amino acids. This implies the return to the body fluids of the amount of the substances required by the body's needs, with the excesses being excreted in the urine.
- Elimination of nitrogenous end products of protein metabolism, primarily urea (uric acid in birds), creatinine and ammonia.
- Elimination of excess H^+ and the maintenance of physiological pH of body fluids.
- Elimination of complex organic compound both endogenous and exogenous.
- Secretion of endocrine substances e.g. erythropoietin which assumes a role in normal hematopoiesis, renin which is involved in the regulation of aldosterone secretion by the adrenal cortex.

C.N.S. contribution to Renal integration

Maximum urine concentration requires the secretion of antidiuretic hormone (ADH) or vasopressin by the hypothalamo – neurohypophyseal complex.

Reflexes from peripheral receptors (e.g. the postulated volume receptors) may influence renal functions by central nervous integration through hypothalamus and autonomic nervous system.

Hypothalamic mediation of the adenohypophyseal secretion represents another pathway through which the CNS may alter the output of hormones that modify renal functions.

Thyroid hormones and adenohypophyseal growth hormone exerts tropic effect on the kidney. The hormones that assume major importance in kidney function regulation are steroid secretions of the adrenal cortex and the hormones of the parathyroid gland e.g. the permissive action of the cortisol-

type steroids is essential for maximal rates of H₂O excretion, while aldosterone regulates transport of K⁺ into urine and the retention of Na⁺ within body fluids.

The hormone of the parathyroid gland influences the rate of Calcium and Phosphate excretion into the urine.

The normal kidney demonstrates considerable functional autonomy and is adequately perfused with blood. Just a small percentage decrease in any given process can be produced by removing a specific neuro-humoral or endocrine mediator. Volumes of fluids passing through the kidney each day are of such magnitude that small percentage decreases in any given function usually represents a major crisis in terms of maintaining the physiological integrity of the body fluid compartments.

Anatomy of the kidney

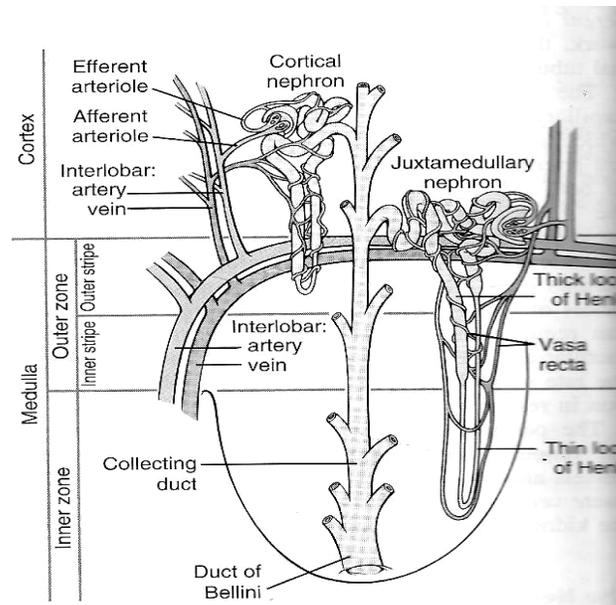
Nephrons, which are the functional units of kidney are of 2 types in mammals and are distinguished by:

- Locus of the origin i.e. the area of the cortex in which the glomeruli are found.
- The extent to which the loops of Henle penetrates the medulla.

Types of Nephron

(1) Cortical / corticomedullary nephrons: They arise from glomeruli located in the *peripheral* and *central area* of the kidney cortex with their loops of Henle extending into the corticomedullary junctional area and to variable levels of the outer medulla.

(2) Juxtamedullary nephrons: They originate from glomeruli situated in the deeper portion of the cortex adjacent to the corticomedullary junctional area with their loop of Henle, particularly the thin segments extending into medullary substance. Many of the longer looped nephrons penetrate to the medullary crest or renal papilla.



Schematic representation of cortical and juxtamedullary nephrons

Principal mechanism of Nephron functions

- A. Nephron filters a large portion of plasma ($\frac{1}{5}$) from glomeruli blood throughout the glomerular membrane into the tubular system.
- B. As filtered fluids pass through the tubular systems, unwanted substances are allowed to pass out into urine, while wanted substances are reabsorbed back into the plasma through the peritubular capillary network

Functions of the renal tubules

Filtration: An average of 21% of the blood pumped by the heart each minute flows through the kidneys. Of the total volume of blood plasma that flow through the glomerular capillaries, about 19% passes through the filtration membrane into the Bowman's capsule to become filtrate. In all of the nephrons of both kidneys, about 180lt of filtrate are produced each day but only about 1% or less of the filtrate becomes urine.

Filtration is the passage of plasma, aqueous, ionic and crystalloid components of blood across the filtrates membrane of the renal corpuscles (Bowman's capsule and glomerulus) into the Bowman's space. Erythrocytes and most of the plasma proteins {albumin, a blood protein with a diameter slightly less than the openings in the filtration barriers enters the filtrate in trace (small) amount} do

not filter through the glomerular membrane. In other respects, the glomerular filtrate prior to its entrance into the proximal convolutions is almost identical in composition and osmolality to plasma.

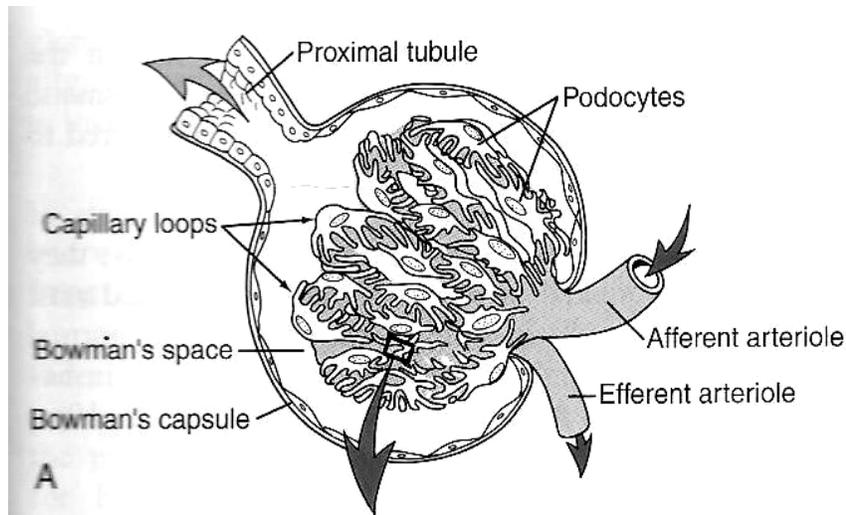


Diagram of the glomerulus and bowman's capsule

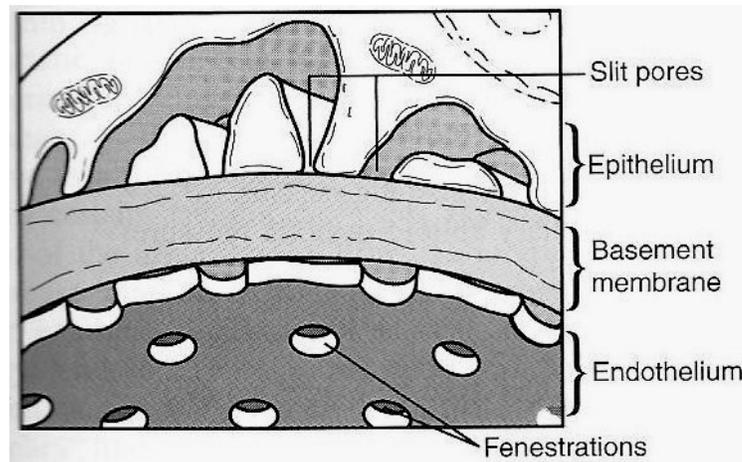


Diagram of the filtration membrane of the glomerulus and bowman's capsule

Re-absorption: About 99% of the filtrate volume is reabsorbed and enters the peritubular capillaries. Reabsorption as used here means that a substance moves from the tubular lumen to the peritubular capillary and it is not allowed to get into the collecting duct. The reabsorbed filtrate flows through the renal vein to enter the general circulation. Excess ions and metabolic waste e.g. urea, uric acid and creatinine are not readily reabsorbed. Therefore the small volume of urine

produced contains a high concentration of metabolic waste products. Tubular reabsorption may result from either passive back diffusion or active cellular transport.

Secretion: Tubular secretion is similar to reabsorption except that substances enter the renal the renal tubules instead of leaving it. Tubular secretion can either be active or passive. e.g. NH_3 diffuses into the lumen of the nephron whereas H^+ , K^+ , creatinine, histamine & penicillin are actively transported into the nephrons.

SPECIFIC FUNCTIONS OF NEPHRON

The glomeruli and the proximal convoluted tubules: The glomeruli function primarily as filters.

The glomeruli membrane is composed of the endothelium of the glomeruli capillaries, a basement membrane and the invaginations of the Bowman's capsule.

The membrane is of differential permeability that permits the passage of aqueous, ionic and crystalloid components of blood into the Bowman's space.

Erythrocytes and most of the plasma proteins do not filter through the membrane.

Proximal convoluted tubule is the primary site for reabsorbing solute and water. Tubular fluid near the end of the PCT is devoid of glucose and amino acids and most of the filtered proteins and has a fluid- plasma osmolal ratio of 1.

Quantitative estimates indicate that only 20% of the original glomerular filtrate remains after its passage through the PCT. In summary, the primary function of the PCT is to return 70% of the glomerular filtrate into the peritubular blood and hence into the systemic circulation.

When plasma glucose concentrations are normal, all of the filtered glucose is transported from the tubular fluid of the PCT into the plasma.

Amino acids are almost entirely removed (reabsorbed) from the proximal tubular fluid. The major determinants of PCT reabsorption apparently are:

1. Active transport of Na against an electrochemical gradient, from the tubular fluid into the peritubular interstitial fluid and capillary blood.
2. H^+ - Na^+ exchange processes
3. Reabsorptions of glucose

Chloride either diffuses along with Na^+ to maintain electrical neutrality or may also be transported by some carrier system.

Other substances that are actively transported from the PCT includes proteins, Na^+ , K^+ , Ca^{2+} , HCO_3^- , Cl^- . The PCT is permeable to water. As solute molecules are transported from the PCT to the peritubular capillaries, water moves by osmosis in the same direction.

N.B: Difference between osmolality & osmolarity, active and passive transport.

Consequently, 65% of the glomerular filtrate volume is reabsorbed from the PCT. Creatinine and urea which are other nitrogenous components of glomerular filtrate are differentially affected by events in the PCT. Creatinine which is not reabsorbed by the nephrons becomes more concentrated as reabsorption proceeds while urea on the other hand diffuses readily across most biological membranes. Approximately 30-40% of filtered urea is reabsorbed in the PCT. H^+ is actively secreted in the PCT.

How? The epithelial cells secrete large quantities of H^+ across the wall of the nephron into the filtrate.

Loop of Henle: Tubular fluids in Henle's loops become increasingly hypertonic as it passes through the medulla. The descending limb of Henle's loop (DLH) is apparently permeable to the passage of ions & crystalloids. Both NaCl and urea are added by passive diffusion to the tubular fluid in this segment from the medullary interstitium. Fluids from the tip of Henle's loop are almost equal in composition and the osmolality to the medullary interstitial fluid. The initial segment of the ascending limb of Henle's loop (ALH) may be less permeable than the descending, but some equilibration occur between tubular fluids and medullary interstitium. **LH, therefore functions as a counter current diffusion system in concert/association with the vasa recta,** as NaCl and urea diffuse circuitously from the ascending segment into the medullary interstitium and into the descending segment.

The medullary segment of the thick ascending LH is relatively impermeable to water and it is the site of active transport system that translocates chloride (accompanied by sodium) against the significant concentration from the tubular fluid into the interstitial fluid of the inner medulla. Since NaCl is reabsorbed at this site into the interstitial fluid, the tubular fluid becomes increasingly dilute.

N.B.: Water excretion (elimination of dilute urine) is not a passive process solely related to the absence of ADH. The active transport of chloride (accompanied by sodium) from the relatively

water- impermeable ascending LH represents an essential energy dependent process in the formation of dilute urine.

Active chloride transport from the thick ascending loop of Henle could supply NaCl to be carried into and sequestered within the **counter current multiplier**. NaCl and particularly urea apparently can be concentrated solely by passive diffusion within the counter current multiplier system of the thin portion of the LH and side by side the apposed descending and ascending vasa recta. The maintenance of the gradient is enhanced by the progressive decrease in medullary blood flow from the inner medulla to the medullary crest or papilla.

N. B. the daily production of primary urine (glomerular filtrate) is about 150 – 180 liters, but due to tubular reabsorption of H₂O and numerous substances from the primary urine, only 1-1.5 liters of the secondary urine is excreted daily.

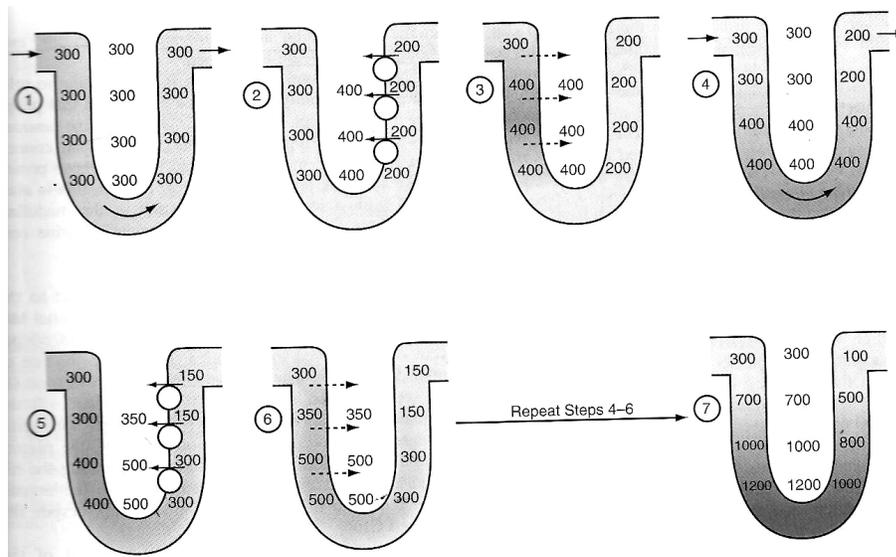
concentrating mechanism of the kidney

By the time the tubular fluid leaves the PCT, its volume has been considerably reduced and certain chemicals have been reabsorbed or excreted, but the osmotic concentration of the urine is still essentially the same as blood. Some additional reabsorption and excretion occurs in the distal convoluted tubule (DCT) and in the collecting duct (CD), but concentration of urine primarily involves movements of Cl⁻, Na⁺ and water. A major function of the LH is to establish differences in osmotic concentration of NaCl in the fluid surrounding the collecting duct from the upper cortex down to the inner medulla of the kidney.

Tubular fluid that enters the descending limb of the LH has an osmotic concentration similar to blood and the membrane of the descending LH is permeable to H₂O but not to NaCl. The membrane of the ascending limb of LH actively transports chloride from tubular fluid to interstitial fluid bathing the nephron. Sodium passively moves from tubular fluid to interstitial fluid but the membrane of the ascending LH is not permeable to H₂O. As a result, NaCl accumulates in fluid surrounding the nephron in increasing concentration from the cortex down through the medulla. The descending LH serves to provide NaCl to be transported out the ascending limb.

N.B.: Water is withdrawn from the tubular fluid in the descending limb.

The LH is called a **counter current multiplier**.



Counter current multiplier system in the loop of Henle for producing a hyperosmotic renal medulla

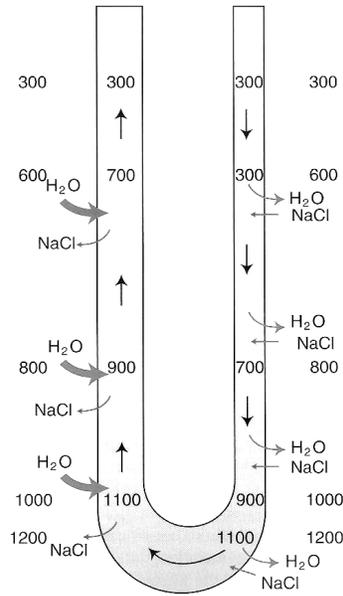
Why? Fluid flow in the ascending limb of LH is counter current to the flow of the descending limb and the collecting duct. In addition energy is expended to produce concentration gradient along the loop and collecting duct. Each small section of membrane on the ascending limb transports a certain amount of NaCl against a particular difference in concentration. This addition of small sections of membrane along the entire length of the ascending limb produces a multiplicative effect because multiplication is a series of successive addition of the same amount.

When tubular fluid reaches the top of the ascending limb, it may be slightly less concentrated than blood plasma resulting in some H₂O movement by osmosis to blood and further reduction of urine volume. As fluid passes back down through the CD, water will move by osmosis out of urine if the CD membranes are permeable to water (i.e. in the presence of ADH).

Because the concentration of fluids surrounding the collecting duct increases along their length, more and more water can be withdrawn by osmosis as the fluid move down the CD.

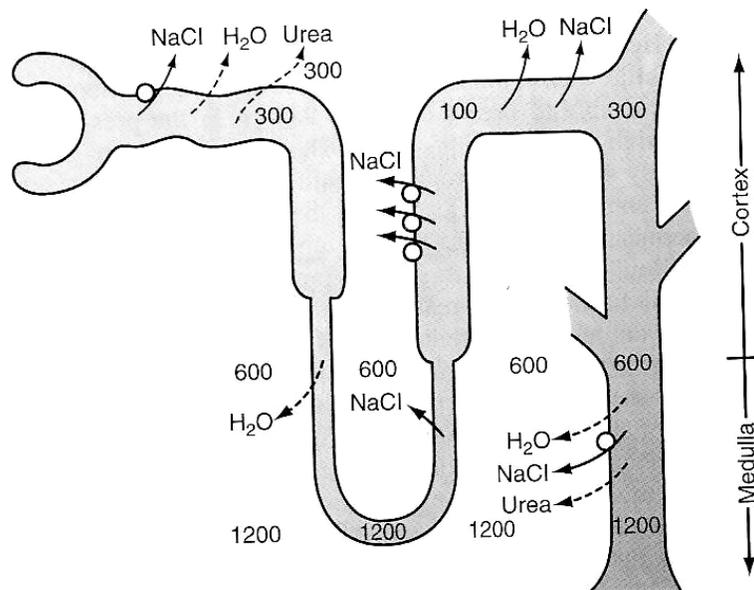
The H₂O that moves from the descending limb of LH and the collecting duct must be removed from the fluid surrounding the nephron tubules; otherwise the gradient of NaCl concentration will be dilute. Water removal occurs with blood flow in the capillary loops called vasa recta.

Counter current exchanger: Venous blood leaving the glomerulus gains NaCl by diffusion and loses water by osmosis on the descending limb of the vasa recta, but by looping back, the blood loses sodium by diffusion and gains water by osmosis on the ascending limb.



Counter current exchanger system in the loop of Henle and Vasa recta for producing a hyperosmotic renal medulla

Urea diffuses across all of the membranes in the nephron tubules and in the vasa recta. Urea is transported passively and becomes more concentrated in tubular fluid in CD as a consequence of the movement of water out of the ducts and into blood. The permeability of the CD to water and urea is variable, depending upon the presence of ADH.



Distal convoluted tubule and collecting duct: The distal CT receives a hypotonic fluid from the medullary region. Isoosmotic equilibration occurs in the 1st 1/3rd of the DCT (assuming that the kidney is elaborating a concentrated urine) as water leaves the tubular fluids in the direction of its concentration gradient. Further isoosmotic reabsorption occurs in the remaining portions of the DCT secondary to Na transport from tubular fluid into plasma. The osmolality of the fluid at the end of DCT is equal to the osmolality of plasma but quantitatively now represents approximately 5% of the original glomerular filtrate.

N.B.: Isoosmotic equilibration of tubular fluid does not occur in the DCT of dog nephrons. Rather the tubular fluid at the end of DCT is still hypotonic to plasma. Some portions of the ascending LH in the dog kidney appear to be involved in the processes that regulate urine concentration and dilution. Fluid entering the DCT shows a fluid – plasma osmolal ratio of 0.5 – 0.6 when the dog is elaborating a concentrated urine. Under conditions of water diuresis, i.e. when the kidney excretes a hypotonic urine, the osmolal ratio may be as low as 0.2.

Final concentration of urine takes place in the collecting duct as these terminal segments of the nephron system carry the urine through the medulla to the renal pelvis. The permeability of the collecting duct to water and urea is variable depending upon the presence of ADH. When the kidney is excreting concentrated urine i.e. in the presence of ADH, the collecting duct becomes increasingly permeable to water and urea. Water, free of solute, then passes in the direction of its concentration, from the lumen of the collecting duct into the hypertonic medullary interstitium. As the fluid in the collecting duct becomes concentrated, urea concentration in the collecting duct fluid increases until it exceeds the urea concentration in the medulla. Urea then diffuses from the collecting duct fluid into the medullary interstitium, thus, obligating the reabsorption of H₂O from the collecting duct fluid.

The collecting duct appears to be relatively impermeable to non-urea solute e.g. Na, K salts of chloride, sulphate, bi-carbonate and to creatinine, and these solutes become increasingly concentrated. The net result of these processes is the excretion of urine that may be 5-7 times the concentration of plasma.

Dilute urine is excreted when the release of ADH is inhibited. The primary target organs of ADH are the collecting duct, but the DCT and ALH in the dog at least, share to some extent as sites of action of this hormone. In the absence of ADH, the DCT, CD and the ALH in the dog become relatively impermeable to water and urea. Na reabsorption still takes place from the fluid in DCT,

but water movement is decreased; concurrently, water reabsorption in the CD is markedly inhibited. Therefore, the absence of ADH, results in water diuresis i.e. the excretion of large volume of urine hypotonic to plasma.

The specialized morphology and metabolism of the medulla permits the mammalian kidney to concentrate urine and thereby conserve water. However, there is evidence that the hyperosmolarity / hyperosmolality may also be detrimental. It has been shown that chronic infectious diseases of the kidney may also be closely associated with the maintenance of the cortico-medullary osmotic gradient.

Reasons are:

- The hyperosmotic environment of the medulla apparently inhibits the migration of leucocytes to the sites of infection, thus depriving the area of one of the primary defense mechanisms against bacteria.
- The relatively small medullary blood flow, will limit the amount of antimicrobial drugs that could be carried into the medulla.

These 2 factors complicate the therapeutic management of renal infection.

The urine concentrating process functions most effectively when protein intake is sufficient to maintain positive nitrogen balance. Protein deficient diet results in impairment in the capacity of the kidney to conserve water.

There may be subtle changes in the permeability characteristics as protein turnover in the kidney responds to unfavorable nitrogen equilibrium. Enzyme synthesis in the kidney may be similarly affected. Urea, however, assumes an important role in the renal responses to changes in protein intake. The urea component of the cortico-medullary osmotic gradient is virtually eliminated by protein deficiency and urea excretion falls to low levels. As urine is concentrated in the CD, there is a minimal reabsorption of urea and the amount of water reabsorption obligated by urea diffusion is greatly reduced.

A decrease in the cortico-medullary osmotic gradient also occurs since the quantity of urea is decreased. Water conservation, therefore, depends to a large extent upon reabsorption and is decreased as the result of the decrease in the osmolality of the medullary interstitium.

GLOMERULOTUBULAR BALANCE

In the dog and probably many other species as well, the glomerular filtration rate (GFR) varies markedly with the diet. The filtration rate in dog may be increased nearly 100% 4-5hrs after a meal of raw beef. Changes in GFR of this magnitude results in a very large increase in the Na load presented to the tubules. If the tubules are unable to adjust their Na reabsorption ability accordingly, the resulting severe Na loss in the urine cannot be tolerated. To prevent such wide fluctuation, the tubules are able to adjust their Na reabsorption proportionately.

Therefore, if GFR increases, tubular reabsorption of kidney increases proportionately and less Na is lost in the urine than would have occurred if Na reabsorption were fixed. This proportionality between Na reabsorption by the tubule and the GFR is termed Glomerulotubular balance.

Changes in Na reabsorptive capacity occurs primarily in the PCT. DCT and CD can only partially alter their reabsorptive rate for Na and the modest changes in GFR may be due at least in part to these incomplete adjustments at the DCT and CD. Glomerulotubular balance appears to be intact over a range of filtration rate, but during acute reductions or elevations in GFR some deviations from perfect balance occurs. How the tubules are informed of the necessity to readjust their reabsorptive ability when the filtration rate changes is still under investigation.

The hypothesis on which there is some evidence suggests that the interactions of some hydrostatic and colloid osmotic pressure at the peritubular capillaries surrounding the PCT are of primary importance. A change in these forces may be brought about by a change in the GFR relative to the renal blood flow.

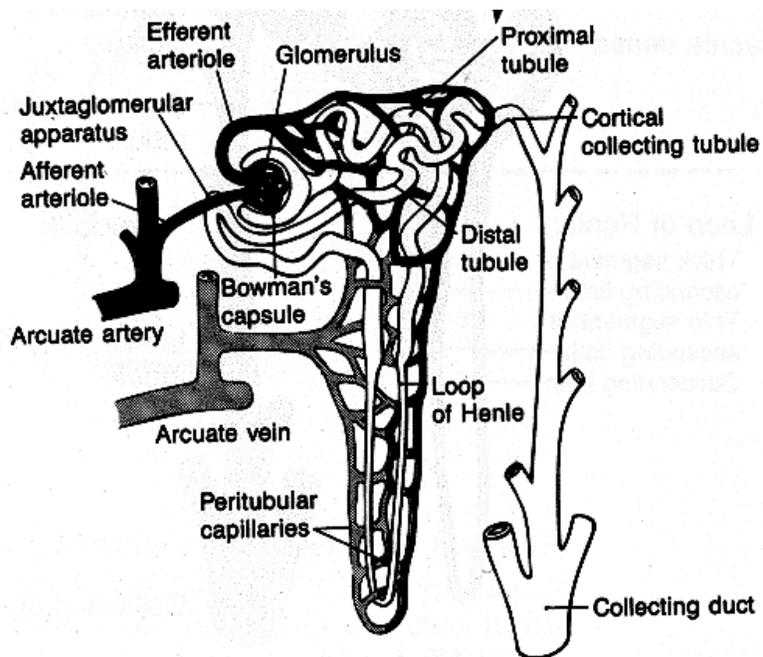
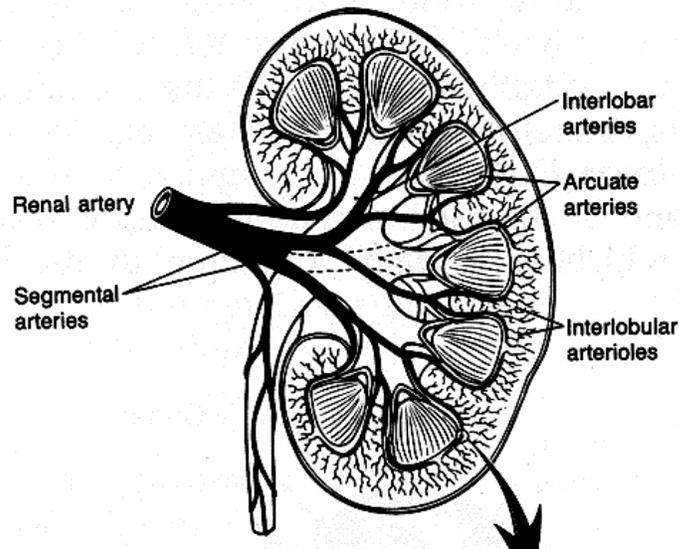
Also, The association of the glomerular arterioles with the macula densa of the DCT provides a system that may participate in the adjustment of glomerular filtration to tubular reabsorption.

RENAL CIRCULATION

The renal arteries branch off the abdominal aorta and enter the kidneys. They give rise to several interlobar arteries which pass between the renal pyramids. The interlobar arteries give rise to arcuate arteries which arch between the cortex and medulla. Interlobular arteries branch off the arcuate arteries to project into the cortex.

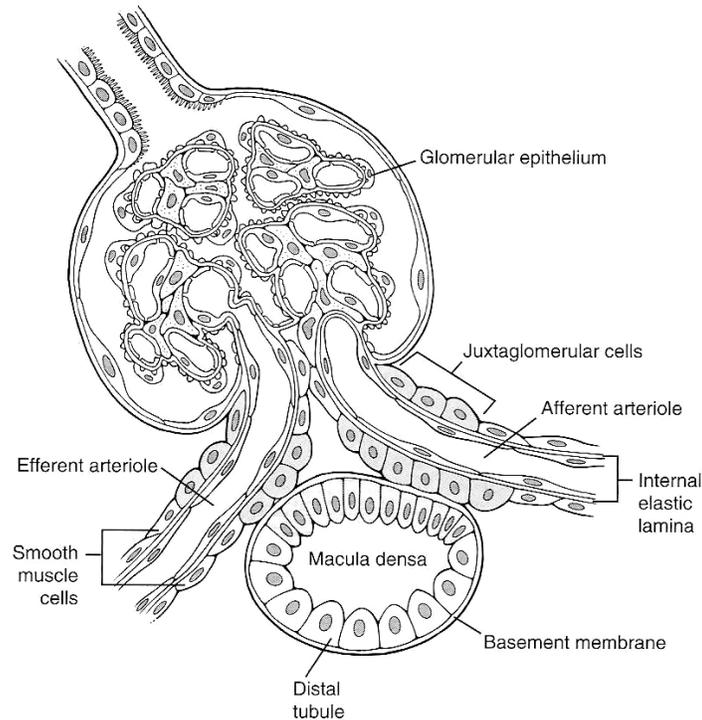
The afferent arterioles, arise from branches of the interlobular arteries and extends to the glomerular capillaries. Efferent arterioles extend from the glomerular capillaries to the peritubular

capillaries, which surround the PCT, DCT and LH. Blood from the peritubular capillaries enters the interlobular veins. The veins of the kidney run parallel to the arteries and have similar names.



Section of the human kidney showing the major vessels that supply the blood flow to the kidney and schematic of the microcirculation of each nephron

JUXTAGLOMERULAR APPARATUS / COMPLEX



This is composed of specialized cells in the walls of the afferent glomerular arterioles which are in intimate contact with the distinctive portion of the DCT known as macula densa. The specialized cells in the arteriolar walls are designated as granular or agranular cells because of the presence or absence in their cytoplasm secretory granules. Endoplasmic reticulum is present in both cell types which suggests the presence of active protein formation. The agranular cells may represent less active cell types. Cells of the macula densa may be differentiated from other cell type of DCT by special staining characteristics. The cells of the macula densa contain fewer mitochondria than the other cells of the DCT. Renin is produced in the macula densa which acts on angiotensinogen (produced by the liver) to produce angiotensin I. Angiotensin I is further hydrolyzed to angiotensin II by angiotensin converting enzyme. Cells of the macula densa exert control on the renin-angiotensin system, which is done through the sensing of changes in Na^+ concentration in tissue fluids. Increased Na^+ leads to decreased renin release, and vice versa.

URINE FORMATION

Formation of urine begins as an ultra filtrate of plasma a cross the glomerular capillary walls and Bowman's capsule into the Glomerular capillary networks.

Energy for this filtration process is provided by the heart in the form of blood pressure within the glomerular capillary and is opposed by the colloid osmotic pressure (COP) of plasma protein plus the intrinsic tissue pressure of the kidney.

Net filtration pressure = Capillary bp – (C.O.P + Tissue pressure)

Under normal circumstances, in which the renal arterial pressure varies between 90 and 100mmHg with mean pressure as blood enters the glomerular afferent arterioles of 75mmHg, then the net filtration pressure will be approximately 45mmHg.

$$\begin{aligned} &= 75 - (25 + 5) \\ &= 45 \text{ mmHg} \end{aligned}$$

N.B.: The mean capillary blood pressure ranges between 60-70mmHg (this promotes filtration).

COP range between 25-30mmHg (this opposes filtration)

Tissue pressure ranges between 5-15mmHg (this opposes filtration)

The net filtration pressure represents the measurement of pressure across the glomerulus. Within the glomerulus there is an additional redistribution of pressures. The hydrostatic pressure drops as blood flows from the afferent arterioles into the glomerular capillaries and COP increases in the efferent portions of glomerular capillaries as fluid is lost during the filtration process.

The ultrafiltration pressure, the net pressure available to force an ultra-filtrate of plasma into the Bowman's space, will be greatest in afferent portions of the glomerular capillaries. Increasing the tissue pressure within the kidney decreases filtration rate by reducing the net filtration pressure. Clamping the ureter permits fluid to accumulate within the nephron. Assuming no change in blood pressure and continued filtration, the pressure within the nephron increases until the intra-tubular pressure reach 45mmHg. At this point, net filtration pressure should be abolished. Ureteral obstruction decreases the filtration rate but continued absorption of tubular fluid into the peritubular blood flow generally prevents complete cessation of the plasma filtering process.

Estimates of regional blood flow, indicates that at least 85% of the effective renal blood flow perfuse the cortex. Total renal blood flow determined quantitatively in unanesthetized dog was found to be 642ml / 100g/min which represent 20% of the cardiac output. This indicates the magnitude of blood flow to an organ that comprises 0.3% of the total body mass.

<u>Area</u>	<u>Blood Flow</u>
Cortex	472ml / 100g/min
Outer medulla	132ml/100g/min
Inner medulla	17ml/100g/min
Hilus and perirenal fat	21ml/100g/min

Blood flow in different parts of the Kidney(Thorburn *et.al.*1963)

Medullary blood flow does not only differ quantitatively from cortical blood flow, but also shows qualitative changes that reflects both the composition of the area it perfuse and the singular arrangement of the vasa recta into a counter current exchange system.

Blood taken by micro puncture from the vasa recta near the medullary crest has an osmolality approximating the osmolality of the medullar interstitium. Generally, blood samples taken at varying levels of the medulla have osmolality indicative of the corticomedullary osmotic gradient.

Mechanisms of Ionic Reabsorption

Na Transport / reabsorption: this is a specific function of the tubular epithelium involving specific enzyme system and which also requires energy. Na is completely reabsorbed in the tubule and is absent in the secondary urine.

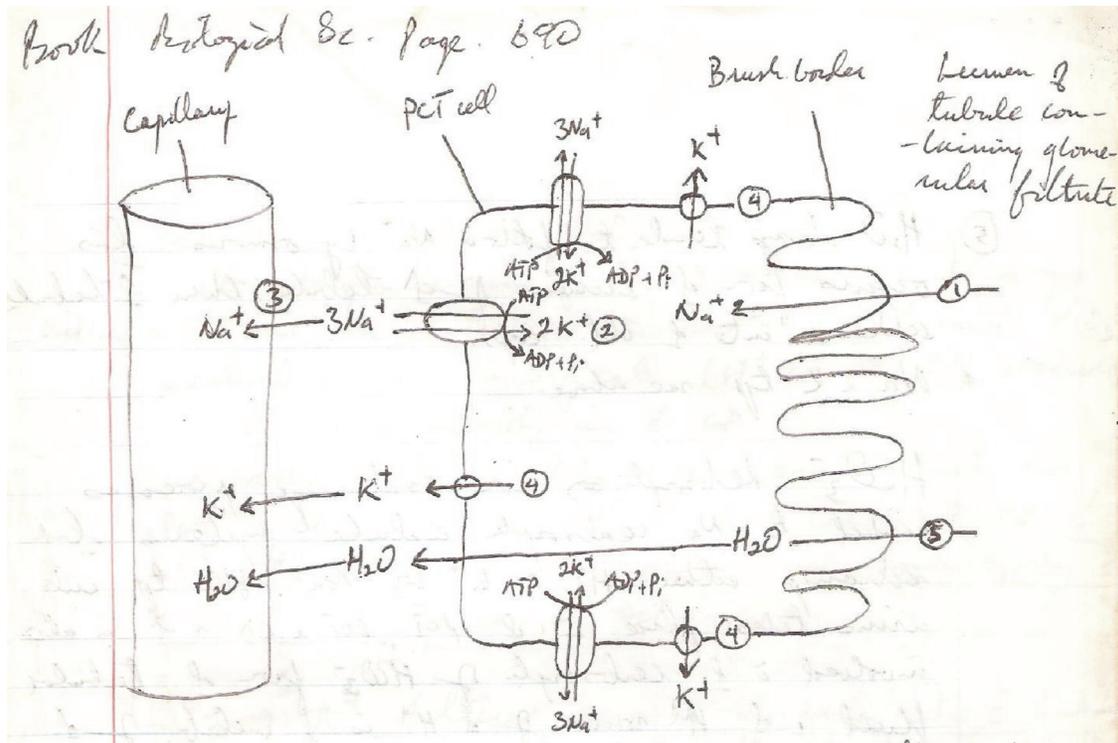
Active Na transport makes possible the reabsorption of Na back into the blood whose blood concentration is normal or higher than normal relative to their tubular concentration. Reabsorption of Na is independent of the concentration (mandatory reabsorption) in the PCT and LH, whereas in the DCT the reabsorption of Na varies with blood Na concentration (optional reabsorption). Therefore Na reabsorption occurs at several nephronal levels: PCT, thick ascending segment of the LH., DCT and CD. Quantitatively, the most significant component of Na reabsorption is accompanied by attendant chloride reabsorption.

Na reabsorption is also linked to ion exchange processes that are of great physiological significance in the maintenance of acid base and ionic equilibrium of the body's fluid compartment. Na transport against its concentration gradient is limited in the PCT and can be inhibited by diluting its concentration in the fluid of the PCT.

Na reabsorption from the DCT can proceed against a much greater concentration gradient. The hypotonic urine excreted during H₂O diuresis is virtually free of Na indicating that Na in the tubular fluid has been conserved despite an increasingly unfavorable concentration gradient.

N. B.: The electrical potential across the PCT has been recorded at approximately -20mV while that of the DCT may be > - 50mV (-35mv to -50mV) emphasizing further the great capacity of Na reabsorption to overcome this electrochemical gradient.

Diagram of Na transport



1. Diffusion of Na down its electrochemical gradient from higher concentration outside the cell to lower concentration inside and towards negatively charged interior of cell (all cells maintain a potential difference across their surface membranes, usually negative on the inside respect to the outside). Na enters through ion channels.
2. Na⁺ /K⁺ ion pumps in the base and sides of the cell, pump out 3Na⁺ for every 2K⁺ pumped in, using ATP as an energy source. This maintains the Na⁺ diffusion gradient into the cell. (6% of the total ATP used in the body is used in the kidney by these pumps)
3. Na⁺ diffuses into the blood capillaries find the spaces around the tubule cells.

4. K^+ diffuses back out of the cell passively through the K^+ channels.
5. H_2O always tends to follow Na^+ by osmosis. This occurs from the lumen of the tubule through the tubule cells and the blood capillaries.

HCO_3^- transport / reabsorption: ion exchange processes linked to Na reabsorption includes systems that exchange either H^+ or K^+ for Na^+ . H^+ transport into urine takes place in the PCT, DCT and CD and it is also involved with the reabsorption of HCO_3^- from the tubular fluid. The source of the H^+ is the metabolism of the renal tubular cells and the hydration of CO_2 to carbonic acid and the dissociation of this acid into H^+ and HCO_3^- .

Secretion of H^+ by the renaltubular cells may account for their relatively high intracellular pH. H^+ when transferred into urine may react with urinary constituent. Under normal conditions, plasma HCO_3^- concentration in the dog is 24-26meq/L. The quantity of bicarbonate ion reabsorbed per minute varies with the GFR; assuming a constant G F R, tubular maximal HCO_3^- reabsorption in the dog ($T_mHCO_3^-$) is about

2 - 3mmol/min/dL filtrate. HCO_3^- reabsorption also depends on plasma PCO_2 . Increased arterial PCO_2 increases the maximal rate of HCO_3^- reabsorption and conversely, decreases in the arterial PCO_2 decreases the kidneys capacity to reabsorb HCO_3^- .

HCO_3^- reabsorption and acidification of urine in the dog's kidneys (nephron) are initiated in the PCT. Continued HCO_3^- reabsorption and urine acidification (H^+ secretion) occurs in the DCT and probably in the CD.

The reactions of H^+ with HCO_3^- and anion such as phosphate and chloride occurs in both the PCT, DCT and CD. The ultimate pH (H^+ concentration) of urine is determined, however by the rate of H^+ transport into the PCT.

K^+ Reabsorption: K^+ filtered across the glomeruli into the tubular filtrate, are almost completely reabsorbed by the PCT via active transport. Reabsorption of K^+ occurs in the DCT and CD via a transport process which functions as an ion exchange process, or from the diffusion of K^+ down a favorable electrochemical gradient from the interior of the tubular cells into the tubular fluid.

The physiological stimulus for H^+ and K^+ secretion is the increased negativity of the tubular fluid which results from the transport of Na^+ from the tubular fluid.

H⁺ and K⁺ appear to utilize a common transport or diffusion pathway and in general a reciprocal relationship exists between the secretion of these ions. The metabolic state of the body, under normal circumstances determines whether H⁺ or K⁺ will be transferred preferentially into urine.

N.B.: The urinary excretion of ions, especially Na⁺ and K⁺ does not always conform to a stoichiometric relationship which would be anticipated on the basis of ion exchange mechanisms.

Administration of excess K⁺ salt to the dog is followed by the rapid excretion of the excess K⁺ into the urine without corresponding increases in Na⁺ reabsorption.

Ca⁺ and Mg⁺ reabsorption: They are reabsorbed primarily from the glomerular filtrate in the PCT. Ca⁺ is also reabsorbed in the ascending limb of LH and in the DCT. Ca⁺ transport is an active process and may be linked to the Na⁺ transport system.

Measurement of Renal Functions

Glomerular Filtration Rate: Glomerular filtration takes place in all the nephrons of both kidneys at the same time but the filtration process are not the same. Also the quality of the glomerular filtration varies from one nephron to another.

The quantity of the glomerular filtrate that is formed in all the nephrons of both kidneys per minute is the glomerular filtration rate.

If U_x = concentration of drugs or substance in urine (mg/ml)

V = flow rate of urine (ml/min) or urine volume

P_x = concentration of drugs / substance in plasma (mg/ml)

The relationship between these factors and glomerular filtration rate is:

$$\text{GFR} = \frac{U_x(\text{mg/ml})_{\text{urine}} \times V(\text{ml/min})}{P_x(\text{mg/ml})_{\text{plasma}}}$$

x can be inulin or creatinine, these 2 substances are physiologically inert.

Glomerular Filtration Rate can be measured in intact animals and humans by measuring the excretion of plasma level of a substance which is freely filtered through the glomerulus and should not be secreted nor reabsorbed by the tubules. The amount of such a substance in the urine per unit time must have been provided by filtering the exact number of ml of plasma which contains these amounts.

Characteristics of substances suitable for measuring glomerular filtration rate by determining its clearance are:

- Freely filtered
- Should not be reabsorbed or secreted by the tubules
- Should not be a metabolite
- Should not be stored in the kidney
- Should not be protein bound (cause substance bound to albumin and globulin are not freely filtered)
- Should not be toxic
- Should not have effect on filtration rate
- Should be easy to measure in the plasma and urine

Renal Clearance / Plasma Clearance: Renal clearance expresses the ability of the kidneys to “clean” or “clear” the plasma of various substances. It is used to indicate the manner of disposition of a given substance known to be excreted into urine e.g. Evans dye.

$$P_c = \frac{U \times V}{P}$$

U = Concentration of substance in urine (mg/ml)
P = Concentration of substance in plasma (mg/ml)
V = Volume in ml of urine formed per minute (ml)

Plasma clearance of a substance is important in estimating kidney function.

Renal Blood Flow

See also Renal Circulation.

At least 85% of the effective renal blood flow perfuses the cortex. In an unanaesthetized dog, the total renal blood flow was found to be 642ml/100g/min which represent approximately 20% of the cardiac output.

Renal Transport Processes for Organic Substances

Glucose: It is reabsorbed from the PCT via an active transport system. It is transported against a concentration gradient (at normal plasma levels of approximately 100mg/dl plasma, all of the filtered glucose is reabsorbed) by a process requiring metabolic energy with glucose not being

chemically altered during reabsorption. The hexose can be reabsorbed up to a maximal rate and when glucose load exceeds this reabsorptive limit, it is excreted into urine.

Amino Acids: Amino acids are reabsorbed by several discrete active transport systems. Basic amino acids like lysine, arginine, histidine share a common tubular transport system and competition among them exists. Other amino acids transport systems include that of leucine and isoleucine; and that of proline, hydroxyl proline and glycine. Amino Acid reabsorption requires the presence of pyridoxal phosphate. A complex is formed by the amino acids, pyridoxal phosphate and a metallic iron (Mg^{2+}) which probably facilitates the transport of amino acids from the tubular fluid into the intracellular pool of amino acids and subsequently into the peritubular blood flow.

Uric acid: It is formed from the degradation of purines, adenines and guanine. Apart from humans and higher apes, mammals convert uric acid to allantoin by the action of the enzyme uricase. Allantoin is water soluble and is rapidly excreted into urine primarily by glomerular filtration. Uric acid or Na urate is excreted into the urine through a combination of glomerular filtration, tubular reabsorption and tubular secretion. Urate has limited solubility in water and its reabsorption is governed by its relationship between pH of tubular fluid, pKa of urate and concentration of urate in plasma and tubular fluid.

Diagram of Na-K-ATPase pump

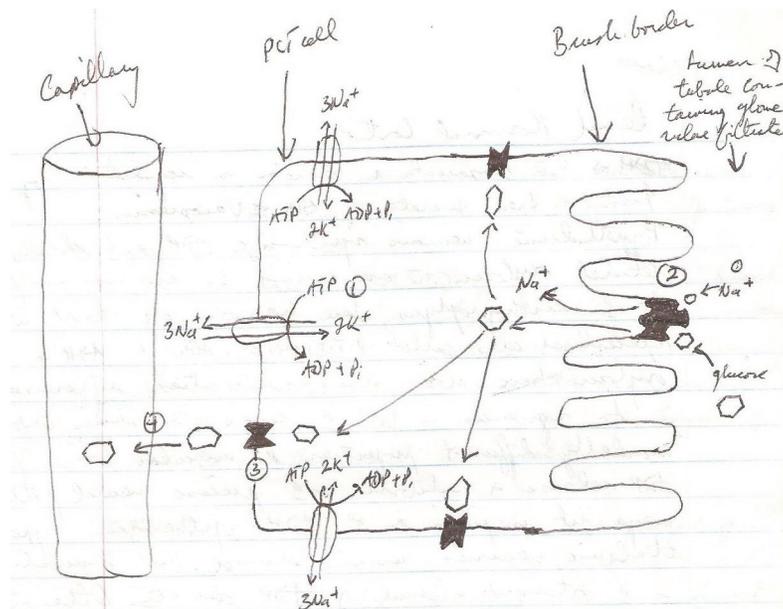


Diagram of active transport of Glucose

1. $Na^+ - K^+$ pump, pumps out Na^+ and reduce concentration of Na^+ inside cell.

2. A special transport protein reabsorbs both Na⁺ and Glucose. Such proteins are called symporters (the movement of the 2 molecules is linked). Na⁺ and glucose are effectively moving down diffusion gradient, but this is only made possible by the active transport of Na⁺-K⁺ pumps. The process is therefore sometimes referred to as secondary active transport.
3. Glucose leaves the cell by facilitated diffusion through the carrier protein.
4. Glucose diffuses into the blood capillaries. Amino acids and some other nutrients follow the same type of route.

Renal Hormonal Control

Antidiuretic Hormone: Water conservation or secretion is regulated by increased or decreased secretion of ADH (aka- Vasopressin). Hypothalamic neurons and the closely related oxytocin, which are carried by axoplasmic flow to the neuro-hypophysis, where hormones are stored in specialized cells called pituicytes. Although ADH and oxytocin have close structural similarities, differences in amino acid sequences in both the ring and side chains confer markedly different properties. The molecular basis for ADH release or inhibition and the precise neural pathways that impinge on the ADH-synthesizing hypothalamic neurons remains elusive.

Water deprivation is the strongest stimuli for ADH secretion. Other stimulus include, fear, increase in extracellular fluid volume and pain. Drugs may also alter the rate of ADH secretion e.g. ethanol which is the most abused but legally available C.N.S. depressant. This ethanol is a potent inhibitor of ADH secretion.

ADH acts on the distal portions of the nephron, most prominently on the collecting duct to alter their permeability to water and urea. When ADH secretion is enhanced, the CD is increasingly permeable to H₂O and urea and they more easily diffuse from the tubular fluid of the CD into the hyper-osmotic medullary interstitium and vice versa.

If the hypothalamo – neurohypophyseal system is destroyed, a syndrome known as diabetes insipidus is produced, which is characterized by excretion of large quantities of water. Inappropriately high concentration of ADH, whether induced iatrogenically or by secretion of ADH by some cancers results in dilution of serum electrolytes, particularly sodium leading to dilutional hyponatremia. This problem may be augmented by the ability of high levels of ADH to promote renal Na excretion.

Aldosterone: it's the recognized primary mediator of the renal regulation of Na and K⁺ equilibrium. This function is due to a direct tubular effect of the hormone that permits normal rate of Na reabsorption and K excretion. The areas of the nephron that are sites of aldosterone secretion have not been determined conclusively, although the distal segments have been implicated i.e. DCT and CD.

Excessive secretion of aldosterone or the long time administration of a mineralocorticoid steroid to dogs or humans results in Na retention for a period of 5-7days, as high levels of mineralocorticoid activity are maintained, 'escape' from Na retention occurs in the form of a saline diuresis. The functional processes that are involved in the escape phenomenon are not yet known. The site of production of aldosterone is the adrenal cortex.

Parathyroid hormone: Ca and phosphate excretion into urine is regulated by this hormone. PTH is synthesized by the parathyroid gland and thyrocalcitonin is synthesized by the thyroid gland. PTH causes a decrease in the phosphate reabsorption and an increase in phosphate excretion in the urine. These changes are due to direct tubular effect. The administration of PTH is accompanied by increases in calcium excretion in the urine, but this effect may not indicate any specific responses in renal tubular transport of Ca. The primary effect of PTH on Ca metabolism is the result of mobilisation of Ca from bones and enhanced absorption of Ca from the intestinal tract. As the result of parathyroid gland stimulation, plasma concentration and consequently the filtered load of Ca are increased to an extent that exceeds the tubular reabsorptive capacity for Ca.

RESPIRATORY SYSTEM

Anatomy

Respiratory zone – respiratory bronchioles, alveolar ducts and sacs.

Conducting zone – bronchioles, bronchi.

Conducting zone does not contribute to gas exchange (anatomical dead space): mucus secreting, ciliated cells line conducting zone airways

Airflow to terminal bronchioles by bulk flow

NON RESPIRATORY FUNCTIONS OF THE LUNG

- (i) Enhances venous return
- (ii) Heat exchange
- (iii) Metabolism – synthesis and catabolism
- (iv) Immunological defense
- (v) Nose; sense of smell
- (vi) Regulates pH by altering the amount of CO₂ exhaled

RESPIRATORY MECHANICS

Respiration

Internal respiration – intracellular metabolic processes carried out in the mitochondria. O₂ is consumed.

External respiration – entire sequence of events involved in the exchange of O₂ and CO₂ between the external environment and the cells of the body.

Ventilation: Exchange of air between the environment and alveoli of the lungs i.e. breathing

Respiratory Cycle

Respiration works by changing the volume of the chest cavity. Before the start of inspiration, respiratory muscle is relaxed. Intravascular pressure = atmospheric pressure and so no air is flowing.

- Atmospheric pressure and so no air is flowing
- At the onset of inspiration, inspiration muscle (diaphragm) contract, which results in enlargement of the thoracic cavity
- As the thoracic cavity enlarges, the lungs are forced to expand to fill the larger cavity
- Because the intraalveolar pressure is less than atmospheric pressure air follows its pressure gradient and flows into the lungs until no further gradient exists.
- Deeper inspirations are accomplished by contracting inspiration muscle more forcefully and by using accessory inspiratory muscle to enlarge the chest cavity.
- At the end of inspirations the inspiratory muscles relax, the chest cavity returns to the original size and the lungs return to the original size.

Respiratory cycles are generally continuous, however during anaesthesia there may be intervals between cycles.

The inspiratory and expiratory phases of the cycles are generally smooth and symmetrical. The horse is however an exception it had 2 phases each during inspiration and expiration.

RESPIRATORY PRESSURES

Air moves from a region of high pressure to low pressure i.e. it flows down a pressure gradient.

Atmospheric (barometric pressure) = pressure exerted by weight of air in atmosphere on objects on earth surface = 760mmHg at sea level. It decreases as altitude increases

Intra alveolar pressure (intrapulmonary pressure) is 760mmHg when equilibrated with atmospheric pressure. Intrapleural pressure (intra thoracic pressure) = 756mmHg

Trans mural pressure = pressure across surface of the lungs – $P_{\text{alveolus}} - P_{\text{pleural space}}$

This trans mural pressure gradient across the lung wall is crucial in expanding the lung to fill the chest cavity.

Although elastic lungs want to collapse, they don't because of the trans mural pressure gradient.

Two forces hold thoracic walls and lungs in close apposition.

- (1) Intrapleural fluid cohesiveness (like H₂O between 2 slides)
- (2) Transmural pressure gradient (most important)

Pneumothorax – air enters pleural cavity, pressure equalizes with atmospheric pressure, trans mural pressure gradient is gone, lung collapse and thoracic wall springs out.

Pulmonary Elasticity

There is a constraint tendency for the lungs to collapse.

The recoil tendency is due to elastic recoil : returning to pre-inspiratory volume at the end of inspiration

Compliance – measure of distensibility magnitude of change in volume for a given trans mural ΔP .

Normal compliance = 200cm/ml H₂O.

Pulmonary elastic behavior depends on

- (a) Connective tissue in the lungs
- (b) Alveolar surface tension: displayed by thin layers of liquid that lines each alveolus.

Pulmonary surfactant, a complex mixture of lipids and proteins secreted by alveolar cells which reduced alveolar surface tension $\xrightarrow{\text{pulmonary compliance}}$ reduces $\xrightarrow{\text{lung's}}$ tendency to recoil.

Smaller airways are more likely to collapse than the larger ones because of greater surface tension

Laplace law $P = 2T/r$ where P = inward directed collapsing pressure. T = surface tension

AIR FLOW

Flow $V = \Delta P/R$

ΔP = pressure gradient between the atmosphere and alveoli

R is primarily determined by the radius.

Poiseuille's law defines relationship between flow and pressure under laminar flow conditions.

$$V = \frac{\Delta P \pi r^4}{8.7 \eta L}$$

Where ΔP = Pressure drop, V = flow rate, η = fluid viscosity, L = length of the tube, r = radius of the tube

$$\text{Resistance} = \frac{87 \eta L}{\pi r^4}$$

Flow can be laminar or turbulent in small airways flow is usually laminar

Laminar flow

- (a) Fluid traveling in center moves fastest because there is no interference
- (b) Fluid in contact with tube wall remains stationary or is slowest due to contact with walls.
- (c) Parabolic velocity profile: Fluid velocity decreases with the square of radial distance away from the center of the tube.
- (d) Average fluid velocity: In the tube is half of the peak velocity at centre of tube
- (e) Pressure difference between two points along the tube is directly proportional to the flow rate $\Delta P = K_1 \cdot V$ where

P = Press difference (cmH₂O)

K_1 = constant for system (cmH₂Osec/ml)

V = flow-rate (ml/sec)

In fully turbulent flow

- i) fluid movement occurs both in radial and axial directions
- ii) Velocity profile across tube is much blunter than the parabolic profile seen in laminar flow.
- iii) because fluid moving in a radial direction can impact on the tube wall, noise is often generated (due to eddy current).
- iv) Since energy is consumed in the process of generating the eddies, chaotic fluid movement, a higher driving press is required to support a given flow rate.

- v) Pressure difference between two points along the tube increases with the square of the flow rate i.e. doubling the flow rate required more than doubling the driving pressure. $\Delta P \propto k \cdot V^2$, ΔP = Pressure difference, k = constant, V = flow rate

During tidal breathing:-

- Flow is highly turbulent in trachea
- Less turbulent in small bronchi
- Laminar-like, in the small peripheral airways

Flow (v) is determined by :- Driving press (ΔP), Resistance to flow (R)

Gas exchange

The composition of a gas mixture can be described by the traditional composition or partial pressure.

Air contains 21% oxygen. The oxygen tension of a dry gas mixture is determined by the barometric pressure.

P_{O_2} in dry air at sea level when barometric pressure = 760mmHg is approximately 160mmHg.

During inhalation, air is warmed to body temperature and humidified in the larger air passages.

The P_{O_2} of humidified gas is therefore approximately 149mmHg. i.e $P_{O_2} = (P_B - P_{H_2O}) \cdot f_{I_{O_2}}$ i.e.

$P_{O_2} = (760-50) \times 0.21 = 149\text{mmHg}$. Where P_{H_2O} in saturated air equals 50mmHg.

Alveolar gas composition is determined by alveolar ventilation and the exchange of O_2 and CO_2 .

P_{ACO_2} is determined by the rate of CO_2 production (V_{CO_2}) in relation to the amount of alveolar ventilation (V_A).

$P_{ACO_2} = K \cdot V_{CO_2} / V_A$ where $K = P_B - P_{H_2O}$

P_{O_2} is lower in the alveolus than in the inspired air because oxygen and CO_2 exchange occurs continuously.

The average oxygen tension in the alveoli of the lung can be calculated from the alveolar gas equation.

$PA_{O_2} = [(P_B - P_{H_2O}) \times f_{I_{O_2}}] - PA_{CO_2} / R$

Where R is the respiratory exchange ratio i.e. the ratio of the rate of CO_2 production to that of O_2 consumption. Alveolar hypoventilation elevates P_{ACO_2} and decrease PA_{O_2} .

Alveolar hyperventilation cause a decrease in PA_{O_2} because ventilation is increased in relation to carbon dioxide production. Therefore according to the alveolar gas equation as P_{ACO_2} decreases PA_{O_2} increases.

A modified form of the alveolar gas equation can be used to determine PAO_2 for clinical purposes as follows.

$$PAO_2 = (PB - H_2O) \times fI_{O_2} \times PaCO_2/R$$

In this equation, arterial carbon dioxide tension ($PaCO_2$) is substituted for alveolar carbon dioxide tension ($PACO_2$).

Average alveolar PO_2 is 100mmHg

Average alveolar PCO_2 is 40mmHg

Average arterial PO_2 is 100mmHg PCO_2 is 40mmHg

Blood entering pulmonary capillaries is systemic venous blood (via pulmonary artery) and systemic venous blood $PO_2 = 40$ mmHg $PCO_2 = 46$ mmHg

Exchange of O_2 and CO_2 between the alveoli and pulmonary capillary blood occurs by diffusion.

The rate of gas movement between the alveolus and the blood (V_{O_2}) is determined by the physical properties of the gas (D) the surface area available for diffusion (A), the thickness of the air-blood barrier (x) and the driving pressure gradient of the gas between the alveolus and capillary blood as follows, $V_{O_2} = D.A. (PA_{O_2} - P_{COPO_2})/x$

D is the diffusion co-efficient. D is related to solubility and molecular weight.

$D \propto \text{solubility}/MW^{1/2}$.

D for CO_2 is 20 x D for O_2 because CO_2 is for more soluble in the body. Faster diffusion rate is offset by CO_2 smaller ΔP (6mmHg), compared to O_2 (60mmHg), so CO_2 and O_2 diffusion more or less equilibrates.

In dissolved lung, O_2 transfer is more seriously impaired than CO_2 transfer because of the difference in D.

In the lung, the barrier separating air and blood is less than 1 μ m thick. This layer include

- (1) Fluid layer lining alveolus containing surfactant
- (2) Alveolar epithelium
- (3) Epithelial basement membrane
- (4) Interstitial space between two basement membrane
- (5) Capillary basement membrane
- (6) Capillary endothelial cell membrane

GAS TRANSPORT

Oxygen

Oxygen is transported in the blood in 2 forms

1. Dissolved in plasma and 2. reversibly bound to hemoglobin

Dissolved Oxygen

Henry's law: The amount of a gas which dissolves in unit volume of a liquid of a given temperature is directly proportional to the partial pressure of the gas in the equilibrium phase.

Ostwald solubility co-efficient for O_2 at $37^\circ C = 0.003 \text{ml}/100 \text{ml blood}/\text{mm Hg}$

Therefore PO_2 of 100mmHg \longrightarrow dissolved $O_2 = 0.3 \text{ml}/100 \text{ml blood}$

Total content of O_2 in arterial blood is 20 ml $O_2/100 \text{ml blood}$

The tissue O_2 consumption is 250ml/min at rest, there is thus a need for extra way to transport O_2 .

Oxygen carriage by Hemoglobin

Each hemoglobin molecule has 4 Fe combining with $4O_2$ molecules. When it is carrying $4O_2$ it is said to be fully saturated. One gram of Hb binds reversibly with 1.34ml O_2 .

PO_2 determines Hb saturation. Percent Hb saturation is a measure of the extent to which the Hb present is combined with oxygen and can vary from 0 to 100%.

The saturation of the Hb with oxygen depends on the PO_2 of the blood: O_2 already bound to Hb does not contribute to PO_2 .

Relationship between PO_2 and percentage saturation is complex

O_2 – Hb dissociation curve is S shaped and not linear

At $PO_2 = 100 \text{mmHg}$, Hb is 97.5% saturated. A large change in PO_2 here results in only a small change in percentage Hb saturation, therefore PO_2 can fall nearly 40% in the lungs. even at $PO_2 = 60 \text{mmHg}$, hemoglobin is 90% saturated. From 60-760mmHg PO_2 , Hb saturation only changes 10%, this provides margin of safety in O_2 carrying capacity of blood.

At $PO_2 = 40 \text{mmHg}$ Hb is 75% saturated. From 0-60mmHg, a small drop leads to a steep drop in the Hb saturation, Hence, when PO_2 falls even a little in systemic capillaries, a large amount of O_2 dissociates from Hb. This facilitates unloading of O_2 from Hb in tissues. Pulse oximeter can non invasively measure oxygen saturation.

Modification of Oxyhemoglobin dissociation curve

Affinity of Hb for O_2 is measured by the P_{50} which is the PO_2 when Hb is 50% saturated.

At a pH = 7.4 T = 37°C and $P_{50} = 26.3$ mmHg. Decreased affinity of hemoglobin for oxygen leads to a shift of the curve to the right (Bohr effect), and an increased P_{50} . Increased affinity of hemoglobin for oxygen leads to a left shift of the curve and a decreased P_{50} .

Increased metabolism leads to increase in tissue temperature, acidity and CO_2 . An increase in all these, right shifts the $O_2 - Hb$ curve.

Carbon monoxide left shifts the $O_2 - Hb$ curve so that less O_2 is delivered to tissues for a given level of PO_2

CO₂ TRANSPORT

CO_2 is transported in the blood in 3 ways

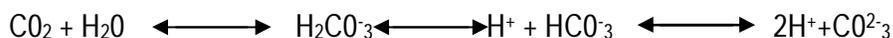
a. 10% is dissolved in plasma. Dissolved CO_2 depends on PCO_2 . It also obeys Henry's law.

CO_2 is 24 times more soluble than oxygen. b. 30% is bound to Hb

CO_2 bound to the globin portion of hemoglobin not heme portion as carbaminohemoglobin. unoxygenated Hb binds tighter to CO_2 than does oxygenated Hb.

Dissolved CO_2 depends on PCO_2 . It also obeys Henry's law. CO_2 is 24 times more soluble than oxygen

c. 60% of CO_2 is transported as HCO_3^- :



Carbonic anhydrase catalyses the 1st reaction in the RBC. HCO_3^- then diffuses out of the RBC.

Erythrocyte membrane is relatively impermeable to H^+ so HCO_3^- diffuses alone. HCO_3^- diffuses out into plasma and chloride diffuses into RBC – chloride shift. Most H^+ that is left binds to Hb (reduced Hb has a greater affinity for Hydrogen ion than HbO_2

These reactions are reversed once the blood reaches the pulmonary capillaries and CO_2 leaves the blood and enters the alveoli.

Haldane effect: removing O_2 from the Hb increases its ability to pick up CO_2 , H^+ . Bohr effect and

Haldane effect feeds into one another. Increased CO_2 and Hydrogen ion lead to an increased oxygen release. The increased release of oxygen increases the CO_2 and Hydrogen ion binding capacity of hemoglobin.

CO_2 dissociation curve depicts relationship between PCO_2 and total content of CO_2 in the blood. In the physiological range, the curve is almost linear.

Therefore changes in PCO_2 are accompanied by corresponding changes in C_{CO_2} .

- The position of the dissociation curve is dependent upon HbO₂ saturation – Haldane effect
- The slope of the CO₂ curve is much steeper in the physiological range than for O₂.

Control of Respiration

Quite unlike the heart where the role of CNS is modulatory. The CNS input is required for breathing to occur at all.

Various part of the brain stem are involved in control of rhythmic breathing.

Neural control of respiration includes

1. factors responsible for alternating inspiration/expiration rhythm
2. factors that regulate magnitude (rate, depth) of ventilation
3. factors that modify respiratory activity to serve other purposes.

Medullary respiratory center

DRG originates from NTS. It lies within the reticular formation of the brain stem. They are mostly inspiratory neurons. Cells within the DRG are thought to possess inherent rhythmicity generating bursts of neuronal activity to the diaphragm and inspiratory muscles.

VRG – nucleus retroambiguus. both inspiratory and expiratory neurons, both remain inactive during quiet breathing. Important in active expiration. Only during active expiration do impulses travel to expiratory muscle. The neurons of the expiratory VRG are quiescent during tidal respiration.

Generation of respiratory rhythm comes from the rostral ventromedial medulla. It drives the rate at which inspiratory neurons fire.

Apneustic Centre

Situated in the lower pons in the floor of the 4th ventricle near the middle cerebellar peduncle. impulses from these neurons ,inspiratory DRG and increased ramp AP's.

Section of the brainstem immediately above this group causes ~~apne~~ apneusis.

Prolonged inspiratory gasps interrupted by transient expiratory efforts. Apneustic center prevents inspiratory neurons from being turned off.

Pneumotoxic Centre

Located in the upper pons. Acts to limit the activity of the inspiratory DRG. Without pneumotoxic brakes, apneusis : prolonged inspiratory gasps with very brief interrupting expirations. It regulates inspired volume and rate of inspiration. It acts only as a modulator, as normal respiratory rhythm can exist in its absence.

Cortex – involved in voluntary control of respiration. the hypothalamus and the limbic system can alter pattern of breathing i.e. affective states like fear, rage.

The brain stem respiratory centers are influenced by

- (a) carotid and aortic chemoreceptors
- (b) central chemoreceptors
- (c) cerebral blood flow
- (d) reflexes from lungs, inflation reflex
- (e) carotid, aortic baroreceptors
- (f) muscle spindles in respiratory muscle
- (g) thoracic chemo-receptors
- (h) peripheral/somatic receptors (1) temperature
 - (2) Pain receptors
 - (3) Mechanoreceptors
- (i) cerebral cortex – emotion, breath holding

Central chemoreceptors

These are located near the ventral surface of medulla in the vicinity of exit of 9th and 10th cranial nerves. They monitor PCO₂. An increase in PCO₂ results in more CO₂ crossing blood-brain barrier. The CO₂ reacts with water to form bicarbonate and H⁺. The increase in H⁺ is detected by the central chemoreceptors.

The central chemoreceptors are bathed in the brain ECF. The composition of ECF is determined by CSF, local blood flow and local metabolism. CSF contain less protein than blood = poorer buffering capacity. Change in PCO₂ will change pH of CSF more than it changes pH of blood.

Peripheral Chemoreceptors

These receptors are very sensitive to change in blood pH and cause changes in ventilation. They respond primarily to decrease PO₂. They are responsible for all the ventilatory response to hypoxia. The peripheral responses to increased PCO₂ are lesser than those of the central chemoreceptors.

Respiratory Cycle

Respiration works by changing the volume of the chest cavity. Before the start of inspiration, respiratory muscle is relaxed. Intravascular pressure = atmospheric pressure and so no air is flowing.

- Atmospheric pressure and so no air is flowing
- At the onset of inspiration, inspiration muscle (diaphragm) contract, which results in enlargement of the thoracic cavity
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LUNG VOLUMES

1. Tidal Volume (TV): The amount of air inspired or expired during normal quiet respiratory cycle.
2. Inspiratory Reserve Volume (IRV): The amount of air which can be inspired above and beyond that which is inspired during normal quiet inspiration.
3. Expiratory Reserve Volume (ERV): The maximal amount of air which may be expired following a normal quiet expiration.
4. Residual volume (RV) : the amount of air remaining in the lungs after a maximal expiratory effort.

In addition to the four volumes which do not overlap, there are four capacities which are made up of two or more of the volumes.

1. Total lung capacities: the amount of air contained in the lungs at the end of maximal inspiration.
2. Vital capacity: the maximal amount of air which can be expired after a maximal inspiration.
3. Functional residual capacity: The amount of air remaining in the lungs after a normal expiration. $FRC = ERV + RV$
4. Inspiratory capacity (IC): The maximal amount of air which can be inspired after a normal expiration.
5. Forced vital capacity (FVC): Total volume expired from maximum inspiration to maximum expiration.
6. Forced expiratory volume in one second (FEV_1): The maximum volume that can be expired in one second. $FEV_1 = 80\%$ of VC.

VENTILATION.

This is the process whereby gas in a closed place is renewed or exchanged. It is the process of exchanging the gas in the airways and alveoli with gas from the environment.

Total Ventilation: is the volume of air moved into or out of the airways and alveoli over a certain period of time.

Minute Ventilation: is the total volume of air moved into or out of the alveoli and airways in one minute. $V_E = fV_T$. Where V_E = minute volume of ventilation (expired), f = respiratory frequency in cycles per minute. V_T = average tidal volume in milliliters.

Dead space ventilation: is the volume of air that does not take part in gas exchange over a certain period of time.

Alveolar Ventilation: is determined by subtracting dead space ventilation from total ventilation.

Alveolar ventilation per minute V_A is the volume of air that contributes to diffusional exchange of gas each minute. $V_A = f(V_T - V_D) = fV_A$. Where f = respiratory frequency, V_T = tidal volume, V_D = dead space volume, V_A = Alveolar volume

VENTILATION AND PERFUSION RELATIONSHIP

The amount of alveolar ventilation in relation to pulmonary capillary blood flow i.e the V/Q ratio determines the adequacy of pulmonary gas exchange. There is no perfect matching of ventilation to perfusion in most alveoli. Non uniform distribution results in alveolar units with varying ratios of ventilation to perfusion. V/Q.

Alveoli at the apex are overall poorly ventilated and perfused but relatively better ventilated than perfused. i.e high V/Q ratio. This results in increased PAO_2 and decreased $PACO_2$.

Alveoli at the base are well ventilated but better perfused than ventilated i.e low V/Q ratio. PAO_2 will be low and $PACO_2$ will be high.

Alveoli at the centre is ideal, it receives ventilation and blood flow with a V/Q ratio of 0.8.

Units with low V/Q ratios have a greater effect on overall gas exchange since they receive greater proportion of total pulmonary blood flow. A high V/Q unit cannot compensate for the impact of low V/Q unit. It raises PO_2 which result in more dissolved oxygen but not HbO_2 .

CARDIAC ELECTRO-PHYSIOLOGY.

Electrical impulses are the result of the flow of cations (mostly Na^+ , K^+ and Ca^{2+}) back and forth across the cardiac cell membrane. A difference in concentration of these ions across the membrane at any give moment provides an electrical potential measured in millivolts.

The resting state of the cardiac cell consists of

- a. high concentration of Na^+ outside the cell membrane (at rest cell membrane is impermeable to Na^+).
- b. a high concentration of K^+ and anions (PO_4^{2-} , SO_4^{2-} and Proteinate) inside the cell. the cell membrane is impermeable to this anions.
- c. A negative electrical potential exist across the cell membrane and the cell is polarized.

Resting potential of myocardial cell and conducting cells is -90millivolts.

The ability of cardiac cells to generate and propagate an normal action potential depends on the level of the resting membrane potentials. The resting membrane potential arises as a result of the selective permeability of the cell membrane to K^+ and transmembrane K^+ gradient which in turn is maintained by the $Na^+K^+ATP_{ASE}$ pump. Normally the RMP is largely determined by the ratio of the extracellular to intracellular K^+ ions activities because the membrane permeability to K^+ far exceeds that of Na^+ , Ca^{2+} , or Cl^- in the resting state. RMP is usually slightly positive to the equilibrium potential for K^+ predicted by the Nernst equation.

The passage of ions across the myocyte membrane is regulated through specific ion channels that cause cyclical depolarisations and repolarisation of the cell called action potential. The AP of a working myocyte begins when the cell is depolarized from its diastolic transmembrane potential of -90 millivolts to a potential of about -50 millivolts. At this TP, voltage dependent fast sodium channels open causing rapid depolarization mediated by Na^+ influx down its steep concentration gradient. The fast Na^+ channel is rapidly inactivated and Na^+ influx stops, but other time and voltage dependent channels opens allowing Ca^{2+} to enter through slow Ca^{2+} channels (a depolarizing event) and K^+ to leave through the K^+ channel (a repolarizing event). At first these two events are balanced maintaining a positive trans-membrane potential and prolonging the plateau phase of AP. During this phase, Calcium entering the cell is responsible for the electromechanical coupling and myocyte contraction. Eventually Ca^{2+} influxes ceases and K^+ efflux increases causing rapid repolarisation of the cell back to the -90 millivolts resting transmembrane potential. While depolarized, the cell is resistant (refractory) to subsequent depolarizing events. Initially a subsequent depolarization is not possible (ARF) and after partial but incomplete repolarisation, a subsequent depolarisation is possible but occurs slowly (RRF). Cardiac tissues can be classified into two based on their automaticity or rhythmicity

- a. Fast channel tissues
- b. Slow channel tissues.

Fast channel tissues : working atrial and ventricular myocytes, His purkinje system) have a high density of fast sodium channel and action potential characterized by little or no spontaneous diastolic depolarization and thus very slow rate of pacemaker activity. very rapid initial depolarization rate and thus very rapid conduction velocity and loss of refractoriness coincident with repolarisation and thus short refractory periods and the ability to conduct repetitive impulses at high frequencies.

Slow channel tissues: SAN and AVN have a low density of fast Na^+ ion channels and action potential characterized by more rapid spontaneous diastolic depolarization and thus more rapid rates of pacemaker activity, slow initial depolarization rate and thus slow conduction velocity and loss of refractoriness that is delayed after repolarisation (and thus long refractory periods and the inability to conduct repetitive impulses at high frequencies).

ACTION POTENTIAL IN SINUATRIAL NODE

Fast Na^+ channels exist in nodal tissue but are sparse. The RMP is less, the upstroke of the AP(phase0) has a slower rise time, a plateau is absent and repolarisation is more gradual.the most distinctive feature is the slow depolarization of the membrane during phase 4-pacemaker potential.

The rate of depolarization during phase4 is due to

- a. i_f : slow inward Na^+ current induced by hyperpolarisation. Activated at the end of phase of 3 and early phase 4 as RMP becomes -50millivolts. The lower the RMP, THE greater the activation.
- b. I_{Si} : slow inward current during phase2, $\text{Ca}^{2+}\text{Na}^+$. They are activated toward the end of phase 4 as $V_M > -55$ millivolts. A decrease in ECF Ca^{2+} will decrease the amplitudeof the AP and rate of phase4 depolarisation
- c. I_{K1} : slow outward current of K^+ variably active in all the phases. It tend to repolarize the cell but progressively decreases throughout phase4 thereby leading to dominance of i_{Si} and i_f depolarizing the cell.

ACTION POTENTIAL IN VENTRICULAR MYOCYTES

Phase 4: the trans-membrane potential is about -90millivolts. The interior of the myocyte is negative relative to the exterior. The interior negativity is maintained by selective permeability of the membrane to K^+ and the activity of the $\text{Na}^+\text{K}^+\text{ATP}_{ASE}$ pump.

Phase 0: this is the phase of rapid depolarization. Fast sodium channels activated when the RMP is raised to -70millivolts. The conduction velocity along the fiber is determined by the following during phase 0.

- a. Absolute amplitude of AP.
- b. The rate of change of RMP

The RMP is an important determinant of conduction velocity. It determines both the amplitude of AP and the rate of rise dv/dt . This potential may be altered by variations in K^+ concentration.

Phase1: early phase of repolarisation. Membrane potential is +10millivolts. There is inactivation of I_{Na^+} and the activation of the short lived outward K^+ current. A notch marks the end of phase1 depolarization and the onset of the plateau phase.

Phase 2: Cellular conductances of all ion channels rapidly decrease to a level lower than that seen at any other time during AP. At the peak of the plateau no net current movement because the depolarization current equals the repolarisation current. The major factors underlying the plateau phase are

- a. depolarizing influence of some Na^+ channels with long latencies.
- b. The influx of Ca^{2+} through the voltage dependent Ca^{2+} channels.
- c. The repolarising effect of outward K^+ current.

Factors that potentiate $I_{\text{Ca}^{2+}}$ include the beta-adrenergic agonist which heightens the plateau. Those that diminishes $I_{\text{Ca}^{2+}}$ normally decrease the plateau voltage and they include calcium channel blockers and acidosis.

Phase 3: it depends on two processes

1. an increase in outward potassium current
2. Inactivation of I_{Si} .

The increase in the K^+ efflux is mediated partly by the increased ICF Ca^{2+}

MECHANISM OF ARRHYTHMIA

Abnormal impulse formation

Sinus pulse

Ectopic pulse

Triggered activity: during TA, heart cells contract twice, although they have been activated once.

The hall mark of TA is after depolarization (EAD & DAD) caused by electrical instability in myocardial cell membrane. factors which may predispose to after depolarization include digoxin, catecholamines, decrease ECF Potassium ion, decreased ECF sodium

Abnormal automaticity: occurs when other cells apart from the the sinuatrial node fire spontaneously. Under normal condition, atrial and ventricular myocardial cells do not exhibit spontaneous diastolic depolarization. If they are however experimentally depolarized, to a membrane potential more positive than about -60 millivolts , spontaneous automaticity may occur and cause repetitive impulse generation.

Abnormal heart impulse conduction

Reentry : is a common cause of arrhythmia. Ventricular arrhythmia and AV nodal reentry are typical examples. In the presence of slow conduction and unidirectional block it is possible to establish in the myocardium a so called reentrant loop of excitation. Under appropriate conditions, an impulse may re-excite some regions of the myocardium through which it has previously passed. This re-entry may be ordered or random.

The two requisite factors for ordered re-entry are

- a. a unidirectional block of conduction
- b. the effective refractory period of the reentered region must be less than the propagation time around the loop.

ELECTROCARDIOGRAM

The ECG is a graphic recording of the changes in magnitude and direction of the electrical current (NOT of contraction and relaxation) generated by depolarization and repolarization of the atria and ventricles. Electrical activity is detected by on the skin by electrodes. The upward deflections are positive deflections. They represent the electrical current moving toward the positive electrode. The downward deflection is negative, which means that the current is moving away from the positive electrode. The magnitude of the deflection represents the thickness of the muscle mass through which the current is being conducted. In regards to "depolarization" – it is the change of the internal electrical potential of the cell from negative to positive (associated with contraction). Repolarization is when the cells regain their electronegative (resting) state.

P wave – atrial depolarization. QRS complex – ventricular depolarization; duration related to HR.

An increase in duration of the QRS complex is a sign of delayed conduction through the ventricle. Q wave – first negative deflection in the complex before the R wave. A large Q wave may indicate recent infarction. R wave – first positive deflection in the complex. S wave – first negative deflection occurring after the R wave. T wave – ventricular repolarization. U wave – occasionally follows a T wave; small positive deflection; terminal phase of ventricular repolarization. Isoelectric line (baseline) – no electrical activity detected; straight, flat line.

ECG INTERVALS

QT interval is measured from the beginning of the QRS complex to the end of the T wave. This is the entire period of electrical activity

The PR segment is normally 0.02 to 0.10 seconds in duration. It represents the time taken for the electrical impulse to spread to the AV node, Bundle of His, bundle branches, and Purkinje fibers to the ventricular myocardium. The ST segment is normally ≤ 0.20 seconds in duration.

It represents the early phase of ventricular repolarization, and it is normally isoelectric.

ECG PAPER: The paper moves at a rate of 25 mm/second. Time is measured horizontally. Each small block is 1 mm and equal to 0.04 seconds and equal to 0.1 mV. Each bold block is equal to 0.2 seconds. Amplitude is measured vertically

Each bipolar lead consists of two electrodes of opposite polarity (one positive and one negative) or one positive electrode and a zero reference point (unipolar lead). There are six limb leads (I, II, III, aVR, aVL, aVF) and six are precordial (chest) leads (V_1 - V_6). For all 12 leads, the right leg serves as the ground or indifferent lead. Using a ground lead minimizes extraneous electrical activity.

Leads I, II, and III are formed by three sides of a triangle (Einthoven's triangle) connecting the right arm, left arm, and left foot. The heart is near the center of the triangle. Bringing the sides of the triangle to the center point creates a triaxial system. A hypothetical line joining the poles of a lead is called the lead axis. A lead axis has polarity and direction.

Leads I, II, and III are Bipolar

They represent the difference in electrical potential between two specific points in the body (i.e., 2 electrodes of opposite polarity). Lead I is the difference in potential between the left arm (LA, +) and right arm (RA, -). Lead II is the difference in potential between the left leg (LL, +) and right arm (-). Lead III is the difference in potential between the left leg (+) and left arm (-). Right arm is always negative; left leg is always positive; left arm is positive and negative. Lead II = lead I plus lead III (e.g., if lead I is 3 mm and lead III is 6 mm, lead 2 should be 9 mm high). If P waves are positive in all three leads, the tallest P wave identifies lead II. Lead II is commonly used to diagnose arrhythmias because it most consistently shows an easily visible P wave. The P wave is often the key to identifying an arrhythmia.

Leads aVR, aVL, and aVF are Unipolar

They represent the difference in electrical potential between one positive lead and the average of the potential between the other two leads, which serve as the negative electrode or a zero reference point. There is only one visible electrode. Lead aVR (augmented voltage right) is the difference in potential between the right arm and the average of the potential of the left arm and left

leg. Lead aVL (augmented voltage left) is the difference in potential between the left arm and the average of the potential of the left leg and right arm. Lead aVF (augmented voltage foot) is the difference in potential between the left leg and the average of the potential of the left arm and right arm. The waveforms of the aV leads are augmented (increased in size) in order to get adequate magnitude for evaluation.