INTRODUCTION & REVIEW OF LITERATURE

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❖ HEART

The heart is present in the left side of chest cavity, its apex located at 5th intercostal space and enclosed in serous sac called pericardium, which is thin and transparent. Along the insertion and at the apex of the heart, it contains fat deposits. It connected with sternum by sternopericardial ligaments. Cranioventrally it is firmly attached to the thymus over a wide area ***(Frank et al., 1994).***

The structure of the heart of the rat is the same as in other mammals. It consists of four chambers, right and left atria as well as right and left ventricles. The atria have relatively weak contractile power sufficient for filling the ventricles. While the ventricles have powerful expulsive contraction forcing the blood into the main arterial trunks ***(Baer, 1964;Basmajian, 1971 and Lawerence et al., 1996).***

The left ventricle is larger than the right one because the interventricular septum is inclined to the right side. The left ventricle has a thicker wall than that of the right ventricle to allow it to do higher amount of work than that performed by the right ventricle. The valves guarding the entrance and exit of the two ventricles enable the rhythmic contraction and relaxation of the myocardium and produce one way flow of blood through the heart ***(Robert and Mathew, 1972; Kelman, 1977 and Ben pansky, 1996).***

Cardiac wall of cardiac chambers consists of three layers. The endocardium, which is the inner layer composed of connective tissue

containing blood vessels and covered by simple squamous epithelium. The epicardium is the outer layer formed of visceral pericardium and consists of connective tissue covered extremely by simple squamous epithelium. The third layer is the myocardium, which is the middle layer. It is thin in the atria and thicker in left ventricle than in the right ventricle ***(Bloom and Fawcett, 1975; Ham, 1979 and Ronald et al., 1996).***

In both atria and ventricles, the myocardium is formed of branching and anastomosing cardiac muscle fibers, that have a very rich supply of capillaries, required for extensive energy requirement of the heart ***(Cormack, 1987).*** Each cardiac muscle fiber is formed of several cardiac myocytes and each cell contains centrally located nucleus .The cells are connected together by junctional complexes at the level of Z-lines, these ~~junctional complexes~~ are called intercalated discs. The intercellular spaces contain fibroblasts, collagen bundles, nerve fibers and capillaries ***(Williams and Warwick, 1980 and Fawcett, 1994).***

The intercalated disc is thick, straight line that lie perpendicular to the axis of the cells. This disc provided attachment to the myofibrils formed of desmosomes and gap junctions but mainly desmosomes. ***(Han and Holmstedt, 1981; Rogers, 1983 and Junqueira et al., 1998).***

The desmosome is formed of two adjacent cell membranes with intercellular space (20 - 25 nm). On the inner side of the inner protein layer of each cell membrane, there is electron dense material called plaque, so the desmosomes has two plaques with tonofilaments attached to each plaque and turn back to the cytoplasm .In the gap junction, there is narrowing of the intercellular space to (2 nm). The desmosome is supportive in function while the gap junction helps the rapid transmission

of impulses throughout the cardiac muscle fibers to function like a syncytium. The sarcoplasm of each cardiac muscle fiber is filled with long and cylindrical fibrils called myofibrils, which are parallel to the long axis of the muscle fibers. The myofibrils are composed of alternating light and dark bands. The dark bands called (A) bands (anisotropic) and the light bands called (I) bands (isotropic). The (A) band contains thick myosin filaments as well as thin actin filaments which extend between the thick myosin but don't extend into the (H) zone which contains only myosin so the (H) zone appear as light band which bisects the (A) band. The (M) band lies in middle of (H) band and contains fine strands connecting myosin filaments. The (I) band contains thin actin filaments only and is bisected by dark line called (Z) line, the distance between each successive (Z) lines form the sarcomere, which is the structural and functional unit of the cardiac muscle fibers ***(Zamzam, 1992 and Junqueira et al., 1998).***

The transverse tubular system (T system) is the invagination of the cell membrane into sarcoplasm. In developing and adult rats it is composed of three, major elements, the transverse tubules, longitudinal tubules and flattened cisternae. The T system serves to transmit the message " action potential "passing across the cell surface to the interior of the cell and stimulate sarcoplasmic reticulum to release calcium ions to bring about contraction of muscle fibers ***(Nakamura et al., 1986 and Fawcett, 1994).***

The sarcoplasmic reticulum of the cardiac muscle consists of anastomosing tubules, which act as a store for calcium ion to release it at the time of need causing muscle contraction ***(Zamzam, 1992 and Barbara and John, 2000).***

The sarcoplasmic reticulum is divided into two parts; the first part is the terminal cisternae, which is located beneath the sarcolema and functions, as a store for calcium ions to release it when needed into sarcoplasm causing the myofibril to contract. The second portion is a network of sarcotubules (non cisternal) that crosses over the surface and to some extent through the myofibrillar contractile material, its function is to lower calcium level after the contraction of the myofibrils, causing it to relax ***(Page and Mcallister, 1973;Bloom and Fawcett, 1975 and David 1998).***

The cardiac myocytes show small Golgi apparatus near one of their poles and may be perinuclear in position ***(Page and Mcallister, 1973; Bloom and Fawcett, 1975 and Bergman et al., 1996).*** Golgi apparatus in the cardiac muscles is formed of multiple stacks of cisternae and associated vesicles and located in the perinuclear area and is well developed in the ventricles than atria ***(Dunphy and Rothman, 1985).***

The most prominent organelle in the cardiac myocytes is the mitochondria, which are the sites of oxidative phosphorylation processes, which constitute the main energy source for the cardiac myocytes ***(Anversa et al., 1971; Gross, 1971; page and Mcallister, 1973 and Ronald et al., 1996).***

Mitochondria are numerous in the cardiac muscle fibers in between myofibrils and at the perinuclear zones of the sarcoplasm ***(Kelly et al., 1984).*** The mitochondria are abundant in cardiac than skeletal muscles and are characterized by their numerous cristae ***(Page and Mcallister, 1973).*** The mitochondria are elongated or spherical with abundant closely packed cristae rich in oxidative enzyme system ***(Burkitt et al., 1995).***

The nuclei of myocytes are large, ovoid or elongated in shape and their nuclear membrane is deeply enfolded, central or eccentric in position and contained small prominent nucleolus and contained mainly euchromatin and few patches of heterochromatin ***(Tay et al., 1983).*** Most cardiac muscle cells posses a single nucleus but few of them contain two, the nuclei are relatively large with pale staining ***(Cormack, 1997).***

Lysosomes, phagosomes and multivesicular bodies are commonly found in the perinuclear region of the sarcoplasm of cardiac muscle, a small number of free ribosome is observed throughout the sarcoplasm and the cisternae of rough endoplasmic reticulum are mostly confined to the perinuclear region and Centriole are rarely observed in myocardial cells ***(Silver, 1983 and Lesson et al., 1988).***

Glycogen granules tend to be more abundant in cardiac than in skeletal muscle. It occurs in the form of 30 –40 nm dense particles located in the areas that contain mitochondria, but particles may be found aligned in rows between myofilaments. Glycogen and lipids are both important energy sources for contractile activity of myocardium ***(Fawcett, 1994).***

Lipid droplets exist as oval or rounded small droplets about (0.3–1um in diameter) devoid of membranes, present between rows of mitochondria ***(Burkitt et al., 1995).*** Lipid droplets and myoglobin present more in cardiac muscles than in skeletal muscles ***(Bergman et al., 1996).***

Lipofuscin pigments are present in small irregular membrane bound bodies about (1–1,5 um in diameter) present between mitochondria. They considered as secondary lysosomes and increase with increasing age. This

pigment may be so extensive to give a brownish tinge to fresh myocardium (brown atrophy of the heart) ***(Leeson et al., 1988; Hulland, 1985 and Zamzam, 1992).*** Lipofuscin pigment is the product of lysosomal degradation of various cellular components especially the mitochondria ***(Skepper and Navaratram, 1987).***

All cardiac muscles fibers are of the red type as they are rich in myoglobin, which is the pigment that functions as hemoglobin in red corpuscles ***(Ham, 1979 and Junqueira et al., 1998).***

The quantitative study of the ultrastructure of myocardial cells revealed that, the normal cell volume is composed of 47,6% myofibrils, 35,8% mitochondria, 1% tubular system, 3,5% endoplasmic reticulum 12,1% sarcoplasm, nuclei and other structures ***(Page and Mcallister, 1973 and Ronald et al., 1996).***

The efficiency of the heart as dual pump depends on contractions in left and right sides being simultaneous and on the different events in the cardiac cycle following each other. The synchronization of these events and their occurrence in an orderly sequence depend on the impulse for contraction sweeping through heart down what is termed as impulse conducting system. This system is composed of a special type of cardiac muscle cell that is specialized for either initiating an impulse for contraction or conducting the impulse through parts of the heart. This system includes the sinoaterial node (S.A.N), the atrioventricular node (A.V.N), the atrioventricular bundle (bundle of His), the atrioventricular bundle branches (A.V bundle branches) and the purkinje fibers ***(Cormack, 1997 and Barbara and John, 2000).***

The S.A.N. is the pace maker of heart which is present at the junction of superior vena Cava and the right atrium beneath the epicardium, the S.A.N is responsible for initiation of the cardiac impulses ***(Zamzam, 1992).*** Microscopically, the S.A.N. is a small mass of specialized cardiac muscle fibers that lies in fibroelastic tissues and it is supplied by nodal artery. The nodal fibers have finer caliber than ordinary cardiac muscle fibers outside the node ***(Barbara and John, 2000).***

The A.V.N. is present in the interatrial septum just above tricuspid valve beneath the endocardium, this ovoid node consists of crossing muscle fibers with spherical nuclei and is surrounded by a thick sheet of muscle fibers with rich blood and nerves from both sympathetic and para sympathetic ***(Anderson and Toylor 1972;Ham, 1979 and Leslie and James, 1997).*** The A.V.B. is formed of specialized cardiac muscle fibers called purkinje fibers ***(Anderson and Taylor, 1972 and Ronald et al., 1996).***

The heart had special conducting system called purkinje system composed of specialized fibers called purkinje fibers, the purkinje system plays an important role in the rapid conduction of the impulses throughout the atrium then to the ventricles ***(Guyton and Hall, 1996).***

The purkinje fibers are different from ordinary cardiac muscle fibers. The purkinje fibers are larger in diameters, contain more glycogen granules, more mitochondria more than one nucleus, few myofibrils which are striated and located peripherally, than in ordinary cardiac muscle fibers, but they have undeveloped sarcoplasmic reticulum and undeveloped intercalated discs ***(Zamzam, 1992 and Barbara and John, 2000).***

Two coronary arteries supply the heart, the right coronary artery run in a dorsocaudal direction over the wall of right ventricle, it sends two twigs to the right atrium and other branches that run dorsally and ventrally across the ventricular wall. The left coronary artery passes around the pulmonary trunk to the left ventricular wall and gives off a circumflex ramous which run parallel with coronary groove to the dorsal aspect of the ventricular wall. It sends twigs to the left atrium and other branches to the left ventricle and interventricular septum. The blood supply of the rat heart is dual, besides the coronary vessels, accessory vessel supply of the heart. A well developed interventricular artery arsises from the right (45%) or the left (55%) coronary artery shortly after its origin. It enters interventricular septum where it gives several septal branches, which anastomose with end twigs of the coronary arteries along the margin of the septum ***(Ts'so et al., 1970; Ts'so et al., 1971 and Gerard, 1995).***

Coronary arteries are modified to prevent occlusion during systole, so they are characterized by the presence of three well developed elastic lamina (internal, middle, external) and a profuse basket like capillary network around the muscle fibers ***(Cormack, 1987).***

The heart has several important functions such as contractility, excitation, rhythmicity, conductivity and hormonal function. The mechanism of contractility which occurs due to sliding of the actin and myosin myofilaments constituting the myofibrils in response to propagation of action potential over and inside the cardiomyocytes ***(Albert, 1979).*** Speed of contraction of cardiomyocytes depends on the amount of myofibrils and mitochondria inside them, which provides the ATP needed for the contractility ***(Brutsaert and Paulus, 1979).***

The heart acts as a pump formed of two parts, right and left, each consists of an atrium and ventricle. The atria are the primary pumps as they forced the blood into ventricle immediately before ventricular contraction. This propulsion of blood into the ventricles make them more efficient as pumps and more powerful as they still pump large quantities of blood even when the atria failed to function. Most of the cardiomyocytes are capable of contracting, rhythmically including group of small cardiac muscle fibers and the S.A.N. The cause of this rhythmicity is the continuous excitation and hyperpolarization of the membrane of the nodal cells with the regeneration of action potential in the node. Normally action potentials originating in the S.A.N spread through the heart and thereby elicit the rhythmic contraction of the heart ***(Guyton, 1984).***

The S.A.N. fibers had the capacity of the self-excitation, which could produce automatic rhythmical discharge and contraction ***(Huizinga, 1995 and Guyton and Hall, 1996).*** Cardiac impulses originated in sinoaterial node can travel along cardiac fibers first in the atrial syncytium producing its contraction ***(Keele et al., 1984).***

The atrial cardiomyocytes has the capacity to produce a polypeptide; this substance affected the sodium excretion by the kidneys and called the natriuretic peptide (NP) or the natriuretic factor (NF) ***(Cantin et al., 1984 and De lean et al., 1984)***

The secretion of atrial natriuretic factor is stimulated by distention and stretching of the cardiac wall as in case of hypertension and chronic renal failure ***(Ballerman and Brenner, 1986; Needleman; Greenwald, 1986 and Rinne et al., 1986).***

The atrial natriuretic peptide affects the functions of other endocrine glands. These effects vary from inhibition of adrenocorticotropic, antiduretic hormone, thyroid hormone, renin and progestrone hormones, to enhancement of testosterone and luteinising hormone secretion ***(Dayanithi and Antoni, 1990; Kovacs and Antoni, 1990 and Steele, 1990).***

These endocrine effects are attributed to the effect of the peptide on the blood electrolyte levels. The peptide might also affect the enzymes responsible for hormonal synthesis ***(Ermirro et al., 1990 and Tseng et al., 1990).***

The atrial peptide has a potent vascular effects including hypotension as result of vascular dilation, fluid leakage and decreased cardiac output ***(Huxley and Meyer, 1990).***

The atrial peptide has a strong effect on the respiratory system; this effect varies from the dilation of the bronchi to the paralysis of the respiratory cilia of the trachea and bronchi ***(Rankin and swift, 1990).***

❖ KIDNEY

The kidneys are a pair of compound tubular glands that clear the blood plasma from metabolic wastes, regulate fluid and salt concentrations of the body, eliminate foreign chemicals, help to maintain the acid base balance of the body and also has excretory functions. Kidneys are the site of production of hormones as renin and erythropoietin directly into blood stream and thus are considered as endocrine organs. Renin is important in regulating blood pressure and sodium ion concentrations and erythropoietin influences hemopoietic activity ***(William and Harry, 1994).*** The renal blood flow is very high; it reaches about 25% of the cardiac output although the kidneys are 4% of total body weight delivering toxic solutes to the renal cortex ***(Barbara and John, 2000).***

Kidneys are situated retropertineally on the posterior wall of the abdomen on either side of the vertebral column; they are paired bean shaped organs. Each kidney contained within a thin but strong connective tissue capsule and is surrounded by a mass of perirenal adipose tissue ***(Schrier and Gotlschalk, 1988 and Fawcett, 1994).***

Hilus is a concavity on the medial border of the kidney where arteries, veins, lymphatics and nerves are present, the Hilus is continuos with renal sinus which is a central cavity containing fat ***(Leslie et al., 1992 and Barbara and John, 2000).***

Renal pelvis is a funnel shaped expansion of upper end of the ureter where it joins the kidney. It also passes through the sinus, and dividing it into two or three short tubular structures called major calyces, these in turn divide into eight to twelve smaller units called minor calyces, which form a cylindrical attachment around a conical projection called renal papilla ***(William and Harry, 1994 and Junqueira et al., 1998).***

The parenchyma of the kidney is divided into two distinct regions, cortex and medulla. The cortex is an outer continuous layer beneath the capsule, which is darker and granular. In the cortex, renal corpuscles and convoluted tubules are present. Medulla is an inner region, which is paler and smoother and consists of 8 to 12 cone shaped structures called medullary pyramids, which separate from each other by inward extensions of cortical tissue called renal columns. The bases of the pyramids direct towards the renal sinus and form the renal papillae. From the bases of the pyramids, groups of tubules extend into the cortex giving it a striated appearance, which are called medullary rays ***(William and Harry, 1994 and Junqueira et al., 1995).***

Renal lobe consists of medullary rays (at its center) and the closely associated cortical tissue surrounding it. All nephrons in single lobules are drained by the same collecting tubule ***(Leslie et al., 1992 and Fawcett, 1994).***

Uriniferous tubules are the basic structural and functional units of the renal parenchyma. Each one consists of a nephron, which produces and modifies the urinary filtrate and collecting tubule, which concentrates urine and conveys it into minor calyces ***(Kurt, 1992; Fawcett, 1994 and Junqueira et al., 1998).***

Each kidney is composed of 1-4 million nephrons. Each one consists of dilated portion called the renal corpuscle, which contains the glomerulus and kidney tubules, the unit of kidney structure is the nephron ***(Junqueira et al., 1995 and Barbara and John, 2000).***

Two types of nephrons have been described; cortical nephrons have short loops of Henle and reach only to outer medulla. They also have a juxta glomerular apparatus and their function varies according to the physiological demands. The second type is juxta medullary nephrons, with large glomeruli and long loops of Henle, which penetrate deep into medulla, their function is adapted for conservation of water and salt ***(Brenner et al., 1982 and Fawcett, 1994).***

The renal corpuscle is situated in the cortex; and forms the upper end of uriniferous tubules; it contains glomerulus and Bowman's capsules. The glomerulus consists of a network of capillaries into which blood enters by an afferent arteriole and leaves through smaller efferent arteriole. Both afferent and efferent arterioles are present in the vascular pole of glomerulus. The glomerulus also has a urinary pole continuous with the lumen of the next segment of nephron ***(Leeson et al., 1988 and Fawcett, 1994).***

Bowman's capsule is a double walled cup around a glomerulus, which is composed of a parietal layer, which is lined with simple squamous epithelium that changes into cubodial epithelium at the start of proximal convoluted tubule and a narrow cavity called Bowman's space ***(Haensly et al., 1982 and Fawcett, 1994).*** The visceral layer closely invests glomerular capillaries; the cells of this layer are called podocytes. They are octopus shaped, have a cell body from which arise several large

primary processes that clasp the glomerular capillaries. Also have smaller secondary processes that arise from the primary one and interdigitate with secondary processes of podocytes. This interdigitation lead to the formation of several narrow slits between the pedicles called slit pores. In transmission electron micrographs, these slits are seen to be bridged by a layer of material of unknown composition that is thinner than cell membranes and is called the filtration slit membranes. The cell bodies of podocytes and their primary processes do not touch the basal lamina. The secondary processes end in feet that are applied firmly to the basement membrane of the capillary wall of the glomerulus. The visceral epithelial cells are the primary site for basement membrane synthesis and a narrow cavity called Bowman's space ***(Schrier and Gotlschalk, 1988 and Junqueira et al., 1998).***

The endothelial cells of glomerular capillaries have a thin cytoplasm that is thicker around the nucleus, which projects into the lumen of the capillary where most of the organelles are clustered. The fenestrae of these cells are larger and more numerous than in the fenestrated capillaries of other organs and they lack the thin diaphragm commonly observed spanning the openings of other fenestrated capillaries ***(Junqueira et al., 1995 and Barbara and John, 2000).***

The glomerular basement membranes are defined as thin exrtacellular matrices that separate epithelial and endothelial cells from the underlying stroma and prevent the passage of certain macromolecules. These membranes are thicker than other basement membranes elsewhere ***(Rohrback et al., 1982 and Cormack, 1987).***

Chemically, the glomerular basement membrane is composed of type IV collagen, fibronectin, laminin and glycoaminoglycan. Heparan sulphate, a highly negatively charged glycoaminoglycan, thought to be important in maintaining the charge barrier properties of the glomerular capillaries ***(Hawthhorne et al., 1986 and Barbara and John, 2000).***

Morphologically, the glomerular basement membrane is composed of three layers, an outer less dense subepithelial layer called lamina rara externa, a central electron dense layer known as lamina densa and an inner subendothelial layer called lamina rara interna, which is continuous with mesangial matrix ***(Schrier and Gotlschalk, 1988 and Junqueira et al., 1998).***

The filtration barrier between blood flowing through the glomerular capillaries and the capsular space, consists of the fenestrated endothelium, the basal lamina and the filtration slits between the interdigitating foot processes of the podocytes. The function of this barrier is that the basal lamina is the main filter; the endothelial fenestrae act only as a coarse sieve holding back the formed elements of the blood and controlling access of its macromolecular constituents to the filtrate ***(Leeson et al., 1988; Fawcett, 1994 and Barbara and John, 2000).***

The intercapillary spaces of the glomerulus occupied by mesangium, consisting of the mesangial cells, which have small dark staining nuclei and are more or less stellate in shape. The cytoplasmic extensions of mesangial cells appear to be engorged with ferritin (an electron scattering iron containing protein) used for easily identification of these cells with electron microscope. In addition, lysosomes and lipofuscin granules are recognizable in the cytoplasm. These cells are similar to pericytes in that

they contain many cytoplasmic filaments and similar to smooth muscle cells due to presence of peripheral dense bodies. These cells provide support for the capillary tufts and may act as macrophages and clean the basal lamina of particulate material that accumulates during filtration process and the mesangium serves to unclog and recondition residues that accumulate against it ***(Schrier and Gotlschalk, 1988 and Junqueira et al., 1995).***

Juxta glomerular apparatus is located at the vascular pole the renal corpuscle and is composed of three different groups of cells, as macula densa, which is formed of tall, thin, columnar cells and Juxta glomerular cells, which are modified smooth muscle cells of the afferent arteriole. These cells contain cytoplasmic granules rich in the enzyme renin. The last cells are mesangial cells, which are pericyte like cells. When blood pressure falls, Juxta glomerular cells release renin, which causes an increase in the blood pressure by way of a homeostatic mechanism. Renin is an enzyme that acts on angiotensinogen in the plasma converting it to angiotensin I, in the capillaries of the lung. Angiotensin I is converted into Angiotensin II, which causes release of aldosterone from zona glomerulosa cells in the adrenal cortex. aldosterone stimulate distal tubule cells to retain sodium ions, water follows the sodium and the fluid volume is increased in the extracellular compartment, which corrects the initial problem, which is decreased extracellular fluid volume ***(Kurt,1992 ; Leslie et al.,1992 and Stevens and Lowe,1997).***

The proximal convoluted tubule begins at urinary pole of the renal corpuscle. It has a convoluted part and a straight part. Because the proximal convoluted tubule is longer, more sections of it can be detected than of the distal tubule. The cells of the proximal tubule are large and

more acidophilic. In cross section, they appear wide and triangular with basal spherical nuclei. The lateral borders of these cells interdigitate very extensively, which make them indistinct in light microscopic sections. The luminal border of these cells is covered with many microvilli and posses abundant glycoprotein in its cell coat. Sodium pump performed by the proximal tubule requires a considerable expenditure of energy and thus abundant elongated mitochondria were present in the base of these cells, which contain considerable amount of oxidoreducatse enzyme ***(Fawcett, 1986 and Junqueira et al., 1998).***

The next segment of the nephron is the loop of Henle, which consists of an initial thick descending portion, a thin descending portion that resemble distal convoluted tubule. The thin segment of loop of Henle has a narrow lumen with a thin wall that is composed of simple squamous epithelium. The luminal surface has a few short microvilli. It plays role in concentrating the urine passing through collecting tubules by the countercurrent multiplier mechanisms ***(Snell, 1984; Junqueira et al., 1995 and Barbara and John, 2000).***

The last segment of the nephron is the distal convoluted tubule; it begins at macula densa, which lie in close association with vascular pole of the renal corpuscle of the same nephron and extends to the region of transition with initial collecting tubule. The cells lining the distal convoluted tubule are not acidophilic as those in the proximal tubule, hence this portion has a large spherical nuclei and its lumen appears wider. The luminal border of these cells has microvilli. The lateral borders are slightly more distinct. Also, have deep basal infoldings and interdigitations of the cell membrane with relatively numerous elongated mitochondria ***(Tisher and Modson, 1991 and Junqueira et al., 1995).***

Its function is resportion of sodium and chloride from the glomerular filtrate. Its Na-K- ATPase activity and its resportive capacity are greatest in the inner stripe of the outer medulla ***(William and Harry, 1994 and Barbara and John, 2000).***

The collecting tubule begins as arched tubule, which empty into straight collecting one. The straight tubules unite after a number of fusion. The papillary ducts formed, which open on the area cribrosa of the papilla then into a minor calyx. The cells lining the collecting tubules are first cubodial, later in the straight duct, they are tall columnar. The cell borders are regular with few interdigitations. The cortical collecting tubules respond to antiduretic hormone, while the medullary collecting tubules play an important role in producing a concentrated urine ***(Cormack, 1987; Leslie et al., 1992 and Junqueira et al., 1998).***

Renal interstitium is the connective tissue compartment in the kidney, which is usually not obvious. In normal kidney, most interstitial tissue occurs around interlobar and interlobular arteries ***(Darmady, 1980 and Fawcett, 1994).*** In the cortex, the interstitium constitutes about 7 percent of the tissue volume, while the vasculature occupies an additional 6 percent. The relative volume of the interstitium increases towards the medulla ***(Bulger and Nagel, 1973).***

In the cortical interstitium, two types of interstitial cells are recognized. The first type is fibroblast, which is greatest in number. The second type is mononuclear cell, which is less frequent. These cells contain numerous lysosomes and are phagocytic in function ***(Leslie et al., 1992 and Fawcett, 1994).***

In the medulla, there are three types of interstitial cells; these cells are the sites for prostaglandin production and the synthesis of ground substance. Type I interstitial cells are highly pleomorphic cells containing multiple small lipid droplets. Type II interstitial cells are generally round and have no lipid droplets and their cytoplasm contains abundant number of free ribosomes and lysosomes. Type III interstitial cells correspond to pericytes, these cells are closely related to the descending vasa recta. They usually lie between layers of basement membrane of these vessels ***(Verberckmoes et al., 1976 and Junqueira et al., 1995).***

Arterial supply to each kidney comes from a single renal artery, which is a lateral branch of abdominal aorta. Then renal artery runs towards the hilum of the kidney and divides into two main branches one anterior and one posterior, each of which divides into a number of interlobar arteries that travel between the renal pyramids, then divide into several arcuate arteries that run along the corticomedullary junction, then small interlobular arteries arise from the arcuate arteries and enter the cortical tissue to pass between lobules. Then interlobular arteries give rise to afferent glomerular arterioles, which supply the glomerular capillary. Efferent glomerular arterioles leave the glomerulus and give rise to an extensive peritubular capillary network that supplies the proximal convoluted tubules from glomerulus of juxta medullary nephrons and from vasa recta, which are long, straight capillaries that extend into medullary pyramids ***(Leslie et al., 1992 and Barbara and John, 2000).***

Veins follow the same course as arteries. Blood from interlobular veins flow into arcuate veins then to the interlobar veins. Interlobar veins converge to form the renal vein through, which blood leaves the kidney. Superficial cortical veins drain outermost layer of cortex, which joins

stellate veins and empty into interlobular and arcuate veins and deep cortical veins drain deep region of cortex ***(Schrier and Gotlschalk (Schrier and Gotlschalk, 1988;Leslie et al., 1992 and Junqueira et al., 1998).***

The kidney regulates the chemical composition of the internal environment by a complex process that involves filtration, active absorption, passive absorption and secretion. Filtration takes place in the glomerulus, where an ultrafiltrate of blood plasma is formed. The tubules of the nephron, primarily the proximal convoluted tubules absorb from this filtrate the substances that are useful for body metabolism such as glucose, amino acids, 85% of sodium chloride, water, calcium and small amount of protein thus maintaining the homeostasis of the internal environment. They also secret creatinine and waste product from blood to the tubular lumen, the collecting ducts are permeable to water, contributing to concentration of urine, which is usually hypertonic in relation to blood plasma ***(Junqueira et al., 1998 and Barbara and John, 2000).***

❖ HYPERTENSION

Arterial hypertension is elevation of systolic blood pressure (SBP) 140 mm Hg or greater and diastolic blood pressure (DPP) of 90 mm Hg or greater, classified primary in which patients have arterial hypertension with no definable cause or secondary in which patients have arterial hypertension with definable cause. Isolated systolic hypertension is defined as a systolic blood pressure 140 mm Hg or more and a diastolic blood pressure of less than 90 mm Hg *(Neaton et al., 1996).*

Whatever the pathogenic mechanisms responsible for primary hypertension, they must lead to increased total peripheral vascular resistance (TPR) by inducing vasoconstriction or increased cardiac output or both. The sympathetic nervous system or renin angiotensin aldosterone system plays an important role in the pathophysiology of hypertension since both can increase cardiac output (CO) and total peripheral vascular resistance (TPR) *(Hung and Ingelfinger, 1993).* The pathological change, which occur in primary hypertension includes generalized arteriolar sclerosis particularly apparent in the kidney and is characterized by medial hypertrophy and hyalinization *(Baker and Tomson, 1994).* The rise in blood pressure develops left ventricular hypertrophy. During the course of arterial hypertension, cardiac hypertrophy is initially a beneficial process that allows the heart to adapt to new environmental requirements both by increasing the number of contractile units and by diminishing the wall stress *(Camm, 1994).* The pathophysiological sequelae of left ventricular hypertrophy (LVH) are reduced ventricular filling; contractility and ventricular dysarrhythmias diminished coronary reserve or myocardial ischemia *(Messerli et al., 1993).*

Myocardial structure is abnormal in left ventricular hypertrophy (LVH) that accompanies arterial hypertension. Abnormal fibrous tissue accumulation is present and expressed as an increase in collagen concentration and accumulation of type I collagen in the interstitium and adventitia of intramyocardial arteries ***(Weber et al., 1988).***

Antihypertensive drugs should not only lower arterial blood pressure but also prevent or improve target organ damage, such as LVH, various classes of antihypertensive drugs that influence the sympathetic or renin angiotensin aldosterone system or modulate the intercellular free calcium concentration have shown to reduce LVH after short-term therapy ***(Fauad et al., 1987; Messerli et al., 1988 and Susic and Frohlich, 1993).*** In contrast, arterial vasodilators and diuretics seen to reduce LVH only after long-term therapy ***(Messerli and Aepfelbacher, 1995).*** Angiotensin converting enzyme inhibitors are the most powerful drug class to reduce LVH, followed by calcium antagonists, alpha and beta- blockers and diuretics, while vasodilators seemed to have only a minimal effect. Reversal of LVH by Angiotensin converting enzyme inhibitors, calcium antagonists and beta- blockers was primarily accomplished by reduction of both posterior wall thickness and interventricular septal thickness, whereas diuretics predominantly reduced the internal diameter of left ventricle ***(Dahlof et al., 1992; Cruikshank et al., 1992 and Schmieder, 1994).***

The components of the renin angiotensin system are found in vascular tissues as in the lung, myocardium, brain, kidney and testis ***(Mac Fadyen et al., 1991).*** These tissue systems result in autocrine and paracrine effects of local angiotensin II formation ***(Dzau, 1987).***

Angiotensin II, is a potent vasocostictor octapeptide, formed from its precursor, angiotensin I, a dectapeptide by the activity of Angiotensin converting enzyme (ACE). Angiotensin I originates from angiotensinogen under the influence of the enzyme renin, which occurs in the liver ***(Dzau and Herrmann, 1982).***

Angiotensinogen is an α_2 globulin formed by the liver and its level decreased after partial hepatectomy. Expression of genes for angiotensinogen and ACE is demonstrated in the heart, brain, kidney, adrenal gland and the vasculature ***(Drexler et al., 1989).*** Angiotensinogen is continuously synthesized and secreted in the plasma, and its synthesis is stimulated by a number of hormones as glucocorticoids, thyroid hormones and angiotensin II itself ***(Ben-Ari and Garrison, 1988).***

Renin and prorenin are stored in juxta glomerular cells and circulate in the blood. Renin release from the kidney cortex is stimulated by reduced renal arterial pressure, sympathetic neural stimulation and reduced sodium delivery or increased sodium concentration at distal renal tubules ***(Seaky et al., 1980 and Osbron et al., 1981).*** On the other hand, renin release is inhibited directly by angiotensin II activity, and indirectly by sodium retention associated with aldosterone levels ***(Seaky et al., 1980).***

Plasma Angiotensin converting enzyme (ACE) originates mainly from pulmonary endothelium. ACE is present on the in luminal surface but absent from the media of the greater vessels and localizes within the adventitia at site of vasavasorum and the adventitia intramyocardial coronary arteries ***(Yamada et al., 1991 and Rogerson et al., 1992).***

The converting enzyme is non-specific because it not only converts angiotensin I to angiotensin II but also inactivates bradykinin. Bradykinin inactivated by kininase I and II, the latter being identical to ACE. Therefore ACE inhibitor should lead to increase formation of bradykinin, which has vasodilator properties ***(Hajj-ali and Zimmerman, 1991).***

There are several antagonists of the renin angiotensin system such as a number of drugs that either inhibit the secretion of renin as propranolol, clonidine and α methyl dopa or saralasin which is a competitive blocker of angiotensin or spironolacton, which is a well known aldosterone inhibitor that acts by causing sodium loss and potassium retention in the distal convoluted tubules, finally angiotensin converting enzyme inhibitors (ACEI) ***(Anderson et al., 1977 and Atlas et al., 1983).***

Angiotensin converting enzyme inhibitors (ACEI) are commonly used drugs in the management of the variety of cardiovascular diseases. They are effective antihypertensive agents ***(Safar et al., 1986).*** Angiotensin converting enzyme inhibitors interfere with formation of angiotensin II, the latter have vasoconstrictor properties of both systemic and coronary arteries ***(Mizuno et al., 1988).*** The effect on the coronary circulation has been shown in experimental studies in which ACEI produced a reduction in infarct size which was explained by increased coronary perfusion of the ischemic area ***(Ertl et al., 1982).***

Michel et al., (1988) found that the effect of ACEI on the peripheral circulation causes a reduction in both afterload and preload and decreases the myocardial oxygen demand as well as a fall in blood

pressure without increase in heart rate, leading to reduced myocardial oxygen consumption.

The major effect of ACEI is to reduce the conversion of angiotensin I to the active vasoconstrictor angiotensin II. It also prevents the breakdown of the vasodilator peptide bradykinin. The ACEI are capable of lowering blood pressure by promoting vasodilatation and reducing intravascular fluid volume ***(John and Laragh, 1992).*** Angiotensin II is capable to stimulate growth of vascular smooth muscle within the wall of blood vessels inducing structural change characteristic of the hypertensive state. These include vascular smooth muscle hypertrophy, an increase in DNA content and increase in collagen production. ACEI is capable of preventing or reversing structural change in both large and small arteries ***(Doyle, 1992).***

Angiotensin converting enzyme inhibitors (ACE) classified into three groups, the sulfhdryl-containing group as captopril, and the phosphoryl-containing group as fosinopril and carboxyl -containing group as enalapril. Captopril has rapid onset with relatively short duration of action, whereas enalapril and fosinopril have slower onset with relatively long duration of action ***(Raia et al., 1990).***

ACE inhibitors tended to be more effective in reducing both posterior wall thickness and interventricular septal thickness than beta-blockers, calcium antagonists and diuretics ***(Koren et al., 1991).***

❖ ENALAPRIL

Enalapril is an angiotensin converting enzyme inhibitor (ACEI), which is given orally in the management of hypertension and congestive heart failure ***(Laurence, 1997).***

Enalapril maleate is a white crystalline powder, sparingly soluble in water, slightly soluble in organic solvents, soluble in alcohol, freely soluble in methyl alcohol and dimethyl formamide. Enalaprilat is a white or nearly white, hygroscopic, crystalline powder, soluble in water, methyl alcohol, slightly soluble in isopropyl alcohol, very slightly soluble in acetone and insoluble in chloroform ***(Chiu et al., 1996).***

Enalapril acts, as a prodrug of enalaprilat. It extensively hydrolyzed in the liver to enalaprilat. Following oral administration about 60%of a dose of enalapril is rapidly absorbed from gastrointestinal tract. Absorption not affected by the presence of food ***(Wong et al., 1996).***

Enalapril haemodynamic effects are seen within 1 hour of a single oral dose and the maximum effect occurs after 4-6 hours. The haemodynamic action lasts for about 24 hours allowing once daily dosing ***(Gottleib et al., 1993 and Pechere et al., 1998).***

Enalaprilat did not absorb oral administration and thus is given intravenous injection and its haemodynamic effects develop within 15 minutes of injection and reach a peak in 1-4 hours. The action lasts for about 6 hours at the recommended doses ***(Wong et al., 1996).*** The terminal half-life for enalaprilat following a single oral dose of enalapril

found to be 35 hours. In patients with congestive heart failure, the half- life was longer and clearance was slower than healthy subjects ***(Rucinska, 1991 and Dickstein and Gabliks, 1995).***

Excretion of enalapril maleate is primarily renal, 61% of the absorbed dose is recovered from the urine (18% as enalapril and 43% as enalaprilat) and 33% from faeces ***(Laurence, 1997).***

Enalapril is supplied as white tablets in three strengths, each containing 5 mg or 10 mg or 20 mg enalapril maleate ***(Product information, 2003).***

The usual daily dose ranges from 10- 40 mg, once or twice daily. In essential hypertension, the initial dose is 10- 20 mg, depending on the degree of hypertension and the maintenance dose is 20 mg once daily ***(Goldberg et al., 1993 and Motero, 1997).*** In renovascular hypertension, the initial dose of 5 mg daily may be given to patients with normal renal function who are not receiving a diuretic but initial dose of 2-5 mg daily should be given to patients with renal impairment or who are receiving a diuretic ***(Rucinska, 1991; Wong et al., 1996 and Keane et al., 1997).*** The usual maintenance dose is 10- 40 mg given once and up to 40 mg daily in severe hypertension ***(Baba, 1993).***

Enalapril is excellent in treatment of all grades of essential hypertension, renovascular hypertension, congestive heart failure, myocardial infarction because it act as coronary vasodilator and increase the vasodilatory prostaglandins and increase formation of bradykinin and decrease its breakdown and thus reduce the patients mortality, and can be used as a safe drug in pediatric patients suffering from circulatory

insufficiency or arterial hypertension ***(Swedberg et al.,1992;Jugdutt et al., 1997 and Rokicki and Borowicka, 1997).***

Enalapril has many side effects such as initial hypotension, which may be severe and prolonged ***(Bittner et al., 1993).*** Headache, paraesthesia, agitation, panic, depression and insomnia appeared 4 weeks after starting of treatment ***(Ahmad, 1991 and Gavras et al., 1998).*** Severe muscle pain and weakness accompanied by morning stiffness have been reported after using the drug ***(Lau, 1993).*** Mucocutaneous reaction, photosenitivity, urticaria, skin events including facial oedma or angioedema depends on an interaction of the drug with hormones regulating vascular resistance such as the kallikrein kinin system and prostaglandin system, also nail changes and vulvovaginal pruritus ***(Heckerling, 1990 ; Yusuf et al., 1992 and Tisch and Maier, 1997).*** Some patients suffer from tachycardia, palpitation, rhythm disturbance and angina pectoris ***(Konstam, 1992 and Gavras et al., 1998).*** Nasal obstruction or mild rhinorrhea, sneezing, cough, sorethorat, bronchospasm and hoarsness of voice may appear as result of a treatment with enalapril ***(Yeo et al., 1991; Simon et al., 1992 and Frenntry,1993).*** Ileus, pancreatitis, hepatocellular or cholestatic hepatitis, jaundice, abdominal pain, dyspepsia, constipation, diarrhea, taste disturbance, anorexia, vomiting have been seen after treatment with enalapril ***(Smith et al., 1992 and Maringhini et al., 1997).*** An increase in blood urea and serum creatinine, elevations of liver enzymes and serum bilirubin, decrease in hemoglobin, neutropenia, thrombocytopenia, bone marrow depression and agranulocytosis have been reported with enalapril ***(Burnier, 1994 and Incalzi et al., 1998).***

Enalapril is contraindicated to patients who are sensitive to any component of the drug and to patient with a history of angioneurotic oedema ***(Smith et al., 1992).***

Enalapril crosses the human placenta, so it is not recommended to be used during pregnancy, if used the patient should be informed about the potential risk to the fetus such as hypotension, skull hypoplasia and renal failure when enalapril is used during the 2^{nd} and 3^{rd} trimester of pregnancy ***(The AIRE study Investigators, 1993).***

Additive effect may occur when enalapril is used with other antihypertensive therapy especially in combination with diuretics ***(Goldberg, 1993).*** The combination of enalapril with beta-adrenergic blocking agents, α methyldopa or calcium entery blockers have been shown to improve the efficacy of lowering the blood pressure ***(Bittner et al., 1993 and Chruysant et al., 1997).*** Propranolol coadministered with enalapril reduces serum enalaprilat concentration ***(Pflugfelder, 1993).*** The effect of enalapril was less favorable among the patient taking aspirin than to the patient not taking aspirin due to drug interaction between enalapril and aspirin ***(Nguyen et al., 1997).***