INTRODUCTON

Acute renal failure (ARF) is a common clinical event affecting 2-5% of hospitalized patients and up to 10-30% of those in intensive care units (ICU), depending on the population studied and the criteria used to define ***(Piccinni et al., 2004).***

Acute renal failure is characterized by a rapid decline in renal function accompanied by retention of nitrogenous waste products and electrolyte disorders, an acute and sustained increase in serum creatinine of 0.5 mg/dL (44.2 mmol/L), if the baseline is less than 2.5 mg/dL (221 mmol/L), or an increase in serum creatinine by more than 20% if the baseline is more than 2.5 mg/dL (221 mmol/L) is important laboratory sign in diagnosis of acute renal failure ***(Amy, 2008).***

Until recently, a systematic definition of acute renal failure (ARF) was lacking, which led to significant confusion both clinically and in the medical literature. In 2004, the Acute Dialysis Quality Initiative (ADQI) group published the RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease) classification of ARF, based on changes from the patient's baseline either in serum creatinine level or in glomerular filtration rate (GFR) or urine output (UO) ***(Bellomo et al., 2004)***.

Acute renal failure is similar to the acute respiratory distress syndrome (ARDS) in that it is not a primary disease, but is a complication of other disease, most notably severe sepsis and septic shock, and is often part of the multiple organ failure (MOF) syndrome. **(*Bellomo, 2005*)**

In critically ill patients, more than 90% of ARF episodes are of ischemic etiology, which is named hypoperfusion renal failure, or toxic etiology, which is named nephrotoxic renal failure or a combination of both. However, numerous other etiologies of ARF have been identified. Examples include obstruction of the urine outflow tract, acute tubulo-interstitialnephritis and acute glomerulonephritis ***(Hoste and Kellum, 2004).***

Clinical problems caused by ARF are metabolic acidosis, electrolytes disturbance from impaired renal excretion of electrolytes and hydrogen ions, and volume overload, which will need in severe cases to urgent dialysis ***(Kathleen, 2008).***

For early diagnosis of ARF, the plasma concentrations of urea, creatinine, and electrolytes should be measured on admission of all critically ill patients, and repeated daily or on alternate days, together with the inspection of daily urine output (to discover oliguria or anuria), fluid-balance charts, daily weighing, and the recording of blood pressure, these measurements will ensure that advanced acute renal failure does

not suddenly appear in patients already in hospital ***(Firth, 1998)*.**

It is important to prevent and early management of even the mildest forms of ARF. The goals of preventive strategies for ARF are to preserve renal functions, to prevent complications of ARF (volume overload, metabolic acidosis and electrolyte abnormalities) and to prevent the need for chronic dialysis. The preventive strategies have been grouped into nonpharmacological and pharmacological types **(*Venkataraman, 2005).***

Clinical advances of pharmacological therapy in the treatment of ARF have been limited. Multiple pharmacologic interventions showed promise in animal models of ARF; however, no agents have proven to be effective in the clinical setting. As a result, the management of ARF remains primarily supportive; renal replacement therapy (RRT) and its modalities serve as the cornerstone of treatment in patients who have persistent severe acute renal dysfunction ***(Palevsky, 2005).***

Intermittent hemodialysis (IHD), continuous renal replacement therapies (CRRT) and sustained low-efficiency dialysis (SLED) are the principal RRT modalities that are used in the acute setting ***(Fieghen et al., 2009).***

Although institutional policies may determine the local availability of these modalities, CRRT and SLED tend to be used in patients with greater hemodynamic instability ***(Fieghen et al., 2009).***

Intermittent hemodialysis is typically administered with conventional dialysis machinery that is used in the chronic dialysis population with session length ranging from 3 to 5 hours ***(Fieghen et al., 2009).***

Continuous renal replacement therapy is applied with an intended treatment time of 24 hours and generally requires dedicated machines that operate at comparatively lower blood and dialysate pump speeds ***(Fieghen et al., 2009).***

Continuous renal replacement therapy may be administered as hemodialysis (continuous venovenous hemodialysis, CVVHD), hemofiltration (continuous venovenous hemofiltration, CVVH) or a combination of these (continuous venovenous hemodiafiltration, CVVHDF) ***(Fieghen et al., 2009).***

Sustained low-efficiency dialysis sometimes referred to as extended dialysis, is considered a 'hybrid' of IHD and CRRT. SLED is administered using conventional dialysis technology but typical sessions run for 8–12 h using blood and dialysis flows that are intermediate to those prescribed in IHD and CRRT ***(Fieghen et al., 2009)***.

AIM OF THE WORK

The aim of this essay is to review on a serious problem which is the acute renal failure (ARF) in the intensive care units which is very common in critically ill patients. Although the condition is common in the ICU and associated with high mortality rate and is often part of multiple organ failure syndrome, we understand little about its pathogenesis and histopathology. Accordingly, accurate classification is difficult.

This essay tries to cover the most recent data on the mechanisms of acute prerenal failure and the potential interference of autoregulation of renal blood flow (RBF) by commonly used drugs. It further summarizes some basic and recent insights into the hemodynamic and cellular pathophysiologic mechanisms of mainly postischemic ARF.

How to early diagnose renal impairment clinically and laboratory by using biomarkers to detect renal injury in trying to prevent development to acute renal failure or end stage renal disease, also to avoid the serious complications of acute renal failure.

Focus on Renal Replacement Therapy (RRT), and answer the three main questions:

- When should RRT be commenced?
- What modality of RRT should be used?
- What dose of RRT should be delivered?

RENAL PHYSIOLOGY

Most people are familiar with one important function of the kidneys - to rid the body of waste materials that are either ingested or produced by metabolism. A second function that is especially critical is to control the volume and composition of the body fluids. For water and virtually all electrolytes in the body, the balance between intake (due to ingestion or metabolic production) and output (due to excretion or metabolic consumption) is maintained in large part by the kidneys. This regulatory function of the kidneys maintains the stable environment of the cells necessary for them to perform their various activities. The kidneys perform their most important functions by filtering the plasma and removing substances from the filtrate at variable rates, depending on the needs of the body. Ultimately, the kidneys clear unwanted substances from the filtrate (and therefore from the blood) by excreting them in the urine while returning substances that are needed back to the blood ***(Guyton & Hall, 2006).***

The kidneys play a dominant role in regulating the composition and volume of the extracellular fluid (ECF). They normally maintain a stable internal environment by excreting appropriate amounts of many substances in the urine. These substances include not only waste products and foreign compounds, but also many useful substances that are present in excess because of eating, drinking, or metabolism ***(Tanner, 2003).***

Physiological functions of the kidney:

First, and very importantly, the kidneys play the central role in regulating the water concentration, inorganic-ion composition, and volume of the internal environment. They do so by excreting just enough water and inorganic ions to keep the amounts of these substances in the body relatively constant.

Second, the kidneys excrete metabolic waste products into the urine as fast as they are produced. This keeps waste products, which can be toxic, from accumulating in the body. These metabolic wastes include urea from the catabolism of protein, uric acid from nucleic acids, creatinine from muscle creatine, the end products of hemoglobin breakdown (which give urine much of its color), and many others.

A third function of the kidneys is the excretion, of some foreign chemicals, such as drugs, pesticides, and food additives, and their metabolites.

A fourth function is gluconeogenesis. During prolonged fasting, the kidneys synthesize glucose from amino acids and other precursors and release it into the blood. The kidneys can supply approximately 20 percent as much glucose as the liver does at such times.

Finally, the kidneys act as endocrine glands, secreting some important hormones like erythropoietin, renin, and **1,25**-dihydroxyvitamin **D3** and Prostaglandin synthesis. Also

catabolism of polypeptide hormones (e.g., parathyroid hormone, insulin) occurs in the kidney ***(Vander et al., 2001).***

Many renal functions are shared with other organs (acid-base control with lung; blood pressure control via the renin-angiotensin-aldosterone axis with liver, lung and adrenal glands). Other functions are not routinely measured (small peptide excretion, tubular metabolism, hormonal production) in the ICU and are not considered clinically important. There are only two physiological functions that are routinely and easily measured in the ICU, which are unique to the kidney and which are considered clinically important: the production of urine and the excretion of water soluble waste products of metabolism. Thus, clinicians have focused on these two aspects of renal function to help them define the presence of acute renal failure ***(Bellomo et al., 2006).***

Renal blood supply:

Blood flow to the two kidneys is normally about 20 % of the cardiac output, or 1100 ml/min. The renal artery enters the kidney through the hilum and then branches progressively to form the interlobar arteries, arcuate arteries, interlobular arteries (also called radial arteries) and afferent arterioles, which lead to the glomerular capillaries, where large amounts of fluid and solutes (except the plasma proteins) are filtered to begin urine formation **(Figure 1)**. The distal ends of the capillaries of each glomerulus coalesce to form the efferent arteriole, which leads to a second capillary network, the peritubular capillaries, that surrounds the renal tubules. The renal circulation is unique in that it has two capillary beds, the glomerular and peritubular

capillaries, which are arranged in series and separated by the efferent arterioles, which help regulate the hydrostatic pressure in both sets of capillaries. High hydrostatic pressure in the glomerular capillaries (about 60 mm Hg) causes rapid fluid filtration, whereas a glomerular filtration, tubular reabsorption, or both in response to body homeostatic demands. The peritubular capillaries empty into the vessels of the venous system, which run parallel to the arteriolar vessels and progressively form the interlobular vein, arcuate vein, interlobar vein, and renal vein, which leaves the kidney beside the renal artery and ureter ***(Guyton & Hall, 2006)***.

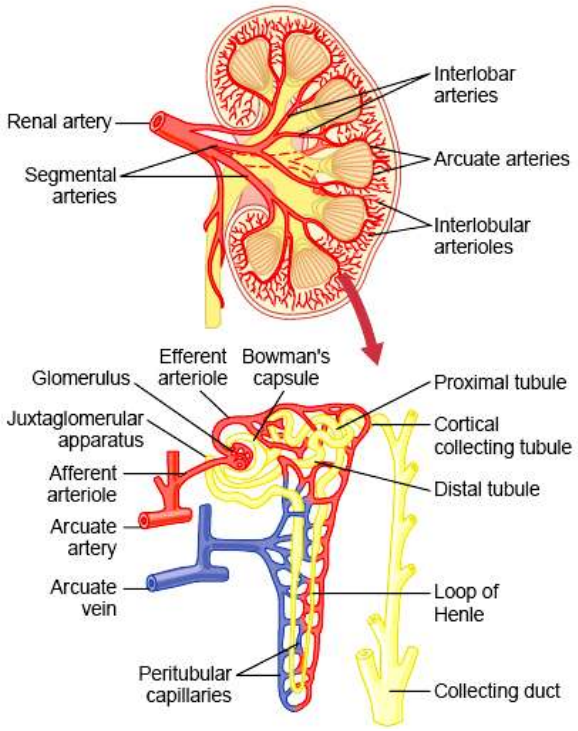

Figure (1): Section of the human kidney showing the major vessels that supply the blood flow to the kidney and schematic of the microcirculation of each nephron ***(Guyton & Hall, 2006).***

Effects of Renal Circulation on Urine Production

The renal circulation affects urine formation in the following ways:

1- The glomerular filtration rate is an important determinant of solute and water excretion.

2- The peritubular capillaries in the cortex return reabsorbed solutes and water to the systemic circulation and can modulate the degree of proximal tubular reabsorption and secretion.

3- The vasa recta capillaries return reabsorbed salt and water to the systemic circulation and participate in the counter-current mechanism.

Abnormalities of renal haemodynamics may be involved in the genesis of acute renal failure, associated with a reduction in total renal blood flow and with the redistribution of intrarenal blood flow away from cortical to juxtamedullary nephrons in order to protect the medulla ***(Banerjee, 2005).***

Autoregulation

The renal circulation is subject to autoregulation by the following mechanisms:

1- A myogenic response, with arteriolar smooth muscle contraction in response to increased vessel wall tension.

2-The intranephron tubuloglomerular feedback system, which describes the coupling of distal nephron flow with single nephron glomerular filtration rate.

(Banerjee, 2005)

Humoral Influences on the Renal Vasculature

Vasoconstrictors:

1) Angiotensin II.

2) Noradrenaline.

3) Thromboxane A2, B2.

4) Leukotrienes D4, C4.

5) Platelet-activating factor.

6) Endothelin-1.

7) Vasopressin**.**

Vasodilators:

1) Prostaglandins E_1, E_2, I_2.

2) Acetylcholine.

3) Bradykinin.

4) Nitric oxide.

5) Atrial natriuretic peptide (ANP).

(Banerjee, 2005)

The nephron is the basic unit of renal structure and function:

Each human kidney contains about one million nephrons **(Figure 2)**, which consist of a renal corpuscle and a renal tubule. The renal corpuscle consists of a tuft of capillaries, the glomerulus, surrounded by Bowman's capsule. The renal tubule is divided into several segments. The part of the tubule nearest the glomerulus is the proximal tubule. This is subdivided into a proximal convoluted tubule and proximal straight tubule. The straight portion heads toward the medulla, away from the surface of the kidney. The loop of Henle includes the proximal straight tubule, thin limb, and thick ascending limb. The next segment, the short distal convoluted tubule, is connected to the collecting duct system by connecting tubules. Several nephrons drain into a cortical collecting duct, which passes into an outer medullary collecting duct. In the inner medulla, inner medullary collecting ducts unite to form large papillary ducts. The collecting ducts perform the same types of functions as the renal tubules, so they are often considered to be part of the nephron. The collecting ducts and nephrons differ, however, in embryological origin, and because the collecting ducts form a branching system, there are many more nephrons than collecting ducts. The entire renal tubule and collecting duct system consists of a single layer of epithelial cells surrounding fluid (urine) in the tubule or duct lumen. Cells in each segment

have a characteristic histological appearance. Each segment has unique transport properties ***(Tanner, 2003).***

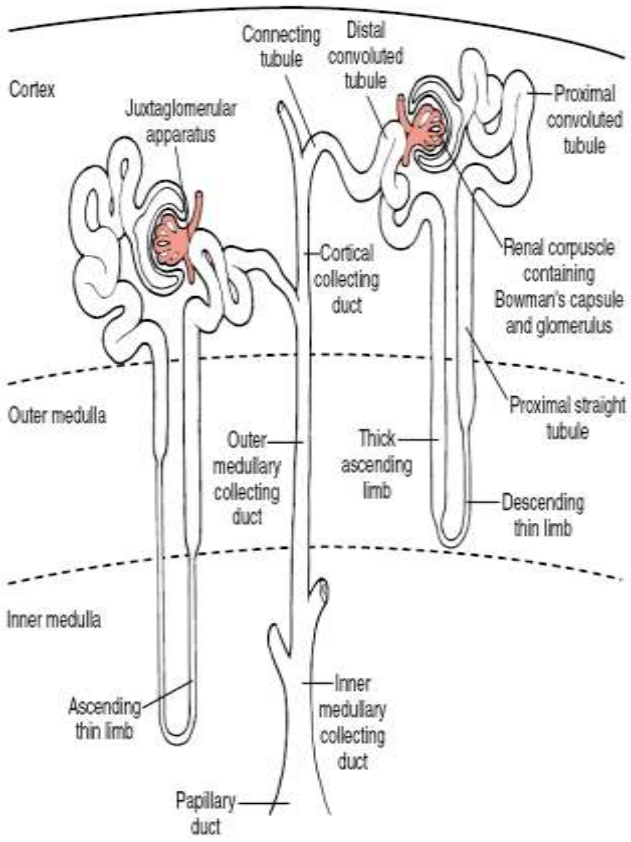

Figure (2): Components of the nephron and the collecting duct system. On the left is a longlooped juxtamedullary nephron; on the right is a superficial cortical nephron ***(Tanner, 2003)***

Three groups of nephrons are distinguished, based on the location of their glomeruli in the cortex: superficial, midcortical, and juxtamedullary nephrons. The juxtamedullary nephrons, whose glomeruli lie in the cortex next to the medulla, comprise about one-eighth of the nephron population. They differ in several ways from the other nephron types: they have a

longer loop of Henle, longer thin limb (both descending and ascending portions), larger glomerulus, lower renin content, different tubular permeability and transport properties, and a different type of postglomerular blood supply ***(Tanner, 2003).***

One additional anatomical detail involving both the tubule and the arterioles must be mentioned. Near its end, the ascending limb of each loop of Henle passes between the afferent and efferent arterioles of that loop's own nephron **(Figure 3)**. At this point there is a patch of cells in the wall of the ascending limb called the macula densa, and the wall of the afferent arteriole contains secretory cells known as juxtaglomerular (JG) cells. The combination of macula densa and juxtaglomerular cells is known as the juxtaglomerular apparatus (JGA) **(Figure 4)**. The juxtaglomerular cells secrete the hormone renin ***(Vander et al., 2001).***

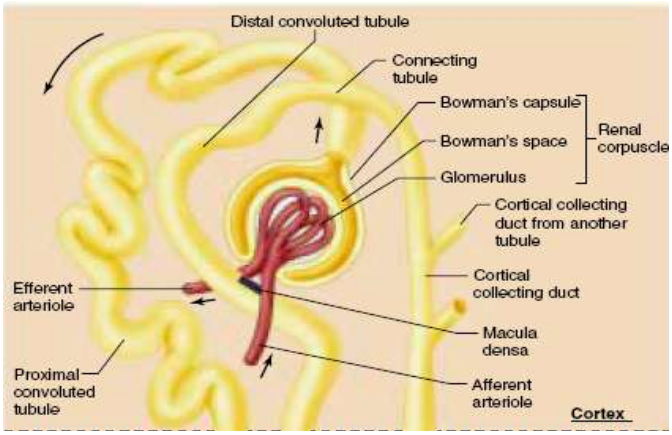

Figure (3): The macula densa is not a distinct segment but a plaque of cells in the ascending loop of Henle where the loop passes between the arterioles supplying its renal corpuscle of origin. The outer area of the kidney is called the cortex and the inner the medulla. The black arrows indicate the direction of urine flow ***(Vander et al., 2001).***

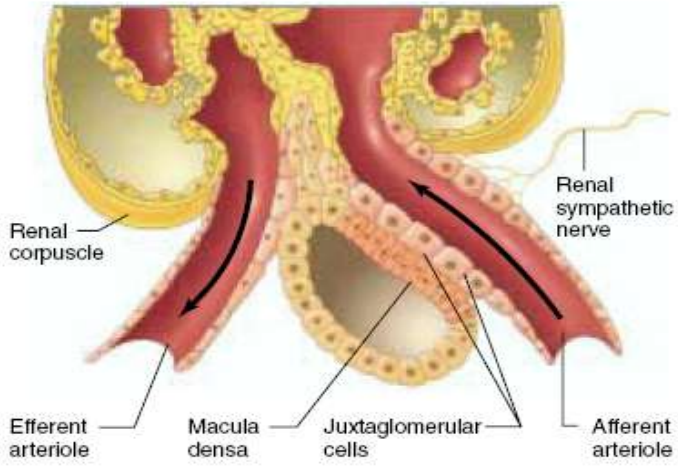

Figure (4): Anatomy of the juxtaglomerular apparatus ***(Vander et al., 2001).***

A- Glomerular filteration: renal solute excretion "the first step in urine formation"

Renal solute excretion is the result of glomerular filtration and the glomerular filtration rate (GFR) is a convenient and time-honoured way of quantifying renal function. However, GFR varies as a function of normal physiology as well as disease. For example, subjects on a vegetarian diet may have a GFR of 45–50 ml/min, while subject on a large animal protein intake may have a GFR of 140–150 ml/min, both with the same normal renal mass ***(Bellomo et al., 2006).***

Glomerular filtration involves the ultrafiltration of plasma. This term reflects the fact that the glomerular filtration barrier is an extremely fine molecular sieve that allows the filtration of small molecules but restricts the passage of macromolecules (e.g., the plasma proteins) ***(Tanner, 2003).***