INTRODUCTION

The adrenal gland is important for the body homeostasis. It secrets amine hormones, adrenaline and noradrenaline, by its medulla which are essential part of the bodies primeval (fight or flight) stress response. It also secrets mineralocorticoids, aldosterone, glucocorticoids, cortisol, and androgens by its cortex which are important in regulating blood volume, immunological and inflammatory processes and proteins anabolism and growth ***(Ganong, 2009).***

Adrenal insufficiency was first identified by Thomas Addison in 1855. It maybe caused by an autoimmune process, infection or surgery. Addison's disease is not usually apparent until over 90% of the adrenal cortex has been destroyed, so that very little adrenal capacity is left. The incidence of adrenal dysfunction in critically ill range from 30-50% with varied population sizes ***(Cohen, 2010).***

Patients with adrenal insufficiency or presenting in crisis require certain considerations for anesthetic management including dehydration and hypovolemia, resulting in hypotension, poor tissue perfusion, metabolic acidemia, and electrolyte changes. If glucocorticoid deficiency is also present, the patient is unlikely to mount a stress response and may not respond to supportive cardiovascular interventions (eg, inotropes) ***(Khursheed, 2012).***

Adrenal insufficiency can be primary or secondary. Addison's disease, the common term for primary adrenal insufficiency, occurs when the adrenal glands are damaged and cannot produce enough of the adrenal hormone cortisol. The adrenal hormone aldosterone may also be lacking. Secondary adrenal insufficiency occurs when the pituitary gland fails to produce enough adrenocorticotropin (ACTH). If ACTH output is too low, cortisol production drops. Eventually, the adrenal glands can shrink due to lack of ACTH stimulation. Secondary adrenal insufficiency is much more common than Addison's disease ***(Betterle, 2011).***

There are several studies documenting increased survival rates in critically ill vasopressordependent septic patients who receive steroids after bouts of refractory hypotension. Steroid doses used in this case should be at physiologic or replacement doses. These are subsequently less than those used for anti-inflammatory or immunosuppressive effects. Hydrocortisone is used in human medicine most frequently ***(Peyton, 2009).***

In the absence of bilateral adrenal hemorrhage, the survival rate of patients with acute adrenal crisis that is diagnosed promptly and treated appropriately approaches that of patients without acute adrenal crisis with similar severity of illness. Patients who developed bilateral adrenal hemorrhage before the availability of hormonal testing or computed

tomography (CT) scanning rarely survived. In one series, patients who were diagnosed using CT scanning had an 85% rate of survival. Because the true incidence of adrenal crisis and bilateral adrenal hemorrhage are unknown, the actual mortality rate also is unknown ***(Lisa, 2014).***

AIM OF THE WORK

This study aims to highlight the clinical implications of adrenal insufficiency, the anaesthetic considerations and post operative ICU management of patients with adrenal insufficiency or adrenal crisis.

Chapter 1
ANATOMY AND PHYSIOLOGY OF ADRENAL GLAND

Anatomy of Adrenal Gland

The adrenal glands also called "suprarenal glands" are present in the abdomen on top of the kidneys and below the diaphragm. They are yellowish in colour due to their high cholesterol content. They are covered by the same membrane that cover the kidneys but are separated from the kidneys by fibrous tissue. Each gland weighs about 5 grams and measures 50 mm vertically, 30 mm horizontally, and 10 mm thick ***(Melmed et al., 2011).***

A cut section in the adrenal gland shows that it is formed of outer yellowish cortex and inner dark red to grey medulla. The cortex is formed of three different zones: zona glumerulosa, zona fasiculata and zona reticularis. Each zone has specific histology and physiology. Zona glumerulosa secrets mineralocorticoids which are responsible for control of salt and water in the body. Zona fasiculata secrets glucocorticoids which is responsible for metabolism regulation in the body. Zona reticularis secrets sex hormones that has a major role in developing sexual characters. Each layer of the three layers has cells called chromaffin cells which have an

unknown function but are thought to be regulating the adrenal function ***(Moore et al., 2013).***

Blood Supply:

Arterial Blood Supply: The adrenal glands are one of the extensively vascularized organs in the body (Figure 1). They receive three sources of arteries to maintain the blood supply:

a) **Superior suprarenal arteries:** are multiple small branches from the inferior phrenic artery

b) **Middle suprarenal artery:** is a direct branch from the abdominal aorta.

c) **Inferior suprarenal artery:** arises from the renal artery on each side.

Venous Drainage: The blood drains through the suprarenal vein to the left renal vein or directly to the inferior vena cava on the right side ***(Sapru et al., 2007).***

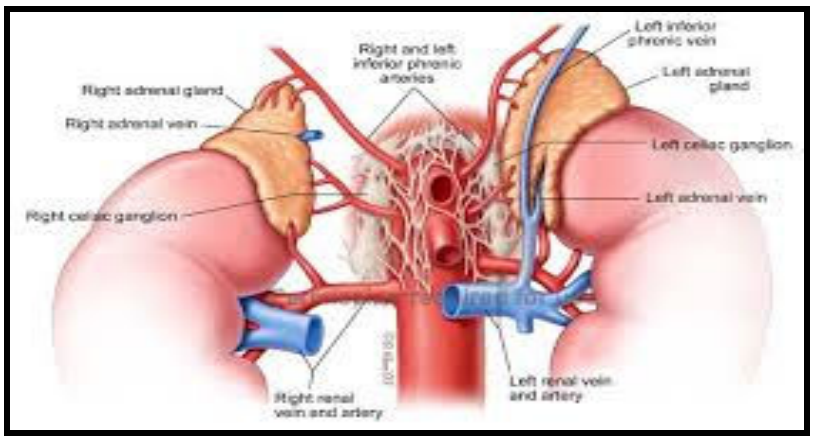

Figure (1): Blood supply of adrenal glands ***(Marieb et al., 2013).***

Lymphatic Drainage:

Lymph drainage is to the lumbar lymph nodes by adrenal lymphatic vessels. These vessels originate from two lymphatic plexuses, one deep to the capsule, and the other in the medulla ***(Skandalakis et al., 2008).***

Nerve Supply:

The adrenal glands are innervated by the celiac plexus and abdominopelvic splanchnic nerves. Sympathetic innervation to the adrenal medulla is via myelinated presynaptic fibers, mainly from the T10 to L1 spinal cord segments ***(Skandalakis et al., 2008).***

Physiology of Adrenal Gland

Introduction:

The adrenal gland secretes multiple types of hormones from its different parts, adrenal cortex and adrenal medulla. The adrenal cortex can be further divided into three layers, zona glumerulosa which is near the surface and secrets the main mineralocorticoids in the body 'Aldosterone', zona fasiculata in midcortex that secrets the main glucocorticoids in the body 'Cortisol' and zona reticularis near corticomedullary junction that secrets sex hormones ***(Funder et al., 2012).***

Both cortisol and aldosterone are derived from cholesterol by multi enzymatic activity and both hormones are

structurally quite similar. However, both hormones are functionally totally different from each other. Cortisol is considered a glucocorticoid because it was noticed early in case of increase blood glucose. Aldosterone is considered a minerlaocorticoids because it controls salt and water retention. The activities of these hormones can overlap especially in high hormonal levels ***(Smith et al., 2012).***

There's only a small difference between the cortisol and aldosterone structurally. Aldosterone has an aldehyde group at position 18 instead of OH group in position 17 that present in cortisol. In spite of this minor chemical different, aldosterone has no glucocorticoid activity at physiological concentration ***(Gordon et al., 2012).***

Adrenal cortex also secrets androgenic steroids, which is considered a byproduct of cortisol. While the chromaffin cells located in the adrenal medulla secrets adrenaline mainly and to a lesser extent its precursor noradrenaline ***(Burnstein et al., 2012).***

The Adrenal Cortex

Cortisol:

Synthesis:

Synthesis of cortisol and steroid hormones starts with the cholesterol (Figure 1-2). The adrenal gland has two sources of cholesterol, circulating LDL the main source and synthesis of cholesterol de novo from the amino acid acetate. Synthesis of

cortisol and aldosterone in adrenal gland is though metabolism of cholesterol by a series of five reactions. The enzymes responsible for these reactions belong to cytochrome P450 family that present in mitochondria and smooth endoplasmic reticulum with exception for 3B hydroxysteroid dehydrogenase ***(Smith et al., 2012).***

The steps of hormonal synthesis in the adrenal gland can be described in detail by the following diagram:

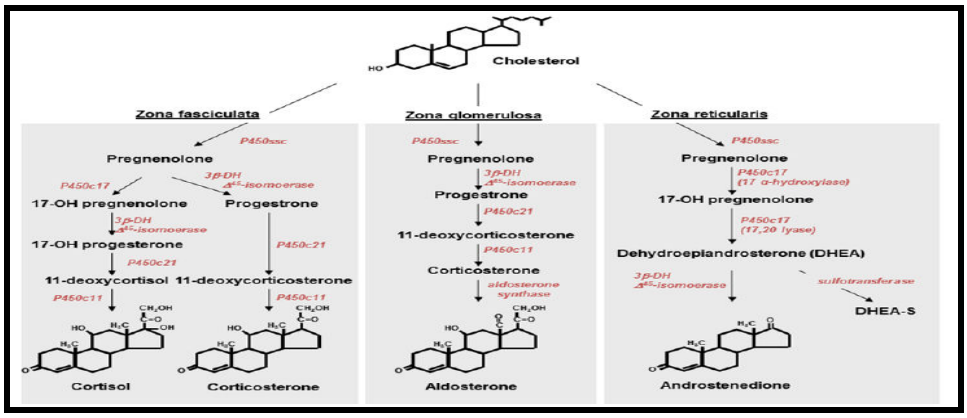

Figure (2): Synthesis of adrenal hormones ***(Henrik Ortsateret al., 2012).***

Cortisol has no storage area. After synthesis, the cortisol diffuses to circulation at which 90% is transported bound to corticosteroid-binding globulin (also known as transcortin) which is synthesized in the liver. Clearance of cortisol from the body is dependant on liver and kidney. Liver and kidney degrade cortisol by formation of inactive cortisone metabolite by 11B hydroxysteroid dehydrogenase (11B HSD). This enzyme has two isozymes, one of the two isozymes of 11B

HSD present in high concentrations of the target tissues of cortisol including liver and adipose tissues. This isozyme can act reversibly by activating the external cortisone drugs. The other isozyme of 11B HSD present in renal distal tubules and collecting ducts. This isozyme act irreversibly on cortisol to form inactive cortisone ***(Young et al., 2012).***

Mechanism of action:

The multiple hydroxylation reactions that convert cholesterol into cortisol changes cortisol to hydrophilic plasma soluble compound. Yet, lipophilic enough to cross cell membrane of target tissues without a need to transporter. Cortisol perform action by binding to intracellular receptor. Generally, all nucleated cells have cortisol receptors. After binding to cortisol receptor that present in the cytoplasm, the cortisol-receptor complex moves to the inside of the nucleus where it perform its action ***(Gordon et al., 2012).***

Action:

Steroid hormones are divided into three major groups according to their action: glucocorticoids, mineralocorticoids and sex steroids. Cortisol is the naturally occurring glucocorticoids. The main action of glucocorticoids is to raise the blood glucose level. It's ability to increase the blood glucose is related to its ability to mobilize the amino acids from tissues into the liver and to enhance the liver to convert these amino

acids into glucose and glycogen by gluconeogenesis. The main target tissues to be affected by cortisol are the glucose regulatory tissues, the liver, fat and muscles. They have an effect on protein and fat metabolism. It also affects bone, skin, viscera and central nervous system. Cortisol also affect bone by decreasing calcium absorption from the GIT. It decreases the ability of osteoblast to synthesize new bone of trabecular bone. Cortisol has a behavioral effect on the CNS and causes alteration of mood and cognition. It has potent immunosuppressive and anti-inflammatory activity. Cortisol allow movement of neutrophils from the bone marrow into circulation and decrease the number of lymphocytes partly by sequestration on the reticulo-endothelial system ***(Turnbull et al., 2012).***

Control:

Cortisol synthesis and secretion is under control of hypothalamus by corticotrophin releasing hormone (CRH) either as a part of normal secretion related to the circadian rhythm or centrally as a part of stress response. CRH stimulates ACTH secretion from the anterior pituitary which in turn stimulate synthesis and release of cortisol. Circulating cortisol perform negative feedback on both CRH and ACTH. Although CRH is main controller of ACTH secretion, argenine vasopressin secreted by hypothalamus has a physiological role also in control of ACTH secretion ***(Autelitano et al., 2012).***

The CNS control of cortisol secretion by the circadian rhythm receives its information from the retina and is located above the optic chiasma. Indeed, blind people loses their circadian rhythm. The secretion of CRH is pulsatile and so is the ACTH secretion. The secretion is increased in the early morning and diminish in the afternoon. The pulsatile mechanism of secretion is yet not completely understood. Due to the longer half-life of cortisol than ACTH, the period of pulsatile change is longer and the magnitude is more dumped than that of ACTH.Other way of CNS control of cortisol secretion is the increased secretion in case of physical, psychological and biochemical stress. Hypoglycemia is an example of biochemical stress and causes increase CRH and ACTH which in turn increases blood glucose ***(Gordon et al., 2012).***

Aldosterone:

Synthesis:

Aldosterone controls the salt and water retention from the renal glomerulus. This allows aldosterone to control the volume of the extra cellular fluid and so, control the arterial blood pressure.

Synthesis of aldosterone had been described in the previous diagram (Figure 2). As with cortisol, there is no storage area for aldosterone after synthesis. So, rate of secretion of aldosterone is dependent on rate of synthesis. Aldosterone secretion is stimulated by increase extra cellular K, angiotensin

2 and ACTH "minimal role". These stimulants control the secretion of aldosterone by controlling the rate limiting step in cascade of synthesis "cytochrome P450 SCC enzyme". Once secreted, 37% of aldosterone remains free in plasma while 63% of aldosterone is bounded to plasma proteins mainly albumin ***(Weitzman et al., 2012).***

Action:

The major action of aldosterone is Na and water retention and K excretion from the distal convoluted renal tubules. Aldosterone has the same action of salt and water retention in salivary gland, sweat gland and colon. Aldosterone increases transcription of Na-K pump, thus augmenting Na reabsorption. The net effect is increased Na reabsorption and K secretion as a secondary effect. Loss of aldosterone regulation of Na reabsorption can lead to major electrolyte disaster in the body including fatal hyperkalemia and hypotension if associated with other compensatory mechanism failure ***(Young et al., 2012).***

Control:

Three known secretagogues for aldosterone are angiotensin 2 through the renin angiotensin cascade, hyperkalemia which is a powerful stimulant and finally and least effective ACTH. Aldosterone has a negative feedback mechanism for controlling renin angiotensin system indirectly

by decreasing plasma K and increasing extra cellular volume ***(Walter et al., 2012).***

Adrenal Medulla

The cells of adrenal medulla are termed chromaffin cells because they contain catecholamines that contains large amount of chromium stain. Chromaffin cells are developed from the neural crest and migrated to the centre of the adrenal cortex which is developed from mesoderm. The Chromaffin cells synthesize and secrets epinephrine and to a lesser extent norepinephrine. They enter the circulation and migrate to act on distal tissues like other hormones. Chromaffin cells are similar to the postganglionic neurons of sympathetic nervous system structurally and functionally. The preganglionic fibers of splanchnic area secrets acetyl choline which is the principle regulator of the adrenal hormones ***(Funder et al., 2012).***

Chromaffin cells of the adrenal medulla has the unique enzymes that allows it to synthesize epinephrine in the body. Norepinephrine present in many other somatic tissues in amounts close to their sympathetic innervation. In other word, norepinephrine can be found in other tissues derived from their sympathetic supply unlike epinephrine, the unique product of the adrenal medulla ***(Fitzsimons et al., 2012).***

Synthesis:

The following figure describes how the medullary hormones are synthesized (Figure 3):

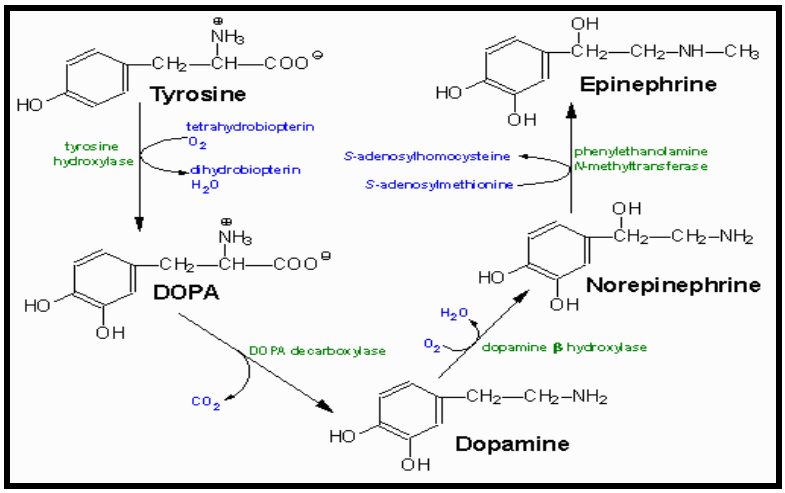

Figure (3): Medullary hormones synthesis ***(Aschenbrenner et al., 2011).***

The catecholamines action is so brief that it doesn't exceed 10 seconds in case of epinephrine. Catecholamine are degraded by the action of Catecholamine-O-methyltransferase (COMT) that present in high concentrations in the endothelium of heart, kidneys and the liver. COMT converts epinephrine and norepinephrine into metanephrine and normetanephrine that are converted by the action of monoamine oxidase into vanillylmandelic acid (VMA). The liver and the gut conjugate these compounds to sulfate and glucuronide to be excreted by the kidney. Measurement of concentrations of catecholamines, metanephrine and VMA in urine can provide an idea about the function of adrenal medulla and sympathetic system ***(Smith et al., 2012).***