

RENAL AND SYSTEMIC HAEMODYNAMICS IN PATIENTS
WITH LIVER CIRRHOSIS AND/OR FIBROSIS WITH
AND WITHOUT HEPATORENAL SYNDROME

Thesis

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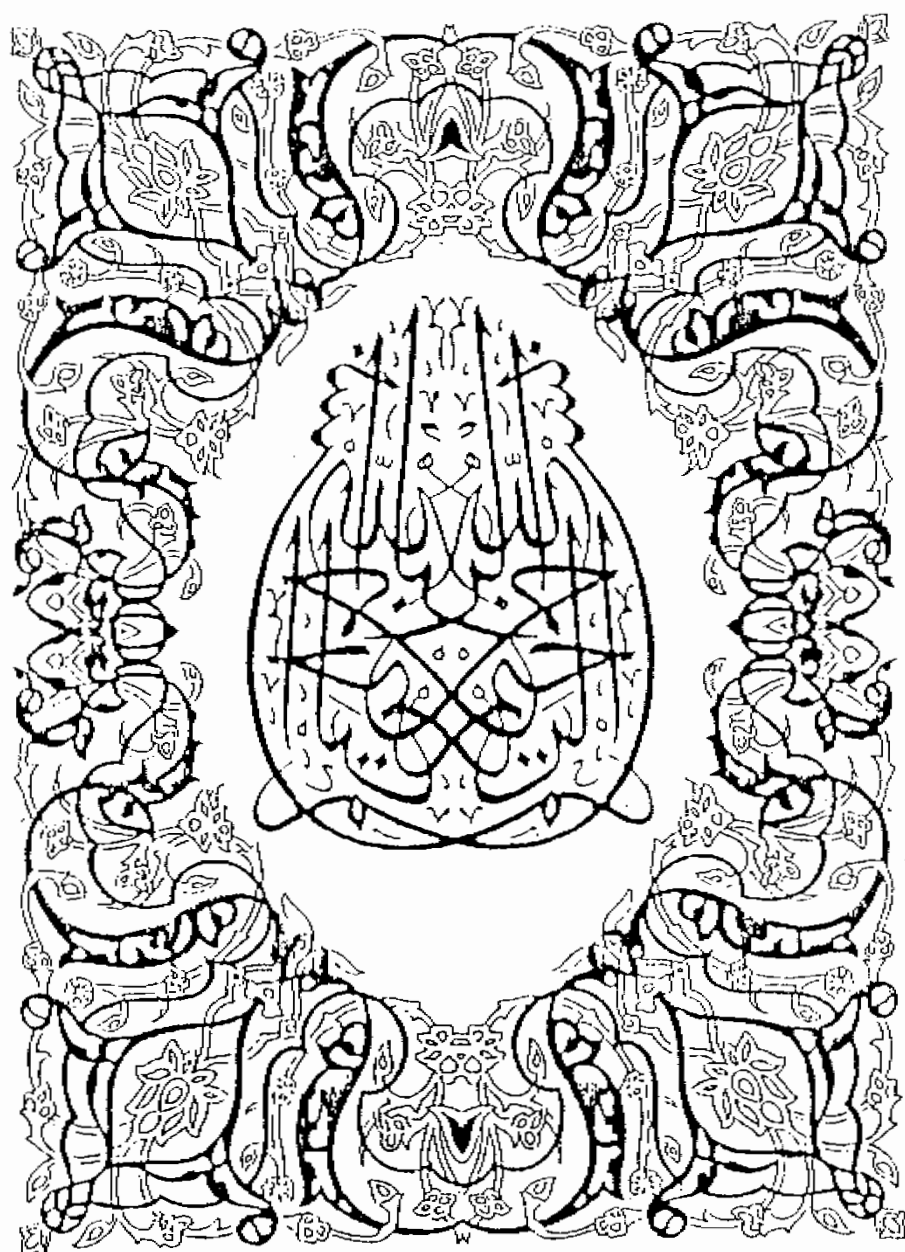
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INTRODUCTION AND AIM OF WORK

INTRODUCTION

Hepatorenal syndrome is defined as functional renal failure in a patient with chronic liver disease (*Sherlock, 1993*). In most instances the uraemia and oliguria arise either spontaneously or in response to changes in blood volume or shifts of fluid within body compartments. The histology of the kidney is virtually normal and the failure is functional one (*Coratelli et al., 1987*).

The aetiology of hepatorenal syndrome is still incompletely understood. To date, most emphasis has center on the hypothesis that it is caused by severe renal arterial vasoconstriction causing reduced renal blood flow and then renal failure (*Moore et al., 1990*).

Renal blood flow is dependent on renal vascular resistance and renal perfusion pressure which is the mean arterial pressure minus the renal venous pressure. In hepatorenal syndrome patients there is a significant fall in the renal blood flow with marked decrease in renal perfusion (*Wilkinson et al., 1991*).

The fall in renal blood flow is due to redistribution of the intravascular volume where systemic vasodilatation is the initiating factor activating homeostatic mechanisms causing rise in plasma renin, aldosterone, noradrenaline and vasopressin concentrations which cause sodium retention and renal vasoconstriction (*Wilkinson, 1982*).

AIM OF THE WORK

The work aims of fulfill two goals:

- 1- Clarification of renal, splanchnic and systemic haemodynamic changes in patients with hepatic cirrhosis and fibrosis with and without hepatorenal syndrome.
- 2- Evaluating the different diagnostic criteria of hepatorenal syndrome and correlating them with haemodynamic alterations.

PATIENTS AND METHODS:

30 patients will be chosen and classified into the following groups:

G 1: Ten patients with proved early cirrhosis or fibrosis without ascites.

G2: Ten patients with proved cirrhosis or fibroses and ascites but without hepatorenal syndrome .

G3: Ten patients with hepatorenal syndrome fulfilling the following criteria:

- a) Plasma creatinine > 1.5 mg/dl.
- b) Urine to plasma creatinine ratio > 30 .
- c) Urine Na conc. < 10 mEq/lit.
- d) No response to approiate diuresis.

G4: Ten normal patients will be included as controls.

All patients will be subjected to.

- 1- Detailed history taking including drug history (salicylates, non steroidal anti inflammatory drugs, gentamycin and diuretics).
- 2- Thorough physical examination.
- 3- The following investigations.
 - a- Urine analysis: concerning protein assessment, urinary sodium and creatinine and microscopic examination.
 - b- Stool examination.

c- Blood picture and ESR.

d- Liver function tests:

Serum bilirubin.

Serum albumin.

SGPT and SGOT.

Alkaline phosphatase.

Prothrombin time.

e- Renal functions:

Serum urea and creatinine.

f- Serum electrolytes: Sodium and potassium.

g- Ascitic fluid studies: Total proteins, leucocytic count and cytology.

h- Hepatitis markers.

i- Liver biopsy.

j- Abdominal ultrasonography.

k- Doppler (duplex) for assessment of:

1- Renal arterial blood flow waves in the main, interlobar and arcuate branches with calculation of pulsatility and resistive indices.

The resistive index (RI) = $\left[\frac{\text{Peak systolic velocity} - \text{Minimum diastolic velocity}}{\text{Peak systolic velocity}} \right]$.

The pulsatility index (PI) = $\left[\frac{\text{Peak systolic velocity} - \text{Minimum diastolic velocity}}{\text{Mean velocity}} \right]$

2- Femoral arterial flow velocity after angle correction with calculation of femoral blood flow volume.

3- Splenic and superior mesenteric arterial blood velocity and volume representing the splanchnic circulation.

REVIEW OF LITERATURE

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THE RENAL CIRCULATION

Blood supply of the kidney: Fig (1 a,b).

The kidney is supplied by the **renal artery**, which arises bilaterally from the sides of abdominal aorta, at the level of the 1st or 2nd lumbar vertebra. Both arteries are frontally covered by the corresponding veins. The right renal artery has an average length of 4.5 cm., and the left artery 4cm. The average diameter on the right 0.53 cm, on the left 0.55 cm. (*Graves, 1971*).

The renal artery enters the kidney at the hilum, then divides into 2 main branches, anterior and posterior. **The anterior main branch** further divides into four segmental arteries, which supply the apex of the kidney, the upper and middle segments of the anterior surface and the entire lower pole, respectively. **The posterior main branch** supplies the remainder of the kidney. These segmental arteries are "end arteries". Where obstruction of an arterial vessel leads to complete ischemia in the tissue of its area of distribution (*Graves, 1971*).

The segmental arteries extend into the kidney and become the interlobar arteries as they course in the columns of Bertini along the sides of pyramids. The interlobar arteries give off small branches to the calyces, renal pelvis before they run toward the cortex. At the junction between the cortex and medulla (base of pyramids) diversion takes place. The vessels running at right angles to the surface, turn, so that the further course runs parallel to the surface (arcuate arteries). From the arcuate arteries the interlobular arteries branch more or less sharply and extend toward the kidney surface. Afferent arterioles leading to glomeruli arise from the smaller branches of interlobular arteries. The capillary network of each glomerulus is connected to the

postglomerular (peritubular) capillary circulation by way of efferent arterioles (*Fourman and Moffat, 1971*).

Venous connections between peritubular capillaries and veins are made at every cortical level. The region near the kidney surface is drained by superficial veins. These lie within the cortex and may run parallel to the capsule before descending along the interlobular axes. Interlobular veins, close to the corresponding arteries, drain the bulk of the cortex. As these converge they are joined by vessels from the medullary rays and veins returning from the medulla in vascular bundles. Unlike the arterial system, which have no collateral pathways, the venous vessels anastomose at several levels. Convergence at the arcuate and interlobar veins give rise to several main trunks that join to form the renal vein. The large veins of the renal hilus have no clear segmental organization and because of the earlier anastomoses obstruction of one large venous channel usually leads to diversion of blood flow to the others (*Tisher and Madson, 1991*).

PHYSIOLOGY OF THE RENAL CIRCULATION

Total renal blood flow:

Under resting conditions, or in the recumbent position, and with normal mean arterial blood pressure, about 20 per cent of the cardiac output, or about 1200ml. of blood per minute passes through both human kidneys. This rate exceeds by three to five folds the flow in such metabolically active organs as the heart, liver and brain. Renal blood flow in women is slightly lower than in men, even when normalized to body surface area (*Altman and Dittmer, 1971*).

From this enormous blood flow (about 1 liter per minute) only a small quantity of urine is formed (about 1 ml per minute). Although, the metabolic

energy requirement of urine production is great, about 10 per cent of basal oxygen consumption. The O₂ consumption of the kidney is about (18-21) ml/m. (*Dworkin and Brenner, 1991*).

Intrarenal blood flow distribution:

It has been recognized that, the perfusion rate in different regions of the kidney is not uniform, especially after trauma, or hemorrhage (*Barger and Herd, 1973*).

Cortical blood flow :

In general, blood flow per gram of tissue declines progressively from outer to inner cortex. The outer cortical flow reaches 5 to 6 ml/gm., thus it is about twice that of the inner cortex (*Chenitz et al., 1976*).

Medullary blood flow:

The entire blood supply of the medulla is derived from efferent vessels of inner cortical glomeruli. The medullary blood flow constitutes about 10 to 15 per cent of total renal blood flow. The outer medullary flow is estimated to be 1 to 2 ml/min/gm of kidney weight, whereas inner medullary flow ranges between 0.1 and 0.5 ml/min/gm. Although these medullary blood flow rates are less than one fourth as high as cortical flow rates, medullary flow is still very substantial. The outer medullary flow exceeds that of liver and inner medullary flow is comparable to that of resting muscle or brain (*Aukland, 1976*).

Regulation of Renal Circulation

Renal vasoconstriction:

The sympathetic nervous system plays an important role in the control of arterial blood pressure (*Folkow et al., 1983*). Thus, a drop in arterial blood pressure will increase sympathetic nervous activity (*DiBona, 1982*). Volume depletion is another powerful stimulus for enhanced sympathetic nervous activity (*Better and Scherier, 1983*). As a result of decrease arterial flow to the kidney, more renin is secreted. Angiotensin II is then formed within the kidney and "shunts down" the renal circulation because of its vasoconstrictive action (*Brown et al., 1970*). Activation of the renin, angiotensin aldosterone system following a decrease in effective plasma volume, has been considered an important factor in inducing sodium retention and hepatorenal syndrome, as it can induce active vasoconstriction of renal blood vessels (*Grentilini et al., 1984*).

Stimulation of the renal nerves causes a marked decrease in renal blood flow. This effect is mediated by $\alpha 1$ -adrenergic receptors and to a lesser extent by post synaptic $\alpha 2$ -adrenergic receptors. Similar renal vasoconstriction can be produced by stimulating the vasomotor center in the medulla, parts of the brain stem, and the cerebellar cortex, especially the anterior tip of the temporal lobe. There is some tonic discharge in the renal nerves at rest. When systemic blood pressure falls, the vasoconstriction response produced by decreased discharge in the baroreceptor nerves includes renal vasoconstriction (*Ganong, 1991*).

Hypoxia is another stimulus to renal vasoconstriction but only when the arterial O_2 content falls to less than 50% of normal. The response is mediated via the chemoreceptors, which stimulate the vasomotor center to produce renal

vasoconstriction when the renal nerves are intact. However, in the range of decreasing arterial oxygen saturation between 100 and about 50%, there seems to be no change in renal blood flow (*Laiken and Fanestil, 1985*).

Catecholamines constrict the renal vessels. Small doses of epinephrine and norepinephrine have a greater effect on the efferent than on the afferent arterioles, so that glomerular capillary pressure and consequently, the glomerular filtration rate are maintained while renal blood flow is decreased; large doses depress the glomerular filtration rate (*Gorgas, 1978*).

Renal vasodilatation:

Various prostaglandins are synthesized by renal cells. Although some e.g., thromboxane A₂ and prostaglandin F₂ are vasoconstrictors, most prostaglandins are vasodilators. Stimuli which increase renal prostaglandins synthesis are: angiotensin II, adrenoreceptor stimulation, renal ischemia and bradykinin (*Kaplan, 1982*).

Prostaglandins synthesized in the walls of the major resistance vessels relax vascular smooth muscle and oppose hormonal and neural-induced vasoconstriction; in their absence vasoconstriction would be augmented and hypertension sustained. Intrarenal prostaglandins attenuate the renal response to various vasoconstrictor stimuli, including angiotensin, norepinephrine and renal nerve stimulation. When these and other stimuli induce renal ischemia, intrarenal prostaglandin synthesis immediately increases and buffers the vasoconstriction (*De Wardener, 1985*). Prostaglandins increase blood flow in the cortex and decrease blood flow in the renal medulla (*Ganong, 1991*).

In the presence of inhibitors of prostaglandin synthesis such as indomethacin, a greater fall in renal blood flow and increase in renal vascular