PLASMA CATECHOLAMINES AND CHANGES IN BLOOD PRESSURE IN PATIENTS WITH LIVER CIRRHOSIS

THESIS

Submitted in partial fulfilment for the Master Degree in General Medicine

Submitted by

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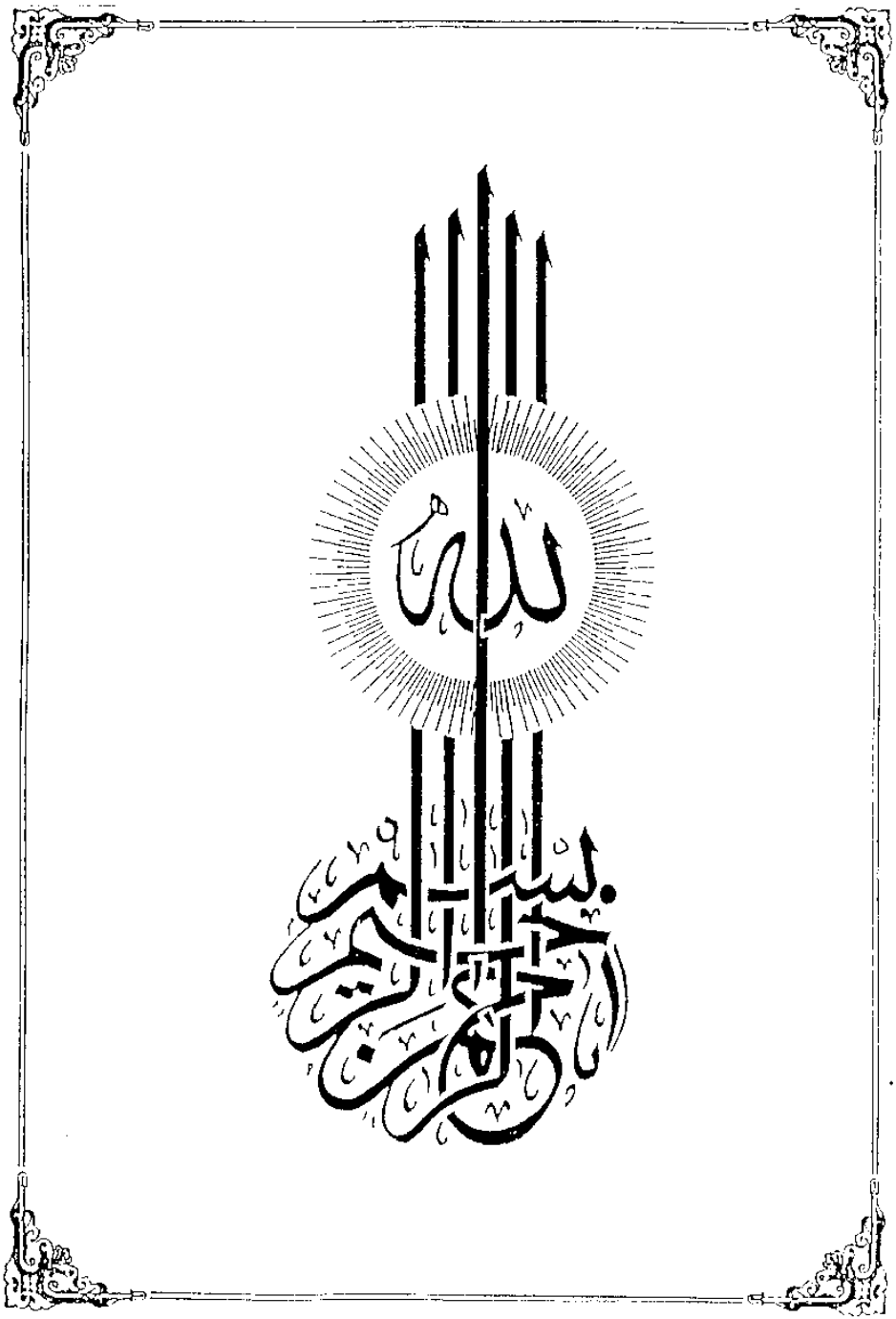
C O N T E N T S



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AIM OF THE WORK

The present subject submitted in a form of a thesis for the award of the Master Degree, explore the study of the correlation of the plasma catecholamines and any change in the arterial blood pressure in patients with liver cirrhosis (Bilharzial fibrosis of the liver) with and without ascites.

The candidate hopes that literature, definitions, results and other informative data, will be of value to all those involved in the subject matter and will clarify the aim of this study, and may give further intensive exploration and developments.

REVIEW OF LITERATURE

CIRCULATORY CHANGES IN LIVER CIRRHOSIS

Cirrhosis is associated with a spectrum of circulatory changes viz. an elevated plasma volume (Mashford, 1962), cardiac output (Epstein, 1977), heart rate (Ring-Larsen, 1977), and possibly muscle perfusion (Kontos, 1964) whereas arterial blood pressure (Mashford, 1962) and renal blood flow are decreased (Epstein, 1970). The mechanisms of changes in vascular resistance in cirrhosis are unknown.

The rise in heart rate during various autonomic reflex stimulation tests has been found significantly reduced in cirrhosis (Lunzer, 1975), and impaired vasoconstriction in skin and muscles during a vertical tilt has been demonstrated even in patients with compensated cirrhosis (Lunzer, 1973). It has been suggested that baroreceptors-mediated sympathetic nervous reactivity is impaired in liver disease (Lunzer, 1973).

Norepinephrine (NE) is the neurotransmitter released from axon terminals of sympathetic postganglionic neurons. Although it is not possible to measure directly the amount of NE released, the amount which escapes into the circulation can be accurately measured by enzymatic isotope-derivative techniques (Cryer, 1976).

Studies in man have shown that plasma NE concentration is an index of sympathetic nervous activity (Christensen, 1973). However, in cirrhosis studies on catecholamines are few, they have been carried out with unreliable methods, and they have

revealed conflicting results (Shaldon, 1961). The use of the sensitive radioemzymatic method demonstrated that plasma norepinephrine levels in cirrhotic patients were decreased in one study (Ciplea, 1979) and increased in another (Henriksen, 1981).

Preliminary studies have reported increased plasma noradrenaline concentration in patients with cirrhosis (Henriksen, 1981), a finding which has been confirmed by others (Bichet, 1982 and Arroyo, 1983).

The raised noreadrenaline in cirrhosis suggests enhanced sympathetic nervous activity in this condition (Ring-Larsen, 1982). Because catecholamines are metabolised in the liver (Vendsolu, 1960), however, the increased plasma noradrenaline might be a consequence of decreased hepatic function in patients with liver disease.

Adrenergic and renin-angiotensin systems are major factors in the regulation of cardiovascular homeostasis. The peculiar cardiovascular changes described in severe liver disease i.e. low peripheral vascular resistance, increased cardiac output, and renal ischaemia (Marray, 1958, Kontos 1964 and Epstein 1970), are therefore, likely to be associated with derangements of these systems, but the intimate mechanism(s) causing such abnormalities is still not clear.

Indirect evaluation of the adrenergic system indicate depletion of catecholamines stores in patients with cirrhosis and hypotension (Mashford, 1962) and impairment of cardiovas-

cular responsiveness to reflex autonomic stimulation in cirrhosis of varied etiology and chronic active hepatitis (Lunzer, 1973). Plasma catecholamines which are assumed to reflect the activity of the sympathetic nervous system (Lake CR, 1976), and which have recently been evaluated in patients with cirrhosis, were found to be elevated (Bernardi, 1982).

Therefore, an absolute deficit of physiological neurotransmitters cannot be considered the key factor accounting for cardiovascular derangements in these patients.

B-Hydroxylated phenylethylamines e.g. octopamine (OCT) and B-phenylethanolamine (PEA), are increased in the plasma of patients with cirrhosis and encephalopathy (Rossi-Fanelly, 1976). Their overproduction has been ascribed to derangements of amino acid metabolism by increased availability of precursor aromatic amino acids (Fisher, 1975). These compounds were considered responsible for both neurological and cardiovascular abnormalities seen in this condition (Fisher, 1971). However, no clear cut relationship has been demonstrated between the elevated plasma concentration of "weak neurotransmitters", hypotension and altered cardiovascular homeostasis (Editorial, 1982).

A hyperactive renin-angiotensin system has been observed in cirrhosis (Schroeder et. al, 1970) and demonstrated to be crucial for maintenance of blood pressure homeostasis in experimental and human post sinusoidal portal hypertension.

This suggests a compensatory role of the system when activity of the sympathetic nervous system is severely impaired (Mathias, 1975).

As a result of improvements in the treatment of bleeding, infections and coma complicating severe liver disease, it has become relatively common for patients with cirrhosis to die in a state characterized by hypotension, which is not due to bleeding, and by oliguria with a rising blood non protein nitrogen concentration (Papper, 1959). This syndrome may last for a week or more and is an almost certain of death. Its pathogenesis is obscure, and hemodynamic measurements have been reported in only a few patients.

A patient described by Hecker and Sherlock (1956) had a high cardiac output, low total peripheral resistance and a decrease response to norepinephrine. Lancestreme et. al., (1962) also reported a high cardiac output and low peripheral resistance in some patients none of whom were in the oligeric, terminal phase of their disease.

In the course of haemodynamic studies on a patient in this phase of cirrhosis, it was found that a reduced pressor response to tyramine. This suggested that the tissue norepinephrine stores may have been depleted since tyramine has its effects solely by releasing such endogenous stores of nonepinephrine (Burn, 1958).

The level of tissue nonepinephrine bears an important

relation to the reactivity of the peripheral sympathetic nervous system (Trendelenburg 1961). Accordingly, the suggestion that the tissue stores are depleted in this condition marked by hypotension, raised the question of their importance in the pathogenesis of this clinical state.

The increase in cardiac output in cirrhotic patients properly represents a response to decrease in systemic resistance (Kowalski, H.J. 1953). If this is the case, identification of the vascular regions in which this decrease in vascular resistance occurs may provide clues concerning the mechanism by which this abnormality is bought about. Studies of the splanchnic, cerebral, renal and coronary circulation in cirrhotic patients, including patients with increased cardiac output, showed that blood flow through these regional vascular beds is either normal or diminished (Zobel, 1962).

On the other hand, the frequent occurance in cirrhotic patients of palmar erythema. warm extremities, capillary pulsations and cutaneous spider, angiomas suggests the presence of cutaneous vasodilatation. This is supported by the finding of elevated blood flow to the hand (plethysmography) in small number of patients with chronic liver disease, by the demonstration of increased elimination of heat from the fingers in a large number of cirrhotic patients and by the finding of reduced arteriovenous oxygen difference from the antecubital venous blood in patients with advanced hepatic

cirrhosis (Tyor, 1959). Blood flow to skeletal muscles has not beenstudied systematically in patients with cirrhosis of the liver, although the finding of increased blood flow in the calf in two cirrhotic patients (Abramson, 1943) suggests that it may be increased.

LIVER CIRRHOSIS

Definition

Cirrhosis is a chronic disease of the liver in which diffuse destruction and regeneration of hepatic parenchymal cells have occurred, and in which a diffuse increase in connective tissue has resulted in disorganization of the lobular architecture (Harold, 1982).

In all cirrhotic patients, regardless of the presence, absence or nature of individual clinical manifestations, the triad of parenchymal necrosis, regeneration and scanning, which was first emphasized by Maxwell et al. (1968), is present. Typical lesions of each of the major types of cirrhosis may be seen to coexist in the same liver (Combs, 1975).

LIVER AND SCHISTOSOMIASIS

Hepatosplenic schistosomiasis is a clinicopathological condition caused by any of the schistosoma parasites or their products, mainly by schistosoma mansoni and japonicum and rarely with schistosoma haematobium (Mousa et al., 1957).

Schistosomiasis is a disease affecting various parts of the world (Manson Bahr., 1966). Bilharzial infection is prevalent with varying degrees throughout Egypt (Kamal and Rizk 1958; Mousa et al., 1960), and after the high dam schistosoma mansoni infection extended to Upper Egypt (Helmy, 1962). The maximum age incidence of infection falls between 10 and 20 years with more prevalence among males (El-Zawahry, 1962).

Andrade (1965) mentioned that the envolvement of the liver is the rule in schistosomiasis, either as a mild chornic granulomatous reaction with few or no symptoms, or severe fibrosis with extensive vascular lesion. Hepatic schistosomiasis is caused by repeated and prolonged embolization of liver by schistosoma ova mainly (Farid, 1977) and to a lesser extent by worms or by the so called Bilharzial toxins and pigments which reach the liver through the portal circulation. The Bilharzial hepatic affection is mainly interstitial granulomata involving the portal tracts which are gradually organized leading to fibrosis that extends through the liver substance. The fibrosis is mainly periportal and leads to splenomegaly which is also due to reticulo-endothelial hyperplasia. The Schistosoma mansoni was found to be responsible for hepatic lesion in 50% of cases where as schistosoma haematobium affect liver in 15% of cases due to Faulty habitat or reach liver through portosystemic collateral circulation (Mousa et al. 1957), but Neoman et al. (1974) reported that schistosoma haematobium can produce hepatosplenic disease almost as serious as schistosoma mansoni.

Splenomegaly was found in half cases affected with Sh, mansoni and in only 15% of cases affected with Sh haematobium (Mousa et. al., 1964).

Pathology of Schistosomiasis

Symmers (1904) described the hepatic pathology of schis-

tosomiasis as a pipe-stem fibrosis. Sorour (1928) found the hepatic lesion to be different from cirrhosis being an interstitial hepatic fibrosis mainly around smaller and larger ducts. Hashem (1947) described two different types of hepatic Bilharzial lesions, the course periportal fibrosis involving the larger portal tracts and the fine periportal fibrosis (diffuse Bilharzial fibrosis) affecting mainly the small portal tracts.

Aidaros and Soliman (1961) found a wide irregular thin walled vascular spaces called angiomatoids in 85% of cases which form a charactiristic feature in the thickened portal tracts, that distinguish Bilharzial liver from other forms of hepatic fibrosis in biopsy. The dilated lymphatics in portal spaces, even remnants of the ovae are diagnostic of schistomiasis (Sherlock, 1975). There may be also diffuse mononuclear infiltration in portal spaces with lymphocytes, plasma and plasmocytoid, histocytes and rarely esinophiles, proportional to the number of the parasites (Andrade, 1965) with little or no bile duct proliferations (Sherlock, 1975).

The hepatic parenchyma is usually well preserved and this is reflected by the good liver function tests, despite the increased portal pressure and extensive collaterals, only the parenchyma is quite liable to mild ischaemia that may be aggravated by massive gastrointestinal bleeding, intrahepatic or extrahepatic portal vein thrombosis, and after sudden cardiac