"ECHOCARDIOGRAPHIC CHANGES, CARDIOVASCULAR AND AUTONOMIC NERVOUS FUNCTION IN PATIENTS WITH DIFFERENT STAGES OF LIVER CIRRHOSIS IN RESPONSE TO THE CONVERTING ENZYME INHIBITOR,CAPTOPRIL"

THESIS

SUBMITTED FOR PARTIAL FULFILLMENT OF MASTER DEGREE IN INTERNAL MEDICINE

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بسم الله الرحمن الرحيم

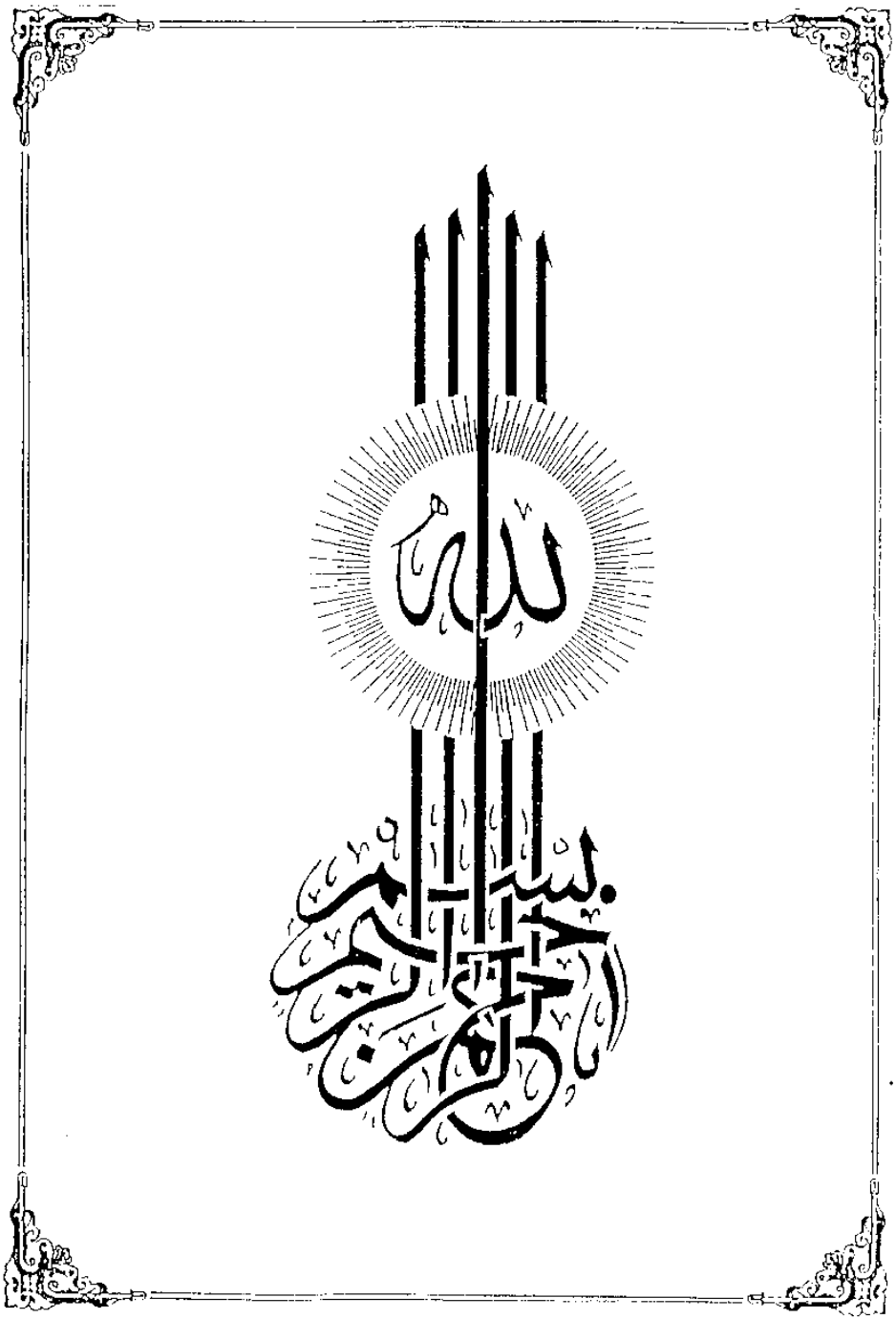
اقرأ باسم ربك الذي خلق

خلق الإنسان من علق

اقرأ وربك الأكرم الذي علم بالقلم

علم الإنسان ما لم يعلم

العلق ١-٥



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To God, to him, who created heavnes and earth, to him, whose knowledge is beyound all knowledges, who guides us to the path of rightfulness. I kneel to express the very humble gratitude of one of his very humble subjects.

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List Of Abreviations

ACE : angiotensin converting enzyme.

ACTH : adrenocorticotropic hormone.

Alk. ph : alkaline phosphatase.

ANP mRNA : atrial natriuretic peptide - messanger radionuclic acid.

At. E. : atrial enlargement.

ATP ase : adenosin triphosphatase.

B., Bilh. : bilharzial.

B. blocker : beta blocker.

BPFs : bradykinin potentiating factors

BUN : blood urea nitrogen.

CAD : coronary artery disease.

CBDL : chronic bile duct ligation.

CDCA : choledco caval anastomosis.

↑C- Th. ratio : increased cardio-thoracic ratio

cold pres. SB : systolic blood pressure before hand immersion in cold water.

" " DB : diastolic blood pressure before hand immersion.

" " SA : systolic blood pressure after hand immersion in cold water.

" " DA : diastolic blood pressure before hand immersion.

D. bilir. : direct serum bilirubin.

dp/dt : rate of increase in systolic pressure over time.

2,3 DPG : 2,3 diphosphglycerate.

E/A : rapid filling phase / atrial contraction.

ERPF :effective renal plasma flow.

GFR : glomerular filteration rate.

Hb : hemoglobin.

HBsAg : hepatitis B surface antigen.

HBsAb : hepatitis B surface antibody.

HBcAb : hepatitis B core antibody.

HBeAg : hepatitis B "e" antigen.

HBeAb : hepatitis B "e" antibody.

HCV Ab : hepatitis "C" virus antibody.

H.R. : heart rate.

H.S. : highly significant.

K : potassium.

LV.ESD : left ventricular end systolic diameter.

LV.ESV : left ventricular end systolic volume.

LV.EDD : left ventricular end diastolic diameter.

LV.EDV : left ventricular end diastolic volume.

LV.EF : left ventricular ejection fraction.

LV.F.S. : left ventricular fractional shortening.

LV.E.T. : left ventricular ejection time.

LVH : left ventricular hypertrophy.

MRC : medical research council.

Na : sodium.

N.S : non-significant.

P++ : pulmonary hypertension.

PEP : pre-ejection period.

pl.eff : pieural effusion.

PRA : plasma renin activity.

PTCA : catheter.

pul. art. press. : main pulmonary artery pressure.

RA : right atrium.

RBBB : right bundle branch block

rhyth : rhythm.

RV : right ventricle.

RVE : right ventricular enlargement.

S. alb. : serum albumin.

S. creat. : serum creatinine.

SD : standard deviation.

SHR : spontaneously hypertensive rat.

SGOT : serum glutamic oxaloacetic transaminase.

SGPT : serum glutamic pyruvic transaminase.

sig. significance, significant.

S - T. seg. : S -T segment.

T. S. bilir. : total serum bilirubin.

T. S. prot. : total serum protein.

V. E. : ventricular enlargement.

V. He. F. T. : Veterans Administration Heart Failure Trial.

Vuls. I : vulsalva maneuver, phase I.

Vuls. II : vulsalva maneuver, phase II.

Vuls. III : vulsalva maneuver, phase III.

Vuls. IV : vulsalva maneuver, phase IV.

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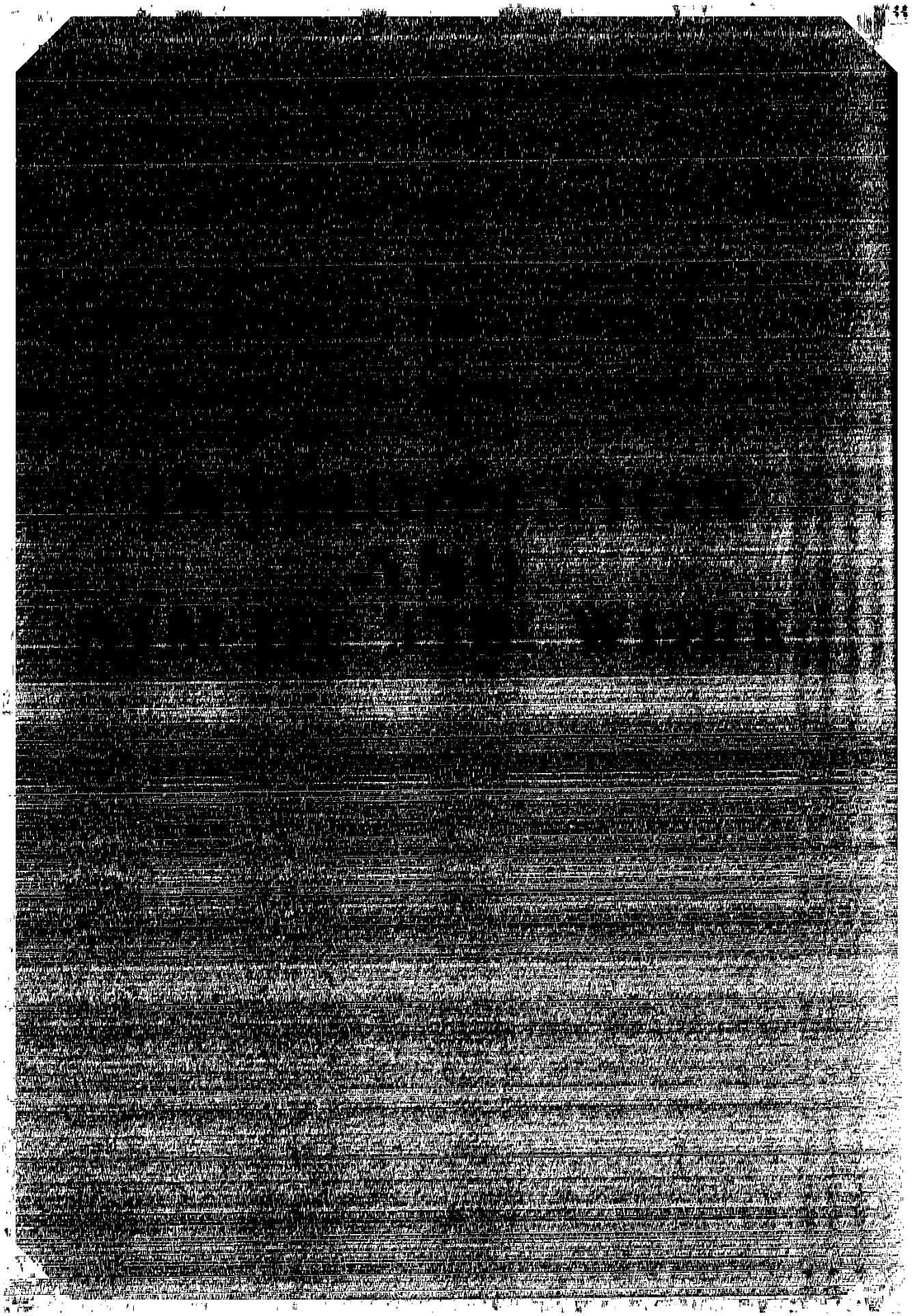


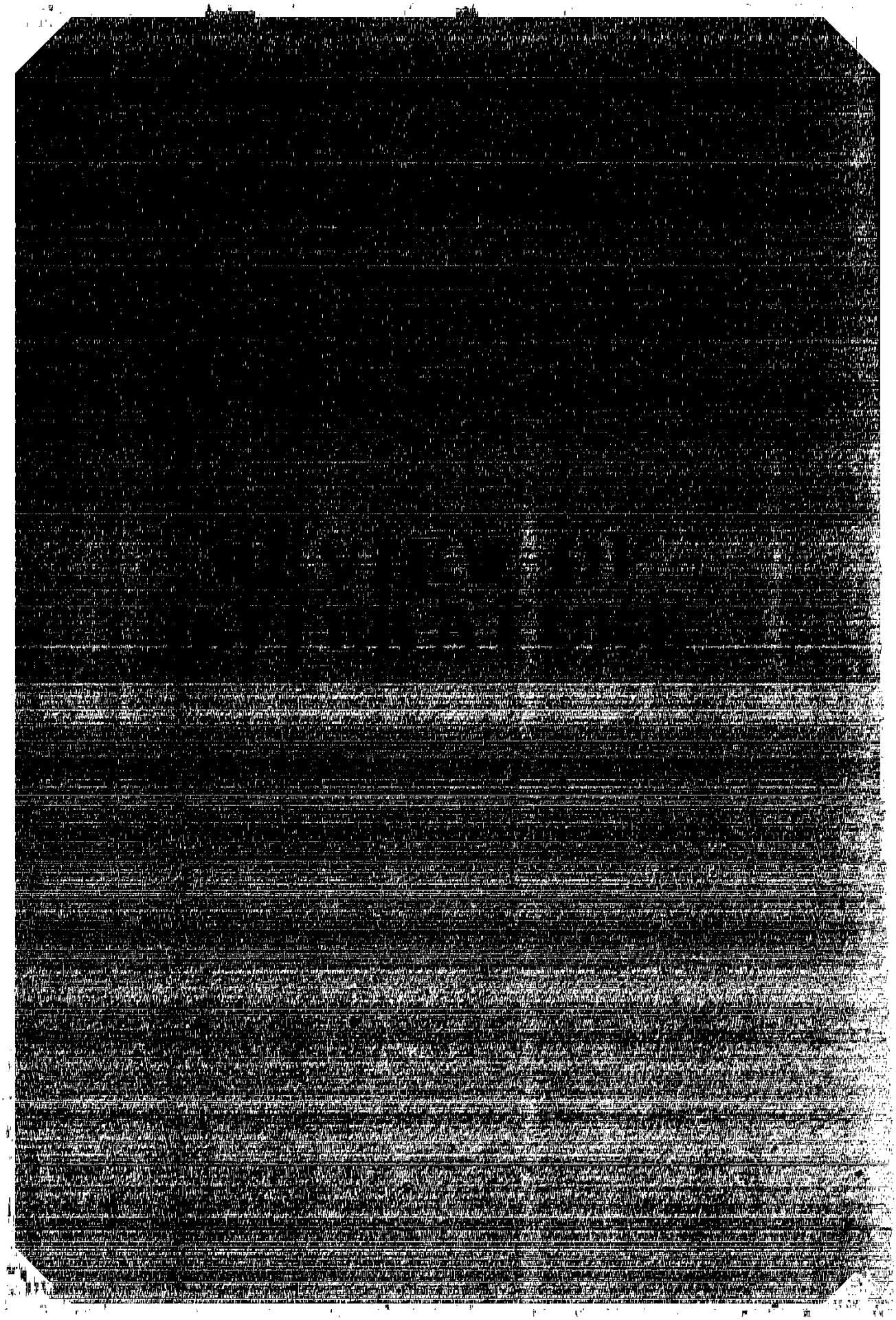
Introduction And Aim Of The Work

Cardiovascular dysfunction in liver diseases ending at terminal stages by hypotension was studied previously by many workers. Diminished venous return due to tense ascites, alcoholic cardiomyopathy and malnutrition, all can interfere with myocardial performance.

Could et al., in 1969 carried out cardiac catheterization in ten patients with alcoholic cirrhosis who had presystolic gallop. When exercising, all ten patients showed an average increase in left ventricular end diastolic pressure and a striking increase was noted in pulmonary pressure. This observation coupled with the finding that correction of hypotension with vasopressors may precipitate pulmonary oedema in patients with cirrhosis suggest that some patients with cirrhosis have latent congestive heart failure, that is ameliorated by the decrease in after load brough about by peripheral vasodilatations as stated by Limas et al.,1974. Moreover, Micheal et al.,1975 found impaired cardiovascular responsivness to reflex autonomic stimulation in patients with cirrhosis compared to controlled subjects. Impaired cardiovascular reactivity in patients with chronic liver disease could predispose to circulatory failure after haemorrhage or surgery and should be considered when prescribing drugs which affect autonomic activity. On the other hand, Lewis B.S. and his collagues in 1980, demonstrated an increase in systolic left ventricular performance in cirrhotics by echocardiography at rest. It is possible that such increase in left ventricular performance in cirrhosis -in this study- is meerly the result of peripheral vasodilatation and reduced left ventricular after load. Thus, it might not necessary imply that a primary increase in cardiac contractility is operative.

Captopril is a known cardioprotective agent against many cardiac insults. it improves myocardial performance and decrease the after load *(Lamas,1989)* without much altering autonomic nervous system as it leaves the vasoactive effect of angiotensin"I" free, which also has enhanced positive inotropic response in presence of captopril, as proved experimentally by *Hirrkate et al.,1987*.

So the aim of this work is to study the effect of different stages of cirrhosis on multiple parameters of cardiac and autonomic function, and whether captopril may be beneficial in reversing or protecting cardiac function in certain stages of the disease.



I- Cardiovascular Effects Of Liver Cirrhosis

Patients with liver cirrhosis may have marked changes in their cardiovascular system. One of the earliest publications noting significant cardiovascular and circulatory changes in patients with hepatic cirrhosis was reported by Fluckiger in Strassburg, the presence of cyanosis and clubbing in a 37 year old woman with liver cirrhosis *(Fluckiger, 1884)*. Undoubtedly, future studies will markedly increase the knowledge of this very important aspect of clinical medicine with findings that may have great significance for other aspects of circulatory regulation and dysfunction.

Many studies about effects of hepatic cirrhosis had proven a slightly or moderatly increased cardiac out put at rest. Lewis B.S et al., in 1980 suggest an increase in systolic left ventricular performance in cirrhosis as documented by echcocardiographic studies. However, in veiw of the reduced total peripheral resistance, as reflected by the tendency to hypotension in the cirrhotic patients, further clarification of the nature of the augmented myocardial function was necessary. It was postulated that increased left ventricular performance in cirrhosis is merely the result of peripheral vasodilatation and reduced left ventricular after load. Thus, it might not necessarily imply that a primary increase in cardiac contractility is operative in the elevated cardiac out put seen in cirrhosis as mentioned by *Veshler RL 1976*.

In most cardiac studies in patients with cirrhosis, the expected increase in cardiac out put during dynamic exercise was fairly well mentained and occasionally greater than normal, although the exercise tolerance was sometimes decreased *(Bayley et al., 1964)*.

However, in some patients with sever cirrhosis and ascites the cardiac output may fail to increase normally during exercise. In contrast to the increased cardiac output in most of the cirrhotics as a result of both peripheral vasodilatation and relative tachycardia (Scalant, 1980), the presence of tense ascites impedes the venous return and have a negative influence on the cardiac function of cirrhotic patients. *Maurizio G and his collague 1976,* studied the effect of paracentesis on the right and left ventricular function in 21 men with cirrhosis and tense ascites during removal of ascitic fluid, it was observed that:

* There was a significant increase in cardiac output, stroke volume, right and left ventricular stroke work and mean rate of systolic ejection.

* That up to a certain stage of drainage (about 5000 ml), there was an inverse relationship between the amount of fluid removed and the intra-abdominal and right atrial pressure.

* That there was a direct relationship between improvement of cardiac functioc and normalization of right atrial pressure.

It was believed that the increased intra- abdominal hydrostatic pressure acting upon the diaphragm affects the intra- thoracic pressure to such an extent that the transmural filling pressure and respiratory pulsations of the right atrium increased all of which impedes venous return. Improved cardiac function during paracentesis appears to be due to an augmented filling of the heart and to larger venous return.