"CARDIOVASCULAR CHANGES IN CHRONIC LIVER DISEASE"

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BONAFIDE CERTIFICATE

This is to certify that this dissertation titled "**CARDIOVASCULAR CHANGES IN CHRONIC LIVER DISEASE**" is a bonafide work done by **Dr.K.KOTTI** Post Graduate Student, Department of Internal Medicine, Government Kilpauk Medical College, Chennai -10 under my guidance and supervision in partial fulfillment of regulations of Tamil nadu Dr.M.G.R. Medical University, for the award of MD Degree Branch I (Internal Medicine) during the academic period of from May 2008 – April 2011.

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CONTENTS

INTRODUCTION

Chronic liver disease is a pathologically defined entity which is associated with a spectrum of characteristic clinical manifestations. The cardinal pathologic features reflect irreversible chronic injury to the hepatic parenchyma and include extensive fibrosis in association with formation of regenerative nodules. These features result from hepatocyte necrosis, collapse of the supporting reticular network with subsequent connective tissue deposition, distortion of the vascular bed, and nodular regeneration of remaining liver parenchyma most common causes of chronic liver disease in general order of frequency are chronic hepatitis C, alcoholic liver disease, non alcoholic steatohepatitis. Chronic hepatitis B, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, haemochromatosis and Wilson'sdisease. These chronic liver disease ultimately develop cirrhosis.

Chronic Liver Disease includes chronic hepatitis and cirrhosis. Chronic hepatitis eventually leads to cirrhosis. Cirrhosis, the end result of all chronic liver disease is, characterized by diffuse destruction and regeneration of hepatic parenchymal cells leading to deposition of connective tissue with resulting disorganization of the lobular and vascular architecture. In spite of the remarkable regenerative capacity of the liver, once hepatic parenchymal

reserve is exceeded, clinically overt or decompensated chronic liver disease ensues. Portal hypertension develops due to resistance to blood flow through the liver resulting increase in portal venous pressure leading to diversion of blood flow through low resistance portosystemic collaterals thereby bypassing the liver.

Liver cirrhosis is associated with a range of cardiovascular abnormalities. This was first described by Kowalski and Abelmann who noted a higher resting cardiac output and decreased systemic vascular resistance in patients with cirrhosis[1, 2]. However, despite the hyperdynamic circulation, impaired ventricular contractility in response to stimuli was described in cirrhotic patients[3-7]. These abnormalities were initially thought to be a manifestation of latent alcoholic cardiomyopathy. But in the mid 1980s, studies in nonalcoholic patients and in experimental animal models showed a similar pattern of blunted cardiac contractile responsiveness[8-10]. Thus these cardiovascular changes are now termed 'Cirrhotic cardiomyopathy'[11-14].

The prevalence of cirrhotic cardiomyopathy remains unknown at present. Features include structural, histological, electrophysiological, systolic and diastolic dysfunction. Multiple factors are considered as responsible, including impaired beta-adrenergic receptor signal transduction, abnormal membrane biophysical characteristics, and increased activity of

cardiodepressant systems mediated by cGMP[15].

Overt heart failure is not generally a feature of cirrhotic cardiomyopathy, because the associated marked vasodilatation accompanying the hyperdynamic circulation significantly reduces ventricular afterload. However, major stresses on the cardiovascular system such as liver transplantation, infections and insertion of transjugular intrahepatic portosystemic shunts (TIPS) can unmask the presence of cirrhotic cardiomyopathy and thereby convert latent to overt heart failure. Cirrhotic cardiomyopathy may also contribute to the pathogenesis of hepatorenal syndrome and circulatory failure in liver cirrhosis[15].

Diastolic dysfunction is present in the vast majority of patients with cirrhotic cardiomyopathy, and that simple echocardiographic indices such as the E/A ratio may detect diastolic dysfunction even at rest. This may therefore represent the best available screening test to diagnose cardiac dysfunction[16].

Due to the limited number of human studies, the management of cirrhotic cardiomyopathy remains largely empirical. Treatment of this condition is mainly supportive. Orthotropic liver transplantation appears to improve or normalize the condition, generally after a period of several months[17]. If overt heart failure develops in these patients, then the same general treatment principles of noncirrhotic congestive heart failure apply,

including bed rest, salt restriction, oxygen, diuretics, and careful preload and afterload reduction[14].

The current study was designed to precisely evaluate the cardiovascular system in a group of patients with **chronic liver disease-cirrhosis** based on clinical examination, elctrocardiography, roentgenography and M-Mode 2-dimensional echocardiography.

AIM OF THE STUDY

1. To clinically evaluate patients with chronic liver disease with respect to changes in heart rate, blood pressure, mean arterial pressure, jugular venous pressure and precordial examination.

2. To document the electrical and morphological alterations in the heart in patients with chronic liver disease by means of non-invasive investigations like electrocardiography, roentghenography and M-Mode 2-Dimensional echocardiography.

3. To determine the relationship between the cardiac and hemodynamic parameters and the severity and extent of chronic liver disease.

REVIEW OF LITERATURE

Liver diseases may be acute or chronic. Most common causes of chronic liver disease in general order of frequency are chronic hepatitis C, alcoholic liver disease, non alcoholic steatohepatitis. Chronic hepatitis B, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, haemochromatosis and Wilson's disease. These chronic liver disease ultimately develop cirrhosis.

Chronic liver disease is a pathologically defined entity which is associated with a spectrum of characteristic clinical manifestations. The cardinal pathologic features reflect irreversible chronic injury to the hepatic parenchyma and include extensive fibrosis in association with formation of regenerative nodules (fig;1). These features result from hepatocyte necrosis, collapse of the supporting reticular network with subsequent connective tissue deposition, distortion of the vascular bed, and nodular regeneration of remaining liver parenchyma. Despite the remarkable regenerative capacity of the liver, once the hepatic parenchymal reserve is exceeded, clinically overt or decompensated cirrhosis ensues.

Classification of Chronic liver disease

1. **Chronic Hepatitis**
2. **Cirrhosis**

1. **Chronic Hepatitis**

   a) Chronic persistent hepatitis

   b) Chronic active hepatitis

   c) Chronic lobular hepatitis

Causes of chronic hepatitis

Chronic hepatitis B

Chronic hepatitis B Plus D

Chronic hepatitis C

Autoimmune hepatitis

Drug related chronic hepatitis

Alcoholic hepatitis

Non alcoholic steatohepatitis

Metabolic causes (Primary billiary cirrhosis, sclerosing cholangitis wilson's disease, haemochromatosis) cryptogenic chronic hepatitis.

Microscopic appearance

Periportal necrosis including piecemeal necrosis and bridging necrosis

Intralobular necrosis

Portal inflammation

Fibrosis

2. **Cirrhosis**

    a) Micro – Nodular cirrhosis

    b) Macro –Nodular Cirrhosis

    c) Mixed cirrhosis.

Cirrhosis Classification:

1. Micro nodular cirrhosis: There is preponderance of parenchymal nodules that are less than 3 mm in diameter. There is involvement of every lobule. The micro nodular liver may represent impaired capacity for regrowth as in alcoholism, malnutrition, old age and anaemia.

2. Macro nodular cirrhosis: In this size of the nodules exceed more than 3 mm in diameter. Nodules are highly variable is size and normal lobules are found amongst larger nodules. Regeneration is reflected by large cells with large nuclei and by cell plates of varying thickness eg. Post necrotic cirrhosis.

3. Mixed Cirrhosis: Combination of micro nodules and macro nodules eg. Biliary cirrhosis.

    Most types of cirrhosis may be conveniently classified by a mixture of etiologically and morphologically defined entities as follows.

1. Alcoholic
2. Cryptogenic
3. Post viral or post necrotic
    - Viral hepatitis [Hepatitis B, Non – A, Non – B]
    - Hepatitis D, hepatitis C, Cytomegalovirus
    - Toxoplasmosis
    - Schistosomiasis
    - Ecchinococcus
    - Brucellosis
4. Inherited and Metabolic disorders :
    - Haemochromatosis
    - Wilson’s disease
    - Alpha 1 – antitrypsin deficiency
    - Galactosaemia
    - Glycogen storage disease
    - Gaucher’s disease
    - Hereditary fructose intolerance
    - Hereditary tyrosinemia
    - Fanconi’s syndrome

5. Drugs and toxins :
    - Methyldopa
    - Methotrexate
    - Isoniazid
    - Perhexilene maleate
    - Oxyphenisatin
    - Arsenicals
    - Oxyphenisatin
    - Arsenicals
6. Biliary Cirrhosis :
    - Primary
    - Secondary
    - Hepatic venous outflow obstruction :
    - Budd Chiari Syndrome
    - Cardiac cirrhosis
    - Veno occlusive disease
7. Miscellaneous:
    - Sarcoidosis
    - Graft Vs Host disease
    - Chronic inflammatory bowel disease

- Cystic fibrosis
- Jejunoileal bypass
- Diabetes mellitus
- Carcinomatous cirrhosis
- Indian childhood cirrhosis
- Immunological – Lupoid hepatitis.

Clinical and Biochemical Classification:

Clinical features of cirrhosis (fig :2) derive from the morphologic alterations and often reflect the severity of liver damage rather than the etiology of underlying liver disease. Loss of functioning hepatocellular mass may lead to jaundice, edema, coagulopathy, spider telangiectasia, palmar erythema , parotid and lacrimal gland enlargement , nail changes, Dupuytren contractures, gynaecomastia, ascites, testicular atrophy as well as confusion and asterexis suggesting hepatic encephalopathy.

Distorted vasculature leads to portal hypertension. Portal hypertension develops when resistance to blood flow through the liver, is increased and resulting increase in portal venous pressure lead to diversion of blood flow through low resistance portosystemic collaterals thereby bypassing the liver. Hyperdynamic circulation, caput medusae, splenomegaly and gastro esophageal varices more directly suggest the presence of portal hypertention.

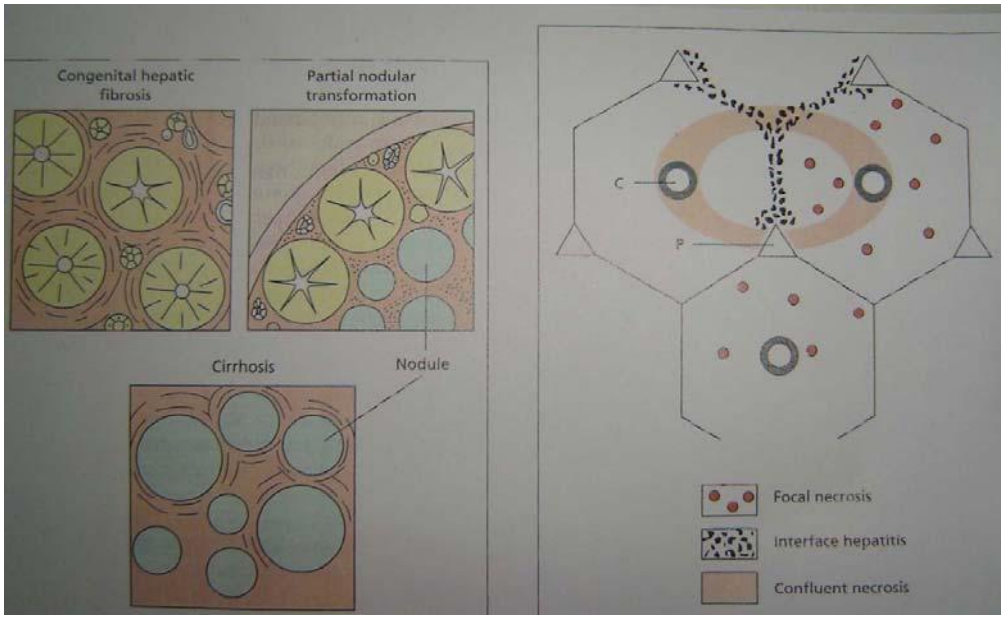


Fig.1.FIBROSIS WITH NODULAR REGENERATION

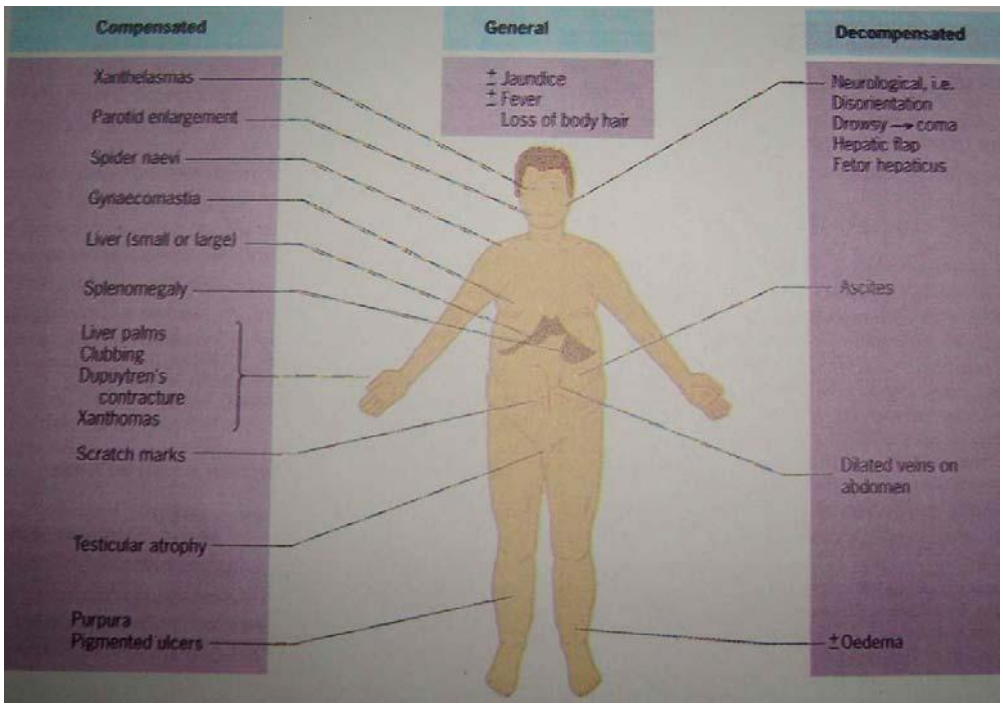


Fig.2.CLINICAL FEATURES OF CIRRHOSIS

Ascites and hepatic encephalopathy result from both hepatocellular insufficiency and portal hypertension.

Compensated Cirrhosis:

This stage is discovered by the following

a) Early symptoms:

- Vague abdominal pain
- Fatigue
- Mild pyrexia
- Vascular spiders (fig : 3)
- Palmar erythema (fig : 4)
- Unexplained epistaxis
- Ankle oedema

b) Detected on a routine check up

- Firm non tender hepatosplenomegaly (fig : 5)
- Elevated transaminases

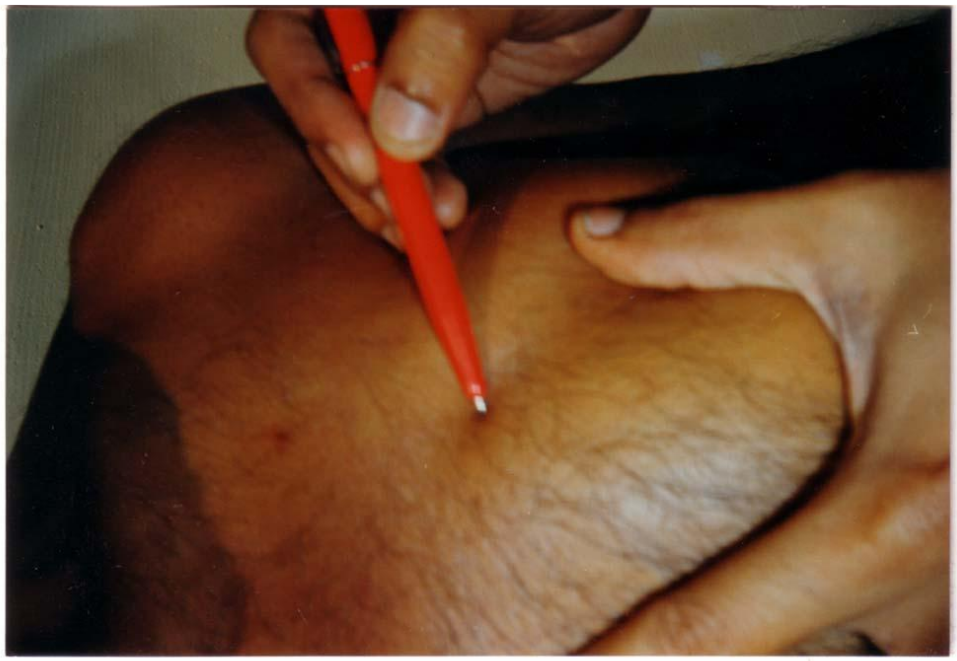


Fig: 3 VASCULAR SPIDERS AND METHOD OF DEMONSTRAITON

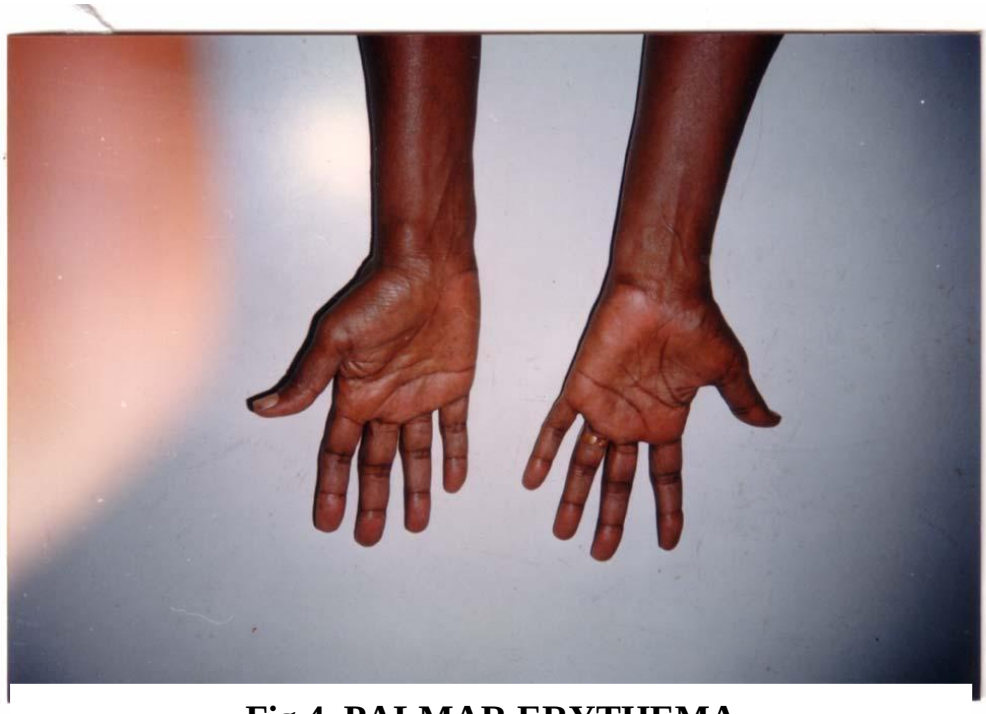


Fig 4 PALMAR ERYTHEMA

c) Background

- Alcoholism
- Hepatitis
- Decompensated Cirrhosis

The patient usually seeks medical advice because of ascites and/or jaundice. Features include poor general health, muscle wasting, weight loss. (fig: 6): Continuous mild fever ($37.5 – 38^0C$) is often due to gram negative bacteremia., to continuing hepatic cell necrosis or to a complicating liver cell carcinoma. Foetor hepaticus may be present. Cirrhosis is the commonest cause of hepatic encephalopathy.

Jaundice (fig : 7) implies that liver cell destruction exceeds the capacity of regeneration and deeper the jaundice, greater the inadequacy of the liver cell function.

The skin may be pigmented. Clubbing of fingers may be present. Purpura over the arms, shoulders and shins may be associated with a low platelet count. Spontaneous bruising and epistaxis reflect a prothrombin deficiency.

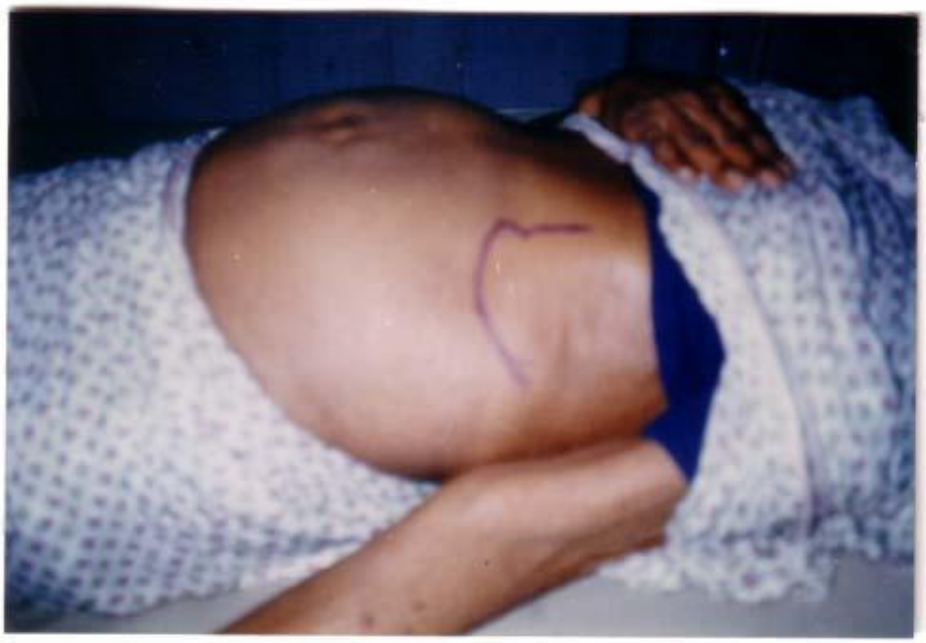


FIG 5: SPLENOMEGALY

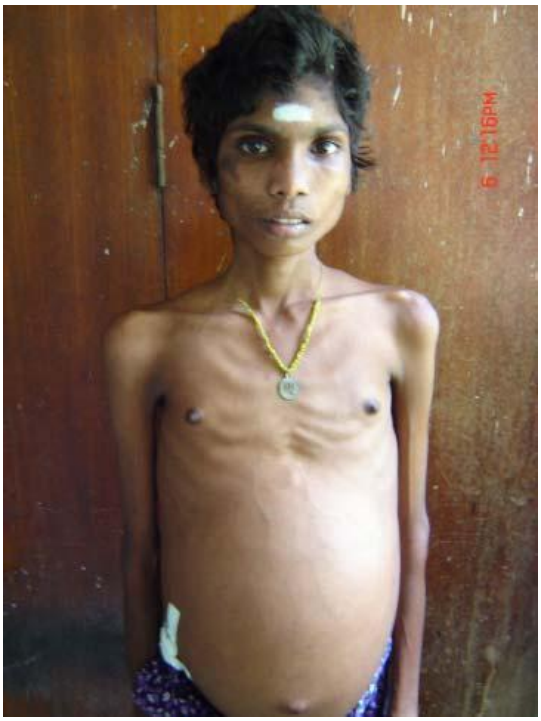


FIG : 6 : DECOMPENSATED CIRRHOSIS

The circulation is overactive. The blood pressure is low. Sparse body hair, vascular spiders, palmar erythema, white nails (Leuconychia) and gonadal atrophy are common.

Ascites is usually preceded by abdominal distention edema of the legs is frequently seen (fig: 8)

The liver may be enlarged and firm or contracted and impalpable. Spleen may be palpable and firm. Haemetological manifestations of Cirrhosis include anemia, leukopenia and thrombocytopenia which may result from splenomegaly and hypersplenism. Clotting factor abnormalities also seen.

A classification scheme based on a combination of several factors, the Child-Turcotte classification has been useful in estimating long term outcome which is represented below.

CHILD TURCOTTE CLASSIFICATION OF SEVERITY OF CIRRHOSIS

INDEX		**CLASS**	
	A	**B**	**C**
Bilirubin (mg/dl)	<2.0	2.0-3.0	>3.0
Albumin (g/dl)	>3.5	3-3.5	<3
Ascites	None	Easily controlled	Poorly Controlled
Encephalopathy	None	Mild	Advanced
Nutritional Status	Excellent	Good	Poor

FIG : 7 : JAUNDICE

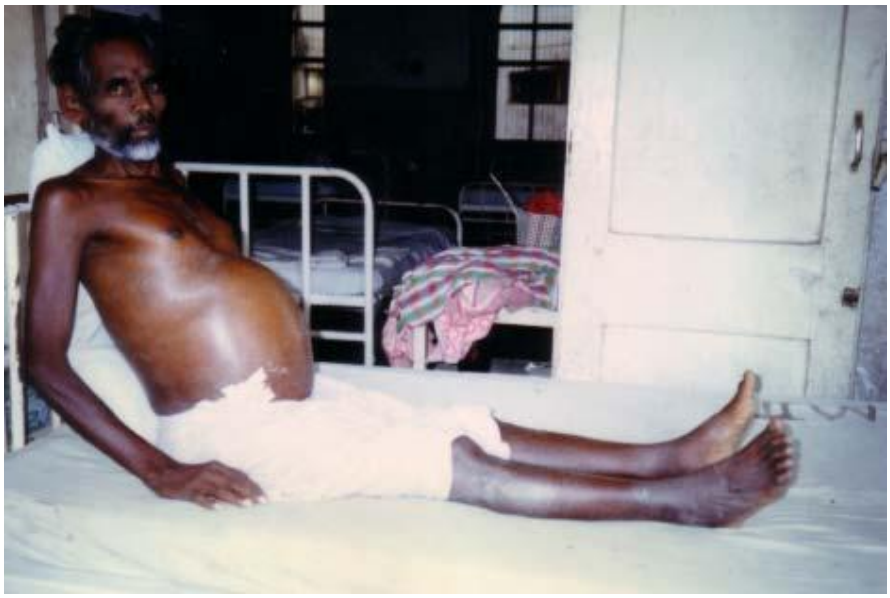


FIG: 8 : ASCITES WITH EDEMA LEGS

PATHOPHYSIOLOGY OF PORTAL HYPERTENSION:

The fundamental hemodynamic abnormality is an increased resistance to portal blood flow. This may be intra hepatic as in cirrhosis or due to obstructed portal vein due to thrombosis. As the portal venous pressure is lowered by the development of collaterals deviating portal blood into systemic veins, the portal hypertention is maintained by increasing the blood flow in the portal system which thus becomes hyperdynamic. Resistance to portal blood flow is exerted along both the hepatic and portal collateral circulation and appears to be modified by vasoactive agents. Portal hypertension is defined as portal venous pressure exceeding 12 mm Hg.

ROLE OF ULTRASOUND:

Ultrasonography has proved to be a useful non invasive and inexpensive method to establish the presence of and aetiology of portal hypertension.

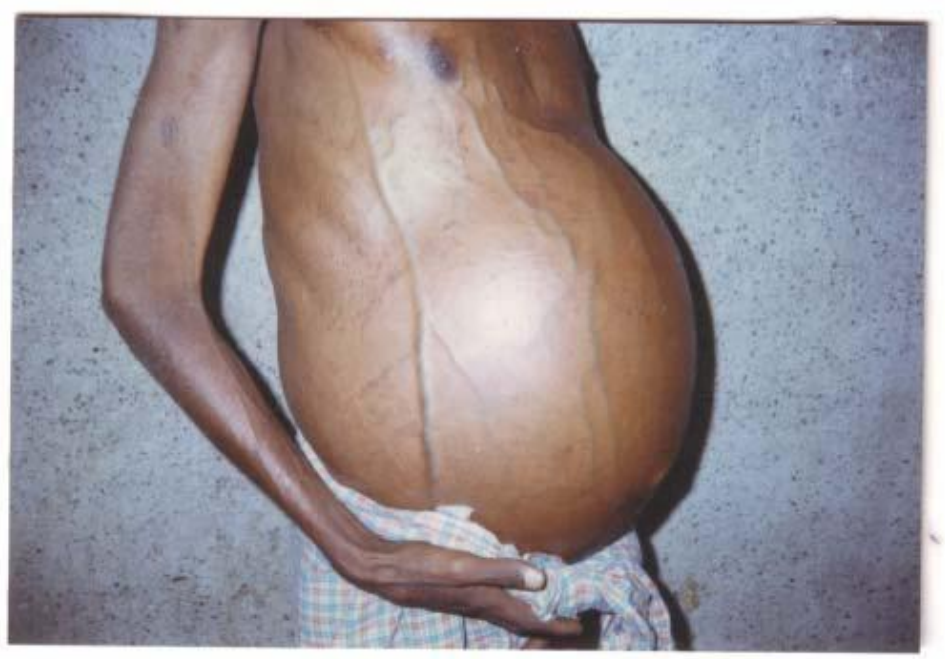
A normal ultrasound shows the liver to have mixed echogenicity. In cirrhosis of the liver the edge of the liver may be irregular and the liver shows coarse echo pattern. It has a fine stippled echogenicity due to increased acoustic attenuation. In end stage cirrhosis the liver is small and very echogenic. It has a nodular border and may be outlined well by ascitic fluid. One portion of the liver may have a different echogenicity from the

remainder and form a bulge. This represents a regenerating nodule. Portal hypertension and splenomegarly are present. Caudate lobe is enlarged relative to the right lobe.

The presence of portal hypertension is sonologically assessed by the following features.

1. Splenomegaly : If the transducer has a 90^0 angle and the superior and inferior border of the spleen cannot fit on an image, the spleen is enlarged. Static scans are helpful if serial exams for splenomegaly are needed. To evaluate splenic size on a static scan a superior view is preferred. The spleen is enlarged when its anterior border lies in front of the aorta and inferior vena cava and it is at least as thick as a normal kidney.
2. Portal vein dilated to >1.3cm. Estimation of portal vein and splenic vein diameter is useful to predict the presence of oesophageal varices. Portal vein and splenic vein size of 12 mm 8 mm are good predictors (93.05% and 94.89% respectively) of oesophageal varices but their size did not differ significantly according to grade of varices.

FIG: 9: COLLARERALS OVER THE ANTERIOR ABDOMINAL WALL



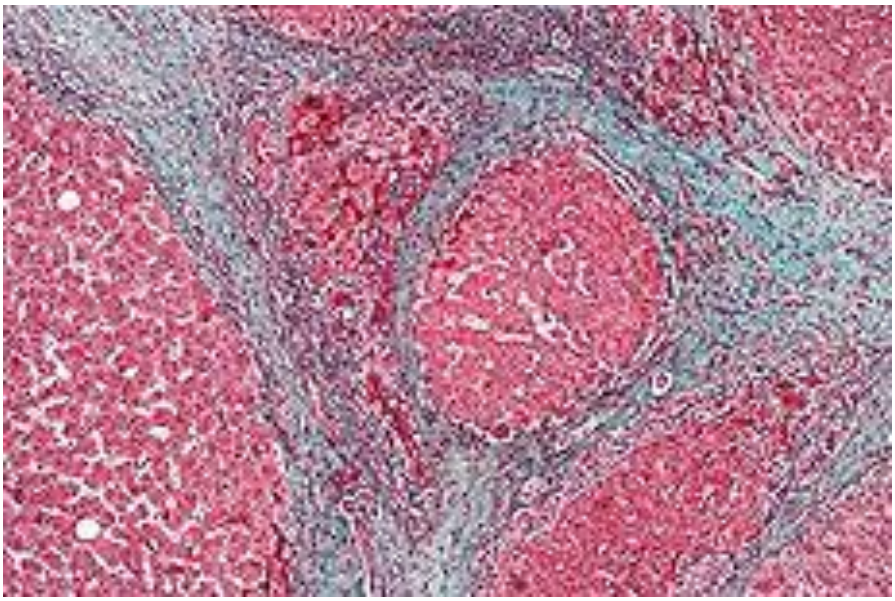


FIG: 9 (a) Liver Biopsy

3. Recanalization of paraumbilical veins with in the ligamentum teres.
4. Collaterals – Small tortuous vessels at porta hepatis gastric fundus, pancreatic beds splenic hilum – Doppler and colour flow detect vessels.
5. Dilated splenic and superior mesenteric veins.
6. Ascites
7. Normal flow in the portal vein and hepatic artery is in the direction to the liver – Hepatopetal. In severe portal hypertension flow in the portal vein is reversed towards the feet – hepatofugal. Colour flow makes this change is direction obvious and Doppler cursor through both vessels simultaneously demonstrates the direction of flow.
8. Fenestrated thickened gall bladder wall is a unique Ultrasonagraphic sign seen in patients with portal hypertention. This appearance is possible due to congestive thickness of the gall bladder wall with collaterals in the wall giving it a fenestrated appearance.

ROLE OF ABDOMINAL PARACENTESIS:

Diagnostic paracentesis of about 50 ml is always performed in case of ascites. Complication like bowel perforation and hemorrhage may rarely occurs in patients with cirrhosis of liver after paracentesis.

Protein concentration rarely exceeds 2.5 g/100 ml. Higher values suggest infection. If serum albumin to ascites albumin gradient (SAAG) is greater than 1.1 g/dl then it indicates presence of portal hypertension. The SAAG reflects a difference in the oncotic pressures and correlates well with the portal venous pressure.

Fluid usually appears straw coloured or clear and sometimes in advanced cirrhosis chylous ascites may result due to accumulation of chylomicrons in the ascitic fluid.

From 1950 onwards abdominal paracentesis was the accepted Treatment of tense ascites. Selection criteria for the therapeutic paracentesis include.

- Tense ascites preferably with edema
- Child's grade B
- Prothrombin > 40 %
- Serum Bilirubin <10 mg/dl
- Platelets > 40,000/cu mm
- Serum creatinine<3 mg /dl
- Urinary sodium>10 mEq/24 hrs

Usually 5-10 litres of fluid is removed followed by replacement of salt poor albumin 1V 6g/litre of fluid removed. Single large paracentesis of about 10 L in 1 hour with intravenous salt poor albumin is also equally effective and safe.

ROLE OF LIVER BIOPSY:

Needle Biopsy of The liver:

Needle biopsy of the liver is indicated in the cirrhosis of liver in that it helps to confirm the diagnosis and may provide a clue for the aetiology of cirrhosis. Since the lesions in most cases of cirrhosis liver are diffuse, such a small biopsy specimen is representive of changes in the whole liver.

The exception to this is macro nodular cirrhosis in which aspiration often large nodule may reveal normal architecture. The diagnostic yield may be improved by three consecutive samples obtained by redirecting the biopsy needle.

Types of needles used:

- Vim Silverman Needle
- Menghini Needle

Trucut needle: For the purpose of the study, the trucut needle was chosen because it is of value in cirrhosis patients as it caused less fragmentation.

Biopsy gun (BIOPTER)

Surecut needle: 0.66 mm, may be used to diagnose cirrhosis when the Menghini needle is contraindicated. Risk of complication is minimal.

Approach For liver Biopsy:

1. Intercostal approach is the most frequent method and it rarely fails.
2. Liver biopsy can also be performed via the transjugular route in patient with small liver, failed transcutaneous approach. Wedged and free hepatic venous pressure can be measured simultaneously.
3. Direct (Guided) liver Biopsy
4. Ultrasound or CT Scan guided liver biopsies give a higher percentage of positivity than the blind percutaneous techniques.

Contraindications:

- Coagulation defects
- Platelet count less than 80,000/cu mm
- Tense ascites
- Very small fibrotic liver
- Known vascular lesions like hemangioma

Naked Eye Appearance:

A satisfactory biopsy is 1-4 cms long and weighs 10-50 mg. The cirrhotic liver tends to crumble into fragments of irregular contour.

The biopsy is usually fixed in 10% formal – saline. Routine stains

include haematoxylin and eosin and a good stain for connective tissue. Orcein staining is useful to show hepatitis B surface antigen in the hepatocyte; and is also an indicator of cholestasis and Wilson's disease.

Microscopic Appearance:

This is characterized by the following : (Fig. 9 (a))

- Parenchymal injury and consequent diffuse fibrosis in the form of delicate bands (portal central, portal-portal, central – central) or broad scars replacing multiple adjacent lobule.
- Reorganized vascular architecture.
- Parenchymal nodules created by regeneration of hepatocytes.

PATHOPHYSIOLOGY OF CARDIAC AND CIRCULATORY CHANGES IN CHRONIC LIVER DISEASE

CHAMBER DYNAMICS AND MYOCARDIAL FUNCTION

Chronic liver diseases like cirrhosis produce high cardiac output states. The mechanisms is uncertain but has been attributed to increased blood volume, intrahepatic arteriovenous shunts, mesenteric arteriovenous shunts and defects in inactivation of circulating vasodilators.

M-Mode 2-Dimenisonal echocardiograph is a useful – invasive method of studying the various morphological and functional parameter. In patients with cirrhosis liver prior studies have shown that right ventricular end diastolic volume and right ventricular end systolic volume where significantly reduced in patients whereas left ventricular end diastolic volume and left ventricular end systolic volume and left atrial volume were normal or slightly increased. The right ejection fraction was significantly increased and the left ejection fraction was slightly decreased. There is also evidence of myocardial contractile function impairment and ventricular hyporesponsiveness to pharmacological or physiological stress. Diastolic dysfunction was found to be 35% in prior studies and more common in alcoholic than in non alcoholics. These changes are reversed following liver transplantation.

Pericardial effusion has been demonstrated in a significant number of patients and is seen as echo free zone surrounding the heart and if large the whole heart can be seen swinging in to it. Pulmonary hypertension was seen in 12% of patients.

The incidence of coronary and aortic atheroma is less than the rest of the population. At autopsy, the incidence of myocardial infarction is about a quarter of that among total cases examined without cirrhosis.

HAEMODYNAMIC CHANGES;

Peripheral Vasodilatation and Hyperkinetic Systemic Circulation:

Vasodilatation is characteristically shown by flushed extremities, bounding pulses and capillary pulsations.

The cardiac output is raised and this is evidence by resting tachycardia and active precordial impulse and frequent systolic murmur. The splenic blood flow is increased. The renal blood flow especially renal cortical perfusion is reduced. Cutaneous micro circulation is reduced due to opening of arterio venous channels and neurohumoral factors. The cardiac index was significantly raised.

The mean arterial pressure and peripheral resistance are markedly reduced. The blood pressure is further lowered and is an ominous sign as it further reduces kidney function.

Hemodynamic changes in cirrhosis

Portal hypertension is one of the salient features of cirrhosis. Cirrhosis of the liver accounts for approximately 90% of cases of portal hypertension. Portal hypertension is a common clinical syndrome defined by a pathologic increase of portal venous pressure. As a consequence, the gradient between portal pressure (PP) and inferior vena cava pressure (IVC) (portal pressure gradient, PPG) is increased above the upper normal value of 5 mm Hg. The importance of portal hypertensive syndrome is defined by the frequency and severity of its complications, including upper gastrointestinal bleeding from ruptured gastroesophageal varices, ascites, and hepatorenal Syndrome, which represent the leading causes of death and of liver transplantation in patients with cirrhosis.

Portal hypertension is considered to be clinically significant (CSPH) when PPG, or its clinical equivalent hepatic venous pressure gradient (HVPG), exceeds 10 to 12 mm Hg, since this is the threshold for the clinical manifestations of portal hypertensive syndrome to appear. The vast majority of patients with cirrhosis develop CSPH along the course of the disease, and data from a recent multicentric study indicate that CSPH is already present at diagnosis in approximately 60% of histologically proven, well-compensated cirrhosis case.

Portal hypertension is related both to vascular resistance and to portal blood flow. The fundamental hemodynamic abnormality is an increased resistance to portal flow. This may be mechanical due to the disturbed architecture and nodularity of cirrhosis or due to an obstructed portal vein. Other intra-hepatic factors such as collagenosis of the space of Disse, hepatocyte swelling and the resistance offered by portal-systemic collaterals contribute. There is also a dynamic increase in intra-hepatic vascular resistance.

Stellate (Ito) cells have contractile properties that can be modulated by vaso-active substances. These include nitric oxide (NO) which is vasodilatory and endothelin which is a vaso-constrictor. These may modulate intra-hepatic resistance and blood flow especially at a sinusoidal level. As the portal venous pressure is lowered by the development of collaterals deviating portal blood into systemic veins, portal hypertension is maintained by increasing portal flow in the portal system which becomes hyperdynamic. It is uncertain whether the hyperdynamic circulation is the cause or the consequence of the portal hypertension or both. It is related to the severity of liver failure. Cardiac output increases and there is generalized vasodilatation. Arterial blood pressure is normal or low. Splanchnic vasodilatation is probably the most important factor in maintaining the hyperdynamic circulation. Azygous blood flow is increased.

The increased portal flow raises the oesophageal variceal transmural pressure. The increased flow refers to total portal flow (hepatic and collaterals). The actual portal flow reaching the liver is, of course, reduced. The factors maintaining the hyperdynamic splanchnic circulation are multiple. There seems to be interplay of vasodilators and vaso-constrictors. These might be formed by the hepatocyte, fail to be inactivated by it or be of gut origin and pass through intra-hepatic or extra-hepatic venous shunts. Endotoxins and cytokines, largely formed in the gut, are important triggers.

NO and endothelin-1 are synthesized by vascular endothelium in response to endotoxin. Prostacyclin is produced by portal vein endothelium and is a potent vasodilator. It may play a major role in the circulatory changes of portal hypertension due to chronic liver disease. Glucagon is vasodilatory after pharmacological doses but does not seem to be vaso-active at physiological doses. It is probably not a primary factor in the maintenance of the hyperkinetic circulation in established liver disease.

Cardiac and vascular changes in cirrhosis

The cardiovascular system in patients with cirrhosis or portal hypertension is abnormal. The circulation becomes hyperdynamic, characterized by increased cardiac output and decreased peripheral vascular resistance and arterial pressure. Moreover, despite the increased cardiac output at rest, with stressful stimuli such as hemorrhage, surgery or

vasoactive drug administration, the ventricular response is blunted, a condition known as cirrhotic cardiomyopathy. These cardiovascular abnormalities have been suggested to induce or aggravate several complications of cirrhosis such as renal salt and water retention, variceal bleeding, hepatopulmonary syndrome, and increased cardiovascular fragility under stress. Recent reviews have detailed the clinical aspects of hyperdynamic circulation[18, 19] and cirrhotic cardiomyopathy[20, 21, 22.]

HYPERDYNAMIC CIRCULATION

Peripheral vasodilatation is central to hyperdynamic circulation and portal hypertension in cirrhosis. However, the factors directly initiating vasodilatation remain obscure. A hypothesis that has received much attention over the past three decades is the "humoral factor" theory. In cirrhosis, increased intrahepatic resistance induces portosystemic collateral formation, allowing gut-derived humoral substances to directly enter the systemic circulation without detoxification by the liver. The following gut-derived or locally-produced humoral factors have been implicated as possible mediators of peripheral vasodilatation in cirrhosis or portal hypertension.

Endocannabinoids

Endocannabinoids are lipid-like substances that act on two inhibitory G protein-coupled receptors, CB1 and CB2. The vasodilatory effect of endogenous cannabinoids in cirrhosis was first reported in 2001[23]

Anandamide, an endogenous cannabinoid or endocannabinoid, is increased in monocytes of cirrhotic rats [23, 24] and its receptor CB1 is also upregulated in the vascular endothelium of patients with cirrhosis [23]. Infusing monocytes isolated from cirrhotic rats into normal rats decreases the mean arterial pressure in the recipients. Furthermore, administering a CB1 receptor antagonist SR141716A to cirrhotic rats increases the total peripheral resistance[23, 24] both studies demonstrated that SR141716A significantly increases the reduced arterial pressure in cirrhosis, and blocks the hypotension induced by the infusion of isolated cirrhotic monocytes into normal rats [23, 24] Batkai and colleagues also found that SR141716A decreases mesenteric blood flow and portal venous pressure in cirrhotic rats[23]. All of these data indicate that the vascular tone in cirrhosis is regulated by CB1 receptors in both the splanchnic and systemic circulations.

Besides vasodilatation, anandamide rapidly and dose-dependently induces apoptosis in primary culture-activated and in vivo-activated hepatic stellate cells, with over 70% cell death after 4 h at 25 μmol/L[25]. This effect could alter the hepatic sinusoidal microcirculation and enhance the development of portal hypertension that leads to hyperdynamic circulation.

How does cirrhosis leads to increased endocannabinoids? Varga and co-workers found that bacterial endotoxin stimulates endocannabinoid production in cirrhosis [26]. The upregulation of CB1 receptors in cirrhotic

vascular endothelium and thus increased end-organ sensitivity may also enhance endocannabinoid vasodilator tone [23].

Nitric oxide

NO has been extensively studied. It is now clear that in cirrhosis, changes in NO activity affect different vascular beds in variable ways. In the liver microcirculation, endothelial-constitutive NO synthase (eNOS or NOS3) expression is decreased in a cirrhotic rat model [27]. Simvastatin enhances hepatic nitric oxide production and decreases the hepatic vascular tone in patients with cirrhosis[28]. An NO donor[29] or NOS3 gene transfection[27], which compensates for the decreased hepatic NOS3 expression, significantly lowers the increased portal pressure in cirrhosis.

In contrast, systemic NO production is increased in cirrhotic patients and animal models[30-32]. Moreover, normalization of NO production in cirrhotic rats, by achieving normal concentrations of aortic cGMP with small doses of the NOS inhibitor L-NAME, normalizes the decreased peripheral vascular resistance and the increased cardiac output [33]. In vitro, an NO inhibitor reverses the hyporeactivity of blood vessels from cirrhotic rats to vasoconstrictors [34]

All these results strongly support the hypothesis that increased NO production is a major factor in the peripheral arterial vasodilation of cirrhosis. Agents promoting nitric oxide production include inflammatory

cytokines and endotoxin. In that regard, selective intestinal decontamination with norfloxacin partially reverses the hyperdynamic circulatory state in cirrhotic patients, suggesting a role for the endotoxin-NO pathway [35]. Where does this endotoxin come from in cirrhosis? First, alcohol is a major cause of cirrhosis in Western countries, and alcoholic gastrointestinal mucosal damage [36], could potentially facilitate transfer of bacteria into the circulation. Second, portosystemic shunting allows gut-derived bacterial endotoxins passage to the systemic circulation. Third, cirrhotic patients with portal hypertension show intestinal structural abnormalities characterized by vascular congestion and edema, which leads to increased intestinal permeability to bacterial toxins [37]. Fourth, intestinal bacterial overgrowth and bacterial translocation are increased in cirrhosis [38]. Besides endotoxins, the other possible factors stimulating NO production include cytokines such as TNF-α, IL-1, IL-6, and IFN-γ[39-41]. Among these, TNF-α has been studied the most. Lopez-Talavera et al found that anti-TNF-α antibody increases mean arterial pressure and systemic vascular resistance, and decreases cardiac index and portal pressure [42]. In 4-week BDL rats, in parallel with increased serum TNF-α, aortic NOS3 expression and serum nitrate/nitrite concentrations were increased [43].

Although the evidence is strong that the increased NOS activity in cirrhosis plays an important role in hyperdynamic circulation in cirrhosis, it

remains obscure which NOS isoform is involved. The majority of previous studies have used a nonspecific NOS inhibitor to diminish NO production. However, a recent study used aminoguanidine, a preferential inhibitor of NOS2 (inducible NOS), and showed that in vivo, the hyperdynamic circulation in portal hypertensive rats is reversed [44]. But in another study aminoguanidine had no in vitro effect on the hyporeactivity of aortic rings from cirrhotic rats [45]. We have recently evaluated the activity of the L-arginine-NO pathway at different levels [43]. Although NOS2 mRNA was detectable in the cirrhotic aorta, no NOS2 protein was observed in our Western blots. It is unclear why the mRNA was not expressed as a protein. It might have been degraded or not been transcribed. It is also possible that our method of Western blotting did not allow the detection of small amounts of NOS2 protein.

A consistent augmentation in the expression of NOS3 mRNA and protein levels is observed in cirrhotic rats. Because NOS3 can be upregulated by stimuli such as shear stress and mechanical deformation, some have suggested that hyperdynamic circulation is the cause rather than the consequence of the activation of the NO pathway [31, 46, 47]. In addition, there may be other reasons for the increased NOS3. Cirrhosis is associated with increased levels of estrogens [48, 49], and these compounds have been shown to upregulate NOS3 activity[50]. Other factors which may stimulate NOS3

expression need further investigation.

What is the role of another isoform of NOS, neuronal NOS (nNOS or NOS1)? Xu and his colleagues have demonstrated that nNOS expression is significantly increased in rat cirrhotic aortae [51]. Furthermore, a nNOS-specific inhibitor, 7-nitroindazole (7-NI), significantly decreased the sodium and water retention and normalized the hyperdynamic indices such as cardiac index, mean arterial pressure, and systemic vascular resistance in these rats [51]. Biecker et al also showed that nNOS partially compensates for the absence of eNOS in producing hyperdynamic circulation in eNOS-gene knockout mice [52]. These data indicate that the nNOS isoform plays a major pathogenic role in hyperdynamic circulation, and perhaps even in renal salt and water retention in cirrhosis.

It seems that endocannabinoids and nitric oxide may both play an important role in hyperdynamic circulation, but what is the relationship between them? The literature remains inconclusive. In a kidney study, Deutsch et al found that the vasodilatation of anandamide is NO dependent, because the NOS inhibitor L-NAME completely blocked the vasodilatory effect of anandamide, similar to a CB1 antagonist [53]. However, another study showed no effect of L-NAME infusion on the hypotensive effects of anandamide [24].

Some studies suggest the possible involvement of other humoral vasodilators, but a definitive pathogenic role for any of these substances remains elusive. This list includes: glucagons [54], prostaglandins [55], GABA[56], VIP [57], bile acids [58], endotoxin, histamine [59] and adenosine[60].

Central neural mechanisms

Although most research has focused on the humoral mediators, in recent years we and others have shown an important mechanistic role of central nervous system (CNS) activation. A decade ago, it was demonstrated that primary afferent denervation by capsaicin reversed the hyperdynamic circulation in rats with cirrhosis or portal hypertension due to portal vein stenosis (PVS)[61]. What is the relationship between the CNS and hyperdynamic circulation in portal hypertension? Using c-fos, an immediate-early gene (whose protein product can be detected by immunohistochemistry as Fos), as a marker of central neuronal activation, it was showed that the brainstem and hypothalamic cardiovascular-regulatory nuclei are activated at the first day after PVS, whereas the hyperdynamic circulation does not start up until 3-5 days after PVS. This time sequence suggests that central neural activation is the initiating signal in the pathogenesis of hyperdynamic circulation.

Subsequently, in portal hypertensive rats, when c-fos antisense oligonucleotide was microinjected into one of the major cardiovascular-

regulatory brainstem nuclei, the nucleus tractus solitarius (NTS), to block local Fos expression. This treatment completely blocked the development of the hyperdynamic circulation, i.e., abnormalities in cardiac output, mean arterial pressure and systemic vascular resistance were completely eliminated [62]. In normal control rats, c-fos antisense oligonucleotides had no effect[62]. These results indicate that central neural activation is a sine qua non for the development of the hyperdynamic circulation in portal hypertension.

The CNS, as the controller of the circulation, presumably would not arbitrarily activate the cardiovascular system without reason. This raises the question of what the initiating signal is. Likely, it is somehow related to the portal hypertension per se. Moreover, the exact route of signaling from the periphery to the CNS remains unclear. The aforementioned capsaicin study suggests that primary afferent nerves may be the signaling pathway from the periphery to the CNS [61]. A subsequent study showed that capsaicin-treated BDL rats improve the renal function and do not develop ascites[63]. Moreover, both BDL-cirrhotic and portal hypertensive rats show diminished Fos expression in NTS after capsaicin-induced denervation of the afferent nerves as neonates[63]. These observations indicate that intact primary afferent innervation is necessary for the central neuronal activation and development or maintenance of hyperdynamic circulation. Additionally, sodium retention and ascites formation is also dependent on either the presence of

hyperdynamic circulation or intact afferent innervation, or both. The complex relationship between CNS activation, local or neurohormonal humoral factor stimulation, and cardiovascular disturbances in cirrhosis/portal hypertension continues to be studied in several labs.

Cirrhotic Cardiomyopathy

This syndrome was first described in the late 1960s, although for many years, it was mistakenly attributed to latent or subclinical alcoholic cardiomyopathy [64-66]. However, studies in human and animal models with nonalcoholic cirrhosis, dating from the mid-1980s showed a similar pattern of increased baseline cardiac output with blunted response to stress [21]. The clinical features of cirrhotic cardiomyopathy include blunted systolic and diastolic contractile responses to stress, in conjunction with evidence of ventricular hypertrophy or chamber dilatation and electrophysiological abnormalities including prolonged QT interval. Recent studies suggest the presence of cirrhotic cardiomyopathy may contribute to the pathogenesis of hepatorenal syndrome precipitated by spontaneous bacterial peritonitis[67] acute heart failure after insertion of transjugular intrahepatic portosystemic shunts (TIPS) [68, 69], and increased cardiovascular morbidity and mortality after liver transplantation[70]. Therefore this syndrome is more than an academic curiosity, but rather an important clinical entity.

Endocannabinoids

Endocannabinoids are known to have a negative inotropic effect on cardiac contractility in both human[71] and rats[72]. The plasma level of an endogenous cannabinoid, anandamide, is known to be increased in cirrhosis [23]. We recently demonstrated a major role for increased local cardiac production of endocannabinoids in cirrhotic cardiomyopathy [73]. This conclusion is based on the restoration of blunted contractile response of isolated left ventricular papillary muscles from BDL-cirrhotic rats after preincubation with a CB1 antagonist, AM251. Additionally, endocannabinoid reuptake blockers (VDM11 and AM404) enhance the relaxant response of cirrhotic papillary muscle to higher frequencies of contraction in an AM251-sensitive fashion, suggesting an increase in the local production of endocannabinoids acting through CB1 receptors. Other in vitro evidence suggests a main neuronal source for the increase in local production of endocannabinoids, as these effects were mostly abolished by pretreatment with the neurotoxin tetrodotoxin.

β -adrenergic signaling

Cardiac-adrenergic signaling is one of the main regulators of cardiac contractility. Adrenergic receptors increase adenylyl cyclase activity through stimulatory G proteins. Increased production of cAMP in turn results in an increase in calcium influx and contractile force mainly through activation of

protein kinase A (PKA). We have previously shown that expression and responsiveness of β-adrenergic receptors[74] as well as its post receptor signaling pathway is blunted in cardiac tissue of cirrhotic rats. Post receptor impairment was found at different levels including content and function of stimulatory Gs-proteins[75], uncoupling of the β-adrenoceptor-ligand complex from G protein[76], and responsiveness of adenylyl cyclase to stimuli[75, 77].

Membrane fluidity

Biochemical and biophysical properties of the cell membrane determines the mobility of membrane-bound protein moieties. This mobility is known as membrane fluidity[78], which is shown to be an important factor in the function of a number of membrane-bound receptors including β-adrenergic receptors[79]. It was shown that membrane fluidity in cardiomyocytes from bile duct-ligated rats is decreased in association with an increase in membrane cholesterol content and cholesterol/phospholipids ratio[75]. Restoration of these abnormalities in vitro results in normalization of blunted response of β-adrenergic receptors[75]. Alterations in membrane fluidity may also play a role in abnormal function of other membrane-bound components in cirrhotic cardiomyocytes including ion channels. The significant decrease in K^+ currents through Ca^{2+}-independent transient outward K^+ channel and the delayed rectifier current reported by Ward et al

is an example that requires further investigation[80].

Nitric oxide

Nitric oxide is known to negatively regulate cardiac contractile function. It has been shown to be involved in some types of cardiac dysfunction including ischemic heart disease[81]. Balligand et al have reported that non-selective blockade of NOS augments the contractile response of rat ventricular myocytes to the β-agonist isoproterenol without affecting the baseline contractility[82]. Whether this effect is mediated by the inhibition of adenylyl cyclase activity by NO[83] or through the second messenger, cyclic guanosine monophosphate (cGMP), remains to be elucidated. Possible effects of NO on cardiac function in physiological and some pathophysiological states were extensively reviewed previously[84, 85].

As noted previously, cirrhosis is known to be associated with NO overproduction[46]. Involvement of NO overproduction in the development of cirrhotic cardiomyopathy was first reported in 1996 by Van Obbergh et al in the BDL rat. They showed that a nonselective NOS inhibitor, L-NMMA, restored the blunted contractile function of isolated heart from cirrhotic rats while it had no significant effect in control animals[86]. A similar effect was reported in isolated left ventricular papillary muscles of cirrhotic rats. Furthermore, it was observed that iNOS and not eNOS mRNA and protein

expression were significantly increased in the heart of a cirrhotic rat [39]. Increased levels of cGMP in cirrhotic ventricles and elevated serum and cardiac levels of cytokines like TNF-α suggest a cytokine/iNOS/cGMP pathway for this effect [39].

Carbon monoxide

Carbon monoxide (CO) is mainly produced in the body through the action of heme oxygenases. These enzymes are responsible for converting heme to biliverdin and CO. Like NO, CO activates soluble guanylate cyclase resulting in increased levels of cGMP [87, 88]. Expression of inducible heme oxygenase (HO-1) mRNA was increased in the right ventricle in a canine model of congestive heart failure [89]. We previously reported an increase in mRNA and protein expression of HO-1 in left ventricle of bile duct-ligated rats, which was associated with an increase in left ventricular cGMP levels [90]. Furthermore, treatment of cirrhotic heart with an HO inhibitor, zinc protoporphyrin IX, restored the elevated cGMP levels [90]. These findings suggest the involvement of an HO-CO-cGMP pathway in the development of cirrhotic cardiomyopathy.

Cardiomyopathies

The cardiomyopathies are a group of diseases that primarily affect the heart muscle and are not the result of congenital, acquired valvular, hypertensive, coronary arterial or pericardial abnormalities. Two

fundamental forms of cardiomyopathy are recognized: (1) a primary type, consisting of heart muscle disease predominantly involving the myocardium and/or of unknown cause; and (2) a secondary type, consisting of myocardial disease of known cause or associated with a systemic disease such as amyloidosis or chronic alcohol use. In many cases it is not possible to arrive at a specific etiologic diagnosis, and thus it is often more desirable to classify the cardiomyopathies into one of three morphologic types (dilated, restrictive, and hypertrophic) on the basis of differences in their pathophysiology and clinical presentation. About one in three cases of congestive heart failure is due to dilated cardiomyopathy (DCM). LV and/or right ventricular (RV) systolic pump function is impaired, leading to progressive cardiac dilatation. The electrocardiogram (ECG) often shows sinus tachycardia or atrial fibrillation, ventricular arrhythmias, left atrial abnormality, low voltage, diffuse nonspecific ST-T-wave abnormalities, and sometimes intraventricular and/or AV conduction defects. Echocardiography shows LV dilatation, with normal, minimally thickened, or thinned walls, and systolic dysfunction. Circulating levels of brain natriuretic peptide are usually elevated. Hypertrophic cardiomyopathy (HCM) is characterized by LV hypertrophy, typically of a nondilated chamber, without obvious cause, such as hypertension or aortic stenosis. The ubiquitous pathophysiologic abnormality is diastolic dysfunction, which can be detected by Doppler

tissue imaging and results in elevated LV end-diastolic pressures; the latter may be present despite a hyperdynamic, nondilated LV. The ECG commonly shows LV hypertrophy and widespread deep, broad Q waves.

The hallmark of the restrictive cardiomyopathies (RCMs) is abnormal diastolic function .The ventricular walls are excessively rigid and impede ventricular filling. In late stages systolic function is also impaired. Myocardial fibrosis, hypertrophy, or infiltration due to a variety of causes is responsible. ECG often shows low-voltage, nonspecific ST-T-wave abnormalities and various arrhythmias. Echocardiography, reveal symmetrically thickened LV walls and normal or slightly reduced ventricular volumes and systolic function; the atria are usually dilated.

Doppler echocardiography typically shows diastolic dysfunction. Cardiac catheterization shows a reduced cardiac output, elevation of the RV and LV end-diastolic pressures, and a dip-and-plateau configuration of the diastolic portion of the ventricular pressure pulses resembling constrictive pericarditis.

Cirrhotic cardiomyopathy

In the absence of specific diagnostic criteria, the exact prevalence of cirrhotic cardiomyopathy remains unclear. At present, cirrhotic cardiomyopathy can be defined as the constellation of one or more of these following factors[74]:

- Normal or increased left ventricular systolic contractility at rest, but attenuated systolic or diastolic responses to stress stimuli,
- Structural or histological changes in cardiac chambers, Electrophysiological abnormalities such as prolonged ectrocardiographic QT interval,
- Serum markers suggestive of cardiac stress.

Systolic dysfunction

Despite the increased or normal cardiac output at rest, under physiological stress cirrhotic patients fail to mount an adequate stimulatory cardiac response. Gould et al documented in cirrhotic patients that with exercise the left ventricular end-diastolic and pulmonary arterial pressures increased with no change in the cardiac index. In other words, cardiac output did not increase despite increased ventricular filling pressures, which indicates a highly impaired ventricular response[91]. Similarly Grose et al showed that when cirrhotic patients underwent maximal exercise, cardiac output increased by only 97%; this is considered inadequate when compared to approximately 300% increase in healthy controls[92]. Similar blunted cardiac systolic response to exercise was also demonstrated by Wong et al[93]; moreover patients with ascites showed greater dysfunction than those with preascitic cirrhosis.

The cardiac response to different physiological stimuli, including Valsalva's maneuver, ice-cold skin stimulation, and mental stress was investigated by Lunzer et al and found to be inadequate[94]. Lee and colleagues showed an inappropriate decrease in the cardiac output in the postprandial state in cirrhotic patients[95]. Blunted cardiac responsiveness has been reported in response to other pharmacological agents. Limas et al showed that angiotensin infusion in cirrhotics resulted in an increase in the pulmonary wedge pressure, which reflects left ventricular filling pressure, without any change in the cardiac output[96]. Blunted cardiac responsivenesshas also been documented in response to catecholamine infusions[97].

Diastolic dysfunction

Diastolic dysfunction is thought to be more prevalent in cirrhotic patients[98]. This is manifested by a stiff, noncompliant ventricle that impairs diastolic filling. Finucci et al compared the diastolic function in 42 cirrhotic patients with 16 healthy controls. The cirrhotic patients had increased left ventricular end-diastolic and left atrial volumes, stroke volume, and late diastolic flow velocity compared to normal controls; these results indicate an impaired left ventricular relaxation in the cirrhotic patients[98]. A widely-used index of diastolic function is the echocardiographic E/A ratio. This is the velocity of the diastolic early filling wave (E) divided by the velocity of the

late (or atrial) filling wave (A). Normally, this ratio is >1. Many studies have demonstrated a low E/A in patients with cirrhosis[99].

Structural/histological changes

Multiple studies were conducted to evaluate the heart mass in patients with liver cirrhosis. Most studies did not show any significant structural changes in liver cirrhotic patients[100]. However, some have reported changes of left ventricular hypertrophy in both humans and in portal hypertensive rats[84]. Studies evaluating the heart mass using echocardiography reported enlarged left atrial volumes with normal ventricular volumes[101]. Others however, reported increases in both the end-diastolic and end-systolic volumes of the left ventricle[102]. Changes involving the right heart chambers are less pronounced and were normal in most studies[103]. These cardiac changes may be related to the hyperdynamic circulation of cirrhosis and were correlated with its severity in some studies. The presence of cardiac histological changes has been described in several autopsy studies. Findings include myocardial hypertrophy, cardiomyocyte edema, fibrosis, nuclear vacuolation, and unusual pigmentation[103]. However, these changes were reported from studies dating back at least 50 years in patients suffering from alcoholic cirrhosis. Lunseth et al studied the autopsies of 108 patients with cirrhosis from all causes (although most were alcoholic) and demonstrated

the same cellular myocardial abnormalities that were described in earlier studies[104]. Other studies conducted on animal models including some of our work on long-term bile duct ligated cirrhotic rats failed to show any histological changes by light microscopy[105]. This discrepancy between the histological changes in human and animal studies is probably related to the long disease duration in cirrhotic patients versus the much shorter periods needed to induce cirrhosis in animal models.

Electrophysiological abnormalities

QT prolongation has been described in patients with liver disease and is significantly related to the severity of the underlying liver disease[106]. However, significant ventricular arrhythmias and sudden cardiac death remain uncommon. The prolonged QT interval is thought to revert to normal following improvement in liver function and liver transplantation[107]. The effect of β-adrenergic blockade on the prolonged QT interval in cirrhotic patients was also evaluated and was found to reduce the prolonged QT interval towards normal[108]. Henriksen et al examined the temporal relation between electrical and mechanical systole in patients with liver cirrhosis and in addition to the prolonged QT interval in their study population they also showed alteration in the cardiac excitation-contraction temporal relationship[109]. In conclusion the prolonged QT interval is well linked to liver disease and is a feature of cirrhotic cardiomyopathy. Its exact

mechanism and its prognostic significance require further study.

Serum markers

Cardiac troponin I and the family of natriuretic peptides were noted to be elevated in cirrhotic cardiomyopathy, possibly reflecting the underlying myocardial strain. Atrial natriuretic peptides (ANP) are released mainly by the atria in response to stretch, and brain or B-type natriuretic peptide (BNP) by the ventricles[110]. Troponin I increases in conditions leading to ventricular hypertrophy or dilatation. Pateron et al showed an increased serum troponin I level in about 1/3 of cirrhotic patients. Elevated levels correlated with decreased ventricular stroke volume index[111]. In cirrhotic patients, BNP levels correlated significantly with septal thickness and end-diastolic left ventricular diameter [112,113]. These results suggest the potential role of these markers for screening patients with cirrhosis for the presence of cirrhotic cardiomyopathy, and thereby identifying such patients for further investigations.

Echocardiography

Echocardiography increasingly has become a key component in the routine evaluation of patients with suspected or known cardiovascular disease. Two-dimensional (2D) echocardiography is able to visualize the heart directly in real time using ultrasound, providing instantaneous assessment of the myocardium, cardiac chambers, valves, pericardium, and

great vessels. Doppler echocardiography measures the velocity of moving red blood cells and has become a noninvasive alternative to cardiac catheterization for assessment of hemodynamics.

2D echocardiography is an ideal imaging modality for assessing left ventricular (LV) size and function. 2D echocardiography is useful in the diagnosis of LV hypertrophy and is the imaging modality of choice for the diagnosis of hypertrophic cardiomyopathy. Other chamber sizes are assessed by visual analysis, including the left atrium and right-sided chambers. Doppler echocardiography uses ultrasound reflecting off moving red blood cells to measure the velocity of blood flow across valves, within cardiac chambers, and through the great vessels. Normal and abnormal blood flow patterns can be assessed noninvasively. Color-flow Doppler imaging displays the blood velocities in real time superimposed upon a 2D echocardiographic image. Doppler echocardiography allows noninvasive evaluation of ventricular diastolic filling. The transmitral velocity curves reflect the relative pressure gradients between the left atrium and ventricle throughout diastole. They are influenced by the rate of ventricular relaxation, the driving force across the valve, and the compliance of the ventricle. There is a progression of diastolic dysfunction, which can be assessed by Doppler flow velocity curves. In the early phase of diastolic dysfunction there is primarily an impairment of LV relaxation, with reduced early transmitral

flow and a compensatory increase in flow during atrial contraction. As disease progresses, and ventricular compliance declines, left atrial pressure rises, resulting in a higher early transmitral velocity and shortening of the deceleration of flow in early diastole so that the filling pattern becomes normal, termed pseudonormalization. In patients with the most severe diastolic dysfunction and further elevation of left atrial pressure, early diastolic flow velocity rises further, termed the restrictive filling pattern. The addition of analysis of Doppler tissue velocities of annular motion provides further information concerning the diastolic properties. The systolic function is evaluated with the following parameters in echocardiography.

Ejection fraction

Simpson's apical biplane method is recommended as the accurate echo measure of LVEF.

- Fractinal shortening at endocardium and midwall
- Stress-shortening relations
- Pressure volume analysis

The prevalence and extent of systolic dysfunction in cirrhotic patients variable. If present, it is unlikely to manifest itself without a stimulus. Stroke volume and contractile indices such as dP/dt (first derivative of ventricular pressure generation) typically are normal or even increased at rest. Conventional Doppler echocardiography is the method of choice in

assessment of diastolic function. The peak velocities of LV filling during the early rapid (E wave), atrial contraction (A wave) phases, the ratio of the 2 filling velocities (E/A ratio), E wave deceleration time and the isovolumetric relaxation time are recorded at end-expiration for 5 consecutive beats at baseline and again during the phase of Valsalva maneuver. Diastolic dysfunction represents a decrease in left ventricular filling and reduced possibility to maintain stroke volume without a compensatory increase of atrial filling pressures. This condition usually precedes the development of systolic dysfunction and is the main determinant of heart failure. Diastolic dysfunction appears to be more prevalent in patients with cirrhotic cardiomyopathy.

Electrocardiogram

The electrocardiogram is a graphic recording of electric potentials generated by the heart. The signals are detected by means of metal electrodes attached to the extremities and chest wall and are then amplified and recorded by the electrocardiograph. ECG leads actually display the instantaneous differences in potential between these electrodes. Electrophysiological changes including prolonged depolarization and impaired cardiac excitation-contraction coupling been demonstrated in cirrhotic patients. Repolarization prolongation manifested by a prolonged QT interval (more than 440 msec) on the electrocardiogram is found in 30–

50% of patients with cirrhosis. Severity of liver disease seems to be correlated to the degree of QT prolongation. These changes disappear after liver transplantation in most patients.

MATERIALS AND METHODS

The present study was conducted in the Kilpauk Medical College Hospital, between November 2009 and October 2010. 100 patients of chronic liver disease were selected for the study. These patients were admitted in the general medical wards.

Criteria followed for selection of patients includes:

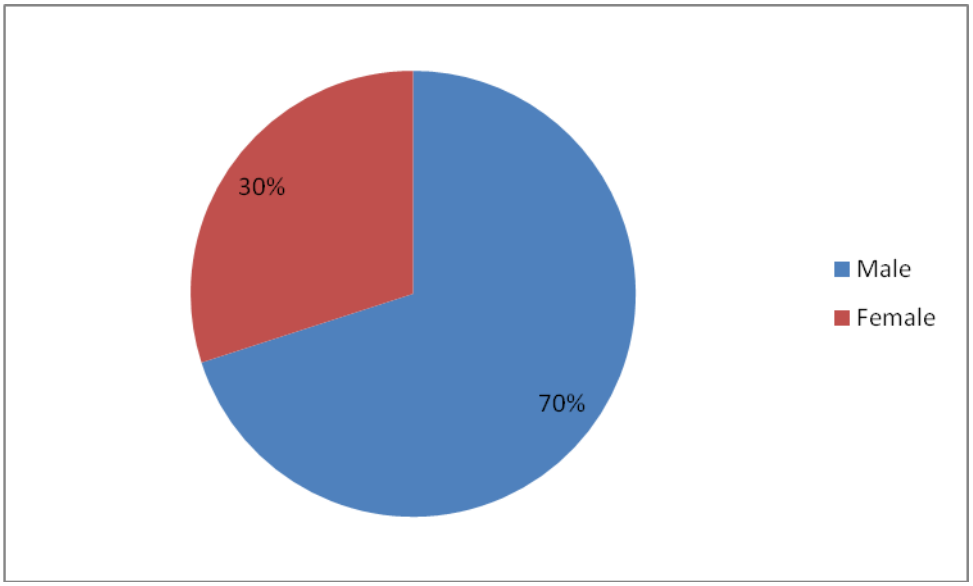
1. Only patients with clinical, biochemical and sonographic evidence of chonic liver disease – cirrhosis were selected.
2. Patients with previously detected heart disease were excluded from the study.
3. Patients with inter current illness and those who were critically ill were excluded from the study.
4. Patients with cardiac cirrhosis were excluded from the study.

A detailed history was elicited from the patient with special reference to cardiovascular symptoms. A thorough physical examination was performed in the patients and a special note was made regarding heart rate & rhythm, blood pressure, jugular venous pulse and pressure and precordial examination.

All patients were subjected to routine investigations viz, Blood urea sugar, complete haemogram, serum cholestrol & liver function tests. All patients were subjected to ultrasound scan abdomen to confirm the diagnosis of chronic liver disease. Patients with ascites underwent abdominal paracentesis and fluid was analyzed for protein content and cells. All patients were then subjected to electrocardiography, chest X-ray and M- mode 2-Dimensional echocardiography.

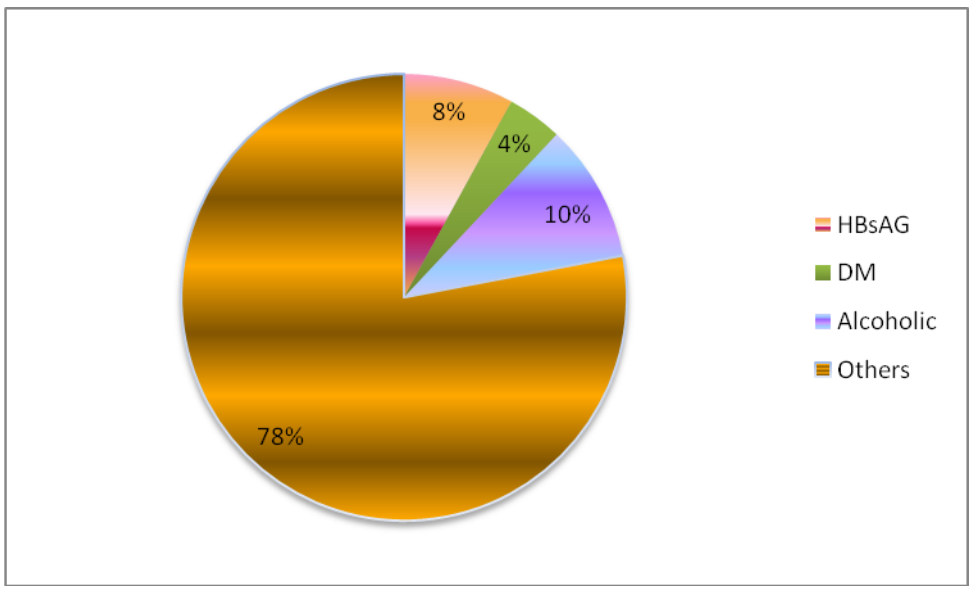
RESULTS AND OBSERVATION

Fig 9



Out of the 100 patients studied 70 (70%) were males and 30 (30%) were females (Fig 9). The age of the patients ranged from 19 years to 75 years.

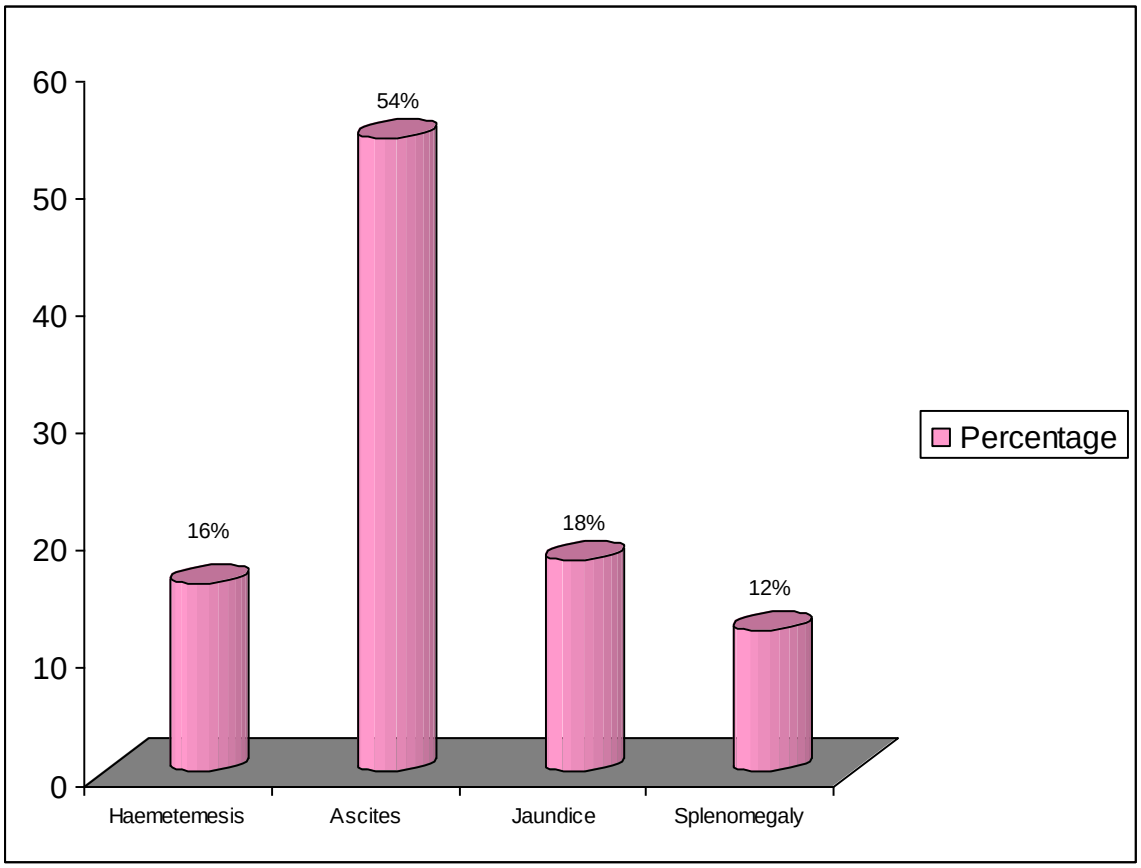
Fig 10



10 Patients (10%) were alcoholics, 28 patients (28%) had past history of jaundice or, 16 patients (16%) presented with haemetemesis (fig : 11) on admission and 54 patients (54%) had ascites, 18 patients (18%) had jaundice and 12 patients (12%) had clinically detectable splenomegaly on admission. Among this 8 patients were HbsAG+ (8%) and 4 patients were diabetics (4% (fig : 10). All patients had sonographic evidence of cirrhosis with portal hypertension.

TYPE OF CLINICAL RESENTATION

Fig 11



Regarding the cardiovascular examination 40 (40 %) out of 100 Patients had symptoms referable to the heart table below :

CARDIO VASCULAR SYMPTOMS AND SIGNS

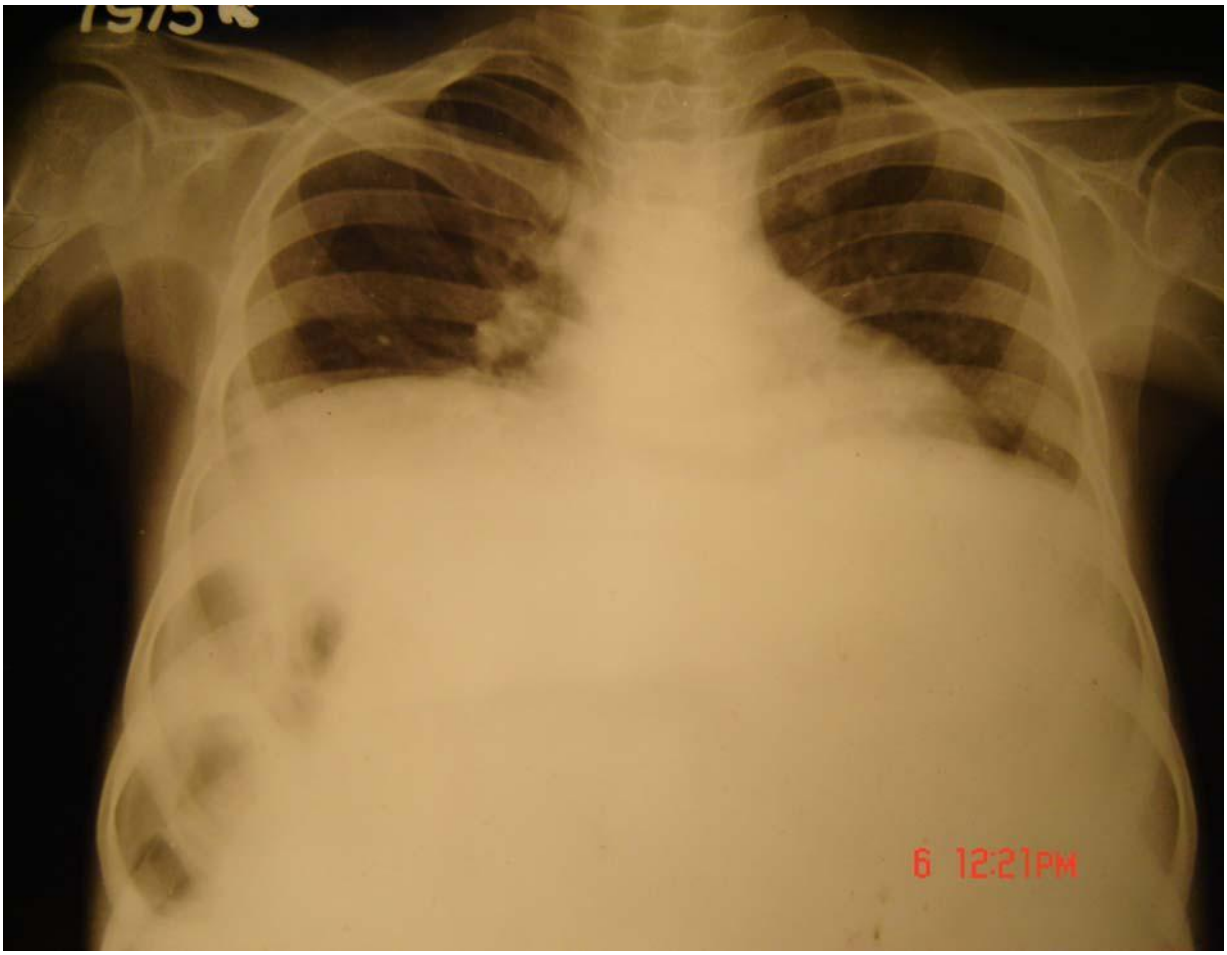
S. No	VARIABLE	MEAN	RANGE
1	SYMPTOMS PRESENT	40	-
2	PULSE RATE	84/min	54 TO 120/MIN
3	JVP ELEVATION	12%	-
4	BLOOD PRESSURE SYSTOLIC DIASTOLIC MAP	 110 mmHg 70 mmHg 84 mmHg	 90 to 160 mmHG 50 to 100 mmHG 70 to 110 mmHG
5	HEART MURMURS	6 %	-
6	CONGESTIVE CARDIAC FAILURE	6 %	-

6 Patients (6%) had congestive cardiac failure. The average pulserate was 84 and it ranged from 54/m to 120/m. The jugular venous pressure was elevated in 12 (12%) patients. The systolic blood pressure ranged from 90mmHg to 160 mm Hg, the average being 110.mmHg. The diastolic blood pressure ranged from 50mmhg to 100 mm Hg, the average being 70 mmHg. The mean arterial pressure ranged from 70 mmHg to 110mmHg the average being 86 mmHg Functional high output systolic flow murmur was detected in 6 (6%) patients.

Out of 100 patients 6 patients had elevated blood pressure. Previous studies shows that the systolic blood pressure more than 160mm HG and diastolic blood pressure more than 95 mmHg are the range for hypertension in cirrhorotic patients.

X- RAY CHEST IN ASCITES PATIENT

Fig 12

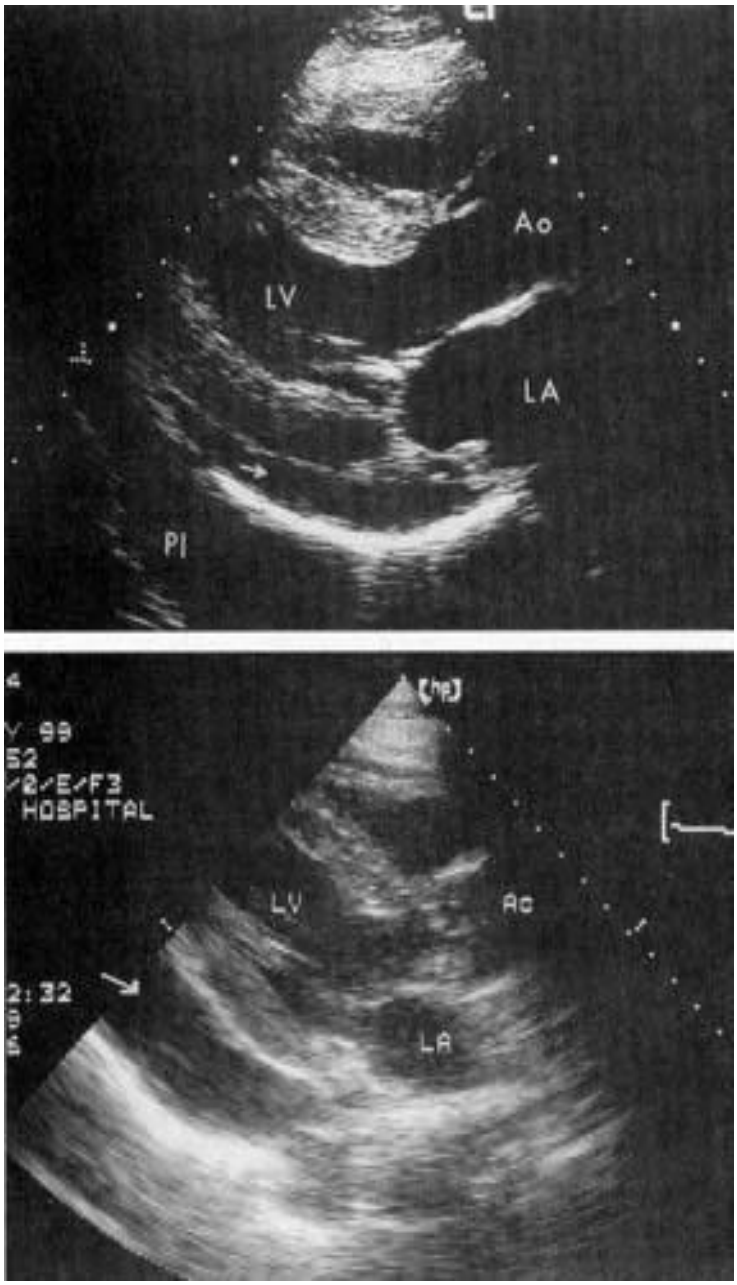


The electro cardiac gram showed an average heart rate of 82 / m. The low QRS voltage in chest leads and limb leads were found in 20 patients. T wave inversion was found in chest leads (V_1 to V_3/ $V_{6)}$ in 8 (8%) patients, in II, III avf in 14 patiens (14%). Regarding Hemiblock 4 (4%) cases were observed in the study. qs complex in anterior & Inferior leads is seen in 8 patients (8%).

The chest roentgenogram showed Hepatic Hydrothorax in 10 patients (10%). Cardio megaly was evident in chest X – ray in 22 patients (22%) (Fig: 12).

M-Mode 2 Dimensional Echocardiographic studies, done showed abnormality in 30 (30%) patients. Pericardial effusion (fig: 13) was detected in 8 (8%) patients. Regarding enlargement of cardiac chambers – all 4 chambers were enlarged in 6 (6%) patients. With global hypokinesia and left ventricular hypertrophy in 2 (2%) patient. Two cases of porto Pulmonary HT was observed in our study (2 %). Akinesia of inferior and anterior wall was seen in 8 (8%) patients and hyperdynamic flow due to anemia was observed in 4 patients (4 %).

FIG.13.ECHO SHOWS MILD PERICARDIAL EFFUSION



DISCUSSION

The aetiology of cirrhosis (chronic liver disease) in patient under study showed a slightly higher incidence of post hepatic or post necrotic cirrhosis as compared to western studies.

With regard to the cardiovascular evaluation, the average heart rate in present study was 84±2 beats per minute. Other studies showed the average heart rate as follows.

Lenz K, Lleinberger G et al 1985	–	101/min +2 Vs 78
Bernard M, Rubbloli et al 1991	-	79/min +2 Vs 71
McCormnick P.A; Chin J et al 1995	-	101/min + 2 Vs 78
Present study 2006	-	84±/ min Vs 74

Thus the present study confirms that there is an increase in heart rate is cirrhosis liver as compared to the average heart rate of healthy subjects, reflecting a hyper dynamic circulatory state.

The average systolic blood pressure, diastolic blood pressure and mean arterial pressure in the present study were 110/ Hg and 70mm/Hg and 86mmHg respectively. In the other studies they were as follows.

Lenz L; Kleinberger G et al 1995 - Diastolic pressure 56 Vs McCormick PA, Chin H et al 1995 -86- Mean arterial pressure.

The present study shows that the mean arterial pressure is comparable with that of the study done by McCormick P.A et al but the diastolic pressure is within the normal range.

The elevation of jugular venous pulse in 12% of patients reflects an increase in the plasma volume and fluid over load. Significant correlation was demonstrated between the heart rate and mean arterial pressure both of which indicate a hyper dynamic circulation and serum albumin and serum bilirubin levels both of which are indicators of liver dysfunction. The present study clearly demonstrated that hyperdynamic circulation progressively increase with the severity of the liver dysfunction. The study quoted for this include Meng HG, Lin HC et al 1994 which also concludes that the severity of cirrhosis is closely related to the degree of hyperkinetic circulatory state and portal hypertension. Signification positive correlation was noted between decreased MAP in 36% and increased HR in 54% similarly decreased serum albumin in 32% and increased serum bilirubin in 44%.

The present study shown that out of 100 patients 6 patients are hypertensive 6%.

Regarding the electrocardiographic findings not many studies are available showing the various electrocardiographic abnormalities in cirrhosis liver. It has been said that cardiac arrhythmias in cirrhosis liver are always due to a definable precipitating event such as hypo or hyper kalemia,

acidosis, hypoxia or cardiac irritation due to insertion of lines, although in older patients the possibility of ischemic heart disease must not be ignored. One study by Walt, Toyonaga A et al 1995 demonstrated that cardiac arthythmias in common during surgery, the commonest arrhythmias is common during surgery, the commonest arrhythmias being premature ventricular contraction. The current study shows that low voltage QRS complexes were present in 20 patients. Out of which 8 had pericardial effusion probably reflecting the presence of occult pericardial effusion. T were inversion was noted in the precordial leads & limb leads in 22 patients and CAHD changes in 8 patients had no symptoms referable to the cardiac system.

S.NO	**ECG ABNORMALITIES**	**INCIDENCE N=48**	**% 48**
1	Low voltage complexes	20	20
2	CAHD old infarction	8	8
	ischemic changes	20	20

Chest roentgenograms showed that the elevated hemidiaphragms were the commonest abnormality detected and all these patients had ascites and the elevated hemidiaphragms probably reflecting increased intra-abdominal

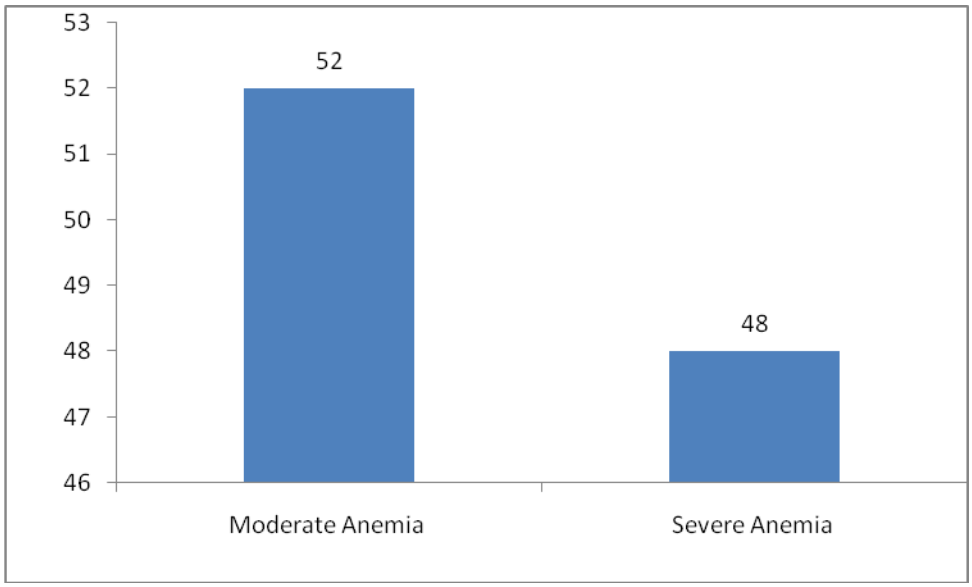
pressure. Cardiomegaly was detected in 22 patients. Hepatic Hydrothorax was found in 10 patients.

Chest roentgenograms evaluation of patients under study is an follows

x-Ray changes	Incidence N=32	% 32
Cardiomegaly	22	22
Hepatic hydrothorax	10	10

Echocardiographic evaluation of patients under study is as follows

S. No	Echo Abnormalities	Incidence N=30	%30
1	Cardiomyopathy Global Hypokinesia & Chamber enlargement Present.	6 (Out of 6, Two patients are alcoholic)	6
2	Pericardial Effusion	8	8
3	CAHD changes	10	10
4	Porto Pulmonary HT	2	2
5	Hyper dynamic flow due to anemia	4	4
6	LV Dysfunction (LUEF <49%)	6	6



Moderate Anemia <10 g % severe Anemia < 7 to 8 gm % (fig 14)

Current study shows that all the 100 patients were anemic that is <10gm %. Among this 48 (48%) patients were severely anemic and 52 (52%) patients are moderately anemic.

CONCLUSION

1. The result of this study clearly show that large number of patients, Chronic liver Disease with hepatic cirrhosis are asymptomatic (40%) with regard to cardiovascular system, have evidence of cardiac involvement in electrocardiography and echo cardiography
2. Cardiac decompensation in cirrhosis is rare despite the high output state and its presence as indicated by left ventricular systolic dysfunction.
3. The incidence of hypertension in chronic liver disease (cirrhosis) patients, our study shows 6 patients (6 %).
4. Electrocardiographic abnormalities includes low voltage complexes due to pericardial effusion non specific T wave abnormalities and CAHD changes.
5. Cardiomyopathy, pericardial effusion, portopulmanary hypertension and CAHD are the Echocardiographic abnor -malities detected in this study.
6. All the patients were anemic, either the hyperdynamic circulation and hyperkinetic syndrome is due to cirrhosis or due to anemia I still in controversy. Further it needs a long term follow up and study.
7. Cardiac evaluation is a pre-requisite in patients with cirrhosis undergoing stress like surgery because the presence of cardiac involvement adds to the morbidity and mortality.

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CARDIOVASCULAR CHANGES IN CHRONIC LIVER DISEASE

PROFORMA

NAME: AGE SEX M/F D.O.A

OCCUPATION : I.P.NO D.O.A

ALCOHOLIC : NON –ALCOHOLIC

KNOWN CARDIAC PATIENT YES / NO

COMPLAINTS

ABDOMINAL PAIN ABD MASS JAVNDICE

ABD DISTENTION HAEMATEMESIS MALENA.

CLINICAL FINDINGS

JAUNDICE HEPATOMEGALY SPLENOMEGALY

PEDAL OEDEMA JVP ↑

PULSE: BP: MAP:

INVESTIGATIONS

Hb : Blood Sugar :

Tc : Blood Urea :

Dc : Serum Creatinine :

RBC : Serum Electrolytes : Na+ :

PLATELETS: K+:

PCV : LET Ascitic Fluid

URINE ALB: Sr Bilirubin:

SUG: SGOT:

DEP: SGPT:

SAP:

HBsAG: Sr Protein:

Sr. Ceruloplasmin : Albumin:

Globulin:

ECG: CXR:

USG ABDOMEN: OGD:

ECHOCARDIOGRAM:

ABBREVIATION

ANP	Atrial Natriuretic Peptide
cAMP	Cyclic Adenosine Monophosphate
cGMP	Cyclic Guanosine Monophosphate
CO	Carbon Monoxide
DCM	Dilated Cardiomyopathy
E/A	E – Early Filling Wave
	A – Atrial Filling Wave
HCM	Hypertrophic Cardiomyopathy
HO-1	Heme Oxygenase
HVPG	Hepatic Venous Pressure Gradient
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
RCM	Restrictive Cardiomyopathy
TIPS	Transjugalar Intrahepatic Portosystemic Shunt
TNFα	Tumour Necrosis Factor α

KEY WORDS TO MASTER CHART

S.No	Serial Number
HR	Heart Rate
Sys BP	Systolic Blood Pressure
Dias BP	Diastolic Blood Pressure
MAP	Mean Arterial Pressure
Hb	Haemoglobin
Sr.Bil	Serum Bilirubin
Sr.Alb	Serum Albumin
Bld.Urea	Blood Urea
USG Abd	Ultra Sonogram Abdomen
CXR	Chest X-ray
Echo	Echocardiogram
Cirrh/PHT	Cirrhosis / Portal Hypertension
CAHD	Coronary Artery Heart Disease
LV Dysfunction	Left Ventricular Dysfunction
IWMI	Inferior Wall Myocardial Infarction
AWMI	Anterior Wall Myocardial Infarction

S. No	Name	Age / Sex	HR	Sys BP	Dias BP	MAP	Hb%	Sr. bil	Sr. alb	BLD Urea	USG ABD	CXR	ECG	ECHO
1	Ramalingam	52/M	84	100	70	80	6.2	6.8	3.5	30	Cirrh/PHT	Cardiomegaly	Ishaemic Changes	CAHD Chages
2	Agbar	55/M	88	110	70	84	5	1	3.5	15	Cirrh/PHT	Normal	Normal	Normal
3	Kamala	58/F	92	110	80	90	7.8	0.9	2	39	Cirrh/PHT	Cardiomegaly	Low voltage complex	Hyperdynamic flow
4	Baby	59/F	76	160	100	120	9.4	1	3.7	30	Cirrh/PHT	Cardiomegaly	Low voltage complex	CAHD Chages
5	Ravi	28/M	89	120	80	94	10.4	6	3	24	Cirrh/PHT	Normal	Normal	Normal
6	Arunchalam	45/M	92	110	70	84	8	1.2	3.4	36	Cirrh/PHT	Normal	Normal	Normal
7	Rathna	55/F	72	120	80	94	9	0.8	3.2	52	Cirrh/PHT	Normal	Normal	Normal
8	Moorthy	39/M	86	100	70	80	5.8	0.6	2.6	182	Cirrh/PHT	Normal	Normal	Normal
9	Karuppaiya	49/M	82	110	60	76	9	5.8	3	34	Cirrh/PHT	Cardiomegaly	Ishaemic Changes	CAHD Chages
10	Dharmaraj	35/M	74	160	96	113	9.2	1.4	2.8	36	Cirrh/PHT	Normal	Normal	Normal
11	Muthu	75/M	88	120	80	94	6	1.4	4.1	35	Cirrh/PHT	Cardiomegaly	Old IWMI	LV Dysfunction
12	Shanmugam	40/M	64	130	80	96	3.4	0.8	3.4	25	Cirrh/PHT	Normal	Low voltage complex	Pulmonary Hypertension
13	Madhavan	46/M	78	130	80	96	9	2.4	3	34	Cirrh/PHT	Normal	Low voltage complex	Normal
14	Balaganesh	39/M	98	100	70	80	6	0.1	2.8	37	Cirrh/PHT	Normal	Normal	Normal
15	Kumar	40/M	88	120	80	94	8.5	1.2	2.5	53	Cirrh/PHT	Hydrothorax	Ishaemic Changes	Pericardial effusion
16	Thiyagarajan	19/M	76	110	70	84	9.2	1.6	3	16	Cirrh/PHT	Normal	Normal	Normal
17	Padma	30/F	76	100	70	80	8	1.4	2.7	16	Cirrh/PHT	Normal	Normal	Normal

18	Babu	50/M	84	120	80	94	8	0.9	3.2	55	Cirrh/PHT	Hydrothorax	Ishaemic Changes	Pericardial effusion
19	Kathaiyan	40/M	86	100	70	80	7.8	1.2	3.4	36	Cirrh/PHT	Hydrothorax	Ishaemic Changes	Pericardial effusion
20	Arumugam	30/M	90	120	80	94	7.2	4	3	28	Cirrh/PHT	Normal	Normal	Normal
21	Sivapakkiam	40/F	88	110	70	83	6.8	1.4	3.3	41	Cirrh/PHT	Normal	Normal	Normal
22	Munusamy	19/M	86	120	70	86	7	1.4	3.4	3.2	Cirrh/PHT	Normal	Normal	Normal
23	Subramani	48/M	80	180	100	126	10.2	1.8	3.1	34	Cirrh/PHT	Normal	Low voltage complex	Normal
24	Jaya	47/F	96	120	80	94	9.2	1	2.3	34	Cirrh/PHT	Normal	Normal	Normal
25	Selvamani	50/M	98	120	70	86	8	3.4	2.7	28	Cirrh/PHT	Normal	Ishaemic Changes	Hyperdynamic flow
26	Suguna	48/F	80	110	80	90	6.4	2	3.4	22	Cirrh/PHT	Normal	Low voltage complex	Normal
27	Noornisha	27/F	88	110	70	84	8.8	0.8	3.2	28	Cirrh/PHT	Normal	Normal	Normal
28	Anand	60/M	90	100	70	80	4.6	0.8	3.3	22	Cirrh/PHT	Hydrothorax	Normal	Pericardial effusion
29	Ramesh	74/M	86	140	80	100	8.2	1.4	3	18	Cirrh/PHT	Cardiomegaly	Old AWMI	LV Dysfunction
30	Porkodi	35/F	82	120	80	94	6.2	1.4	2.8	24	Cirrh/PHT	Normal	Normal	Normal
31	Yusuf	39/M	96	110	70	84	7.2	8.2	3.4	18	Cirrh/PHT	Normal	Normal	Normal
32	Mani	63/M	88	120	70	86	2.8	0.9	3.2	32	Cirrh/PHT	Normal	Ishaemic Changes	Normal
33	Arumugam	65/M	86	110	80	90	9.2	0.8	3	28	Cirrh/PHT	Cardiomegaly	Old IWMI	LV Dysfunction
34	Ragumansha	52/M	98	100	80	86	6.4	1.6	2.8	23	Cirrh/PHT	Normal	Normal	Normal
35	Hema	50/F	80	130	80	96	8.2	1.4	2.7	17	Cirrh/PHT	Normal	Normal	Normal

36	Ratha	40/F	92	110	70	84	8.6	0.8	2.7	21	Cirrh/PHT	Normal	Normal	Normal
37	Padmavathi	30/F	84	110	70	83	8.8	0.8	3.5	15	Cirrh/PHT	Normal	Normal	Normal
38	Raman	47/M	80	110	80	90	9.2	1.2	3.2	24	Cirrh/PHT	Normal	Low voltage complex	Normal
39	Muthu	60/M	84	120	80	94	8.6	0.8	3.5	36	Cirrh/PHT	Cardiomegaly	Ishaemic Changes	Normal
40	Raja	45/M	80	110	80	90	5.6	2.6	3	43	Cirrh/PHT	Cardiomegaly	Ishaemic Changes	Normal
41	Dakshinamoorthy	65/M	96	120	80	94	9.2	1.2	2.5	46	Cirrh/PHT	Normal	Old AWMI	Normal
42	Arockia Mary	52/F	85	140	70	84	8	0.8	3.5	33	Cirrh/PHT	Normal	Normal	Normal
43	Ragavan	51/M	88	110	70	84	9.4	0.6	2.3	40	Cirrh/PHT	Normal	Low voltage complex	Normal
44	Kannan	50/M	84	110	80	90	4	0.8	2.8	38	Cirrh/PHT	Normal	Normal	Normal
45	Kaliaperumal	55/M	84	120	80	94	9.2	0.8	3.3	30	Cirrh/PHT	Cardiomegaly	Low voltage complex	Normal
46	Senthil	42/M	90	110	70	84	8.6	1	4	19	Cirrh/PHT	Cardiomegaly	Ishaemic Changes	CAHD Chages
47	Kamatchi	40/F	96	110	80	90	9.8	4	3	21	Cirrh/PHT	Normal	Normal	Normal
48	Lakshmi	35/F	80	110	70	84	7.6	1.2	2.6	94	Cirrh/PHT	Normal	Normal	Normal
49	Samikannu	65/M	98	120	80	94	6.4	3	2.4	56	Cirrh/PHT	Cardiomegaly	Low voltage complex	Normal
50	Dhatayuthapani	53/M	76	130	80	96	8.2	2.8	3.7	42	Cirrh/PHT	Normal	Normal	Normal
51	Subbiah	42/M	64	130	80	96	3.4	0.8	3.4	25	Cirrh/PHT	Normal	Low voltage complex	Normal
52	Sreedhar	38/M	98	100	70	80	6	0.1	2.8	37	Cirrh/PHT	Normal	Normal	Normal
53	Hari Krishnan	74/M	86	140	80	100	8.2	1.4	3	18	Cirrh/PHT	Cardiomegaly	Old AWMI	LV Dysfunction

54	Pandi	74/M	88	120	80	94	6	1.4	4.1	35	Cirrh/PHT	Cardiomegaly	Old IWMI	LV Dysfunction (Diastolic)
55	Duraisamy	60/M	90	100	70	80	4.6	0.8	3.3	22	Cirrh/PHT	Normal	Ishaemic Changes	Normal
56	Adhikesavan	21/M	76	110	70	84	9.2	1.6	3	16	Cirrh/PHT	Normal	Normal	Normal
57	Sanmugam	52/M	84	100	70	80	6.2	6.8	3.5	30	Cirrh/PHT	Normal	Low voltage complex	Hyperdynamic flow
58	Natesan	48/M	78	130	80	96	9	2.4	3	34	Cirrh/PHT	Hydrothorax	Normal	Normal
59	Gowri	32/F	88	110	70	84	8.8	0.8	3.2	28	Cirrh/PHT	Normal	Normal	Normal
60	Murali	55/M	86	110	70	84	5	1	3.5	15	Cirrh/PHT	Normal	Ishaemic Changes	Normal
61	Nelson	48/M	80	180	100	126	10.2	1.8	3.1	34	Cirrh/PHT	Normal	Ishaemic Changes	Normal
62	Parasuraman	30/M	82	120	80	94	10.4	6	3	24	Cirrh/PHT	Normal	Normal	Normal
63	Vinayagam	40/M	86	100	70	80	7.8	1.2	3.4	36	Cirrh/PHT	Hydrothorax	Normal	Pericardial effusion
64	Arusiya	52/F	72	120	80	94	9	0.8	3.2	52	Cirrh/PHT	Normal	Normal	Normal
65	Kumarasen	50/M	84	120	80	94	8	0.9	3.2	55	Cirrh/PHT	Hydrothorax	Normal	Pericardial effusion
66	Ramakrishnan	45/M	92	110	70	84	8	1.2	3.4	36	Cirrh/PHT	Normal	Low voltage complex	Normal
67	Perumal	53/M	82	110	60	76	9	5.8	3	34	Cirrh/PHT	Normal	Ishaemic Changes	Normal
68	Jayasankar	35/M	74	160	96	113	9.2	1.4	2.8	36	Cirrh/PHT	Normal	Normal	Normal
69	Kajendran	41/M	86	100	70	80	5.8	0.6	2.6	182	Cirrh/PHT	Normal	Low voltage complex	Normal
70	Manivannan	65/M	84	120	80	94	9.2	1.2	2.5	46	Cirrh/PHT	Cardiomegaly	Ishaemic Changes	CAHD Chages
71	Malliga	35/F	82	120	80	94	6.2	1.4	2.8	24	Cirrh/PHT	Normal	Normal	Normal

72	Kesavan	60/M	84	120	80	94	9.2	0.8	3.3	30	Cirrh/PHT	Hydrothorax	Normal	Pericardial effusion
73	Loganathan	64/M	88	120	70	86	2.8	0.9	3.2	32	Cirrh/PHT	Cardiomegaly	Low voltage complex	Normal
74	Narayani	35/F	80	110	70	84	7.6	1.2	2.6	94	Cirrh/PHT	Normal	Normal	Normal
75	Manickam	39/M	94	110	70	84	7.2	8.2	3.4	18	Cirrh/PHT	Normal	Low voltage complex	Normal
76	Jayaraman	65/M	98	120	80	94	6.4	3	2.4	56	Cirrh/PHT	Normal	Ishaemic Changes	Normal
77	Malar	31/F	84	110	70	83	8.8	0.8	3.5	15	Cirrh/PHT	Normal	Normal	Normal
78	Kuppasamy	65/M	86	110	80	90	9.2	0.8	3	28	Cirrh/PHT	Cardiomegaly	Old AWMI	Normal
79	Kanniyappan	53/M	78	130	80	96	8.2	2.8	3.7	42	Cirrh/PHT	Normal	Normal	Normal
80	Krishnan	58/M	84	120	80	94	8.6	0.8	3.5	36	Cirrh/PHT	Cardiomegaly	Ishaemic Changes	CAHD Chages
81	Anusa	45/F	80	110	80	90	6.4	2	3.4	22	Cirrh/PHT	Cardiomegaly	Normal	CAHD Chages
82	Murali	40/M	88	120	80	94	8.5	1.2	2.5	53	Cirrh/PHT	Normal	Normal	CAHD Chages
83	Amudha	61/F	76	160	100	120	9.4	1	3.7	30	Cirrh/PHT	Cardiomegaly	Normal	Normal
84	Easwari	35/F	90	120	80	94	7.2	4	3	28	Cirrh/PHT	Normal	Normal	Normal
85	Balammal	30/F	74	100	70	80	8	1.4	2.7	16	Cirrh/PHT	Normal	Normal	Normal
86	Fathima	58/F	90	110	80	90	7.8	0.9	2	39	Cirrh/PHT	Cardiomegaly	Old IWMI	LV Dyfunction (Diastolic)
87	Karthikeyan	25/M	86	120	70	86	7	1.4	3.4	32	Cirrh/PHT	Normal	Normal	Normal
88	Shanthi	47/F	94	120	80	94	9.2	1	2.3	34	Cirrh/PHT	Cardiomegaly	Ishaemic Changes	Normal
89	Savithri	43/F	88	110	70	83	6.8	1.4	3.3	41	Cirrh/PHT	Normal	Normal	Normal

90	Kuppan	50/M	98	120	70	86	8	3.4	2.7	28	Cirrh/PHT	Normal	Low voltage complex	Pulmonary Hypertension
91	Vetrivel	47/M	80	110	80	90	9.2	1.2	3.2	24	Cirrh/PHT	Normal	Low voltage complex	Normal
92	Gandhimathy	50/F	82	130	80	96	8.2	1.4	2.7	17	Cirrh/PHT	Hydrothorax	Normal	Pericardial effusion
93	Parthiban	45/M	80	110	80	90	5.6	2.6	3	43	Cirrh/PHT	Normal	Normal	Normal
94	Ellamma	41/F	92	110	70	84	8.6	0.8	2.7	21	Cirrh/PHT	Normal	Ishaemic Changes	Normal
95	Jamuna	52/F	80	140	70	84	8	0.8	3.5	33	Cirrh/PHT	Normal	Low voltage complex	Normal
96	Vivek	55/M	86	110	80	90	4	0.8	2.8	38	Cirrh/PHT	Cardiomegaly	Normal	Hyperdynamic flow
97	Kasi	42/M	80	110	70	84	8.6	1	4	19	Cirrh/PHT	Normal	Normal	Normal
98	Mariyappan	52/M	98	100	80	86	6.4	1.6	2.8	23	Cirrh/PHT	Normal	Low voltage complex	Normal
99	Arivazhagan	51/M	88	110	70	84	9.4	0.6	2.3	40	Cirrh/PHT	Cardiomegaly	Ishaemic Changes	Normal
100	Kalpana	40/F	94	110	80	90	9.8	4	3	21	Cirrh/PHT	Normal	Normal	Normal