Cardiovascular Disease in Patients with Liver Cirrhosis

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1 Introduction

Cardiovascular diseases (CVD), mainly regarded as coronary artery disease and stroke, are the leading cause of mortality in western countries. Its incidence in patients with liver cirrhosis (LC) is still confounding but specific cardiovascular pathology in these patients is now well established. These include cirrhotic cardiomyopathy, hepatopulmonary syndrome and porto-pulmonary hypertension.

Nonetheless, cardiovascular complications in the patient with LC are a major cause of perioperative mortality and graft loss even in donor liver transplant recipients [1-4]. For these reasons, research has focused on this pathology, studying the potential reversibility of these cardiovascular alterations, early diagnosis and effective treatment. Although the specific cardiovascular conditions of LC are known for almost 60 years [5], its true prevalence remains unknown, perhaps because it was not observed in all patients with LC, but only in those with more advanced disease. Only recently the distinctive characteristics of ethanol-induced cardiomyopathy and LC-induced cardiomyopathy were recognized, and regular and careful previous cardiological evaluation usually fails its detection [6].

Apart from these facts, the hemodynamic profile of patients with LC is distinctive and deserves our best understanding. This may compromise patients in stressful situations, such as sepsis and after major surgery, including liver transplantation (LT).

2 Overview of Cardiovascular Disease in Liver Cirrhosis

Patients with LC present a higher mortality when compared to the general population [7,8]. For an adequate and accurate approach for this theme, it should be considered that the aetiology of LC is quite diverse, although in an end-stage condition there can be more unifying syndromes [9]. So, the natural history of each disease that evolves into LC must be taken into account: post-necrotic (viral), biliary tract diseases, liver steatosis, genetic conditions, alcohol consumption or even the presence of two or more risk factors.

Co-morbidities are important in this risk stratification and it includes the presence of CVD. Several authors studied the incidence of CVD in patients with LC. Kalaitzakis et al [10] studied this issue in a European population and found that although the incidence of coronary artery disease (CAD) was higher in patients with liver cirrhosis, it was independently related to the presence of diabetes, alcoholic aetiology and age. The same fact is reported for the risk of stroke in LC, although the incidence of intracranial bleeding is higher in these patients [11, 12], due to the inherent coagulopathy. It means that the actual incidence of CVD in patients with LC appears not to differ from general population although one finds it difficult to consider LC as a protective factor for CVD.

Patients with advanced LC have frequently lower levels of serum cholesterol and higher levels of serum triglycerides. However, it does not contribute to a hypothetical lower incidence of CVD in this group of patients. Nonetheless, known risk factors for the development of CVD in the general population are the most relevant, such as obesity, hypertension, hypercholesterolemia and diabetes. A distinctive incidence of CVD was observed in patients with LC due to specific conditions, such as non-alcoholic fatty liver disease and primary biliary cirrhosis [13-18]. In the first condition there is a plurimetabolic syndrome with severe fatty liver disease that can evolve into LC; the second condition regards a biliary system disease that, as a rule, is accompanied by hypercholesterolemia.
Heavy alcohol consumption is frequently present in patients with LC. The protective role of alcohol intake regarding CVD is to be established. In a nationwide study covering the years 1950 to 2002, Kerr et al. [19] found that a protective effect was noted for beer and wine consumption and a deleterious effect for stronger beverages. But it was also pointed that the incidence of CVD increased 1% per year and per litre of alcohol consumed, regardless of origin. This study may unveil other bias in this type of analysis, such as culture of drinking, genetic background and type of diet (Mediterranean versus non-Mediterranean). Another study by Kokolis et al. [20] verified that in a population which presented with chest pain, alcohol consumption was related with lower incidence of angiographically determined CAD, but related to systolic dysfunction. Based on these facts, it is not possible to determine that alcohol consumption protects from CVD, neither the right amount of consumption; it is not possible to distinguish the frontier between a healthy consumption and the development of other side effects, namely on the cardiac muscle.

There are muscular changes induced by alcohol consumption, called alcoholic myopathy [21]. It is characterized by atrophy of Type I muscle fibres (anaerobic, white glycolic), while Type II are relatively protected (aerobic, red oxidative). The clinical effect is reduced muscle mass, cramps, myalgia and difficulty in gait. It seems to affect more often chronic alcoholics than patients with pure alcoholic LC (incidence from 40-60% for the first group; 15-20% for the second). These changes also include the formation of acetaldehyde adducts, membrane changes and increases in cholesterol hyperoxides, inducing a radical-mediated damage to membrane. Although myopathy related to LC may be different, these patients are at increased risk for development of acute myopathy and rhabdomyolysis [22, 23], as well as, more benign clinical entities such as muscle cramps [24]. Myocardial changes due to alcohol intake are also well known, and are mainly characterized by a pattern of dilated cardiomyopathy, undistinguished from other aetiologies. However, little data is available on myocardial changes due solely to LC. The course of progressive damage to the cardiovascular system can be silent and precipitate after stress manoeuvres, making both diagnosis and treatment, in most cases, late and difficult. This particular issue will be presented ahead as cirrhotic cardiomyopathy.

3 Electrophysiological Alterations in Liver Cirrhosis

In a study by Bernardi et al. [25] the incidence of prolonged corrected QT interval (QTc) was observed in 46.8% of patients. The factors associated with it were the CTP class and the serum norepinephrine levels. Other electrophysiological changes have been described in patients with cirrhosis such as rhythm disturbances, ventricular desynchrony and chronotropic incompetence. The rhythm disturbances more frequently reported are atrial fibrillation, atrial flutter and extrasystoles. These may be due to changes in the permeability of the cell plasma membrane [26]. The QTc interval is an indicator of ventricular depolarization and repolarization. Therefore, QTc prolongation is due to changes in myocardial repolarization and can lead to ventricular arrhythmias such as Torsade de Pointes, ventricular tachycardia, ventricular fibrillation and even sudden death [27]. The QT prolongation is more common when the etiology of cirrhosis is alcoholic than viral (83.3% vs 20%) [28]. Liver transplantation can improve the QTc interval of patients who have it prolonged [29]. Table 1 presents a list of common drugs that can prolong the QT interval.
It has been suggested that an enhanced sympathetic activity can be responsible for this electrophysiological abnormality. Of notice, it was recently found that beta-blockers can induce higher mortality in patients with LC and refractory ascites [30]. This medication is part of the treatment for variceal bleeding as it decreases the porto-systemic pressure gradient. There is no plausible explanation for this fact, but it can be attributed to the influence of this class of drugs on the QT interval. Also, beta-blockers are nowadays a standard therapy for patients with heart failure. To understand this point one must look to the distinguishing hemodynamic profile of heart failure and LC.

### 4 Hemodynamic Alterations in Liver Cirrhosis

The main characteristics of the hemodynamic profile of heart failure patients are low cardiac output (CO), high peripheral vascular resistance (PVR) and signs of vascular congestion (high central venous pressure, high pulmonary capillary wedge pressure, dilated inferior vena cava without respiratory variation) [31].

In patients with heart failure the density of the beta receptors on the surface of the cardiomyocytes is low due to the internalization of the beta receptors secondary to the excess sympathetic activity; in this situation, the response to adrenergic stimuli can be affected. In patients, the use of beta-blockers can expose the internalized adrenergic receptors in a process that requires several weeks and that can initially worsen the symptoms; but with time, the higher density of these receptors on the surface of the cardiomyocytes can enhance the inotropic response to adrenergic stimuli and thus improve the systolic performance of the left ventricle.

The main cardiovascular disorders of the LC are portal hypertension and a permanent state of hyperdynamic circulation. The increased blood flow in the splanchnic bed exacerbates the portal hypertension and consequently increases the incidence of esophageal varices, variceal bleeding and ascites. Peripheral vasodilation also contributes to the pathophysiology of ascites, resulting in a decreased effective circulating volume, which is sensed by the kidney as hypovolemia, leading to salt and water retention.

In this state of hyperdynamic circulation of LC, heart rate (HR), CO and Left Ventricular Ejection Fraction (LVEF) are increased, and PVR, mean arterial pressure (MAP) and blood vessel contraction

| Risk of torsades de points (strong evidence of QT prolongation when used as directed in label) | Amiodarone; Astemizol; Azithromycin; Chloroquine; Chlorpromazine; Cisapride; Citalopram; Clarithromycin; Disopyramide; domperidon; droperidol; erythromycin; escitalopram; flecainide; haloperidol; levomethadyl; mezoridasine; methadone; moxifloxacine; pentamidine; probucol; procainamide; quinidine; servoflurane; solalol; thioridazine. |
| Potential risk (substantial evidence, but insufficient evidence as the effect if used as directed in the label) | Amantadine; atazanavir; chloral hydrate; clozapine; dolasetron; dronedarone; famotidine; fingolimod; foscarnet; phenytoin; gemifloxacin; ganisetron; indapamide; isradipine; levofloxacin; lithium; mirtazapine; nortriptyline; octreotide; ofloxacin; olanzapine; ondasetron; oxytocin; quetiapine; risperidone; sunitinib; tacrolimus; tamoxifen; vardenafil; venlafaxine; voriconazole. |
| Conditional risk (evidence existing but only under certain conditions (overdosage, drug interactions) | Amisulpiride; amitriptyline; ciprofloxacin; diphenydramine; fluconazol; fluoxetine; imipramide; itraconazol; ketoconazol; paroxetine; ritonavir; sertraline; trazodone; trimethoprim/sulfamethoxazol; |

Table 1: Common drugs that can prolong the QT interval
are decreased. The pathophysiology is multifactorial. It has been reported that arterial vasodilation activates the sympathetic nervous system and the renin-angiotensin-aldosterone system, resulting in a tachycardic response. Blood volume is decreased at a central level (heart, lungs and great vessels) and increased in the periphery (mainly the splanchnic circulation). With the evolution of the illness, there are other precipitating factors of clinical worsening such as autonomic dysfunction and desensitization of myocardial beta-adrenergic receptors [32, 33] - conditioning hypo-responsiveness to treatment with vasoactive drugs - or nitration of cardiac proteins [34].

In an experimental model with rats with induced portal hypertension, a reduction in myocardial contractility and beta-adrenergic response was observed and the authors associated these findings with a possible altered excitation-contraction coupling, decreased sarcolemma L-type calcium channel density and reduced calcium in the sarcoplasmic reticulum [35]. In recent reports, an inadequate adrenergic stimulus due to the presence of a relative suprarenal insufficiency has been noticed. This inadequacy of the adrenergic system can lie on the basis of the incompetent response to stressful situations, ranging from exercise to severe medical conditions like sepsis or major surgery. Thus, it may not be possible to further increase the cardiac output or further decrease the peripheral systemic vascular resistance, the known adaptive phenomena to stress situations. If beta-blockers are added to the medication, this inadequate response can also be further compromised.

## 5 Cirrhotic Cardiomyopathy

For many years cirrhotic cardiomyopathy was thought to be due to alcoholic heart muscle disease. However, “cirrhotic cardiomyopathy” (CCM) is the term used to describe a group of features indicative of abnormal cardiac performance in cirrhotic patients which seems to be an independent entity, different from ethanol-induced cardiomyopathy [36].

Only scattered clinical studies have specifically studied the features of the CCM, which would justify that there are no diagnostic criteria widely accepted between experts. The working definition was proposed in the World Congress of Gastroenterology in Montreal (Canada) in 2005 and is detailed in Table 2. The main characteristics of this condition are depicted in Table 3.

CCM is defined as a chronic cardiac dysfunction in patients with LC characterized by a blunted response to stress, with systolic and/or diastolic dysfunction, electrophysiological changes and without known history of heart disease. There is little information about the epidemiology of such entity since its diagnosis is difficult due to near normal cardiac function at rest. Most of the patients are diagnosed during an episode of cirrhosis decompensation, probably having been asymptomatic during the first stages of the disease [37]. If CCM is not diagnosed in time or is treated improperly, it can lead to cardiac failure [38]. There have been reported rates up to 50% of pulmonary edema and 27% of haemodynamically significant arrhythmias in the perioperative period of orthotopic liver transplant (OLT) [39]. Fouad et al. in a study of 197 post-OLT patients found a prevalence close to 50% of cardiac decompensation, which was the main cause of death in these patients [40].

The pathogenesis of CCM is likely to be attributed to the increase of intra-abdominal pressure in cirrhotic patients, particularly those with ascites, resulting in an increased intrathoracic pressure and consequent myocardial dysfunction. However, as the CCM has been described in patients without ascites, it appears that other factors, not mechanical, could cause progressive cardiac deterioration. Within these
factors, nitric oxide, TNFα, bile acids, endotoxin and beta-adrenergic receptor dysfunction have been proposed.

<table>
<thead>
<tr>
<th>Systolic dysfunction</th>
<th>Diastolic dysfunction</th>
<th>Supportive criteria</th>
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<tbody>
<tr>
<td>● Blunted increase in cardiac output with stress</td>
<td>● E/A ratio &lt;1</td>
<td>● Electrophysiological abnormalities</td>
</tr>
<tr>
<td>● Resting LVEF &lt;55%</td>
<td>● Prolonged DT (&gt;200 msec)</td>
<td>● Altered chronotropic response</td>
</tr>
<tr>
<td></td>
<td>● Prolonged IVRT (&gt;80 msec)</td>
<td>● Electromechanical desynchrony</td>
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<td></td>
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<td>● Prolonged QTc</td>
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<td></td>
<td></td>
<td>● Enlarged LA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Increased cardiac mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Increased BNP/proBNP</td>
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<tr>
<td></td>
<td></td>
<td>● Increased troponin I</td>
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</tbody>
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Table 2: The working definition of cirrhotic cardiomyopathy (Montreal, 2005)

<table>
<thead>
<tr>
<th>Altered function of β-adrenergic receptor: Several studies have demonstrated a reduced receptor density in cirrhotic patients and animal models.</th>
</tr>
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<tr>
<td>Enhanced muscarinic tone that could contribute to the negative inotropic effect on the myocardium.</td>
</tr>
<tr>
<td>Altered membrane fluidity, these changes have a profound effect on the β-adrenoceptor function that includes impairing the receptor-ligand interaction; affects the function of membrane-bound ion channels (Ca^{++} and K^{+}) (3)</td>
</tr>
<tr>
<td>NO, carbon monoxide and endocannabinoids exerts a negative effect on cardiac contractility.</td>
</tr>
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Table 3: Pathophysiological characteristics of cirrhotic cardiomyopathy

The histopathology of the CCM is nonspecific. The autopsy findings are increased ventricular volumes and mass, hypertrophy of cardiomyocytes, interstitial and intracellular edema and signs of cellular injury. The left ventricle (LV) is thickened and less compliant. These findings are more evident in patients with ascites [41], and they are more frequent in the LV that in the right ventricle [42].

Ventricular systolic function has been the most studied feature of CCM, which is normal at rest but, in situations of physical stress (surgery, infection, bleeding and exercise), psychological or pharmacological stress (dobutamine, sodium load) is affected [43]. In CCM the ejective period is shortened and pre-ejective time is lengthened [44].

Diastolic dysfunction is due to a defect in ventricular compliance that alters its physiological filling, which usually precedes systolic dysfunction in ischemic heart disease. However, this has not yet been demonstrated in cirrhotic patients. Some authors suggest that diastolic dysfunction is present in all
cases of CCM and that the echocardiographic findings of a pathological E/A ratio may be sufficient for diagnosis [45] (see Figure 1). However, it has been described in most cirrhotic patients without cardiomyopathy, so its individual use for diagnosis is not enough.

Figure 1: Diastolic dysfunction in a cirrhotic patient diagnosed during pre-transplantation echocardiographic study (E/A ratio <0.8, DTE >240).

Diastolic dysfunction in CCM may also be due to left ventricular hypertrophy, fibrosis or interstitial edema. If diastolic dysfunction is present, it will be more deteriorated after OLT, especially in the first 3 months [45]. It appears to be more common in patients with ascites and paracentesis improves diastolic and systolic functions [46]. Left ventricular hypertrophy (LVH) leads to an increased myocardial stiffness and, therefore, changes in contractility, relaxation and conductivity. In patients with LC, LVH is thought to be an adaptive phenomenon to the chronic overload of blood volume by retaining sodium and water. Therefore, in CCM we find a heart with increased ventricular mass, rigid, less compliant and pro-arrhythmogenic. Chronotropic incompetence is associated with increased risk of perioperative complications, greater incidence of arrhythmia and myocardial infarction. The failure to achieve 82% of predicted heart rate after dobutamine echocardiography was associated with an increased risk of death of almost 4 times in the first months after liver transplantation (22% versus 6%) [47]. We cannot however conclude that chronotropic incompetence is an independent predictor of mortality in patients with cirrhosis.

Limited studies suggested that, in an earlier stage of CCM, mechanical desynchrony preceded LV dysfunction - in fact, mechanical desynchrony is one of the diagnostic criteria in the working definition of CCM. Recently, Aljaroudi et al. [48] performed a study with 178 patients with LC who underwent stress-gated Tc-99m sestamibi myocardial perfusion imaging and found no differences in desynchrony indexes between survivors and non-survivors, and then concluded that in patients with LC there is insufficient evidence of a higher incidence of LV desynchrony.
The Transjugular Porto-systemic Shunt (TIPS) produces an acute increase in preload by shifting traffic from the portal vein circulation to the systemic circulation, leading to a worsening of the hyperdynamic state by increasing CO, bi-atrial end-diastolic volume and a decrease in SVR. It is estimated that 1% of cirrhotic patients without cardiac history developed heart failure after TIPS [49]. With TIPS, the central filling pressure increases more than 2 times and the stroke volume index increases up to 20% immediately [50]. Within two years, both CO and SVR tend to normalize, also occurring mild LV hypertrophy. These consequences are responsible for an increased probability of death in patients with CCM immediately after TIPS [51]. Another trigger for CCM is LT. In the perioperative period of LT, CCM is the third leading cause of death after rejection and infection [52]. 47% of patients have radiographic acute pulmonary edema immediately after OLT [53] and 3% developed new dilated cardiomyopathy in the first 6 months [54].

Several studies support the correlation between CCM and elevated laboratory parameters such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), pro-BNP and troponin I, which could be used in screening. It seems that ANP is less specific, since its alteration is related to atrial distension or distortion that can sometimes exist alongside effective hypovolemia [55]. Several studies have shown that when pro-BNP and BNP are elevated, these are related to the severity of cirrhosis, myocardial dysfunction, myocardial hypertrophy and QT prolongation [56, 57]. B-type natriuretic peptide (BNP) concentrations are higher in cirrhosis possibly due to the hyperdynamic state and cirrhotic cardiomyopathy. Pimenta et al. [58], in a study that included 83 patients hospitalized with decompensated cirrhosis, observed that BNP levels in cirrhosis reflects cardiac systolic function and is an independent predictor of medium-term survival in advanced cirrhosis. Median BNP levels were 130.3 (65.2 – 363.3) pg/ml, BNP levels above the median were associated with an increased occurrence of death within 6 months of discharge (p=0.023).

Troponin I is a key parameter for the diagnosis of myocardial ischemia and has also proved to be useful for diagnosis of other entities such as sepsis-induced myocardial dysfunction, hypertrophic cardiomyopathy and LC. Pateron et al. [59] showed that in patients with LC who had elevated serum troponin I, it correlated with lower left ventricular stroke volume and mass index.

Risk assessment with ECG, coronary angiography and myocardial perfusion scintigraphy has failed to predict a perioperative CCM. Late gadolinium enhancement (LGE) in cardiac magnetic resonance (CMR) was traditionally considered to be associated with cardiac fibrosis in ischemic heart disease, but it is also described in infiltrative cardiomyopathies, myocarditis and sepsis [60, 61]. Lössnitzer et al. [62] performed CMR in 20 patients with end-liver disease listed for liver transplantation and found hyperdynamic state and LGE in all of them, suggesting a common mechanism originating from cirrhosis. The pattern of LGE was patchy, similar to myocarditis [63], so it cannot be ruled a possible partial reversibility of LGE. A greater extent of LGE was found in patients with ethanol-induced cardiomyopathy. The authors suggested that CMR should be the gold standard for diagnosis of CCM [64].

The most common form to study the LV systolic function is by using the LVEF calculus measured by two-dimensional echocardiography and Simpson's modified biplane method. However, this approach has serious limitations because LVEF is preload and afterload-dependent. For the analysis of diastolic function, E / A ratio has been analysed in most reported studies of CCM, concluding that a ratio ≤1 is associated with increased mortality risk. The E / A ≤ 1 is present in 50-70% of patients with end-stage liver disease, being more evident with the progression of the disease (MELD ≥ 20), and lowest in patients with ascites [65]. However, E/A ratio is also preload dependent [66], which doesn’t allow the diagnosis of a
pseudo normal pattern (grade II diastolic dysfunction) and thus leads to underestimation of the real incidence of diastolic dysfunction in patients with LC.

For these reasons, recent studies using new echocardiographic technologies such as Doppler Tissue Imaging (DTI) are promising, since it lacks the limitations above cited and, therefore, becomes an attractive diagnostic tool [67]. Kazantov et al. [68], in a pioneer study using DTI, studied LV systolic and diastolic function at rest in 44 cirrhotic patients without previous known heart disease, and simultaneously analysed tissue velocities and strain rate in various segments of the LV in the same cineloop. They noted that all patients had systolic dysfunction and 54% had diastolic dysfunction (25% impaired diastolic relaxation pattern, 27% pseudo normal filling pattern and 2% restrictive filling pattern) at rest. These findings suggest that the current characterization of CCM is doubtful, further studies are needed in this field and that advanced methods such as echocardiography with DTI and Speckle Tracking may become the gold standard for diagnosis of CCM. Accumulating evidence also suggest that dobutamine stress echo test cannot be recommended routinely for the diagnosis of CCM, being reserved for patients with severe ischemic heart disease before transplantation [69].

Unfortunately there is no specific treatment for CCM [70]. Few treatments have been proposed to date and many of them are just experimental. The clinical management of patients with CCM will be, therefore, with supportive measures, treating heart failure as if it they were not cirrhotic patients. Accumulating evidence also suggests the use of cardioprotective therapy - beta-blockers, statins, angiotensin-converting enzyme inhibitors or anti-aldosterone agents could have a very important role [71-74].

Albumin dialysis using the Molecular Adsorbent Recirculating System (MARS) has been shown to improve hemodynamic status of patients with end-liver disease decreasing the levels of nitric oxide, TNFα and intrahepatic vasoconstriction. These effects disappeared four days after cessation of MARS. (75, 76). However, it has not shown improved survival in patients treated. LT is one of the treatments proposed for the CCM, but the high incidence of perioperative complications in these patients makes this option be reconsidered.

6 Porto-pulmonary Hypertension (PPH)

PPH is defined by criteria obtained by right heart catheterization in patients with portal hypertension (PoH): elevated mean pulmonary artery pressure (>25 mmHg at rest or > 30 mmHg with exercise), increased pulmonary vascular resistance (> 240 dynes s/cm^5), normal pulmonary artery occlusion pressure (<15 mmHg). Its prevalence varies according to the population studied being that in patients with end-stage liver disease it can range from 3.5 to 16.1% [77, 78].

PoH either precedes or is diagnosed concurrently with PPH, supporting the hypothesis that the pathogenesis of PPH may be related to vasoactive substances not metabolized or produced by the cirrhotic liver that are found in the pulmonary circulation. It is thought that these mediators possibly induce vasoconstriction or direct toxic damage to the pulmonary arteries, since high concentrations of mediators such as serotonin, interleukin-1, endothelin-1, glucagon, secretin and thromboxane A2 have been found in plasma of patients with PoH [79, 80].

Early stage of PPH is generally asymptomatic or patients may have symptoms of the underlying liver disease. With advancing disease exertional dyspnea is the most frequent presenting symptom of PPH (81%); other symptoms, such as syncope, chest pain, and fatigue, are seen in a third of the patients. Most importantly, this specific entity is quite important, due to the fact that is a contraindication for liver
transplantation. The pre-transplant screening of signs of right heart overload using echocardiography is therefore mandatory.

7 **Hepato-pulmonary Syndrome (HPS)**

The HPS is characterized by a defect in arterial oxygenation induced by pulmonary vascular dilation and pulmonary arterial-venous shunting in the setting of liver disease. It has been reported to be present in 4 to 29% of patients with liver disease [81-83] and from 15 to 30% in patients waiting for LT.

HPS can affect all ages and occasionally occur in non-cirrhotic patients with portal hypertension (PoH) and may also be reported in mild liver disease. The exact mechanism of pathogenesis is unclear but it can be the result of alteration in the production or clearance of chemical mediators causing intrapulmonary vascular vasodilatation and arteriovenous shunting through the lungs with a ventilation-perfusion mismatch. Hypoxia occurs as a result of inability of oxygen to diffuse through the markedly dilated lung capillaries. The capillaries are known to dilate to 15–500 µm (n = 8–15 µm) in HPS. There is a pulmonary vascular dilation, intrapulmonary shunts and low pulmonary vascular resistance, which seems to be due to the effect of multiple vasoactive substances; some studies point to increase NO levels in cirrhotic patients. According to the alveolar-capillary dis-equilibrium hypothesis, pulmonary vascular dilation and intrapulmonary shunts in patients with liver cirrhosis are the leading contributors to hypoxemia in advanced liver disease. The low pulmonary vascular resistance leads to a reduction in the intrapulmonary transit time, subsequently a decreased oxygen diffusion across the dilated pulmonary vessels. Another pattern of intrapulmonary vascular dilation is characterized by localized dilation of parts of the pulmonary vasculature and is associated with large arteriovenous shunting, with poor response to oxygen supplementation (84). This syndrome is characterized by the presence of liver disease, pulmonary vascular vasodilatation, associated with significant arteriovenous shunting (AVS) and hypoxemia; capillary vasodilatation is most pronounced at the lung bases, explaining orthodeoxia and platypnea associated with HPS. VQ mismatch appears to be a major event in the pathogenesis of hypoxemia in HPS as a result of extensive pulmonary vasodilatation, a decrease in V/Q ratio in alveolar-capillary units and resultant low PO₂ and O₂ content of blood leaving the lungs; defect in oxygenation, Due to pulmonary capillaries dilatation oxygen encounters difficulty in diffusing into the center of the larger capillaries. Increased cardiac output and the associated reduced transition time of blood through the pulmonary vascular bed also impair diffusion, leading to a diffusion–perfusion defect or alveolar capillary oxygen dis-equilibrium.

Clinical presentation is characterized by dyspnea of insidious onset associated with cyanosis in 90% of all cases, platypnea and orthodeoxia. The presence of clubbing has the highest positive predictive value (75%) and dyspnea the highest negative predictive value (100%) for HPS. Spider nevi are a common clinical feature of patients with HPS with significant relationship between cutaneous spider angiomata and systemic and pulmonary vasodilatation suggesting that spider nevi may represent a cutaneous marker for intrapulmonary vascular dilatation.

Two types of HPS have been described: Type I is associated with vascular dilation at the precapillary level close to the normal gas exchange units of the lung and Type II with focal larger dilations amounting to AVS distant from the gas exchange units. Supplementary oxygen improves Type I HPS PaO₂ but not Type 2 HPS [84].

The HPS is associated with an increased risk of death - the median survival time in cirrhotic patients has been reported as 10,6 months compared to 40,8 months in cirrhotic patients without HPS. The
leading cause of death is hemorrhagic shock due to gastrointestinal bleeding. Survival is worse with baseline PaO$_2$ < 50 mmHg irrespective of the decision to perform LT [85, 86]. The diagnosis relies on imaging techniques and arterial gas analysis. The cut-off values for PaO$_2$ are controversial. Schenk and colleagues suggested that arterial hypoxemia defined as a PaO$_2$<70 mmHg or below the age-related threshold predicted the presence of HPS with high probability in the absence of intrinsic cardiopulmonary diseases. A chest radiograph (CXR) and pulmonary function tests must be used to help exclude other causes of hypoxia such as pulmonary atelectasis, ascites, chronic obstructive pulmonary disease, hepatic hydrothorax. A definitive diagnosis of HPS can be made by demonstration of pulmonary vasodilation associated with functional arteriovenous shunting. Imaging studies that can identify such shunts include contrast echocardiography and perfusion scintigraphy with 99mTc, which are usually carried out following analysis of arterial gases to identify elevated alveolar-arterial differences in O$_2$ or hypoxemia.

Most patients being cared for in hospital setting have undergone a conventional CXR, which is not only useful in the diagnosis of HPS but is crucial for excluding other causes of hypoxemia. A CXR in HPS shows bibasilar nodular or reticulonodular opacities in 5–13.8% of patients with chronic liver disease and 46–100% of patients with HPS. High-resolution computed tomography (CT) is useful in excluding pulmonary fibrosis or emphysema as the cause of these opacities.

Liver transplantation is the only definitive treatment for HPS with at least 85% of patients experiencing significant improvement or complete resolution of hypoxemia following surgery; however these patients have a higher post-transplant mortality rate related to pulmonary hypertension, cerebral embolic hemorrhages and prolonged mechanical ventilation. [84] Several therapeutic trials in HPS have shown poor results such as somatostatin analogues, cyclooxygenase inhibitors, and immunosuppressive agents such as corticosteroids and cyclophosphamide. [87] Some reports have shown improvement in gas exchange with the use of TIPS in HPS [88]. Martínez-Pallí G et al. [89] in another study concluded that TIPS neither improved nor worsened pulmonary gas exchange in patients with portal hypertension and the data does not support the use of TIPS as a specific treatment for HPS.

8 Non Alcoholic Fatty Liver Disease (NAFLD)

NAFLD is defined as the presence of hepatic steatosis in the absence of other cause for secondary hepatic fat accumulation. It is known that it can progress to cirrhosis and is thought to be a major cause of cryptogenic cirrhosis [90]. The prevalence of NAFLD in the US is 20-30%, with a greatest incidence in the fifth decade of life [91]. It is associated with other metabolic disorders such as diabetes, dyslipidemia, hypertension and obesity and is, thus, a known risk factor for cardiovascular disease [92]. However, recent studies have also shown that patients with NAFLD but with no hypertension, diabetes or previous heart condition, have cardiac function abnormalities, such as echocardiographic features of early LV diastolic dysfunction and impaired LV energy metabolism [93-95].

Rijzewijk et al. [96] has conducted a study on diabetic type 2 patients where it was found that on those with a higher degree of liver steatosis, there was an impaired myocardial perfusion and lower high-energy phosphates content on P-magnetic resonance spectroscopy but similar values of LV function and morphology on MRI. Abnormalities, such as echocardiographic features of early LV diastolic dysfunction and impaired LV energy.

Another recent study by Bonapace et al [97] has made a similar evaluation and it is proposed that the systemic release of inflammatory mediators from the steatotic liver may lead to the abnormality of
cardiac function, whether possibly through subclinical myocardial infarction or ectopic deposition of fat in different organs, including the myocardium [98]. Nevertheless, recent data are conflicting, suggesting a complex relationship between these entities. Further studies are necessary to enlighten the mechanisms through which NAFLD leads to diastolic cardiac dysfunction [99, 100].

References


