Cirrhotic Cardiomyopathy

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Alterations in cardiovascular function in patients with liver cirrhosis have been extensively described during the last decades. The observation of a "hyperdynamic" state in the circulation of these patients, characterized by decreased peripheral vascular resistance and increased cardiac output, was followed by the description of a novel type of "cardiomyopathy", with specific functional and electrocardiographic characteristics[1]. There have been efforts to correlate the cardiovascular disturbances with the etiology or the severity of the hepatic failure, often with controversial results. Although nowadays cirrhotic cardiomyopathy is considered to be a well-described clinical entity, its clinical significance in cirrhotic patients remains unclear.

Hyperdynamic circulation in liver cirrhosis

The presence of a hyperdynamic circulation in cirrhotic patients was first described during the 1950s[2]. This hyperdynamic state is characterized by decreased peripheral resistance, increased cardiac output and stroke volume, increased organ blood flow, low systolic arterial blood pressure and decreased arteriovenous oxygen difference. Most patients suffer from advanced hepatic failure, irrespective of the etiology of cirrhosis.

The pathogenetic mechanism of hyperdynamic circulation in cirrhosis remains unclear, even though many theories have been postulated. Investigators have mostly focused on the evaluation of the role of circulating vasoactive substances, which may not be deactivated because of liver failure[3,4]. Glucagone, vasoactive intestinal peptide (VIP), endotoxins, tumor necrosis factor-a (TNF-a), prostacycline, biliary salts, endothelin 1 and 3 (ET-1 and ET-3) natriuretic peptide and nitric oxide (NO) are some of the substances implicated in the pathophysiology of the hyperdynamic state[5]. According to recent reports, the role of NO seems to be the most important.

As was firstly suggested by Vallance and Moncada in 1991, the peripheral vasodilation of cirrhosis can be attributed to the increased synthesis and release of NO from the vascular endothelium, which is initiated by the circulating endotoxins or cytokines in cirrhotic patients[6]. Although the contribution of NO to the maintenance of the hyperdynamic state is not currently disputed, it seems that NO is not the only vasoactive substance implicated in this mechanism[7]. Sympathetic nervous system hyperactivation, anemia, arteriovenous anatomic and functional shunts, low oxygen partial pressure and increased circulatory plasma volume, all seem to contribute to the pathogenesis[2]. Recent reports characterize this hyperdynamic state as a "stealing" phenomenon, from the splachnic to the peripheral circulation[8].

The clinical significance of this hyperdynamic situation, apart from these characteristic circulatory alterations, has not yet been clarified. It has been proposed that it may contribute to the pathophysiology of the syndrome of portal hy-

pertension, hepatopulmonary syndrome, renal retention of sodium and water, and cerebral edema in patients with hepatic cirrhosis[2]. Nevertheless, the hyperdynamic circulation of cirrhotic patients, through the peripheral vasodilation and the decreased cardiac afterload, may be associated with the subclinical manifestation of cirrhotic cardiomyopathy, as will be described[9].

Cardiac dysfunction in liver cirrhosis

Cardiac dysfunction in cirrhotic patients was first described in patients with alcoholic cirrhosis and was attributed to the direct toxic effect of alcohol (alcoholic cardiomyopathy). Impaired cardiac performance in cirrhotic patients was firstly reported during the 1970s. This phenomenon was not correlated with the etiology of the cirrhosis[10]. Nowadays, it is well-documented that cirrhosis, as a clinical entity, is related to a characteristic form of mild, asymptomatic heart dysfunction, characterized by increased cardiac output, that is called "cirrhotic cardiomyopathy"[11]. Although these patients manifest a normal or hyperdynamic circulatory state at rest, they may exhibit an impaired cardiac response to pharmacological or physical stress.

a) Response to pharmacological or physical stress

Cirrhotic patients who are challenged by physical stress test display an abnormal response, consisting of an impaired increase of ejection fraction, chronotropic incompetence and a lower cardiac index, while they also present decreased oxygen consumption and a decreased anaerobic metabolism threshold. In a recent study, Wong et al. speculated that asymptomatic cirrhotic patients undergoing physical stress test may manifest decreased chronotropic response, lower stroke volume and abnormally low maximum heart rate[12]. Impaired cardiac performance is present in both alcoholics and non-alcoholic cirrhotic patients, while the severity of the disorder appears to be proportional to the degree of the hepatic failure[13].

The findings of studies that used pharmacological stress in cirrhotic patients are also indicative of an abnormal inotropic and chronotropic response. Administration of dobutamine in cirrhotic patients resulted in a mild increase of stroke volume, while the dose of isoproterenol that was needed to achieve an increase of 25 bpm in heart rate was significantly higher in cirrhotic patients than in non-cirrhotic subjects[11,14].

b) The "cirrhotic" heart

As described above, in liver cirrhosis the heart manifests a mild dysfunction, called "cirrhotic cardiomyopathy", which becomes evident under increased circulatory demands. This disorder differs from the previously known alcoholic cardiomyopathy and is not dependent on the etiology of cirrhosis. Although studies in the literature have reported conflicting results, it seems that these patients display primarily diastolic dysfunction, with left ventricular hypertrophy, left atrial enlargement, isovolumic relaxation time (IVRT) prolongation and a decreased early to late diastolic flow ratio (E/A ratio). In contrast, systolic function remains normal at rest and systolic dysfunction becomes evident only during stress, in the form of an impaired chronotropic and inotropic response[9,12]. Right ventricular and pulmonary artery pressure, as well as pulmonary capillary wedge pressure (PCWP), range around the upper normal limits[15]. It could be postulated that the hyperdynamic state of cirrhosis, because of the increase in the cardiac output and circulatory intravascular plasma volume, induces a volume overload in cardiac muscle which subsequently may contribute to the myocardial hypertrophy. However, the decreased left ventricular afterload, due to peripheral vasodilation, conceals the cardiac dysfunction at rest[5,16].

Pathologically, the cirrhotic heart has characteristically increased weight, with myocardial hypertrophy, dilation of the cardiac chambers and structural changes, such as extracellular and myocardial cell edema, nuclear vacuolation, fibrosis, exudates and pigmentation[11,16]. Increased troponine-I levels in the plasma of cirrhotic patients may represent a biochemical marker of myocardial damage in these patients[17].

c) Pathogenetic mechanisms

The pathogenesis of cirrhotic cardiomyopathy has not yet been clarified, though it could be suggested that it is closely related to the hyperdynamic circulatory state described above. Although various humoral and neurohormonal factors have been implicated, the mechanism seems to be more complicated and may be the result of the interaction of a variety of factors.

i) β-adrenergic receptor dysfunction

The myocardial β-adrenergic receptor signaling pathway regulates the ventricular contractility, by a complicated pathway of signal transduction. In this pathway, the activated β-adrenergic receptor is attached to the stimulatory transmembrane G protein (consisting of three heterogeneous subunits: a_s, b and g) .The transmission of the signal from the receptor to the G-protein system induces the activation of the a_s subunit, which is able to activate adenyl cyclase, an enzyme that causes the transformation of ATP to cAMP. The cAMP is the second messenger of this pathway and promotes the phosphorylation and the activation of various cellular proteins by the stimulation of protein kinase, resulting finally in increased intracellular calcium levels and a positive inotropic response[18].

Research efforts have been focused on the study of this pathway, considering that a dysfunction at certain levels may contribute to the pathogenesis of cirrhotic cardiomyopathy. Ma et al. reported decreased expression of G_{sa} protein in experimental models (probably because of circulating endotoxins or increased biliary salts levels) and they pointed out that increased plasma catecholamine levels in cirrhotic patients may also play an important role[18]. Desensitization of β-adrenergic receptors has also been attributed to alterations in the fluidity and biochemical properties of the cellular membrane, due to the abnormal lipid metabolism of cirrhosis, which may result in a deficit in anchoring of G-protein in the lipid bilayer[19]. On the other hand, the blunted muscarinic response (M_2) in cirrhotic myocardium seems to be compensatory, because of the abnormal hyperstimulation of the β-adrenergic receptor system, and is not related to the pathogenesis of myocardial dysfunction[20].

ii) Calcium channel dysfunction

Myocardial calcium homeostasis is regulated via the ATP-pumps, which transport ions from the cytoplasm into the sarcoplasmic reticulum (SR), and calcium channels, which promote calcium release from the SR, resulting in the contraction of the muscular fiber. An initial influx of calcium ions through special (L-type) channels of cellular membrane is the stimulus for calcium release from the SR. It has been suggested that any abnormality of the initial influx phase may result in impaired calcium release from the SR and may explain the abnormal muscular contraction of cirrhotic myocardium[21]. Decreased density, as well as electrophysiological dysfunction of L type channels, could attenuate muscular contraction in cirrhotic myocardium. In contrast, the intracellular calcium homeostasis system presents no structural or functional abnormalities.

Some have speculated that this phenomenon may be attributed to: (a) the abnormal lipid metabolism, which impairs the fluidity of cellular membrane and subsequently the function of transmembrane proteins; (b) the overproduction of NO, which probably attenuates the activation of L-type channels (via cGMP); (c) the decreased G_s-protein and cAMP-dependent protein kinase levels, (both represent calcium channel activators), and (d) circulating bile components (most likely the biliary salts) with inhibiting adenyl cyclase properties[21].

iii) Impaired cellular membrane fluidity

It is well-known that the cellular membrane, representing the "organ" of interaction and communication between cells, mostly consists of a lipid bilayer. Moreover, the cellular membrane represents the micro-environment of a number of transmembrane G protein receptors, which are involved in the regulation of a variety of cellular functions. It is reasonable, therefore, that changes in the composition and the physiological properties of the membrane may influence the receptor function, resulting in abnormal cellular performance[11,29].

The abnormal lipid metabolism in patients with hepatic failure leads to an increased membrane cholesterol content. The sterol ring in the cholesterol molecule interacts with fatty acids, thus increasing its rigidity. This disturbed membrane fluidity has been associated with β-adrenergic receptor system dysfunction, causing impaired cAMP production[19]. In addition, the abnormal lipid environment has also been implicated in the dysfunction of transmembrane calcium channels[21].

iv) The action of NO

Nitric oxide is a humoral substance with a variety of effects on the cardiovascular system. It is a free radical that is produced by the L–arginine in the vascular endothelium via NO-synthetase. The plasma

levels of NO are increased in cirrhotic patients as a consequence of transient bacteremia and increased levels of endotoxins and cytokines (especially TNF-a and interleukins), which seem to stimulate NO-synthetase. Some of the more important cardiovascular alterations of cirrhosis have been considered as an effect of multiorgan NO action[22,23].

The increased NO-synthetase activity recorded in cirrhotic myocardium, as well as the improvement of myocardial contractility after the administration of an NO-synthetase inhibitor, are indications of NO implication in the pathophysiology of cirrhotic cardiomyopathy[24]. Albornoz et al. reported an increased production of NO in the splachnic circulation and high NO-synthetase activity in the hepatic artery[25]. Furthermore, cGMP is considered to be the mediator of the inhibition of cardiac contractile function of NO in cirrhotic patients. Increased cGMP levels have been reported in the myocardium of cirrhotic patients and cGMP seems to inhibit signal propagation in the β-receptor pathway or calcium release from the SR[14,24].

v) Role of other humoral substances

Hepatocellular dysfunction and porto-systemic shunts are responsible for the increased absorption and impaired neutralization of bacteria and endotoxins from the gastrointestinal tract. The prolonged presence of bacteria and toxins in the systematic circulation of cirrhotic patients leads to an overproduction of cytokines (interleukins and TNF-a), which exert an inhibitory effect on the contractility of myocardium, either directly or by induction of NO-synthetase and NO overproduction[5,14].

Carbon monoxide (CO) is considered to have similar biochemical properties to NO. The hypothesis that increased CO production may play a role in cirrhotic cardiomyopathy is supported by the finding of elevated heme oxygenase activity in the myocardium of cirrhotic patients. In addition, it has been shown experimentally that pharmacological inhibition of enzyme activity results in improvement of myocardial contractility[26]. This inhibitory action of CO in myocardium has been associated with guanyl cyclase induction and cGMP overproduction, via a mechanism that has already been described.

Increased levels of biliary salts in the plasma of patients with jaundice have been correlated with impaired cardiac function, even in the absence of liver cirrhosis. An inhibitory action of biliary salts on the calcium channels has been postulated (although the study in question referred to vascular wall myocytes and not to cardiomyocytes)[27]. Recent reports consider that elevated plasma bile salt levels influence the β-adrenergic receptor signal transmission system, by inhibiting adenyl cyclase and causing decreased cAMP production[28].

Dysfunction and desensitization of the β-adrenergic receptor pathway may be associated with the increased catecholamine levels in the plasma of cirrhotic patients. Some researchers have suggested that an overstimulation of the myocardial α-adrenergic receptor, because of elevated catecholamine levels, may contribute to the pathophysiology of cirrhotic cardiomyopathy by the induction of prolonged coronary artery vasoconstriction and an increase of energy demands[29].

Electrocardiographic abnormalities

The presence of electrocardiographic (ECG) abnormalities in patients with hepatic failure was firstly reported in patients with alcoholic liver disease. A prolongation of the QT interval, which was correlated with a higher incidence of sudden cardiac death compared with controls, has been described in patients with alcoholic cirrhosis[30]. In this initial report, the authors assumed that the ECG abnormalities should be a consequence of the effect of alcohol on the myocardium and not of hepatic failure, although abnormalities were detected more frequently in alcoholic patients with cirrhosis than in alcoholics with normal hepatic function.

Bernardi et al. detected QTc interval prolongation (>440 ms) in a significantly higher proportion of cirrhotic patients than healthy subjects (46.8% versus 5.4%). This abnormality was irrespective of the etiology of cirrhosis (42.9% in alcoholic versus 47.1% in non-alcoholic cirrhosis). However, the frequency was dependent on the degree of hepatic failure according to the Child-Pugh classification[31]. Patients with QTc interval prolongation exhibited high mortality, more likely due to the advanced hepatic disease than to a higher incidence of sudden cardiac death in this special group of patients.

The pathogenetic mechanisms of ECG abnormalities in liver cirrhosis remain unclear. An initial hypothesis involving autonomous nervous system dysfunction was rejected by a more recent study of

Puthumana et al[32]. The impaired membrane fluidity of cardiomyocyte, by compromising the function of the calcium and potassium pumps, may be related with the repolarization phase abnormality and QT interval prolongation[29]. Finally, increased plasma estrogen levels in cirrhosis have also been implicated in the increased incidence of QT interval prolongation. Nevertheless, it is well-known that this ECG abnormality is more frequent in females and QT prolongation has been considered to be a hormone-dependent finding[33].

Clinical problems and therapeutics

Cirrhotic cardiomyopathy, as a subclinical form of heart failure with no symptoms at rest, is not considered to need any special treatment. Patients with non-compensated liver cirrhosis are usually subjects with limited exercise capacity and are usually under salt restriction (to prevent water and sodium retention) leading to decreased left ventricular preload. Additionally, peripheral vasodilation, as described above, decreases left ventricular afterload and cardiac energy demands.

The pharmacological treatment usually received by patients with non-compensated liver cirrhosis includes drugs with a direct or indirect beneficial effect on the cardiovascular system. The diuretic furosemide contributes to decreased renal reabsorption of sodium and water, decreasing the total plasma volume, while spironolactone is considered to cause both inhibition of the renin-angiotensin axis and an improvement in left ventricular remodeling[1]. The use of β-blockers (propranolol) in cirrhotic patients with portal hypertension and esophageal varices seems to have a beneficial effect on β-adrenergic receptor density, which is supposed to be down-regulated in cirrhosis. In patients with portal hypertension, β-blockers are usually combined with nitrates, which are known to affect the coronary arteries and also have venodilatory effects leading to preload reduction.

Liver transplantation and cardiac dysfunction

Orthotopic liver transplantation constitutes a great physical stress for the cardiovascular system, during both the trans-operative and the postoperative period. Characteristically, 56% of patients in certain series exhibited acute pulmonary edema during the early postoperative period, while 7-21% of post-operative deaths were attributed to heart failure[14].

Beyond the trans-operative stress, cardiac performance may be aggravated postoperatively due to alterations in the cardiovascular system. The progressive normalization of the hyperdynamic circulation state, which is accompanied by elevation of the peripheral resistance and arterial pressure, may contribute to the occurrence of heart failure because of the increase in afterload. Sampathkumar et al. have described a reversible form of dilated cardiomyopathy during the early post-transplant period, with clinical manifestations of acute pulmonary edema and respiratory failure[34]. Cardiac ultrasonography revealed dilatation of all cardiac chambers, with reduction of ejection fraction.

Cardiovascular system alterations during the post-transplant period remain a controversial issue among researchers. Navasa et al. maintained that most of the humoral and hemodynamic alterations in terminal stage liver disease are restored during the post-transplant period[35]. However, Henderson et al. suggested a residual state of hyperdynamic circulation in transplanted patients[36], while Acosta et al. claimed that cirrhotic patients presented normal cardiac performance during both pre- and post-transplant period, disputing the existence of cirrhotic cardiomyopathy[37]. QT interval prolongation is also considered by some authors to be a phenomenon that is reversible during the post-transplant period[38,39].

Obviously, there is a need for further investigation to evaluate the effect of liver transplantation on the cardiovascular status of cirrhotic patients. In the meantime, evaluation of pre-transplant cardiovascular function is deemed to be necessary. Recent reports support the use of dobutamine stress-echo[40] or myocardial scintigraphy[41], but further research is needed.

Conclusions

Myocardial dysfunction in patients with liver cirrhosis and serious hepatic failure is described by the term “cirrhotic cardiomyopathy”. Because of its mild, subclinical course this entity remains underestimated, since these patients usually exhibit a variety of more serious complications related to hepatic failure and portal hypertension. Further re-

search is needed to evaluate whether this entity influences morbidity and mortality under certain circumstances that modify cardiovascular status, such as liver transplantation.

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