Cirrhotic cardiomyopathy is a clinical syndrome in patients with liver cirrhosis characterized by an abnormal and blunted response to physiologic, pathologic, or pharmacologic stress but normal to increased cardiac output and contractility at rest. As many as 50% of cirrhotic patients undergoing liver transplantation show signs of cardiac dysfunction, and 7% to 21% of deaths after orthotopic liver transplantation result from overt heart failure. In this review, we critically evaluate the existing literature on the pathophysiology and clinical implications of cirrhotic cardiomyopathy. (J Am Coll Cardiol 2010;56:539–49) © 2010 by the American College of Cardiology Foundation

More than 50 years ago, it was noted that persons with alcohol-related cirrhosis had increased cardiac output, and it was attributed to either impaired thiamine utilization or the presence of an endogenous vasodilator (1). Cardiac hypertrophy and cardiomyocyte edema in the absence of coronary artery disease, hypertension, or valvular disease were next described in an autopsy series of subjects with cirrhosis (2). Subsequent studies described an impaired hemodynamic response to physiologic (exercise) and pharmacologic stress despite a high resting cardiac output (3).

These findings were then confirmed in animal models of alcoholic cirrhosis and found to be related to decreased myocardial contractile function (4), and finally were corroborated by additional human studies (5,6).

This syndrome is formally described as cirrhotic cardiomyopathy, which is defined as chronic cardiac dysfunction in patients with cirrhosis characterized by blunted contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of known cardiac disease and irrespective of the causes of cirrhosis, although some etiologies (e.g., iron overload and alcohol consumption) further impact on myocardial structure and function.

This syndrome is considered to be related to both portal hypertension and cirrhosis (7) and is characterized by intrinsic alterations in myocardial function.

Pathophysiology

Vascular Dysfunction

Systemic vascular resistance and cardiac dysfunction. Advanced liver disease is associated with marked changes in systemic vascular resistance. In a model of pre-sinusoidal portal hypertension in rats, splanchnic arterial vasodilation is observed and is accompanied by a decreased contractile response to nitroprusside or isoproterenol and impaired myocyte calcium signaling, showing that portal vascular change and portosystemic shunting cause cirrhotic cardiomyopathy independent, at least in part, of parenchymal liver disease (8–10).

Sinusoidal portal hypertension, in contrast, is characterized by increased hepatic sinusoidal resistance to blood flow. This has both a fixed component due to fibrotic disruption of the architecture and a dynamic component due to changes in the contractility of the hepatic stellate cells and myofibroblasts in the hepatic sinusoids (11). These cells are sensitive to a number of vasoactive mediators, for example, endothelins, prostaglandins, and nitric oxide (NO). Sinusoidal NO production is impaired in subjects with cirrhosis because of increased caveolin expression (12,13). In contrast, there is an increased NO drive in the peripheral arterial circulation, especially in the splanchnic bed, that causes vasodilation. Other mediators implicated in the splanchnic arterial vasodilation seen in cirrhosis include carbon monoxide (CO) and endogenous cannabinoids (14,15).

The resting hyperdynamic state in cirrhosis reflects, therefore, an initial appropriate response to splanchnic arterial vasodilation (15,16).

Volume expansion. In patients with cirrhosis, blood volume expansion occurs before ascites formation. With progressive hepatic decompensation, there is a redistribution of this expanded blood volume with a relative decrease in the central circulation and increment in the
splanchnic bed (17). Moreover, despite an absolute increase in blood volume, there is marked activation of sodium (Na\(^+\)) and water retentive pathways, which become more pronounced as cirrhosis worsens. This is driven mainly by the state of progressive arterial vasodilation and imbalance between the blood volume on one hand and the space it has to occupy on the other (Fig. 1).

**Arterial compliance.** Peripheral arterial vasodilation and arterial compliance are closely associated. With progression of cirrhosis, there is a decrease in the thickness of the vessel walls as well as a decrease in total vascular wall area (14). The vascular tone is also decreased, possibly because of reduced smooth muscle mass secondary to NO overproduction or altered endothelial function as well as alterations in extracellular matrix turnover (18). Increased expression of large conductance, calcium-activated potassium (K\(^+\)) channel \(\alpha\) subunits have also been implicated as a cause of vascular remodeling and altered arterial compliance in cirrhosis (14).

**Epidemiology, Natural History, and Clinical Presentation**

Limited information is available about the epidemiology of cirrhotic cardiomyopathy in humans, as its diagnosis is difficult because of near normal cardiac function at rest. The majority of patients are diagnosed during phases of clinical decompensation of cirrhosis in which they present with features of diastolic heart failure and/or high-output heart failure (5) (Table 1). The actual prevalence of this condition is unknown. Therefore, not much is known also regarding the natural history of the disease. The condition is undoubtedly well tolerated and asymptomatic for months to years, and in many cases the symptoms are not easily distinguished from those of the underlying disease. Similarly, the natural history in terms of response to treatment and prognosis is unclear. Increased arterial compliance in cirrhosis leads to a functional hypovolemia (decreased pre-load) despite a volume overload in absolute terms. The blunted cardiac response of cirrhotic cardiomyopathy fails to overcome the decrease in effective circulating volume because of arterial vasodilation. Conversely, splanchnic arterial vasodilation unloads the ventricle and may mask the presence of ventricular insufficiency. Autonomic dysfunction and impaired volume and baroreceptor reflexes may also contribute to the blunted cardiac response. In a calcium tetrachloride model of...
of cirrhosis, rapid correction of the functional hypovolemia with saline infusion caused a rapid drop in cardiac output (19). The human corollary of this experiment is the development of heart failure and pulmonary hypertension after rapid increase in venous return after transjugular intrahepatic portosystemic shunt (TIPS) or liver transplantation (20).

Therefore, the presence of a reduced cardiac workload, favored by splanchic arterial vasodilation, which is in turn caused by progressive hepatic decompensation, may mask cardiac insufficiency. In fact, echocardiography often shows that patients with decompensated cirrhosis have normal cardiac function; however, physiologic or pharmacological stress, bacterial infections (e.g., spontaneous bacterial peritonitis), TIPS, or liver transplantation may unmask alterations in myocardial function, thus revealing the presence of cirrhotic cardiomyopathy.

A broad spectrum of cardiac alterations characterizes the clinical presentation of cirrhotic cardiomyopathy (Fig. 2), that may be distinctively viewed as a high-output heart failure (Table 1) (21,22), although the chronological sequence in which abnormalities develop is not fully defined.

**Electrophysiologic changes.** Multiple electrical abnormalities have been recognized in cirrhosis (QT-interval abnormalities, electrical and mechanical dyssynchrony, chrontropic incompetence) whose development seems linked to autonomic dysfunction (defects in the sympathetic nervous system [SNS] and vagal impairment), severe portal hypertension and liver dysfunction, cytokines, and endotoxins (23,24). These electric abnormalities are independent of the cause of cirrhosis.

**QT-INTERVAL PROLONGATION.** Prolongation of the QT-interval is well known to increase the risk for ventricular tachyarrhythmias. Prolongation of the QT-interval (>0.44 s) is seen even with mild increments in portal pressure in subjects with cirrhosis (24) and in noncirrhotic patients with portal hypertension, whereas a further increase has been described after TIPS insertion (21). Both delayed repolarization of cardiomyocytes due to K+ channel abnormalities and sympathoadrenergic hyperactivity may contribute to QT-interval prolongation (23,25). The QT-interval dispersion has been associated with the severity of liver dysfunction (26). It also varies from daytime to nighttime, probably reflecting diurnal variations in autonomic tone, circulatory status, and respiratory and oxygen demand (26). The QT-interval corrects itself in only 50% of subjects after a liver transplant (23). A recalculation of QT intervals based on heart rate and other liver-related parameters are now indicated to better dissect out the contribution of changes in QT-interval to heart-related morbidity and mortality in subjects with cirrhosis (27). According to some authors, QT-interval prolongation might be an important sign helpful to identify patients with cirrhosis at risk of cirrhotic cardiomyopathy (22).

**ELECTRICAL AND MECHANICAL DYSSYNCHRONY.** Some cases of sudden death from ventricular arrhythmias have been reported in patients treated with vasopressin during variceal bleeding or when undergoing plasma exchange (28). In animal models, chronic ligation of the portal vein has been shown to reduce excitation-contraction coupling due to decreased density of the L-type calcium channel (10). Disturbances of

<table>
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<tr>
<th>Table 1: Clinical Presentation of Cirrhotic Cardiomyopathy</th>
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<tr>
<td><strong>Diagnosis Methods</strong></td>
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<td>-------------------------------------------------------------</td>
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<tr>
<td>Echocardiography</td>
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<td>Dynamic magnetic resonance cardiac imaging</td>
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<td>Radionuclide angiography multigated acquisition</td>
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<td>Myocardial perfusion imaging with gating</td>
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<td>Systolic time intervals (measured through simultaneous recording of electrocardiogram, phonocardiogram, and external carotid arterial pulse tracing using multichannel photographic recording system)</td>
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<tr>
<td>Electrocardiography after necessary adjustment</td>
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<tr>
<td>Cardiac serum markers</td>
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<tr>
<td>Presence of BNP concentration</td>
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<tr>
<td>Elevated pro-BNP concentration</td>
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<td>Vasodilator serum markers</td>
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<td>Carbon monoxide</td>
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<td>Endocannabinoids</td>
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<td>Endothelin-3</td>
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<td>Endothelin-1</td>
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<td>Vasopressin</td>
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BNP = brain natriuretic peptide; LV = left ventricular; PGI2 = prostacyclin.
Excitation-contraction coupling have also been observed in cirrhotic patients with QT-interval prolongation, which may be attributable to defective K⁺ channel function in ventricular cardiomyocytes (29). The role of changes in intracellular calcium (Ca²⁺) and potassium (K⁺) in the extracellular milieu particularly after variceal hemorrhage and blood transfusion in mediating electromechanical dyssynchrony remains to be fully elucidated.

Inotropic and chronotropic incompetence. In a study of cirrhotic subjects without ascites, Na⁺ loading caused an increased end-systolic volume even though the resting hemodynamics were relatively normal (6). After the development of ascites, there was more overt evidence of contractile dysfunction despite a decrease in both afterload (arterial vasodilation) and pre-load (venous return) (6). Both hypertensive and normotensive subjects with compensated cirrhosis show a reduction in cardiac index and an increase in systemic vascular resistance (30). These data have been considered to represent underlying “pump dysfunction.” The hearts of cirrhotic subjects show a blunted ability to increase heart rate or left ventricular ejection fraction after appropriate stimulation with exercise, drug infusion, or postural challenge (31). These data are corroborated by other studies where an infusion of atrial natriuretic factor in cirrhotic subjects led to a decrease in stroke volume and cardiac index despite an increase in heart rate (32).

Another cause of decreased cardiac response to exercise is a decrease in maximal heart rate. This is closely correlated with the decreased cardiac output response. It is hypothesized that impaired cardiovascular reflex regulation and diminished sensitivity to SNS activation might contribute to the observed chronotropic incompetence (33).

Diastolic dysfunction. Diastolic dysfunction in cirrhosis was first reported in 1997 (5). Although some diastolic alterations may precede the systolic disturbances, both forms of dysfunction may develop simultaneously in cirrhotic patients. Eccentric left ventricular hypertrophy develops in bile duct ligated rats in conjunction with development of a hyperdynamic syndrome; this is associated with increased collagen content and increased ventricular stiffness (34) that induces a prolonged, slowed, or incomplete ventricular relaxation. Diastolic dysfunction has also been reported in noncirrhotic portal hypertension and in patients with ascites but without cardiac hypertrophy (35). Whereas the increased venous return seen after TIPS is expected to increase myocardial stretch and thus stroke volume, in a study of alcohol-related cirrhosis, diastolic dysfunction was unmasked by TIPS causing, in some cases, pulmonary edema and heart failure (36). Diastolic dysfunction may also result from impaired myocardial relaxation. This is related to the on-off rate of Ca²⁺ from troponin and the rate at which Ca²⁺ returns to the sarcoplasmic reticulum through the Ca²⁺-adenosine triphosphatase pump or Na⁺/Ca²⁺ exchanger. Interestingly, after paracentesis, patients with cirrhosis show an improvement of diastolic dysfunction, as demonstrated by an increased ratio of early to late diastolic filling (E/A ratio) and a decreased deceleration time (5) (Table 1). In fact, parvalbumin improves diastolic dysfunc-
tion (37), suggesting that improved hemodynamic outcomes after albumin infusion in subjects with spontaneous bacterial peritonitis may be partly due to a direct effect on the myocardium. Clinically, subjects with a thicker ventricle and more severe diastolic dysfunction are more likely to have heart failure after liver transplantation (22). The diastolic dysfunction tends to return to normal 6 to 12 months after a liver transplant (38).

**Systolic dysfunction.** A number of animal and human studies on cirrhosis have shown evidence that systolic function is apparently normal or even increased at rest, yet becomes impaired after stress, exercise, or other forms of stimuli (4–6). Ventricular function is impaired after pharmacologically induced stress in patients with alcoholic cirrhosis (39). Several studies of cirrhotic patients showed a decreased cardiac response with inotropic and chronotropic incompetence after pharmacologic or exercise-induced increase in afterload or heart rate (22,31); in fact, contrary to the expected increase, left ventricular ejection fraction did not change.

Although the systolic dysfunction has been attributed to the effects of alcohol on the myocardium in subjects with cirrhosis, it is also present in those with nonalcoholic causes of cirrhosis (4), as has been evaluated by assessing ventricular contractile performance, at rest and after exercise, through the measurement of systolic time intervals (derived from the simultaneous tracings of electrocardiogram, carotid artery pulse, and phonocardiogram) (28) (Table 1). In these cirrhotic patients, total electromechanical systole was prolonged because of the lengthening of systolic time intervals influenced by electromechanical coupling such as electromechanical delay and pre-ejection period, probably related to a reduced response to the adrenergic drive (28).

Systolic dysfunction, however, worsens with increasing liver failure. The presence of ascites does not affect the systolic dysfunction, and it is also unaffected by therapeu tic paracentesis (5). It has been suggested that systolic dysfunction may be influenced by pre-load, afterload, and diastolic dysfunction, but reduced myocardial reserve and impaired oxygen extraction (probably due to the local imbalanced NO production and function) emerge to be the main factors (22).

Recently, endocannabinoids have been implicated as potential cause of impaired myocardial contractility in a carbon tetrachloride mouse model of cirrhosis (40).

**Pathogenic Mechanisms**

The series of cardiac alterations that characterize the clinical presentation of cirrhotic cardiomyopathy depend on the several pathogenic mechanisms listed in the following text.

**Impaired Receptor Function**

Several potential molecular causes for impaired myocardial function in cirrhosis have been identified. These include changes in cardiomyocyte plasma membranes, β-adrenoceptor density and function, altered K⁺ channels, altered L-type Ca²⁺ channels, and altered Na⁺/Ca²⁺ exchanger (41).

**Role of cardiomyocyte plasma membrane changes.** In a study of a bile duct-ligated cirrhotic rat model, cardiomyocytes had significant increases in plasma membrane cholesterol content and cholesterol-to-phospholipid molar ratio resulting in a decrease in plasma membrane fluidity compared with sham-operated controls (42). In this model, cyclic adenosine monophosphate (cAMP) production in response to adrenergic stimulation was decreased; this was restored with correction of the membrane fluidity (Fig. 3). In a separate study of cholestatic cirrhotic rats, bile acid itself decreased plasma membrane fluidity in cardiac ventricles (43).

**Role of ventricular β-adrenoceptors.** The observed decrease in chronotropic and inotropic responses to β-adrenergic stimulation (9) in cirrhosis may be due to either decreased β-adrenergic receptor density or function. Indeed, a decrease in β-adrenoceptor density has been observed concomitantly with the changes in membrane fluidity noted in the preceding text (42). The decrease in membrane fluidity from increased cholesterol further impairs signaling from the remaining receptors after ligand binding by inhibition of β-adrenergic receptor coupling with stimulatory G proteins (44). Given the key role of altered membrane fluidity in β-adrenergic receptor dysfunction and the presence of decreased membrane fluidity in many animal models of cirrhosis, it appears that defective β-adrenergic receptor function is universally present in cirrhotic cardiomyopathy.

**Role of ventricular muscarinic receptors.** Five muscarinic acetylcholine receptor subtypes are known: M1, M3, and M5 muscarinic receptors couple to stimulate phospholipase C, whereas M2 and M4 muscarinic receptors inhibit adenylyl cyclase (44). However, only M2 and M3 receptors are expressed in heart tissue, and M1, M2, and M3 receptors are detected in vascular endothelial cells (45). In particular, muscarinic receptors reside in both the atria and ventricles but have a greater density in the former (46). They are more prevalent in the endocardium than in the epicardium. Muscarinic receptors exist on T tubules in cardiomyocytes, coronary arteries (including small vessels), and endothelial cell membranes of capillaries. Muscarinic receptors are abundant on sinoatrial and atrioventricular nodal cells (47). The antagonistic effects of muscarinic versus β-adrenergic stimulation are well described in ventricular myocytes (48). In a rat model of bile duct ligated cirrhosis, investigators reported blunted muscarinic (M2) responsiveness and defective signal transduction to cAMP (49).

However, as discussed previously, plasma membrane alterations in cirrhosis models may impair all post-receptor cardiomyocyte systems involving cAMP. The potential role of altered M1 and M3 receptors in cirrhotic cardiomyopathy remains to be described.

**Role of ventricular K⁺ channels.** Ventricular K⁺ channels are activated by a fall in cytoplasmic adenosine triphosphate concentration and function as a voltage-independent “brake” to modulate myocyte depolarization (50). Activation of K⁺ channels is essential for both early
and final repolarization. The K⁺ channel activators (calcitonin gene-related peptide, adenosine, and so forth) promote hyperpolarization and relaxation whereas inhibitors (noradrenaline, 5-hydroxytryptamine, neuropeptide Y, angiotensin II, endothelin-1, and so forth) cause depolarization and contraction. A rat model of bile duct ligated cirrhosis found decreased current density for all 3 types of K⁺/H11001 channels in isolated ventricular myocytes (Ca²⁺-independent transient outward K⁺ current, delayed rectifying K⁺ current, and inward rectifying K⁺ current) (25). As a consequence of the decreased K⁺ current density, cirrhotic rats exhibited a longer duration of baseline action potential as compared with ventricular myocytes of sham-operated rats (25). These observations may contribute to the QT-interval prolongation previously described in cirrhotic patients.

A rapid change from a "short" to a "long" action potential command waveform may cause an immediate decrease in peak Ca²⁺-dependent current and a marked slowing of its decline (51).

Therefore, a marked prolongation of the action potential might maintain the cardiomyocyte in a contracted state and impair relaxation (49). The inwardly rectifying background K⁺ current is believed to be the main ionic current responsible for setting the resting membrane potential in mammalian heart cells and also to influence the late phase of repolarization (52); therefore, the inwardly rectifying background K⁺ current may have some effect on cardiomyocyte inotropy depending on the overall status of regulation of intracellular Ca²⁺ concentration, the key driver of the myocardial contractility.

**Role of extracellular and sarcoplasmic reticulum calcium channels.** In cardiac myocytes, depolarization of the plasma membrane opens L-type voltage-gated Ca²⁺ channels that cause activation of Ca²⁺-stimulated Ca²⁺ release from the sarcoplasmic reticulum through ryanodine receptors (RyR2). Phosphorylation of RyR2 and decreased sarcoplasmic reticulum Ca²⁺ can decrease the calcium available for release (53). The decline of Ca²⁺ content and the consequent myocardial relaxation occur through Ca²⁺ reuptake in the sarcoplasmic reticulum and expulsion of Ca²⁺ from the cytosol into the extracellular space by adenosine triphosphate-driven calcium pumps and ion gradient-dependent Na⁺/Ca²⁺ exchangers. A decrease in initial
Ca\(^{2+}\) entry as well as decreased Ca\(^{2+}\)-stimulated Ca\(^{2+}\) release have been noted in cardiac myocytes in a bile duct ligated model of cirrhosis (54) (Fig. 4). A decrease in density of L-type channels and sarcolemmal calcium content has been reported in other studies (16). Crosstalk between sarcolemmal L-type Ca\(^{2+}\) channels and the sarcoplasmic reticulum might be fundamentally important to ensure adequate Ca\(^{2+}\) kinetics for long-term excitation-contraction coupling. Dysregulation of this process remains to be described in detail.

**Role of Na\(^+/Ca^{2+}\) exchanger.** The Na\(^+/Ca^{2+}\) exchanger plays an important role in maintaining a balance between Ca\(^{2+}\) influx and efflux. The Na\(^+/Ca^{2+}\) exchanger is present in all "external" membranes and exchanges 3 Na\(^+\) ions for 1 Ca\(^{2+}\) ion (or 4 Na\(^+\) ions for 1 Ca\(^{2+}\) ion) (55). The Na\(^+/Ca^{2+}\) exchanger is, therefore, responsible for maintenance of steady-state intracellular free Ca\(^{2+}\) concentration, although a small fraction of the Ca\(^{2+}\) transport also depends on a sarcolemmal Ca\(^{2+}\) adenosine triphosphatase (56). Since excess Ca\(^{2+}\) influx contributes to cardiomyocyte apoptosis (57), abnormalities of the Na\(^+/Ca^{2+}\) exchanger might contribute the cirrhotic cardiomyopathy. This, however, remains to be elucidated.

**Molecular Mediators of Impaired Myocardial Function in Cirrhosis**

**Role of carbon monoxide.** Carbon monoxide is an endogenously produced short-lived gas that favors splanchnic arterial vasodilation. Cirrhosis may stimulate carbon monoxide production through activation of the SNS, increased levels of norepinephrine, or increased cytokinemia from the enhanced portal venous bacteremia and endotoxemia. Carbon monoxide may decrease ventricular contractility through increased cyclic guanosine monophosphate (cGMP) and depressed calcium influx. In a rat model of bile duct-ligated cirrhosis, heme oxygenase messenger ribonucleic acid transcription, protein expression, and total heme oxygenase activity were significantly upregulated in cirrhotic rat hearts but not in sham-operated control rat hearts (58).

**Role of cannabinoids and their receptors.** Endocannabinoids (e.g., anandamide) are lipids that are the endogenous ligands for cannabinoid receptors (59). Several mammalian tissues express 1 of 2 types of cannabinoid receptors: CB1,
expressed in the brain and in several peripheral tissues including heart, endothelial cells (hepatic sinusoidal endothelial cells), smooth muscle cells, and perivascular nerves; and CB2, expressed in immune system cells. Cannabinoids induce splanchnic arterial vasodilation and have negative inotropic effects on cardiac contractility in cirrhosis. In a rat model of bile duct ligated cirrhosis, increased endocannabinoid signaling blunted the ventricular responsiveness to β-adrenergic stimuli by the CB1 receptor (60). A study in a rat model of carbon tetrachloride-induced cirrhosis showed that increased activity of the endocannabinoid/CB1 receptor system directly impaired cardiac contractility, whereas endocannabinoid/CB1 receptor blockade restored the normal contractile function (40). The negative inotropic effect of CB1 receptor might be the result of L-type calcium channel inhibition and cAMP reduction.

**Role of NO.** Nitric oxide is produced in cardiac microvascular endothelial cells and cardiomyocytes from either constitutive or inducible nitric oxide synthase (NOS), which catalyses the conversion of L-arginine to L-citrulline. Cardiomyocytes principally express endothelial NOS, localized near invaginations of the plasmalemma termed caveolae, and neuronal NOS, localized on the sarcoplasmic reticulum (61). A third isoform, the inducible nitric oxide synthase (iNOS), may be expressed upon stimulation with inflammatory mediators. While NO synthesized by neuronal NOS and endothelial NOS has cardioprotective effects through improvement of perfusion and inhibition of apoptosis, NO derived from iNOS has a cardiotoxic effect through the suppression of muscle wall contractility and induction of apoptosis (62). Nitric oxide is released in a pulsatile manner from the beating heart. Changes in ventricular filling induce parallel increases or decreases in cardiac NO synthesis, which, in turn, modulate the function of ion channels and transporters involved in cardiac excitation-contraction coupling (63).

Preliminary observations indicated that NO overproduction-induced hyperdynamic circulation in cirrhosis and the consequent splanchnic arterial vasodilation masked the presence of blunted cardiac function (19,20). However, experimental studies on cirrhotic animal models revealed the link between NOS, NO, and blunted cardiac response. Van Obbergh et al. (64) first elucidated the role of NOS in cirrhotic cardiomyopathy by demonstrating that treatment with the nonspecific NOS inhibitor, L-NMMA (N omega-monomethyl-L-arginine), significantly increased ventricular contractility of isolated working hearts in cirrhotic rats. Thereafter, Liu et al. (65) showed that high levels of NO were cardiopres- sant and that the heart and aorta of cirrhotic rats expressed high levels of iNOS messenger ribonucleic acid and endothelial NOS, respectively. Some lines of evidences support the role of tumor necrosis factor-α as a potent inducer of iNOS and, thereby, NO production (66). Conversely, NO stimulation of soluble guanylyl cyclase produces a 160- to 400-fold increase in cGMP as the second messenger effector and may cause bradycardia by blocking L-type channels and impairing the responsiveness of cardiac pacemaker cells to adrenergic stimuli (54,66). Overproduction of NO and neuronal NOS overactivity may impair RyR2 function through both classic cGMP-signaling and direct redox modification of specific thiol residues in the RyR2 protein (63). In a rat model of bile duct-ligated cirrhosis, both tumor necrosis factor-α and interleukin-1β exerted a negative inotropic effect in control papillary muscles through an NO-dependent mechanism, leading to the hypothesis that NO production played an important role in the pathogenesis of cirrhotic cardiomyopathy (65).

Other molecular pathways have also been investigated to explain the role of NO in cirrhotic cardiomyopathy. Peroxynitrite is a reactive oxygen species, formed by the reaction of NO with superoxide anion (O2−), that may inhibit cardiac function through nitration (or S-nitrosation) of cardiac contractile proteins, such as actin (67). In a rat model of bile duct ligated cirrhosis, increased protein nitration in cardiac tissue was associated with reduced chronotropic function (68). In a separate study of L-NAME (NG-L-nitro-arginine methyl ester) and N-acetylcysteine, decreased cardiac nitrotyrosine levels favored normalization of cardiac function and further confirmed the inhibitory effect of nitration.

**Role of Apoptosis in Impaired Myocardial Function in Cirrhosis**

Apoptosis is a key cellular process that plays an important role of myocardial remodeling in heart failure (69). Mitogen-activated protein kinases (MAPKs) are signaling proteins that respond to a variety of stimuli. Of the MAPK family, p38-MAPK is particularly involved with growth, proliferation, differentiation, and apoptosis (70). Several cirrhotis- inducing agents specifically activate p38-MAPK in myofibroblasts (71). Gene transfer techniques show that the p38-MAPK isoform, p38α, contributes to cell death after ischemia and cardiomyocyte apoptosis (72). A selective p38α/p38β isoform inhibitor, SB203580, protects cardiac myocytes from ischemic damage, further confirming the pro-apoptotic role for p38α (73). These effects are due to inhibition of the α rather than the β isoform (74). Transforming growth factor-β is a potent pro-fibrogenic and pro-apoptotic cytokine that causes its effects through smad proteins and non-smad pathways, including the p38 MAPK and JUN NH2-terminal kinases. These, as well as transforming growth factor-β activity, are increased in cirrhosis.

**Prognosis**

The patient with cirrhosis is a severely ill patient with an overall unfavorable prognosis if liver transplant is not safely performed. While cirrhosis directly provides an increased risk of cancer, bleeding, or infection, additional conditions may worsen the already poor prognosis of such patients. As previously stated, impaired cardiac function is often undiagnosed in cirrhosis yet leads to an increased risk of death especially in the setting of acute decompensated cirrhosis, conditions in which the inability of increasing cardiac...
output likely contributes to unfavorable outcomes (28). The impaired cardiac output may indeed favor a decrease in renal perfusion contributing to the pathogenesis of hepatorenal syndrome (75). That is favored by the ensuing sympathetic activation that tries to increase cardiac contractility but stimulates renal sodium and water retention also through the activation of the renin-angiotensin-aldosterone system (76). Furthermore, when there is a rapid hemodynamic change (e.g., after TIPS or liver transplantation), the increased filling pressure may favor the development of congestive heart failure. That is due both to the impaired diastolic relaxation, already present but still unrevealed, that causes elevated ventricular pressure thus favoring left atrium dilation, and to the impaired heart rate and intrinsic alterations of myocardium contractility. The ensuing blunted cardiac function causes a decrease in the effective circulatory volume, which induces a further increase in sodium retention. Thus, increasing sodium excretion through diuretics, aldosterone-blockers especially, leads to improved function (77). The β-adrenergic blockers are often used for patients with cirrhosis to reduce the portal hypertension and prevent the gastroesophageal variceal hemorrhage; β-blockers also ameliorate the cardiac contraction and function, both reducing QT-interval prolongation time and opposing the downregulation of β-adrenoceptor density (44). However, no longitudinal studies of diuretics and β-blockers for cirrhotic cardiomyopathy are available. Conflicting results have also been obtained by the use of angiotensin-II receptor antagonists, which, despite a good increase in sodium excretion without a change in renal and systemic hemodynamics (78), have not produced substantial clinical results after long-term treatment (79). On the contrary, according to some authors, angiotensin-converting enzyme inhibitors could be of benefit (77), but further studies are necessary to prove their efficacy in cirrhotic cardiomyopathy.

Because of the rapid shift of a large volume of blood from the splanchnic area to the heart, TIPS, used to treat refractory ascites and gastroesophageal variceal hemorrhage, often produces a worsening of the cardiac function in patients with cirrhosis, especially in those with impaired cardiac diastolic function (E/A ratio ≤1) (80).

Liver transplantation is also associated with cardiovascular complications (affecting almost 25% of patients), and patients with an abnormal heart function during surgery are at higher risk for post-operative pulmonary edema (81,82).

An improvement after liver transplant is expected and validates the concept that the cardiomyopathy is truly cirrhotic in origin (38). A study of 40 patients with cirrhosis undergoing liver transplantation reported the disappearance of left ventricular hypertrophy and diastolic dysfunction as well as normalization of systolic response and exercise capacity during stress (38).

In case of concomitant severe cardiomyopathy, heart transplantation has been considered (83).

**Potential Therapeutic Approaches**

No accepted pharmacologic treatment for cirrhotic cardiomyopathy exists. Liver transplant is the cure for cirrhosis and is likely to cure the associated cardiomyopathy. While waiting for targeted clinical trials, general knowledge and considerations used for heart failure should be applied to patients with cirrhosis (84). Agonists of farnesoid X receptor (a gene involved in intrahepatic generation of vasodilator hydrogen sulfide) and NCX-1000 (a new compound that releases NO in the liver) are interesting new attempts aimed at correcting the diminished production of endogenous hepatic vasodilators during cirrhosis (85,86), but their usefulness is not yet clear in cirrhotic cardiomyopathy.

At present, investigations on the gene expression pattern of the cardiomyocyte adrenergic pathway in animal models of cirrhosis are an attempt to better understand the causes of the blunted cardiac response (87). New gene-targeting pharmacological strategies might be the future direction toward which research will move.

**Conclusions**

A significant proportion of patients with cirrhosis affected by ascites, volume overload, and signs of hyperdynamic circulation have normal resting echocardiographic parameters but abnormal cardiac responses during exertion, stress, TIPS, or liver transplantation, consistent with the existence of a cirrhotic cardiomyopathy (81). Strict diagnostic criteria for cirrhotic cardiomyopathy are lacking, and this syndrome is often not recognized. Inability to increase cardiac output when necessary is likely a cofactor in cirrhosis complications such as hepatorenal syndrome or shock. No specific treatment or management strategies has been tested for patients with cirrhotic cardiomyopathy. The presence of the cardiomyopathy should be suspected in patients with worsening hemodynamics, and such patients may benefit from more aggressive monitoring and treatment of the underlying pathology leading to decompensation, and close monitoring during procedures likely to cause decompensation (i.e., TIPS, paracentesis, transplant). Clinical trials in this area are eagerly awaited. In the meantime, management of cirrhotic cardiomyopathy, once identified, should follow the recommendations of the American College of Cardiology/American Heart Association guidelines for the treatment of patients with heart failure (84). A better comprehension of both the complex hemodynamic changes during cirrhosis and the molecular pathways involved in the contractile dysfunction of the cardiomyocyte may lead to improved care of patients with cirrhotic cardiomyopathy.

Reprint requests and correspondence: Dr. Enrico M. Zardi, Università “Campus Bio-Medico,” Via Alvaro del Portillo, Rome 200-00128, Italy. E-mail: e.zardi@unicampus.it.
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