

Cirrhotic cardiomyopathy

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Creation Date: January 2005

Scientific Editor: Professor Dominique Valla

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Abstract

Most patients with cirrhosis have hemodynamic alterations characterized by increased cardiac output, and decreased systemic vascular resistance and arterial pressure. Despite the increased resting cardiac output, ventricular contractile response to stimuli is attenuated, a condition termed cirrhotic cardiomyopathy. The prevalence of cirrhotic cardiomyopathy remains unknown at present. It is generally latent, but shows itself when the patient is subjected to stress such as exercise, drugs, hemorrhage and surgery. Generally, cirrhotic cardiomyopathy with overt severe heart failure is rare. Major stresses on the cardiovascular system such as liver transplantation, infections and insertion of transjugular intrahepatic portosystemic stent-shunts (TIPS) have been demonstrated to unmask the presence of cirrhotic cardiomyopathy, and sometimes convert latent to overt heart failure. Cirrhotic cardiomyopathy may also contribute to the pathogenesis of hepatorenal syndrome. Clinical features include structural, histological, electrophysiological, systolic and diastolic functional abnormalities. Studies in experimental animal models of cirrhosis indicate that multiple factors are responsible, including abnormal membrane biophysical characteristics, impaired β -adrenergic receptor signal transduction and increased activity of negative-inotropic pathways mediated by cGMP. Because of the marked paucity of treatment studies, current management recommendations are empirical, nonspecific measures. Further studies in this area are required.

Keywords

cirrhosis, cardiac, heart failure, cAMP, cGMP

Disease name

Cirrhotic cardiomyopathy

Definition/Diagnostic criteria

In cirrhosis, cardiac output increases whereas systemic vascular resistance and arterial pressure decrease (Kowalski and Abelmann, 1953; Abelmann *et al.*, 1955). Despite the increased basal cardiac output, cardiac response to physiologic or pharmacologic stimuli

is known to be subnormal (Ma and Lee, 1996; Liu and Lee, 1999; Myers and Lee, 2000), a phenomenon called "cirrhotic cardiomyopathy" (Lee, 1989; Liu *et al.*, 2002). When first described more than 3 decades ago in cirrhotic patients, cardiac dysfunction was presumed to result from alcoholic cardiotoxicity, specifically a latent alcoholic cardiomyopathy (Gould *et al.*, 1969; Limas *et al.*, 1974). However, during the past 2 decades, it has become clear that blunted ventricular contractility with stress is also

present in nonalcoholic patients and animal models of cirrhosis (Caramelo *et al.*, 1986; Ingles *et al.*, 1991; Lee *et al.*, 1990). In the 1990s, numerous studies in patients with nonalcoholic cirrhosis conclusively demonstrated that depressed ventricular contractile responses to stimuli are found in *all* forms of cirrhosis (Kelbaek *et al.*, 1984; Grose *et al.*, 1995; Finucci *et al.*, 1996; Pozzi *et al.*, 1997; Wong *et al.*, 1999; Wong *et al.*, 2001).

In the absence of consensus definitions (currently in progress with results expected in 2006), the term "cirrhotic cardiomyopathy" is defined at present as: 1) baseline increased cardiac output but blunted ventricular response to stimuli, 2) systolic and/or diastolic dysfunction, 3) absence of overt left ventricular failure at rest, 4) electrophysiological abnormalities including prolonged Q-T interval on electrocardiography and chronotropic incompetence (Ma and Lee, 1996; Myers and Lee, 2000; Blendis and Wong, 2000; Liu *et al.*, 2002; Moller and Henriksen, 2002). Not all features are required for the diagnosis; for example, only 30-60% of patients show a prolonged QT interval.

Without firm diagnostic criteria, the exact prevalence of cirrhotic cardiomyopathy remains unknown. We believe that diastolic dysfunction is present in virtually all patients with cirrhotic cardiomyopathy, and that simple echocardiographic indices such as the E/A ratio may detect diastolic dysfunction even at rest. Indeed, once cirrhosis has advanced to a moderate stage, with the accumulation of peripheral edema or ascites, it appears that some element of diastolic dysfunction is universally present. For now, tests of diastolic function by echocardiography or dynamic magnetic resonance cardiac imaging may therefore represent the best available screening test to diagnose the syndrome.

Etiology and pathogenic mechanisms

Possible pathogenic mechanisms include defects in the cardiac β -adrenergic receptor system, abnormal membrane biophysical/biochemical function, overactivity of cardiodepressant substances such as nitric oxide, fibrosis/edema of cardiac muscle, and electrophysiologic abnormalities (Ma and Lee, 1996; Ma *et al.*, 1996; Liu and Lee, 1999; Myers and Lee, 2000; Liu *et al.*, 2002).

Heart cell contractility is mainly determined by the stimulatory β -adrenergic receptor system. When stimulated by norepinephrine or other catecholamines, the β -adrenergic receptor-ligand complex couples with G-protein to stimulate membrane-bound adenylate cyclase, generating cAMP which phosphorylates several

proteins leading to intracellular calcium fluxes. The calcium then causes actin-myosin cross-linking, and thus cellular contraction.

Cardiomyocyte plasma membranes isolated from a rat model of cirrhosis show multiple defects in the β -adrenergic signaling pathway and lipid composition of the membrane bilayer (Ma *et al.*, 1994; Ma *et al.*, 1996). Due to increased cholesterol in the membrane, the ratio of cholesterol:phospholipids increases, leading to a biophysical change termed decreased membrane fluidity (Ma *et al.*, 1994; Ma *et al.*, 1996). Decreased membrane fluidity hampers the conformational movement ability and thus the function of protein receptors embedded in the membrane, such as calcium channels and β -adrenergic receptors (le Grimellec *et al.*, 1992). Other mechanisms include increased inducible nitric oxide synthase (iNOS) activity with overproduction of NO (van Obbergh *et al.*, 1996; Liu *et al.*, 2000; Garcia-Estan *et al.*, 2002), and increased heme oxygenase-1 activity that overproduces carbon monoxide (Liu *et al.*, 2001). Both gases inhibit cardiomyocyte contractility by stimulating soluble guanylate cyclase to produce cGMP. cGMP inhibits contractility by several mechanisms, mainly by inhibiting calcium release from the sarcoplasmic reticulum of the cardiomyocyte (Cohen *et al.*, 1999).

Clinical features and diagnostic tests

Many aspects of cardiac contraction have been described to be abnormal in cirrhosis, including histology and structure, chronotropic, systolic and diastolic function, and electrophysiological changes. Functional and structural changes in the cardiac chambers have been seen in the left heart, rather than the right. Most studies have found dilatation of the left atrium, and hypertrophy or dilatation of the left ventricle. The right atrium and right ventricle generally have normal dimensions and wall thickness in the absence of the uncommon syndrome of portopulmonary hypertension. Histological changes of cirrhotic cardiomyopathy include myocardial fibrosis, subendocardial edema, and nuclear and cytoplasmic vacuolation of cardiomyocytes (Ma and Lee, 1996; Liu and Lee, 1999; Myers and Lee, 2000; Liu *et al.*, 2002). However, these conclusions are based on old autopsy studies in patients with alcoholic cirrhosis, some dating back almost 8 decades. Whether some of these findings may simply reflect mild alcoholic cardiotoxicity remains uncertain.

The chronotropic response to the β -adrenergic agonist isoproterenol is attenuated in cirrhotic humans and rats (Ramond *et al.*, 1986; Lee *et*

al., 1990). Cardiac response to physical exercise in cirrhotic patients is blunted, with subnormal responses in echocardiographic ejection fraction and contraction time. Moreover, both ventricular systolic and diastolic function are impaired in cirrhosis (Ma and Lee, 1996; Liu and Lee, 1999; Myers and Lee, 2000; Liu *et al.*, 2002). Stroke volume and contractile indices are typically normal or even increased at rest. However, under stressor stimuli such as exercise, hemorrhage or drug infusions, cirrhotic patients may show an attenuated systolic function compared to healthy controls (Kelbaek *et al.*, 1984; Lee, 1989; Grose *et al.*, 1995; Finucci *et al.*, 1996; Pozzi *et al.*, 1997; Wong *et al.*, 1999; Wong *et al.*, 2001). For example, normal subjects can easily triple their cardiac output with submaximal exercise; cirrhotic patients do not exceed a doubling of cardiac output with exercise (Kelbaek *et al.*, 1984). The prevalence and extent of systolic dysfunction in cirrhotic patients appear to be variable.

In contrast, some element of diastolic dysfunction appears to be much more common. Indeed, some authorities contend that some degree of diastolic dysfunction is present in virtually every patient with cirrhosis (Finucci *et al.*, 1996; Pozzi *et al.*, 1997; Wong *et al.*, 1999; Wong *et al.*, 2001). Diastolic dysfunction manifests as a stiff, noncompliant ventricle, and is often seen in patients with some degree of left ventricular hypertrophy or dilatation. However, overt structural changes in the ventricle are not a prerequisite for diastolic dysfunction. Impaired passive and active filling of the left ventricle in early and middle-late diastole, respectively, lead to an inability to adequately increase stroke volume in response to stimuli. Again, in contrast to systolic dysfunction, a significant stimulus may not be required to detect diastolic dysfunction. Echocardiography may reveal abnormal diastolic function even at rest (Liu *et al.*, 2002).

Electrophysiological changes including prolonged repolarization and impaired cardiac excitation-contraction coupling have been demonstrated in cirrhotic patients (Kempler *et al.*, 1993; Bernadi *et al.*, 1998; Finucci *et al.*, 1998; Trevisani *et al.*, 2003; Bal and Thuluvath, 2003). Repolarization prolongation is manifested by a prolonged QT interval on the electrocardiogram. Rate-corrected prolongation of the QT (>440 msec) is found in 30-60% of patients with cirrhosis (Bernardi *et al.*, 1998; Finucci *et al.*, 1998; Trevisani *et al.*, 2003; Bal and Thuluvath, 2003). Prolongation of QT interval can be associated with an increased risk of certain ventricular arrhythmias, particularly the "torsade de pointes" type of ventricular tachycardia. However, sudden cardiac death is

rare in cirrhosis, and torsade de pointes has only been described in a few patients, all of whom had other risk factors for this type of ventricular tachycardia. For example, torsade de pointes has been reported in patients with variceal bleeding receiving vasopressin (Stein *et al.*, 1992; Faigel *et al.*, 1995). Therefore, the clinical significance of QT prolongation in cirrhosis remains unclear.

In addition to QT prolongation, Henriksen and colleagues have recently reported that cirrhotic patients show a dispersion of the normal interval between the onset of electrical systole (the electrocardiographic QRS complex) and mechanical systole itself (Henriksen *et al.*, 2002). In other words, this normally tightly-regulated time interval is subject to wider variability in cirrhotic patients, either earlier or later than normal. Again the clinical relevance of this interesting observation remains unknown at present.

The exact mechanism leading to these electrophysiological changes is unclear. In clinical studies, severity of liver disease and circulatory dysfunction are related to prolonged Q-T interval. Moreover, these changes disappear after liver transplantation in most patients (Bernadi *et al.*, 1998; Finucci *et al.*, 1998; Trevisani *et al.*, 2003; Bal and Thuluvath, 2003). Studies in the cirrhotic rat suggest that functional alterations of ion channels, particularly one or more types of potassium channels, in cardiac plasma membranes play a role in initiating and maintaining cardiac electrophysiological abnormalities (Ward *et al.*, 1997; Ward *et al.*, 2001).

Differential diagnosis

Many cardiac conditions resulting in mild or moderate left ventricular failure may mimic cirrhotic cardiomyopathy. Patients with liver disease may also have concomitant primary cardiac diseases such as ischemic heart disease, hypertensive cardiomyopathy or alcoholic cardiotoxicity. Whether patients with cirrhosis are somehow protected from developing coronary atherosclerosis remains unclear. Although this was formerly accepted as dogma, more recent evidence suggests that cirrhotic patients can indeed manifest severe coronary artery disease (Plotkin *et al.*, 2000). In Western countries, alcohol remains a significant cause of cirrhosis. In that regard, alcohol may precipitate or aggravate heart disease in two ways. First, it is well known that hypertension becomes more severe or uncontrolled in alcoholic patients (although if end-stage cirrhosis supervenes, then arterial pressure often normalizes due to peripheral vasodilatation).

Second, chronic excessive alcohol is directly cardiotoxic, with alcoholic cardiomyopathy a well-described syndrome.

A careful history of excessive alcohol, physical examination for signs of hypertension such as retinal vascular changes, and appropriate diagnostic tests such as exercise stress electrocardiography, nuclear cardiographic scans and coronary angiography will help distinguish these conditions from cirrhotic cardiomyopathy.

Clinical consequences

Overt heart failure is rare because of the peripheral vasodilatation characteristic of cirrhosis, in effect "autotreating" the ventricle by reducing afterload, and compensatory diminution of inhibitory influences such as the cardiac muscarinic system (Ma *et al.*, 1996; Jaue *et al.*, 1997). However, stresses such as liver transplantation, infection and procedures such as insertion of transjugular intrahepatic portosystemic stent-shunts (TIPS) can convert latent to overt heart failure. Indeed, heart failure is responsible for 7-15% of mortality following liver transplantation (Rayes *et al.*, 1995; Myers and Lee, 2000), and in some series is the third-leading cause of death after rejection and infection. Numerous studies report acute left ventricular failure or subtler indices of cardiac dysfunction following liver transplantation, even in patients with no previous cardiac history or risk factors (Park *et al.*, 1985; Glauser, 1990; Nasraway *et al.*, 1995; Donovan *et al.*, 1996; Sampathkumar *et al.*, 1998).

TIPS are often used to treat recurrent or intractable variceal bleeding, or ascites. The abrupt shift of a significant portion of the mesenteric venous blood directly into the systemic venous circulation through these portosystemic shunts dramatically increases the cardiac preload. Several studies have reported abnormal cardiac response to this abrupt increase in preload (Wong *et al.*, 1995; Huonker *et al.*, 1999; Lotterer *et al.*, 1999; Merli *et al.*, 2002). There are also several case reports and small series of patients with precipitation of overt left ventricular failure after TIPS insertion (Braverman *et al.*, 1995; Gines *et al.*, 2002). Indeed, a recent Spanish-American multicentre study of TIPS vs large volume paracentesis for treatment of ascites, reported that 12% of the TIPS group developed heart failure compared to none in the paracentesis group (Gines *et al.*, 2002).

Severe bacterial infections resulting in septic shock syndrome are known to induce cardiodepression. This is mediated by negative-inotropic cytokines such as TNF α and

interleukins. In that regard, Ruiz del Arbol and colleagues studied 23 patients with proven spontaneous bacterial peritonitis, whose infection cleared with appropriate antibiotic therapy (Ruiz-del-Arbol *et al.*, 2003). The 8 patients who went on to develop the well-known complication of spontaneous bacterial peritonitis, hepatorenal syndrome, had a distinctly different cardiac response compared to the 15 who did not develop renal dysfunction. The former group had a lower baseline cardiac output, which declined even further with infection resolution, compared to the latter. In the group that developed hepatorenal syndrome, the further decline in cardiac output was associated with arterial hypotension, indicating decreased renal perfusion. These results suggest that an inadequate cardiac contractile response to the stress of infection may play an important role in the pathogenesis of hepatorenal syndrome (Lee, 2003).

Management

The optimum management of cirrhotic cardiomyopathy has not been established since there are neither "gold standard" diagnostic criteria nor specific treatments at present. Currently, an expert consensus committee is formulating diagnostic criteria with the initial results expected in 2005/06. Until then, recognition of cirrhotic cardiomyopathy depends on a high level of awareness for the presence of this syndrome, particularly in patients with advanced cirrhosis who undergo significant surgical, pharmacological or physiological stresses. If heart failure becomes overt, the usual treatments should be initiated as for all forms of congestive heart failure, including bedrest, oxygen, diuretics and careful preload reduction by drugs (Ma and Lee, 1999; Liu *et al.*, 2002).

Because the β -adrenergic receptor is desensitized in cirrhotic cardiomyopathy, inotropic β -agonists such as dobutamine and isoproterenol may not benefit patients with cirrhotic cardiomyopathy. Previous studies have demonstrated markedly attenuated vascular responses to dobutamine and isoproterenol in cirrhotic patients without overt heart failure (Mikulic *et al.*, 1983; Ramond *et al.*, 1986).

There remains a marked lack of human or animal data about specific pharmacological treatments (Ma and Lee, 1999; Orii *et al.*, 2000). Specific therapies such as β -blockade and angiotensin/aldosterone inhibitors remain untested in humans or animals with cirrhosis. Henriksen and colleagues have reported that acute administration of a single dose of the β -blocker propranolol improves the prolonged

electrocardiographic QT interval in cirrhotic patients (Henriksen *et al.*, 2004), but whether there is also an improvement in contractile dysfunction with chronic dosing remains unknown. Cardiac glycoside therapy may not be beneficial; the short-acting glycoside ouabain was ineffective in patients with severe alcoholic cirrhosis in a study that dates back 3 decades (Limas *et al.*, 1974). Much future research, both clinical and experimental, is needed in this area.

Acknowledgments

Dr. Baik was supported by a sabbatical leave from Yonsei University Wonju College of Medicine, Wonju, Korea, and research fellowship funding from the Korean Association for Study of the Liver and GlaxoSmithKline Korea. Dr. Lee is supported by a Senior Scholarship award from the Alberta Heritage Foundation for Medical Research. Our studies reported in this review were funded by the Canadian Institutes of Health Research.

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