COR ET VASA 55 (2013) E391–E396

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/crvasa

Review Article — *Special issue: Heart Failure*

Heart failure in patients with liver cirrhosis

Radek Pudil[a,*], *Radek Pelouch*[a], *Rudolf Praus*[a], *Martina Vašatová*[b], *Petr Hůlek*[c]

[a]1st Dept. of Internal Medicine – Cardioangiology, Medical Faculty and University Hospital, Hradec Králové
[b]Dept. of Clinical Biochemistry and Diagnostics, Medical Faculty and University Hospital, Hradec Králové
[c]2nd Dept. of Internal Medicine – Gastroenterology, Medical Faculty and University Hospital, Hradec Králové

ARTICLE INFO

Article history:
Received 19 December 2012
Received in revised form
4 June 2013
Accepted 8 June 2013
Available online 14 June 2013

Keywords:
Liver cirrhosis
Cirrhotic cardiomyopathy
Heart failure
Transjugular portosystemic shunt

ABSTRACT

Liver cirrhosis is associated with severe hemodynamic changes which include hyperdynamic circulation with increased cardiac output, heart rate and reduced systemic vascular resistance. The term cirrhotic cardiomyopathy is defined as the presence of chronic cardiac dysfunction, characterized by blunted contractile responsiveness to stress and altered diastolic relaxation with electrophysiological abnormalities (QT interval prolongation), all occurring in the absence of any other cardiac disease. The key role in diagnosis is played by 2-dimensional echocardiography, electrocardiography and various serum markers (natriuretic peptides). The prognosis of the patients with cirrhotic cardiomyopathy is affected by heart failure, which can develop during invasive procedures (surgery, insertion of a transjugular intrahepatic portosystemic shunting and liver transplantation). No accepted specific treatment of cirrhotic cardiomyopathy exists. The therapy should follow the recommendations for the treatment of liver cirrhosis and heart failure.

Contents

*Correspondence to: 1st Dept. of Internal Medicine – Cardioangiology, Medical Faculty and University Hospital, Sokolská 585, Hradec Králové 500 05, Czech Republic.
Tel.: +420 49 5833249; fax: +420 49 5832006.
E-mail addresses: radek.pudil@fnhk.cz, pudilradek@atlas.cz (R. Pudil).

0010-8650/$ - see front matter © 2013 The Czech Society of Cardiology. Published by Elsevier Urban & Partner Sp.z.o.o. All rights reserved.
http://dx.doi.org/10.1016/j.crvasa.2013.06.002

1. Introduction

In 1953 Kowalski and Abelman observed the elevation of the resting cardiac output, increased stroke volume, normal blood pressure and low systemic vascular resistance in patients with a history of alcoholism, inadequate diet, and liver cirrhosis [1]. Later unexpected deaths due to heart failure were reported in the patients following liver transplantation, transjugular intrahepatic portosystemic shunts (TIPS) insertion, and surgical portocaval shunts [2]. These facts increased interest in study of the myocardial dysfunction in patients with liver cirrhosis. Now, it is clear that similar changes can develop also in patients with non-alcoholic liver cirrhosis. The studies showed that liver cirrhosis *per se* is associated with significant cardiovascular abnormalities [3,4]. It became clear that liver cirrhosis is associated with increased resting cardiac output (CO), decreased systemic vascular resistance (SVR), reduced myocardial contractility or systolic incompetence, especially under the stress conditions, increased left ventricular thickness associated with diastolic dysfunction and ecg abnormalities (QTc interval prolongation) [5]. These abnormalities are formally described as "cirrhotic cardiomyopathy (CCM)," which is defined as chronic cardiac dysfunction in patients with liver cirrhosis. It is 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 cause of cirrhosis [6,7].

These patients can present with dyspnea, fluid retention and limited exercise capacity. Now there is evidence that impaired liver function and portal hypertension with splanchnic vasodilatation lead to the development of the hyperdynamic syndrome. This review discusses the possible pathogenic mechanisms, clinical presentation and potential treatment of cirrhotic cardiomyopathy.

2. Pathophysiology

Impaired liver function and portal hypertension with splanchnic and systemic vasodilatation led to development of hyperdynamic syndrome, which is characterized with increased cardiac output, heart rate, decreased peripheral systemic resistance and normal or decreased arterial pressure. Furthermore, other factors may play an important role: increased sympathetic nervous activity, increased blood volume and the presence of arteriovenous communications [8,9]. This further aggravates the hyperdynamic circulation and can progress into impaired myocardial contractility with electrophysiological abnormalities called cirrhotic cardiomyopathy.

2.1. *Systemic vascular resistance*

In patients with liver cirrhosis, the SVR is reduced as a complex result of the presence of arteriovenous communications, increased level of circulating vasodilators, reduced resistance to vasoconstrictors and increased sensitivity to vasodilators. Increased level of circulating vasodilators is augmented by vasodilators escaping degradation in the diseased liver or their bypassing through portosystemic collaterals [10]. The recent studies show the important role of nitric oxide, carbon monoxide, endogenous cannabinoids, brain natriuretic peptide, calcitonin gene-related peptide, and endothelin-3 as potent vasodilators in patients with liver cirrhosis [7,11,12]. Furthermore, vascular endothelial growth factor (VEGF) seems to stimulate angiogenesis and the development of portosystemic collaterals [13].

2.2. *Volume expansion*

In patients with liver cirrhosis, blood and plasma volumes are increased, but the distribution between central and peripheral vascular areas is unequal [10,14]. Central and arterial blood volumes (i.e. blood volume in the heart, lungs and central arterial tree) are decreased compared to non-central blood volume (splanchnic). This redistribution results in central (effective) hypovolemia. Low effective blood volume in combination with arterial hypotension leads to volume and baroreceptor activation of potent vasoconstriction systems such as sympathetic nervous system and renin angiotensin aldosterone system [15,16]. This can result in further water retention and further redistribution.

2.3. *Myocardial dysfunction*

It has been shown that left ventricular systolic function is normal or even increased at rest, but after stress, exercise or other stimuli it becomes impaired [2–4]. Furthermore, other studies showed a decreased myocardial response with inotropic and chronotropic incompetence after exercise-induced or pharmacologic increase in afterload or heart rate [6]. All these findings were reported in patients with alcoholic and non-alcoholic cirrhosis.

Diastolic dysfunction is relatively frequent in patients with liver cirrhosis and is associated with increased mortality [17–19]. The recent studies of left ventricular filling in cirrhosis support the presence of a subclinical myocardial disease with diastolic dysfunction [13,20]. It has been shown that myocardial fibrosis and increased myocardial mass lead to increased stiffness of the myocardial wall resulting in impaired ventricular filling and diastolic dysfunction.

Therefore, early diagnosis of diastolic heart failure could help to identify risk patients [21].

2.4. *Heart pressures*

Initial phases of liver cirrhosis are associated with upper normal values of right ventricular pressure, right atrial

pressure, pulmonary artery pressure and pulmonary capillary wedge pressure. Actual values of these parameters depend on the degree of the volume status: fluid retention with formation of ascites may result in increase of right atrial pressure; paracenthesis with removal of ascetic fluid and diuretic treatment may decrease these parameters. It has been shown, that physical exercise, pharmacological stress, and therapeutic procedures may affect cardiac pressures (the left ventricular end diastolic pressure increases but the cardiac stroke index and left ventricular ejection fraction fall during exercise, which indicates an abnormal ventricular response to an increase in ventricular filling pressure) [6–10]. Reduced left ventricle afterload (due to decrease of systemic vascular resistance) may mask left ventricle failure for a long time. But, in late stages of cirrhotic cardiomyopathy, the heart is not able to compensate for all volume changes. In these patients cardiac output decreases and left ventricle filling pressure increases. This is a sign of poor prognosis.

2.5. *Pulmonary circulation*

Hemodynamic studies in patients with liver cirrhosis showed significant changes of pulmonary circulation. There are two different entities in patients with liver cirrhosis: portopulmonary hypertension and hepatopulmonary syndrome. Portopulmonary hypertension is characterized with increased mean pulmonary artery pressure and pulmonary vascular resistance in the presence of portal hypertension. The key factors in development of portopulmonary hypertension are abnormal vasoconstriction and obliterative remodeling of lung circulation. In clinical studies, 2–10% of cirrhotic patients have been estimated to be at risk of developing pulmonary hypertension. Portopulmonary hypertension seems to be a significant prognostic factor in patients with liver cirrhosis [22].

Hepatopulmonary syndrome (HPS) is characterized by intrapulmonary vasodilatation (increased production and decreased elimination of vasodilators), the presence of intrapulmonal arterio-venous shunts and development of ventilation/perfusion mismatch. The reported frequency of hepatopulmonary syndrome in patients with liver disease is between 4% and 29% [7,9,22]. The main clinical features of HPS are hypoxemia, othodeoxia and plathypnea.

2.6. *Electrophysiological changes*

In patients with liver cirrhosis, multiple electrophysiological abnormalities have been recognized. They include QT-interval prolongation, electrical and mechanical dyssynchrony and chronotropic incompetence. Prolongation of QT-interval is attributed to delayed repolarization of cardiomyocytes due to K channel abnormalities and sympatoadrenergic hyperactivity [23,24]. The defect in electromechanical coupling leading to dyssynchrony between electrical and mechanical systoles was proven by Bernardi et al. [23]. and Henriksen et al. [25] They reported significant prolongation of pre-ejection time, and the difference between electrical and mechanical systole was evaluated using catheterization curves.

Chronotropic incompetence defined as the failure of the heart rate to respond to physiological and pharmacological stimuli was observed by both alcoholic and nonalcoholic patients and is proportional to the severity of cirrhosis.

3. Diagnostic criteria for cirrhotic cardiomyopathy

A working definition was proposed in the World Congress of Gastroenterology in Montreal (Canada) in 2005 and is detailed in Table 1.

3.1. *Serum markers*

Cirrhotic cardiomyopathy is associated with increased production of natriuretic peptides. Brain natriuretic peptide (BNP) emerged as a sensitive marker of left ventricular

Table 1 Proposed Diagnostic Criteria for Cirrhotic Cardiomyopathy. Adopted from Figueiredo et al. [26]

A working definition of cirrhotic cardiomyopathy
- A cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease

Systolic dysfunction
- Blunted increase in cardiac output with exercise, volume challenge or pharmacological stimuli
- Resting EF < 55%

Diastolic dysfunction
- E/A ratio < 1.0 (age-corrected)
- Prolonged deceleration time (> 200 ms)
- Prolonged isovolumetric relaxation time (> 80 ms)

Supportive criteria
- Electrophysiological abnormalities
- Abnormal chronotropic response
- Electromechanical uncoupling/dyssynchrony
- Prolonged QTc interval
- Enlarged left atrium
- Increased myocardial mass
- Increased BNP and pro-BNP
- Increased troponin

dysfunction also in patients with liver cirrhosis. La Villa et al. [27] and Wong et al. [28] showed that liver cirrhosis is associated with increased production of BNP in ascitic and preascitic phase. Plasma BNP and NT-proBNP level is associated with the severity of the cirrhosis and with the degree of cardiac dysfunction [29]. Cirrhotic cardiomyopathy is frequently associated with increased troponin level [30]. Liver cirrhosis and cardiac dysfunction is also associated with the increase of other markers, such as adrenomedullin, glycogen phosphorylase BB and heart fatty acid binding proteins [31,32]. It has been shown that the levels of these markers of cardiac dysfunction are generally higher in ascitic than nonascitic cirrhotic patients. The assessment of serum markers could be helpful in risk stratification and therapy monitoring in patients with liver cirrhosis [32].

3.2. *Transjugular intrahepatic portosystemic shunt*

A transjugular intrahepatic portosystemic shunt (TIPS) is a percutaneous created connection within the liver between the portal and systemic circulation. A TIPS is placed to reduce portal pressure in patients with severe complications of portal hypertension (variceal bleeding, refractory ascites and hepatorenal syndrome) [33,34]. However, TIPS placement can be associated with potential complications and negative side effects [35]. TIPS placement is associated with increased heart rate, cardiac output and plasma volume, and reduced systemic vascular resistance and arterial blood pressure [36]. Furthermore, liver cirrhosis per se is frequently associated with cardiac dysfunction and abnormalities in the central, splanchnic and peripheral circulation, and hemodynamic changes caused by humoral and nervous dysregulation [7,37].

Transjugular intrahepatic portosystemic shunt (TIPS) insertion represents a stressful situation in this group of patients. Thus, the prognosis of the patients after TIPS procedure can be affected by the development of heart failure, especially in those who have preexisting myocardial dysfunction. Therefore, early diagnosis of dysfunction of the myocardium is essential not only before, but also after the TIPS procedure. In our study, we evaluated the use of echocardiography for monitoring of the hemodynamic changes in the group of 55 patients with liver cirrhosis [38]. We have found that liver cirrhosis is frequently associated with diastolic dysfunction; transjugular portosystemic shunt creation is associated with significant hemodynamic changes. These changes can be monitored using echocardiography. Our study confirmed the need of hemodynamic monitoring of patients undergoing TIPS procedures and showed that echocardiography as a non-invasive method can be very useful for this purpose.

3.3. *Management of cirrhotic cardiomyopathy*

No accepted pharmacologic treatment for cirrhotic cardiomyopathy exists. To date, there are no clinical studies on the management of cirrhotic cardiomyopathy. Once cardiac failure becomes evident following some forms of stress, management should follow similar guidelines as in noncirrhotic patients, although cardiac afterload reduction will not be well tolerated in patients with advanced cirrhosis who are significantly vasodilated. Vasodilators, like ACE-inhibitors, should be used very carefully because of the risk of further aggravation of the systemic vasodilatory state [10]. The treatment with diuretics is indicated in patients with water retention. Aldosterone antagonists may have beneficial effects in the reduction of left ventricular dilatation, wall thickness, and are potentially useful in the improvement of diastolic function. It has been shown that β-adrenergic blockade can lower portal pressure and potentially reduce the degree of shunting of cardiotoxins from the splanchnic to the systemic circulation. Zambruni and colleagues showed beneficial effect of chronic administration of β-blocker on QT intervals in a cohort of cirrhotic patients with varying degrees of decompensation [39].

New therapeutic approaches are under investigation. Pozzi et al. demonstrated favorable effect of k-cancreolate (aldosterone antagonist), which was able to reduce circulatory volume and to decrease left ventricular wall thickness [40]. Similarly, 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, but their usefulness is not yet clear in cirrhotic cardiomyopathy [10,40].

4. Conclusion

Liver cirrhosis is frequently associated with syndrome of hyperdynamic circulation (increased cardiac output, decreased peripheral systemic vascular resistance and normal or decreased arterial pressure). The recent evidence indicates the presence of a subclinical myocardial disease with increased myocardial fibrosis and increased myocardial mass. This can lead to increased stiffness of the myocardial wall and can result in impaired ventricular filling and diastolic dysfunction. It can progress into systolic dysfunction of the left ventricle. These abnormalities are associated with electrophysiological changes (QT interval prolongation).

The presence of the cardiomyopathy should be suspected in patients with worsening hemodynamics. 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, and liver transplant).

The management of cirrhotic cardiomyopathy, once identified, should follow the guidelines for the treatment of patients with heart failure. No specific treatment or management strategies have been tested for patients with cirrhotic cardiomyopathy.

Acknowledgments

This review was supported by the research project PRVOUK 37/03.

REFERENCES

[1] H.J. Kowalski, W.H. Abelmannn, The cardiac output at rest in Laennec's cirrhosis, Journal of Clinical Investigation 32 (10) (1953) 1025–1033.

[2] C. Caramelo, D. Fernandez-Muñoz, J.C. Santos, et al., Effect of volume expansion on hemodynamics, capillary permeability and renal function in conscious, cirrhotic rats, Hepatology 6 (1986) 129–134.

[3] M. Pozzi, S. Carugo, G. Boari, et al., Evidence of functional and structural cardiac abnormalities in cirrhotic patients with and without ascites, Hepatology 26 (1997) 1131–1137.

[4] F. Wong, P. Liu, L. Lilly, et al., Role of cardiac structural and functional abnormalities in the pathogenesis of hyperdynamic circulation and renal sodium retention in cirrhosis, Clinical Science (London) 97 (1999) 259–267.

[5] H. Kelbaek, A. Rabøl, I. Brynjolf, et al., Haemodynamic response to exercise in patients with alcoholic liver cirrhosis, Clinical Physiology 7 (1987) 35–41.

[6] S. Møller, J.H. Henriksen, Cardiovascular complications of cirrhosis, Postgraduate Medical Journal 85 (2009) 44–54.

[7] E.M. Zardi, A. Abbate, D.M. Zardi, et al., Cirrhotic cardiomyopathy, Journal of the American College of Cardiology 56 (7) (2010) 539–549.

[8] S. Møller, J.H. Henriksen, Cardiovascular dysfunction in cirrhosis. Pathophysiological evidence of a cirrhotic cardiomyopathy, Scandinavian Journal of Gastroenterology 36 (2001) 785–794.

[9] M.R. Zile, D.L. Brutsaert, New concepts in diastolic dysfunction and diastolic heart failure: part I. Diagnosis, prognosis and measurements of diastolic function, Circulation 105 (2002) 1387–1393.

[10] S. Møller, J.H. Henriksen, Cardiovascular complications of cirrhosis, Gut 57 (2008) 268–278.

[11] R. Wiest, R.J. Groszmann, The paradox of nitric oxide in cirrhosis and portal hypertension: too much, not enough, Hepatology 35 (2002) 478–491.

[12] J.H. Henriksen, S. Møller, S. Schifter, et al., High arterial compliance in cirrhosis is related to elevated circulating calcitonin gene-related peptide (CGRP) and low adrenaline, but not to activated vasoconstrictor systems, Gut 49 (2001) 112–118.

[13] J.G. Abraldes, Y. Iwakiri, M. Loureiro-Silva, et al., Mild increases in portal pressure upregulate vascular endothelial growth factor and endothelial nitric oxide synthase in the intestinal microcirculatory bed, leading to a hyperdynamic state, American Journal of Physiology—Gastrointestinal and Liver Physiology 290 (2006) G980–G987.

[14] S. Møller, H. Burchardt, C.G. Ogard, et al., Pulmonary blood volume and transit time in cirrhosis: relation to lung function, Liver International 26 (2006) 1072–1078.

[15] R.W. Schrier, Water and sodium retention in edematous disorders: role of vasopressin and aldosterone, American Journal of Medicine 119 (2006) S47–S53.

[16] K. Brinch, S. Møller, F. Bendtsen, et al., Plasma volume expansion by albumin in cirrhosis. Relation to blood volume distribution, arterial compliance and severity of disease, Journal of Hepatology 39 (2003) 24–31.

[17] A. Umgelter, W. Reindl, F. Geisler, et al., Effects of TIPS on global end-diastolic volume and cardiac output and renal resistive index in ICU patients with advanced alcoholic cirrhosis, Annals of Hepatology 9 (1) (2010) 40–45.

[18] G.P. Aurigemma, W.H. Gaasch, Diastolic heart failure, The New England Journal of Medicine 351 (2004) 1097–1105.

[19] W.C. Little, D.W. Kitzman, C.P. Cheng, Diastolic dysfunction as a cause of exercise intolerance, Heart Failure Reviews 5 (2000) 301–306.

[20] N.X. Ortiz-Olvera, G. Castellanos-Pallares, L.M. Gómez-Jiménez, et al., Anatomical cardiac alterations in liver cirrhosis: an autopsy study, Annals of Hepatology 10 (3) (2011) 321–326.

[21] M. Cazzaniga, F. Salerno, G. Pagnozzi, et al., Diastolic dysfunction is associated with poor survival in cirrhotic patients with transjugular intrahepatic portosystemic shunt, Gut 56 (2007) 869–875.

[22] M. Hoeper, M. Krowka, C. Strassburg, Portopulmonary hypertension and hepatopulmonary syndrome, Lancet 363 (2004) 1461–1468.

[23] M. Bernardi, S. Calandra, A. Colantoni, et al., Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors, Hepatology 27 (1998) 28–34.

[24] M.T. Hendrickse, D.R. Triger, Vagal dysfunction and impaired urinary sodium and water excretion in cirrhosis, American Journal of Gastroenterology 89 (1994) 750–757.

[25] J.H. Henriksen, S. Fuglsang, F. Bendtsen, et al., Dyssynchronous electrical and mechanical systole in patients with cirrhosis, Journal of Hepatology 36 (2002) 513–520.

[26] A. Figueiredo, F. Romero-Bermejo, R. Perdigoto, P. Marcelino, The end-organ impairment in liver cirrhosis: appointments for critical care, Critical Care Research and Practice 12 (2012) http://dx.doi.org/10.1155/2012/539412.

[27] G. La Villa, G. Barletta, P. Pantaleo, et al., Hemodynamic, renal, and endocrine effects of acute inhibition of nitric oxide synthase in compensated cirrhosis, Hepatology 34 (2001) 19–27.

[28] F. Wong, S. Siu, P. Liu, L. Blendis, Brain natriuretic peptide, is it a predictor of cardiomyopathy in cirrhosis?, Clinical Science 101 (2001) 651–657, http://dx.doi.org/10.1042/CS20010183.

[29] J.H. Henriksen, J.P. Gotze, S. Fuglsang, et al., Increased circulating pro-brain natriuretic peptide (proBNP) and brain natriuretic peptide (BNP) in patients with cirrhosis: relation to cardiovascular dysfunction and severity of disease, Gut 52 (2003) 1511–1517.

[30] D. Pateron, P. Beyne, T. Laperche, et al., Elevated circulating cardiac troponin I in patients with cirrhosis, Hepatology 29 (1999) 640–643.

[31] J. Genesca, A. Gonzalez, R. Catalan, et al., Adrenomedullin, a vasodilator peptide implicated in hemodynamic alterations of liver cirrhosis. Relationship to nitric oxide, Digestive Diseases and Sciences 44 (1999) 372–376.

[32] M. Vasatova, R. Pudil, V. Safka, et al., Elevated cardiac markers are associated with higher mortality in patients after transjugular intrahepatic portosystemic shunt insertion, Annals of Clinical Biochemistry 50 (2013) 122–126.

[33] J.C. García-Pagán, K. Caca, C. Bureau, et al., Early use of TIPS in patients with cirrhosis and variceal bleeding, The New England Journal of Medicine 362 (25) (2010) 2370–2379.

[34] T.D. Boyer, Z.J. Haskal, American Association for the Study of Liver Diseases. The role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension: update 2009, Hepatology 51 (1) (2010) 306.

[35] M. Huonker, Y.O. Schumacher, S. Soricher, et al., Cardiac function and haemodynamics in alcoholic cirrhosis and effects of the transjugular intrahepatic portosystemic stent shunt, Gut 44 (1999) 743–748.

[36] E. Lotterer, A. Wengert, W.E. Fleig, Transjugular intrahepatic portosystemic shunt: short-term and long-term effects on hepatic and systemic hemodynamics in patients with cirrhosis, Hepatology 29 (1999) 632–639.

[37] A. Montgomery, H. Ferral, R. Vasan, D.W. Postoak, MELD score as a predictor of early death in patients undergoing

elective transjugular intrahepatic portosystemic shunt (TIPS) procedures, Cardiovascular and Interventional Radiology 28 (3) (2005) 307–312.

[38] R. Pudil, R. Praus, P. Hulek, et al., Transjugular intrahepatic portosystemic shunt is associated with significant changes in mitral inflow parameters, Annals of Hepatology 12 (3) (2013) 464–470.

[39] A. Zambruni, F. Trevisani, P. Caraceni, M. Bernardi, Cardiac electrophysiological abnormalities in patients with cirrhosis, Journal of Hepatology 44 (2006) 994–1002.

[40] F. Wong, Cirrhotic cardiomyopathy, Hepatology International 3 (1) (2009) 294–304.