ORIGINAL ARTICLE

Alcoholic liver cirrhosis increases the risk of left ventricular diastolic dysfunction

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Submitted: 2013-06-21 Accepted: 2013-08-30 Published online: 2013-11-10

Key words: **ethanol; alcoholic cirrhosis; liver damage; diastolic dysfunction; patients**

Neuroendocrinol Lett 2013; **34**(Suppl.2):64–70 **PMID:** 24362094 NEL341013A09

Abstract

OBJECTIVES: The aim of this study was to prove that the incidence of the more unusual and largely under-researched cardiac dysfunction, i.e. diastolic, is more frequent in patients with alcoholic cirrhosis. Comparison of the incidence of left ventricular diastolic dysfunction in medical-ward patients with no prior history of cardiovascular disease to that of the patients with hepatic cirrhosis caused by alcohol abuse was carried out. The study is original from the point of view of examination of patients with cirrhosis of solely alcoholic aetiology in one Central-European university hospital.
METHODS: Three methods of echocardiographic examination were used: (i) pulse Doppler echocardiography to assess blood flow through the mitral valve and in the pulmonary veins, (ii) tissue Doppler imaging (TDI) to assess mitral annular motion, and (iii) colour M-mode Doppler echocardiography to assess blood flow from the left atrium into the left ventricle.
RESULTS: The results found confirmed that the incidence of left ventricular diastolic dysfunction in patients with alcohol-related liver cirrhosis, classified as Child-Pugh grade A and B, was significantly higher than in the controls without any prior liver disease. Furthermore, our research team has newly noticed how the severity of diastolic dysfunction affects the morbidity and mortality of patients undergoing such treatments as the transjugular intrahepatic portosystemic shunt (TIPS), liver transplantation and other surgical interventions resulting from different indications.
CONCLUSION: The high incidence of diastolic dysfunction in cirrhotic alcoholics should not be underestimated. Examination of diastolic dysfunction should be a standard procedure for making clinical decisions about these patients.

Abbreviations:

ACE	- angiotensin-converting enzyme
AT 1	- angiotensin type 1
CAD	- coronary artery disease
DMS IV	- Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
GMT	- gamma-glutamyl-transferase
IDC 10	- Alcohol Dependence Syndrome
RAS	- renin–angiotensin system
TDI	- tissue Doppler imaging
TIPS	- transjugular intrahepatic portosystemic shunt
Vp	- velocity propagation

INTRODUCTION

Chronic excessive alcohol consumption can lead to many cardiovascular diseases or disorders, such as cardiomyopathy, chronic heart failure, arterial hypertension, arrhythmias, strokes and sudden cardiac death. About one third of all diagnosed dilated cardiomyopathies is of alcoholic aetiology. This alcoholic cardiomyopathy causes heart failure in approximately two thirds of alcoholics. Dilated cardiomyopathy usually develops after more than 10 years of alcohol consumption and a daily intake of 80 g (Balk 2000; Laonigro *et al.* 2009; Janu *et al.* 2012). This cardiomyopathy most commonly occurs in males between thirty and fifty years of age; in females, it appears even sooner and after a lower intake of alcohol.

One of the organs typically affected by ethanol ingestion is the myocardium. Alcoholic damage of the myocardium has previously been considered to be the result of deficient diet, but it is now generally accepted that alcoholic cardiomyopathy occurs even without thiamine deficiency. This finding supports suggestion that even well-off and educated people often succumb to alcohol abuse (Ren & Wold 2008; Laonigro *et al.* 2009; Iacovoni *et al.* 2010; George & Figueredo 2011).

Alcohol consumption leads to rapid and chronic deterioration of contractility, and can cause a reversible dysfunction even in non-drinkers. However, the mechanisms that are responsible for stimulation of the transition from the acute reversible effect to permanent myocardial damage are still a matter of debate. The exact mechanism behind the negative impact on the myocardium is not known, but it is undeniable that alcohol has a direct toxic effect on the striated muscles (a myopathy of skeletal muscles frequently occurs in cases of alcohol addiction). Various studies have proved that alcohol and its metabolite, acetaldehyde, influence cell functions and the functions of cell membranes – for example, calcium transport, mitochondrial metabolism, lipid metabolism in the myocardium and the synthesis of myocardial proteins. It also affects the contractility by inhibiting the interaction between calcium ions and myofilaments. The damage of the myocardium is also caused by the impact of free radicals (Braunwald *et al.* 2001; Laonigro *et al.* 2009). Neurohormonal systems, such as the sympathetic nervous system and the renin–angiotensin system (RAS), have also a negative influence on the development of alcoholic cardiomyopathy.

The pathological picture of alcohol-induced myopathy is nonspecific and includes interstitial myocytolysis, fibrosis, hypertrophy of myocytes and slight damage of coronary arteries. Electron microscopy reveals enlarged mitochondria with big glycogen vacuoles. A large amount of alcohol consumption can also provoke arrhythmias, even in cases that show totally normal cardiac functions ("Holiday Heart Syndrome"). Most common arrhythmias occurring in alcoholic cardiomyopathies are atrial flutter and atrial fibrillation. Hypokalaemia is often involved in the genesis of arrhythmias.

Left ventricular systolic dysfunction is common in alcoholics. Diastolic dysfunction has, however, often been ignored by researchers, as its occurrence is scarce. This feature is a reason why our attention focused precisely on this more unusual dysfunction. The target of this work was to prove that the incidence of the more unusual and largely under-researched cardiac dysfunction (diastolic) is more frequent in patients with alcoholic cirrhosis.

METHODS

Patients

We enrolled 97 patients in our trial: (1) cirrhotic group – 49 alcohol dependent patients according to "Harmful Use of Alcohol" or "Alcohol Dependence Syndrome" (ICD 10) (American Psychiatric Association 1994) and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association 1994; Robins *et al.* 2000); (2) control group – 48 patients. The control group was carefully matched for age and sex with the analyzed cases. The group of the 49 alcohol-dependent cirrhotic patients contained 30 males (61.2%) and 19 females (38.8%) between 30 to 55 years of age. These patients had consumed more than 60 g of alcohol per day in the case of men, and more than 20 g of alcohol per day in the case of women, for more than 10 years. Further, the laboratory test results corresponded to the liver damage caused by alcohol – there was a higher level of gamma-glutamyl-transferase (GMT) and macrocythaemia in the blood count. The prothrombin time, which is a very sensitive indicator of liver function, was likewise tested. The parameters of this group are shown in Table 1.

The Child-Pugh score to classify the severity of liver cirrhosis was used in the study. To confirm the diagnosis of alcoholic liver cirrhosis as described by the pathologist, liver biopsy of all patients was performed. Persons with cirrhosis due to another etiologic factor – that is, cirrhosis due to chronic viral hepatitis, autoimmune hepatitis and hepatitis caused by metabolic diseases – have been excluded from the study. Likewise, patients with the established diagnosis of diabetes mellitus, hypertension and coronary artery disease (CAD) were excluded, as these may contribute to the development of

diastolic dysfunction. Another exclusion criterion was chronic atrial fibrillation, as it is not possible to detect diastolic dysfunction in patients with this disease. Since the risk of diastolic dysfunction increases with age, the top limit of the studied group was fixed at 55 years of age. Within the cirrhotic group, 43 patients (87.8%) – 25 men and 18 women, were classified as Child-Pugh A, and 6 patients (12.2%) – 5 men and 1 woman – as Child-Pugh B. Esophageal varices were detected by gastroscopy in 7 patients (14.3%) – 6 men and 1 woman; 4 male patients had undergone the sclerotisation of esophageal varices in the past. Portal hypertension gastropathy was observed in 5 patients – 4 men and 1 woman; portal hypertension colopathy was found in 2 male patients.

The control group consisted of 48 patients – 29 males (60.4%) and 19 females (39.6%) – between 30 and 55 years of age. These patients were admitted to our hospital mostly because of viral infections and gastro-enteritis. They had no prior history of diabetes mellitus, hypertension and cardiac diseases. Nor did they have any prior history of liver disease, and their laboratory tests were completely normal. Patients with regular alcohol consumption have not been included. The assessment of diastolic dysfunction was made once the acute stage of the disease was over, using exactly the same procedure, the echocardiographic examination, in these controls as in the cirrhotic group.

The anthropometric data and laboratory values of both the cirrhotic and control groups are summarized in Table 1. The differences between the two groups are clearly indicated.

Tab. 1. Anthropometric data and laboratory parameters of alcohol-dependent patients with alcoholic liver cirrhosis and of the control groups. The numbers in the table are averages from patients in both groups and minimum and maximum values (in brackets).

Parameter	Cirrhotics	Controls	Diff.
Height [cm]	173 (155-190)	175 (153-193)	NS
Weight [kg]	75 (48-100)	77 (53-115)	$p<0.001$
BMI [kg/m^2]	25 (20-30)	27 (23-35)	$p<0.05$
Pulse [bpm]	87 (64-105)	77 (50-92)	$p<0.001$
sBP [mmHg]	110 (95-140)	113 (95-140)	$p<0.001$
dBP [mmHg]	69 (50-90)	72 (60-85)	$p<0.05$
Prothrombin time [INR]	1.26 (1.00-2.32)	1.05 (1.00-1.23)	$p<0.001$
ALT [μkat/l]	1.60 (0.50-3.84)	0.53 (0.37-0.70)	$p<0.001$
AST [μkat/l]	2.47 (0.76-4.21)	0.50 (0.39-0.71)	$p<0.001$
GMT [μkat/l]	3.85 (0.68-13.52)	0.66 (0.48-0.89)	$p<0.001$
Bilirubin [μmol/l]	34 (17-86)	18 (16-23)	$p<0.001$
Albumin [g/l]	36 (28-47)	44 (40-50)	$p<0.001$
MCV [fl]	98 (91-106)	91 (86-93)	$p<0.001$

BMI – body mass index, sBP – systolic blood pressure; dBP – diastolic blood pressure; ALT – alanin aminotransferase; AST – aspartate aminotransferase; GMT – gamma-glutamyl transferase; MCV – mean corpuscular volume; NS – not significant

Assessment of diastolic dysfunction by echocardiography

One of the commercially available ultrasound systems (specifically, ALOKA ProSound ALPHA 5) was used. All patients underwent a comprehensive examination, including the pulse Doppler method, tissue Doppler imaging and colour M-mode Doppler echocardiography. To eliminate any possible individual differences in observation, all the echocardiographic examinations (Yarman *et al.* 2012) were performed by one physician. The following three ultrasound methods were used for the analysis of left ventricular diastolic dysfunction: (i) the pulse Doppler method of blood flow through the mitral valve and in the pulmonary veins (E/A), (ii) the echocardiographic tissue Doppler imaging (TDI) of the motion of mitral annulus (E/E´), and (iii) the colour M-mode Doppler echocardiography of blood flow from the left atrium into the left ventricle.

(i) The pulse Doppler method of blood flow through the mitral valve and in the pulmonary veins (E/A)

Pulse Doppler echocardiography is based on assessing blood flow through the mitral valve and blood flow in the pulmonary veins. Two parameters are measured: the velocities of wave E and wave A. The E/A ratio is then established, which describes global left ventricular diastolic function. While the E wave reflects the passive transmitral flow, which is predominant at the beginning of diastole, the A wave reflects the active flow predominant at the end of it. Normal diastolic function is characterized by E/A>1, the beginning of diastolic dysfunction by E/A<1, advanced diastolic dysfunction also by E/A>1 (this phase is known as pseudonormalization), and progressive diastolic dysfunction by E/A>2 (a restrictive mitral inflow pattern) (for the velocities of wave E and wave A, see Figure 1). To distinguish between the normal diastolic function and the pseudonormalization, the Valsalva manoeuvre was performed and the flow in the pulmonary veins was examined (Pirat & Zoghbi 2007; Nagueh *et al.* 2009).

(ii) The echocardiographic tissue Doppler imaging (TDI) of the motion of mitral annulus (E/E´)

Pulse tissue Doppler echocardiography is a modification of conventional Doppler echocardiography. It records the systolic and diastolic velocities of either the heart muscle or the annuli of the valves. It allows us to assess the relaxation of the left ventricle and to evaluate the filling pressures in it. In our study, the movements of the mitral valve were measured. In contrast to the preceding method, the pulse TDI has no problem with analysing pseudonormalization (Nagueh *et al.* 2009).

(iii) The colour M-mode Doppler echocardiography of blood flow from the left atrium into the left ventricle

Colour M-mode Doppler echocardiography is a useful tool for the evaluation of diastolic dysfunction, which

measures the velocity propagation of blood flow into the left ventricle. In healthy people, velocity propagation (Vp) is about 800 mm/s, but it drops below 500 mm/s in ill persons suffering from the damage of left ventricular relaxation. This method is to an extent independent of the changes of preload and thus enables us to identify ill persons with impaired cardiac relaxation in quite a reliable way even in situations where the classical pulse Doppler indexes have failed (Braunwald *et al.* 2001; Nagueh *et al.* 2009).

Statistical analysis

The statistical analysis was undertaken employing the STATISTICA software (StatSoft, Tulsa, OK). The laboratory and anthropometric data were individually compared by the Mann-Whitney test. The results from the echocardiographic examinations were analysed using Fisher's exact test for categorical data and were accepted as significant at $p<0.05$.

RESULTS

Using pulse Doppler echocardiography, we found left ventricular diastolic dysfunction in 40 alcohol-dependent patients with cirrhosis (n=49) (Table 2). The reversed E/A ratio (as a sign of diastolic dysfunction) was detected in 38 patients, the restrictive pattern of transmitral flow was confirmed in two persons. Only 9 cirrhotic patients (5 men and 4 women) had normal mitral valve flow (Table 2). Abnormal blood flow was confirmed in all 6 Child-Pugh B patients. On the other hand, within the control group, we discovered only one person with diastolic dysfunction. Fisher's exact test has shown that the differences between the cirrhotic and the control groups are, in the case of pulse-Doppler echocardiography use, significant at $p<0.01$ (Table 2).

Using tissue Doppler echocardiography in patients yielded pathological results in 36 persons within the cirrhotic group. Abnormal records were detected in all 6 Child-Pugh B patients. Of the persons of the control group, only one patient was found to have diastolic dysfunction (the same patient with diastolic dysfunction detected by the preceding technique, pulse Doppler echocardiography). Fisher's exact test has revealed that the differences between the patients of the cirrhotic and the control groups are, with the aid of tissue Doppler echocardiography, significant at $p<0.01$ (Table 2).

Using colour M-mode Doppler echocardiography, we detected diastolic dysfunction in 37 persons from the cirrhotic group. Diastolic pathology was identified in 5 patients with Child-Pugh B cirrhosis. Only one person with diastolic dysfunction (again the same patient as detected using the previous two methods) was found in the control group. Fisher's exact test has revealed that the differences between the cirrhotic and the control groups are, in the case of colour M-mode Doppler employment, significant at $p<0.01$ (Table 2).

All three applied ultrasound methods revealed consistent results. A significantly higher incidence of left ventricular diastolic dysfunction was found in alcohol-dependent cirrhotic patients in contrast to the control patients with no history of liver disease. All the results are shown in Tables 2 and 3.

DISCUSSION

Liver cirrhosis often combines with frequent and serious abnormalities of the cardiovascular apparatus. Cardiovascular complications associated with cirrhosis include diastolic and systolic dysfunctions and abnormalities of the central, peripheral and splanchnic circulations. The systemic circulation in cirrhotic patients is

Tab. 2. Results of three examinations of diastolic dysfunction, using three different Doppler methods. Statistical differences based on Fisher's exact test resulted in $p<0.01$ in all three methods used.

	Echocardiopathy method									
	Pulse Doppler Diastolic dysfunction			Tissue Doppler imaging Diastolic dysfunction			M-mode Doppler Diastolic dysfunction			
Group	+	–		+	–		+	–		n
Cirrhotics	40	9	p<0.01	36	13	p<0.01	37	12	p<0.01	49
Controls	1	47		1	47		1	47		48

Tab. 3. Distribution of the E/A ratio in cirrhotic patients found using pulse Doppler echocardiography.

Ratio E/A	Normal pattern (E/A>1)	Reversed pattern (E/A<1)	Pseudonormalization (E/A>1)	Restrictive pattern (E/A>2)
No. (%) of patients	9 (18.4%)	38 (77.6%)	0 (0%)	2 (4.0%)

E/A – the pulse Doppler method of blood flow through the mitral valve and in the pulmonary veins. The E/A ratio – the ratio of the velocities of wave E to those of wave A. For normal pattern (E/A>1), reversed pattern (E/A<1) pseudonormalization (E/A>1) and restrictive pattern (E/A>2), see the Material section.

usually hyperkinetic, and the increase in their cardiac output, tachycardia and reduced peripheral vascular resistance lead to heart dysfunction. Their response to stress is reduced. This phenomenon has been described previously as cirrhotic cardiomyopathy (Moller & Henriksen 2002; Baik *et al.* 2007; Cazzaniga *et al.* 2007). The impairment of neurohumoral reactivity also contributes to its development; the diminution in β-adrenergic signalling plays a very important role, too. The dysfunction of cardiomyocyte cell membranes and the increase in the activity of cardiodepressive substances (such as cytokines, endorphins and nitric oxide) also participate in the pathogenesis of cirrhotic cardiomyopathy, so does the actual toxic effect of alcohol (Braunwald *et al.* 2001; Alquahtani *et al.* 2008).

Diastolic and/or systolic dysfunctions often go unnoticed in patients with liver cirrhosis. The former can manifest itself during physical stress and pharmacological load (i.e. physical exertion and pharmacological therapy). Physical stress does not involve only physical exercise, but also decompensation, which can occur for example when a large quantity of ascites is released without an adequate refill of plasma volume during surgical interventions, or after performing TIPS or peritoneal vein anastomosis (Grose *et al.* 1995; Cazzaniga *et al.* 2007; Moller & Henriksen 2008).

Heart failure is also a major cause of mortality after liver transplantation despite the fact that orthotopic liver transplantation often leads to improvement, or regress, of cardial abnormalities. Cirrhotic cardiomyopathy can also play a role in the pathogenesis of hepatorenal syndrome (Alquahtani *et al.* 2008).

In this study, we have focused exclusively on persons with alcoholic liver cirrhosis. This diagnosis has been confirmed by the anamnestic data, adequate laboratory test results and ultrasound image, and it was also verified by the histology obtained from untargeted liver biopsy or during laparoscopy.

Our investigation has disclosed that diastolic dysfunction occurs much more frequently in patients with alcohol-induced liver damage (the Fisher exact test, $p<0.01$) than in patients with no hepatic disease. Our application of three different methods of echocardiographic detection has supplied evidence of a virtually identical incidence of diastolic dysfunction. Any potential differences between the individual methods are due to the patients' individual physical conditions: some are more difficult to examine than others. The combined use of various ultrasound methods in evaluating diastolic dysfunction diminishes potential uncertainties.

Diastolic dysfunction occurs in about 70–80% of the investigated cirrhotic alcoholics even when these are Child–Pugh grade A (the relative risk of diastolic dysfunction in comparison to non-cirrhotics is about 40). This incidence is high and should not be underestimated. The statistical analysis has revealed no correlation between the occurrence of diastolic dysfunction and the severity of liver damage. Our findings accord with the results found in a study that was carried out by Alexander *et al.* (2007) in India that included more Child-Pugh B cases. But 50% of patients examined in their study had cirrhosis of different aetiology, that is, other than alcoholic (Alexander *et al.* 2007). Our work, however, has included only patients with alcoholic cirrhosis.

We found diastolic dysfunction only in one man from the control patients with no history of liver disease. This outcome was confirmed in the same patient by all the three methods used; however, we were unable to identify the aetiology of his diastolic dysfunction. The incidence of diastolic dysfunction is commonly estimated to be much higher, from 10 to 30% in a general population (Fischer *et al.* 2003; Kuznetsova *et al.* 2009). The low proportion of cases in the control group – only one patient – is most probably the consequence of our exclusion criterion whereby all patients in each

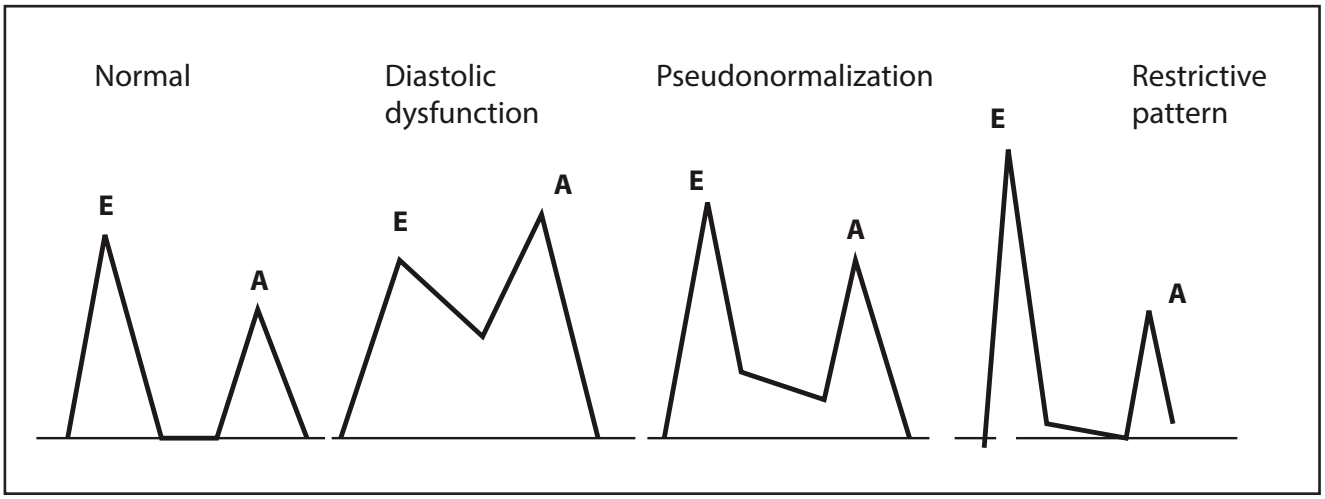

Fig. 1. A schematic view of the velocities of wave E and wave A in control patients with normal diastolic function and patients suffering from diastolic dysfunction using pulse Doppler echocardiography.

group who had a history of CAD and hypertension were excluded (see Methods).

As shown in our present study, the tested cirrhotic patients yielded considerably lower systolic and diastolic blood pressures and significantly higher pulse frequency. All these are signs of hyperkinetic circulation, which occur frequently in patients suffering from liver diseases and are probably instrumental in the development of left ventricular diastolic dysfunction.

Hyperkinetic circulation, increased heart output and increased plasma and blood volume occur regularly in cirrhosis of any aetiology. Factors such as heart frequency, preload and afterload volumes and changes in the vegetative nervous system tone modify the relaxation of the left ventricle and its filling ability. As Pozzi *et al.* (2005) have shown, diastolic dysfunction has been observed not only in patients with alcoholic cirrhosis, but also in those with chronic hepatitis C. Alexander *et al.* (2007) has found no differences in the occurrence of left ventricular diastolic dysfunction among cases with cirrhosis of different aetiology. This implies that there may be a similar incidence of diastolic dysfunctions in cirrhosis of various origins (Baik *et al.* 2007).

It seems that diastolic dysfunction is an important survival factor in patients on whom TIPS has been performed. Cazzaniga *et al.* (2007) studied patients with and without diastolic dysfunction one year after the TIPS intervention. While one-year mortality in patients with diastolic dysfunction was more than 50%, no patient without diastolic dysfunction died. This analysis has demonstrated that diastolic dysfunction is an independent predictor of death in liver cirrhosis treated by TIPS. Thus, we can predict the costs and benefits in patients planning to have a TIPS (Cazzaniga *et al.* 2007).

In this work, we examined patients who underwent other surgical interventions apart from TIPS. Four from five cirrhotic patients underwent intra-abdominal operation and one patient underwent TIPS (all these patients were male). Three patients were Child-Pugh A. Two of them had no established diastolic dysfunction and survived the operation without complications. The third patient had protracted hypotension. The other 2 patients were Child-Pugh B. One of them died of uncontrollable heart failure after the operation. The other suffered from an episode of left-sided heart failure. From the above cases we have examined, it can be inferred that it is possible to evaluate diastolic dysfunction as a rewarding factor for pre-operative risk stratification. It can also help us to predict the prognosis of further post-operative development.

Although a fair amount of information about diastolic dysfunction has been uncovered and gathered in recent years, it is not quite clear how the disease should be treated. While dozens of extensive and thorough randomized trials that have given rise to the adequate treatment of systolic heart failure are available, only one completed mortality and morbidity trial that concerns heart failure with preserved ejection fraction exists (CHARM-Preserved) (Yusuf *et al.* 2003). For the purposes of medical practice, it is possible to establish general aims for treating diastolic dysfunction that leads to heart failure. Such aims include: elimination of congestion using diuretics, elimination of tachycardia using beta blockers or calcium channel blockers, slow down neurohumoral activation using angiotensin-converting enzyme (ACE) inhibitors or angiotensin type 1 (AT 1) receptor blockers (Galderisi 2005). These medicaments are commonly used also in the treatment of liver cirrhosis, but they have their limits. For instance, if a tendency towards hypotension exists, it is problematic to use medicaments lowering blood pressure. We still do not have a specific medicine that would improve the relaxation of the ventricles.

CONCLUSION

This study has discovered a significantly higher incidence of left ventricular diastolic dysfunction in a cohort of alcohol-dependent cirrhotic patients in contrast to the control group of patients with no history of either liver disease or alcohol abuse. Patients from both these groups had no prior coronary artery disease. Because cirrhotic patients are often indicated for a transjugular intrahepatic portosystemic shunt (TIPS) and other surgical interventions, and left ventricular diastolic dysfunction is a predictor of death for patients awaiting this procedure, it seems important to base clinical decisions regarding alcohol-dependent patients also on the examination of this cardiac dysfunction. Our investigation indicates that there seems to be a direct relation between diastolic dysfunction and the severity of liver damage, but because more research is needed, this will be the subject of our future study.

ACKNOWLEDGEMENTS

This work was supported by the grants from the Academy of Sciences of the Czech Republic (AVOZ 50110509), the Ministry of Education, Youth and Sports of the Czech Republic (1M0517) and Charles University in Prague (grant UNCE 204025/2012).

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