Cirrhotic Cardiomyopathy

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In cirrhosis…

The **impaired liver function** and particularly the **portal hypertension** result in:

- **Splachnic arterial vasodilation**
- **Low systemic vascular resistance**
- **Low blood pressure**
- **Reduced central blood volume with central or "effective" hypovolemia**

Initial phases…

- **Sympathetic nervous system** is activated
- **Heart rate and cardiac output** are increased

As liver function and portal hypertension are worsening…

- **Renin-angiotensin-aldosterone axis** is stimulated
- Non-osmotic release of **vasopressin**

Advanced cirrhosis: perhaps **blunted cardiac dysfunction**

***Cirrhotic cardiomyopathy* (CC)**

CC aggravates underfilling of arterial circulation & worsens circulatory dysfunction

This may contribute to the development of hepatorenal syndrome (HRS)

CC is characterised by:

- **Altered diastolic relaxation**
- **Electrophysiological abnormalities (prolongation of QT)**
- **Impaired contractility under physiological or pharmacological stress**
- **Absence of other known cardiac disease**

Pathogenetic mechanisms underlying CC

- **Down regulation of β-adrenergic receptors**

  (Lee SS et al Hepatology 1990)

- **Blunted post-beta adrenoceptor signal transduction**

  (Ma Z et al Gastroenterology 1996)

- **Changed expression of regulators of G-protein signaling**

  (Ma Z et al J Hepatol 1997)

- **Cardiodepressive effect of NO, TNF-α, endogenous cannabinoids, bacterial endotoxin and bile acids**

  (Liu H et al Gastroenterology 2000, Yang YY et al J Hepatol 2010, Gaskari SE et al Br J Pharmacol 2005, Karagiannakis DS et al Dig Dis Sci 2013, Jacob J et al Am J Physiol 1993)

- **Altered ratio of collagen I/III** *(Glenn TK et al J Hepatol 1011)*

- **Altered cholesterol/phospholipid ratio** *(Ma Z et al Am J Physiol 1994)*

Diagnostic criteria of CC

(World Congress of Gastroenterology, Montreal 2005)

- **Systolic dysfunction**

  Resting EF<55%

  Blunted increase in CO after exercise or pharmacological stress test

- **Diastolic dysfunction**

  Early diastolic/atrial filling (E/A) (age corrected) <1

  Deceleration time (DT) > 200 ms

  Isovolumetric relaxation time (IVRT) > 80 ms

- **Supportive criteria**

  Prolongation of QT

  Abnormal chronotropic response

  Electromechanical uncoupling

  Enlarged left atrium

  Increased myocardial mass

  Increased BNP and pro-BNP

Diastolic dysfunction (DD) (I)

- **Appears before the futures of systolic dysfunction**

- **Its prevalence is 50-70% (according to E/A)**

  (Torregrosa M et al J Hepatol 2005, Pozzi et al Hepatology 1997)

- **E/A is neither sensitive, nor specific (influenced by changes in preload and afterload)** *(Ho CY et al Circulation 2006, Kazankov K et al Liver Int 2011)*

Latest guidelines of American Society of Echocardiography

(Nagueh SF et al J Am Soc Echocardiogr 2009)

Diastolic dysfunction	e´ septal <8 cm/s and e´ lateral <10 cm/s
Grade I	E/e´ av ≤8 cm/s
Grade II	E/e´ av ≤9-12 cm/s
Grade III	E/e´ av ≥13 cm/s

Tissue Doppler Imaging (TDI): E, early diastolic mitral inflow velocity; e´ septal, early diastolic mitral annular velocity from the septal side; e´ lateral, early diastolic mitral annular velocity from the lateral side; e´ av (e´ septal + e´ lateral)/2

Diastolic dysfunction (II)

- **According to new guidelines, the prevalence is lower, about 40-45%** *(Sampaio F et al Liver Int 2013, Karagiannakis DS et al Dig Dis Sci 2013, Ruiz-del Arbol L et al Hepatology 2013)*
- **It is not related to the aetiology of liver disease**
- **Its presence does not depend on the stage of liver disease (compensated vs decompensated cirrhosis)**
- **Its severity correlates with the degree of liver failure (association between DD grade and Child-Pugh score)**

Karagiannakis DS et al Dig Dis Sci 2013

Diastolic dysfunction and prognosis

- **DD affects the prognosis of patients undergoing TIPS insertion or liver transplantation**

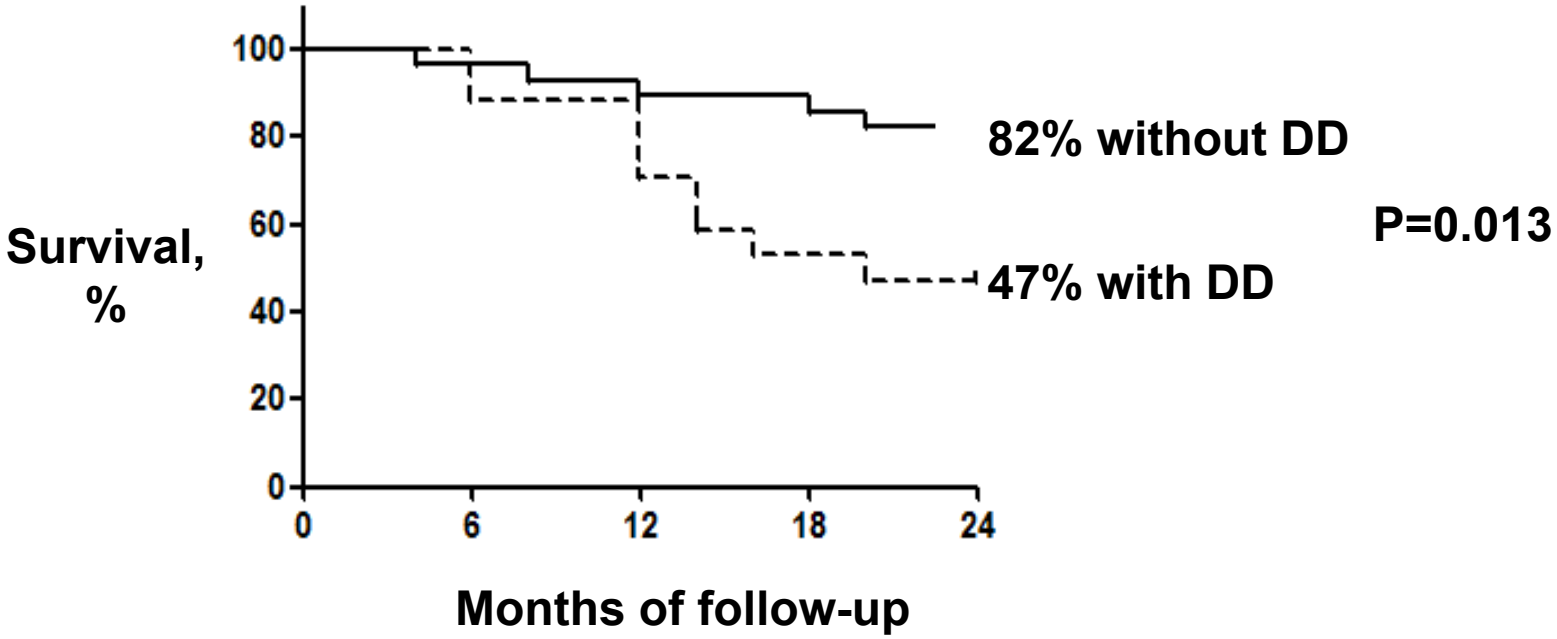
  (Merli et al Am J Gastroenterol 2002, Cazzaniga M et al Gut 2007, Kovacs A et al Cardiovasc Intervent Radiol 2010)

- **Patients with DD cannot “afford” preload increase**

Impact of DD on survival of patients not undergoing invasive interventions

1st author (Ref)	Pts, n	F-up (mos)	Survival Normal vs DD
Najar et al (J Hepatol 2013)	152	12	72% vs 66%, p=NS
Alexopoulou et al (Transpl Int 2012)	76	25	52% vs 37%, p=0.094
Merli et al (Eur J Intern Med 2013)	74	12	73% vs 64%, p=NS
Ruiz-del Arbol L (Hepatology 2013)	80	12	95% vs 79% DD grade I, p=0.016 vs 39% DD grade II, p=0.006

Impact of DD on survival of 45 cirrhotic patients



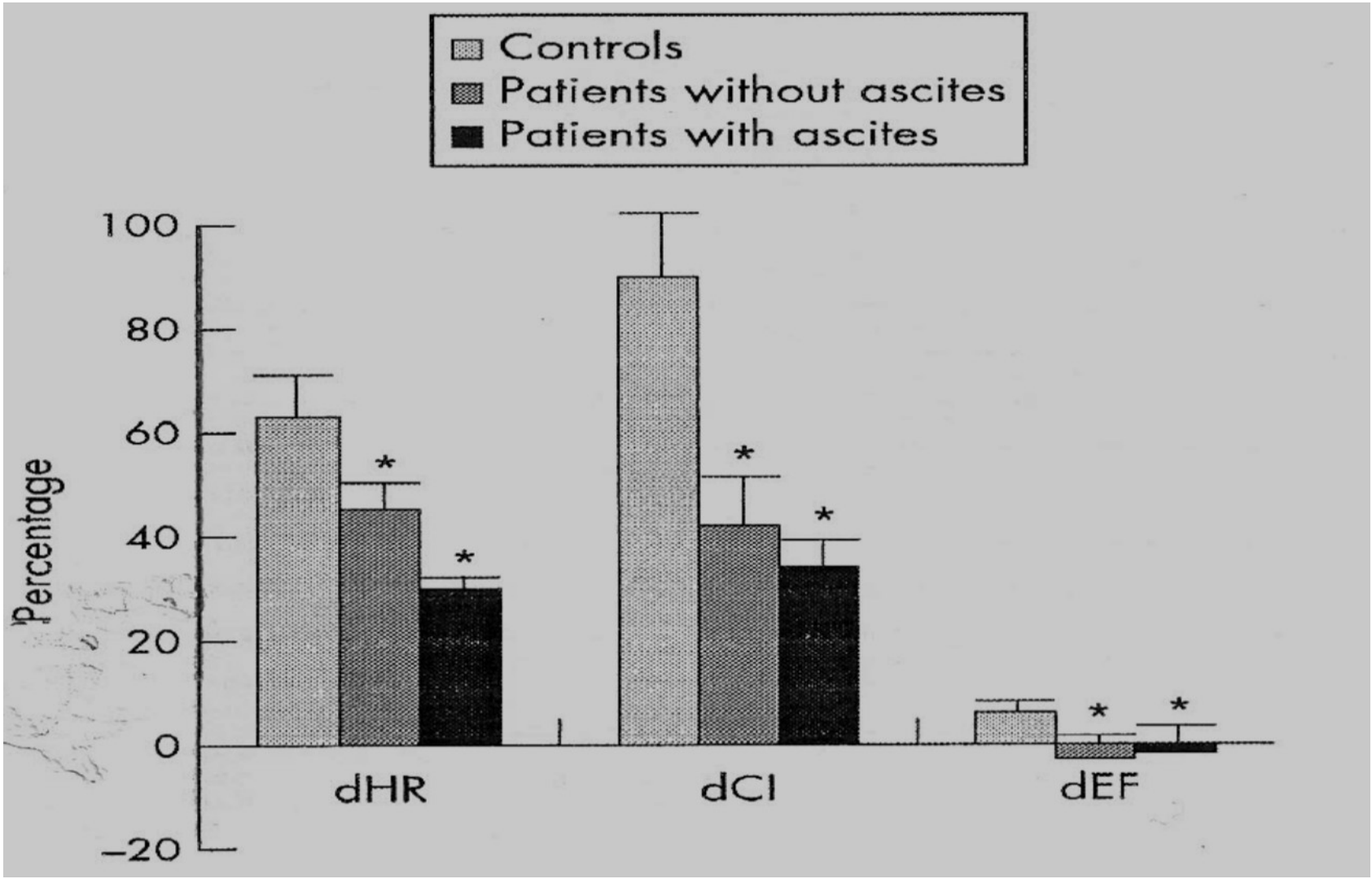
Multivariate analysis - independent prognostic factors of survival: presence of DD (p=0.017) & low albumin (p=0.003)

Karagiannakis DS et al Hepatol Int 2014

Systolic dysfunction (SD)

- **Difficult to be diagnosed at rest in cirrhotic patients**
  - Splachnic vasodilation-reduced afterload-normal EF%

- **Possible to be unmasked during stress**
  - Decrease or smaller increase in EF% than expected



HR, heart rate; EF, ejection fraction; CI, cardiac index

Torregrosa M et al, J Hepatol 2005

Systolic dysfunction & hepatorenal syndrome (HRS)

- **Patients with HRS have lower CO, and lower blood pressure. Higher risk when CO <6 l/min** *(Ruiz-del-Arbol L et al Hepatology 2005)*

- **Lower Cardiac Index is associated with higher creatinine, lower GFR and increased risk of HRS** *(Krag A et al Gut 2010)*

- **Higher risk in case of infection like SBP (suppressive effect of cytokines)** *(Ruiz-del-Arbol L et al Hepatology 2003)*

BNP as a marker of cardiac dysfunction

- **BNP correlates with liver disease severity, degree of cardiac failure and QT prolongation**

  (Henriksen JH et al Gut 2003, Pimenta J et al Liver Int 2010)

- **Poor outcome in case of liver transplantation**

  (Saner FH et al Transpl Int 2011)

Prolongation of QT

- **It is the main electrocardiographic characteristic of cirrhotic cardiomyopathy**

- **It is detected in 40-50% of cirrhotics**

- **Getting worse in parallel with the severity of liver dysfunction**

(Bernardi M et al Hepatology 1998, Bernardi M et al Expert Rev Gastroenterol Hepatol 2012)

Therapeutic approach of patients with CC

- **ACE inhibitors: not studied in CC, to be avoided in cirrhotics with ascites**
- **Diuretics: useful in congestive heart failure**
- **IV human albumin: ameliorates cardiac dysfunction by binding cardiodepressant factors**
- **Erythropoietin: in severe heart failure and low hemoglobin?**

  (Manchini DM et al Circulation 2003, Liu L et al Dig Liver Dis 2012)
- **Potential future therapies: inhibitors of NO and TNF-α, antagonists of CB-1 receptors or farnesoid X receptor agonists?**

  (Yao J et al World J Gastroenterol 2014)

β-blockers?

- **The mainstay of heart failure therapy and decline heart failure mortality**
- **Their role on CC: not evaluated so far**
- **In patients with refractory ascites: may increase the risk of paracentesis-induced circulatory dysfunction & worsen the outcome** *(Serste T et al Hepatology 2010, Serste T et al J Hepatol 2011)*
- **Possible cardiodepressive activity?**
- **Not validated in randomized trials, so any state against the use of β-blockers on patients with CC is misleading**

Cirrhotic Cardiomyopathy (CC) - Conclusions

- CC is a frequent complication of cirrhosis (~40-45% of patients)
- Diastolic dysfunction (DD): the first manifestation of CC
- DD: better detected by TDI echocardiography
- DD's presence not related to stage of liver disease but DD's severity correlates with Child-Pugh score
- Systolic dysfunction (SD) often latent, unmasked during stress
- SD predisposes to HRS development, especially with infection
- No specific treatment aiming to the pathophysiological