3rd Paris NASH Symposium

French-US Meetings
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Organized by
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With the partnership of
Myocardium in Nonalcoholic Fatty Liver Disease

M. Shadab Siddiqui, M.D.
Virginia Commonwealth University
All Cause and Disease Specific Mortality in NAFLD

Ekstedt et al. Hepatology 2006

Adams et al., Gastroenterology 2005
The Liver-Heart Axis

Normal

Subclinical Disease

Clinical Disease

NAFLD

Symptoms

Systolic Heart Failure

Diastolic Heart Failure

Impaired LV relaxation

Increased Filling Pressure
NAFLD Associated with Diastolic Dysfunction

- Abnormal LV Relaxation
- Increased LV Filling Pressures

P < 0.0001
P = 0.0001
## ECHO Parameters of Diastolic Dysfunction

<table>
<thead>
<tr>
<th>ECHO Parameter</th>
<th>ANALYSIS</th>
<th>Value in DD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak E-wave velocity (cm/s)</td>
<td>Peak velocity in early diastole (<strong>Passive filling</strong>)</td>
<td>↓</td>
</tr>
<tr>
<td>Peak A-wave velocity (cm/s)</td>
<td>Peak velocity in late diastole (<strong>Active filling</strong>)</td>
<td>↑</td>
</tr>
<tr>
<td>E/A Ratio</td>
<td>E velocity divided by A-wave velocity</td>
<td>Variable</td>
</tr>
<tr>
<td>TDI e’veolcity</td>
<td>Peak modal velocity in early diastole (<strong>abnormal LV relaxation</strong>)</td>
<td>↓</td>
</tr>
<tr>
<td>E/e’</td>
<td>E velocity divided by mitral annular e’ velocity (<strong>Increased LV pressure</strong>)</td>
<td>↑</td>
</tr>
<tr>
<td>Left atrial volume index (LAVI)</td>
<td>Left atrial volume (<strong>increased LV pressure</strong>)</td>
<td>↑</td>
</tr>
</tbody>
</table>

NAFLD is a Multisystem Disease

- OSA
- MetS
- T2DM
- LIPIDS
- HTN
- Obesity

Fan et al. J Gastro Hepatol 2005
Dixon et al. Gastro 2001
Bugianesi et al. Dig Liver Dis 2004
Diabetes and Hypertension Are Associated with Abnormal LV Relaxation

*P<0.05: HTN-DM vs. HTN/DM alone
Visceral Fat and Hepatic Fat Are Associated with Abnormal LV Structure and Function
Diabetes
Hypertension
Obesity

NAFLD

Diastolic Dysfunction
Metabolic Defects Maybe An Early Alteration in LV of Patients with NAFLD

Normal LV Morphology
Normal Systolic and Diastolic Function
Mechanistic Link Between NAFLD and Diastolic Dysfunction

↑FFA

Release of Adipokines
Lipotoxicity
↑Epicardial Fat

Energy homeostasis impairment (Early Change)

Contractile Dysfunction (Late Change)

Kankaanpaa M, Lehto et al. J Clin Endocrinol Metab 2006
Perseghin et al. Hepatology 2007
De las Fuentes et al. Hypertension 2003
Diabetes
Hypertension
Obesity

Lipotoxicity
Low-grade inflammation

NAFLD

Diastolic Dysfunction
Alterations in LV Morphology Without Changes in Cardiac Metabolism

- PCr/ATP: P=NS
- Wall Thickness: P=0.003
- Eccentricity Ratio: P=0.003
NAFLD Associated with Altered LV Geometry and Early Diastolic Dysfunction

**Bar Chart 1:**
- **Control** vs. **NAFLD**
- **LV Mass (g/m²)**
- **P = 0.001**

**Bar Chart 2:**
- **Control** vs. **NAFLD**
- **E/A Ratio**
- **P < 0.0001**
Diabetes
Hypertension
Obesity

Lipotoxicity
Low-grade inflammation

Cardiac Structure and Function (Independent of Metabolism)

NAFLD

Diastolic Dysfunction
Hepatic Steatosis Linked to Epicardial and Pericardial Fat

Myocardial Triglyceride Content is Linked to Diastolic Dysfunction
Association between NAFLD and DD is Independent of Traditional Risk Factors

Relationship between NAFLD and DD independent of: Age, Sex, BMI, Duration of DM, HbA1c, HTN, and eGFR
Greater Diastolic Dysfunction in Patients with NASH

Petta et al. J Hepatol 2015
Decline in Diastolic Dysfunction Associated with NAFLD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β-Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.03</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-2.1</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.7</td>
<td>ns</td>
</tr>
<tr>
<td>NASH vs NAFL</td>
<td>-14</td>
<td>&lt; 0.007</td>
</tr>
</tbody>
</table>

* p< 0.04 for both
Diabetes
Hypertension
Obesity

Lipotoxicity
Low-grade inflammation

Cardiac Structure and Function (Independent of Metabolism)

Cardiac & Hepatic Steatosis

Diastolic Dysfunction

NAFLD
Hepatic Fibrosis is Linked to Epicardial Fat and Diastolic Dysfunction

Relationship between Fibrosis & DD independent: age >50 yrs, gender, visceral adiposity, hypertension, IFG/Diabetes, statin use, epicardial fat
LV Mass For Given Cardiac Volume Increases Progressively From Controls to NASH

Parameter | β-Coefficient | P
---|---|---
Steatosis | 3.3 | ns
Fibrosis | 5.6 | 0.02
Inflammation | 1.03 | n.s
Hepatic Fibrosis Linked to Diastolic Dysfunction

![Graph showing the relationship between hepatic fibrosis stage and Exericse E/E'].

- Stage 0: Exericse E/E' = 5
- Stage 1: Exericse E/E' = 7
- Stage 2: Exericse E/E' = 10
- Stage 3: Exericse E/E' = 15

P<0.001 for trend

UNPUBLISHED DATA
Fibrosis Linked to Exercise Time and Peak VO$_2$ Consumption

**Hepatic Fibrosis**

- **Exercise Time (min)**
  - Stage 0
  - Stage 1
  - Stage 2
  - Stage 3

  *P*<0.001 for trend

**Fibrosis Stage**

- **Peak VO$_2$ (ml/kg/min)**
  - Stage 0
  - Stage 1
  - Stage 2
  - Stage 3

  *P*=0.025 for trend
The Liver Heart Axis: Summary

Normal Liver — Metabolic Changes — Steatosis — Inflammation — Fibrogenesis — Cirrhosis

Normal Heart — Diastolic Heart Failure
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