Fatigue in patients with heart disease

Measurement & mechanisms

Dr. Nina Kupper
Outline

• The significance and mechanisms of fatigue in heart disease
  – Vital exhaustion in CAD
  – Fatigue in HF
• Measuring fatigue
• Future directions
Fatigue & Heart disease

Prevalence of fatigue in heart disease
- 30-70%

Not only a correlate of prevalent CAD, but also a premonitory symptom
* In month preceding MI: fatigue 71% and chest pain <15% (in women) (McSweeney et al. Circulation 2004)

Common correlates of fatigue in CAD
- co-morbidity, sleep problems & apnea, inflammation, lifestyle factors (physical inactivity, overweight, smoking), depression

Symptoms of MI in women:
- dyspnea 57%
- weakness 55%
- unusual fatigue 43%
- chest pain 31%
- jaw pain 10%
Fatigue

I am dead tired (‘kei kapot’)

Doctor, when I do nothing, I can do everything

When I get up, I want to go to bed again

Dog tired (‘muug muug muug’)

Every month I compromise a little bit more

Tiredness could be worse, but I cannot go anywhere anymore
If all you have is a hammer, everything looks like a nail
unusual tiredness, increased irritability, and feelings of demoralization (Appels, 1987).

Vital exhaustion
Measuring vital exhaustion

**Maastricht Questionnaire**

**Exhaustion**
- Feeling tired, weak,
- Sleeping problems
- Not accomplishing much, not coping
- Don’t have what it takes
- Come to dead end
- Battery loosing power

**Depression**
- Listless, anhedonia,
- Hopelessness,
- giving up,
- death wish, crying,
- trouble concentrating

**Irritation**
- Little things irritate

5-10 minutes
Scoring No - ? - Yes

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Vital exhaustion predicted incident ischemic heart disease (HR=1.78-2.57) in a large Danish population sample and the ARIC population sample (HR= 1.69 (1.40–2.05))

Background correlates

<table>
<thead>
<tr>
<th>Vital exhaustion item score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>n = 1350 (25.8%)</td>
</tr>
<tr>
<td>1–4</td>
</tr>
<tr>
<td>n = 2333 (44.5%)</td>
</tr>
<tr>
<td>5–9</td>
</tr>
<tr>
<td>n = 1072 (20.5%)</td>
</tr>
<tr>
<td>10–17</td>
</tr>
<tr>
<td>n = 486 (9.3%)</td>
</tr>
<tr>
<td>Test for trend P-value²</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Women</th>
<th>0</th>
<th>1–4</th>
<th>5–9</th>
<th>10–17</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.5 (14.1)</td>
<td>57.5 (15.9)</td>
<td>57.7 (15.7)</td>
<td>60.7 (14.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Waist–hip ratio x 100</td>
<td>82.0 (7.3)</td>
<td>82.1 (7.8)</td>
<td>83.1 (8.1)</td>
<td>84.4 (8.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.2 (4.4)</td>
<td>25.0 (4.4)</td>
<td>25.4 (4.9)</td>
<td>25.8 (5.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>140.1 (23.6)</td>
<td>136.9 (24.6)</td>
<td>136.0 (23.7)</td>
<td>137.6 (23.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Plasma total cholesterol (mmol/l)</td>
<td>6.49 (1.36)</td>
<td>6.20 (1.34)</td>
<td>6.21 (1.26)</td>
<td>6.41 (1.34)</td>
<td>0.006</td>
</tr>
<tr>
<td>Self-reported diabetes</td>
<td>23 (1.7)</td>
<td>48 (2.1)</td>
<td>26 (2.4)</td>
<td>23 (4.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Family history of IHD²</td>
<td>231 (17.1)</td>
<td>417 (17.9)</td>
<td>208 (19.4)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>562 (40.5)</td>
<td>1079 (45.1)</td>
<td>525 (49.0)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Physically inactive</td>
<td>93 (6.9)</td>
<td>243 (10.4)</td>
<td>167 (15.6)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No daily consumption</td>
<td>389 (28.8)</td>
<td>628 (26.9)</td>
<td>322 (30.0)</td>
<td>188 (45.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt;3 drinks/day</td>
<td>58 (4.3)</td>
<td>108 (4.6)</td>
<td>62 (5.8)</td>
<td>37 (7.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Living alone</td>
<td>611 (45.3)</td>
<td>972 (41.7)</td>
<td>460 (42.9)</td>
<td>250 (51.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>School education (&lt;8 years)</td>
<td>461 (34.2)</td>
<td>721 (30.9)</td>
<td>380 (35.5)</td>
<td>216 (34.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Household income (Low)</td>
<td>305 (23.3)</td>
<td>505 (22.3)</td>
<td>283 (26.4)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

56% smokers
28% physically inactive
37% lower income
The mechanism

Chronic stressors
- Marital stress
- Long-term care giving
- Work stress
- Financial problems
- Overtime

Negative affect
- Hypothalamus-pituitary-adrenal (HPA) axis (cortisol)
- Vagally-mediated HRV

Fatigue
- Coagulability
- Viral reactivation
- Immune mediated inflammation
- Sympatho-adrenomedullary axis (NE)
- Fibrinolysis

Impairment of adaptive mechanisms

Crescendo atherosclerosis

Agitability
Universality: not only relevant post-MI

- cardiovascular hospital readmission or cardiovascular death, with a mean follow-up of 25 months

Increased risk of cardiovascular readmission or death in those patients with increasing or persistent VE

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>0.97</td>
<td>(0.71–1.32)</td>
<td>0.82</td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>1.16</td>
<td>(0.86–1.58)</td>
<td>0.33</td>
</tr>
<tr>
<td>Having no partner</td>
<td>0.95</td>
<td>(0.69–1.31)</td>
<td>0.76</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.08</td>
<td>(0.81–1.43)</td>
<td>0.61</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.32</td>
<td>(0.99–1.75)</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.28</td>
<td>(0.93–1.77)</td>
<td>0.14</td>
</tr>
<tr>
<td>LVEF &lt;40%</td>
<td>1.94</td>
<td>(1.36–2.75)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>0.80</td>
<td>(0.60–1.06)</td>
<td>0.13</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>0.81</td>
<td>(0.56–1.18)</td>
<td>0.27</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.84</td>
<td>(0.63–1.11)</td>
<td>0.21</td>
</tr>
<tr>
<td>Psychotropic medication</td>
<td>1.26</td>
<td>(0.84–1.91)</td>
<td>0.27</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>1.13</td>
<td>(0.82–1.54)</td>
<td>0.45</td>
</tr>
<tr>
<td>Decreasing vital exhaustion</td>
<td>1.06</td>
<td>(0.66–1.69)</td>
<td>0.81</td>
</tr>
<tr>
<td>Increasing vital exhaustion</td>
<td>2.04</td>
<td>(1.15–3.61)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Severe vital exhaustion</td>
<td>1.69</td>
<td>(1.08–2.64)</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

Heart failure
Fatigue in heart failure: multiple sources

**Exertion fatigue**
fatigue directly related to the performing of activities in daily living.

Consequence of widespread systemic changes in muscle mass, metabolism, endurance, and blood flow.

**General, mental fatigue**
overwhelming, sustained sense of exhaustion and decreased capacity for mental work.

Due to chronic activation of systems set in place to deal with acute stress (which also has mental consequences).

- Exertion fatigue
- General, mental fatigue

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Exercise capacity (6MWT)  
Hypertension  
Depression  
Dyspnea  
Distressed personality  
Anxiety  


Measuring fatigue in heart disease

28 instruments to assess subjective fatigue

Discriminate between generic & ‘disease specific’ instruments

NB. fatigue questions remain the same

- General, mental fatigue
- Exertion fatigue
- Fatigue associated with depression
- Vital exhaustion

Multi-question instruments

MFI-20
(general, physical, reduced activity, reduced motivation, mental)

DEFS-10/FAS-10
(exertion, general, mental)

Maastricht Questionnaire
(21/23)
(vital exhaustion: fatigue, irritability, depression)

‘Objective’ exercise capacity/exertion fatigue indicators:

NYHA class rating during exercise, Borg scale, 6 minute walk test, \( V_O_2 \) max, \( V_E/V_CO_2 \) Slope, Anaerobic threshold

Fatigue affects outcome

- Both general mental fatigue and exertion fatigue impacted survival chances negatively

Fatigue affects self care & consulting behavior

- Both general and exertion fatigue were associated with poorer self-care and poorer consulting behavior (N=545)
- Adjusted for age, gender, SES, partner status, NYHA class, LVEF, diabetes, COPD, kidney disease & BMI
- Independent of sleep problems and mood symptoms
Towards a potential mechanism: inflammation

- Inflammation was relatively stable across the time period
- Higher levels of inflammation across a 1-year period were associated with
  - Higher levels of baseline general fatigue *but not exertion fatigue*
  - Larger increases of general fatigue over the time period

Adjusted for clinical and demographic covariates

NB. Health behaviors

[Diagram with nodes labeled BL Mental fatigue, Change in Mental fatigue, Chronic inflammation, Smoking, Exertion capacity, BMI]
Relation between Exhaustion and C-reactive Protein

Kop et al., AJC, 2002

p interaction = 0.01
CoRPS

summarizing

Fatigue

Vital exhaustion

exertion

mental

Self-care

Consultation

Adherence

Inflammation

Stress adaptive mechanisms

Prognosis

QoL
FUTURE DIRECTIONS
Directions for research

- Measure fatigue more consistently using standardized and reliable instruments (e.g. MFI, FAS, DEFS, MQ)
- Examine fatigue mechanisms (behavioral & biological) more closely
- Intervention on fatigue
Extending the physician toolbox

Treating anemia

Treating sleep disorders

Multimodal exercise interventions aimed at alleviating fatigue, and including psychosocial support and self-care education

Low threshold referral to medical psychologist for fatigue. Extreme fatigue is also debilitating in the non-depressed

Adjusting medication
More fatigue research @ CoRPS

**Diabetes**

Nefs et al. Subjective sleep impairment in adults with type 1 or type 2 diabetes: Results from Diabetes MILES-The Netherlands. Diabetes Res Clin Pract. 2015

Poor subjective sleep quality is prevalent both in adults with type 1 and type 2 diabetes, and is related to poor daytime functioning and higher self-care burden.

**Cancer**

Husson et al. Variation in fatigue among 6011 (long-term) cancer survivors and a normative population: a study from the population-based PROFILES registry. Support Care Cancer 2015.

Fatigue levels are substantial in (long-term) cancer survivors and vary depending on cancer type, time since diagnosis, age, gender, treatment with chemotherapy, number of comorbid conditions, educational level, and partnership.

**Sarcoidosis**


Nature of fatigue moderates the relationships between fatigue and anxiety and fatigue and depressive symptoms in sarcoidosis. Hence, beside fatigue, depressive symptoms and anxiety should be an integral part of the multidisciplinary management of sarcoidosis patients.

**Heart disease**


This prospective study demonstrated that general and exertion fatigue were both associated with poor HF self-care, which could not be explained by sleep problems or mood symptoms, and was independent of clinical indicators of disease severity.
Collaborators:

Robert Smith – Fatigue at the interface of body and mind in chronic heart failure patients (2009)


Acknowledgments for this presentation:

Current projects (PI):