Physical fatigue in relation to clinical context

Bautmans Ivan
Frailty in Ageing research department

Sarcopenia
Rosenberg J Nutr 1997
Age-related loss of muscle mass and muscle strength

Roubenoff R. J Gerontol 2003
Muscle Endurance

- Fatigue & physical exhaustion
  - Often reported symptom in elderly
  - Central characteristic of frailty

- Barriers in frail & ill elderly
  - Bed rest
  - Classic max. exercise tests impossible

- Bed-side evaluation muscle function
  - ≠ large mechanical devices

  → Development of easy test procedures

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Table 3. Reference values (in Kpa) for maximal grip strength

<table>
<thead>
<tr>
<th>Age</th>
<th>Male Threshold value</th>
<th>Male Median</th>
<th>Female Threshold value</th>
<th>Female Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-74 years</td>
<td>66 KPa</td>
<td>91 KPa</td>
<td>54 KPa</td>
<td>67 KPa</td>
</tr>
<tr>
<td>75-79 years</td>
<td>57 KPa</td>
<td>82 KPa</td>
<td>48 KPa</td>
<td>63 KPa</td>
</tr>
<tr>
<td>80-84 years</td>
<td>50 KPa</td>
<td>75 KPa</td>
<td>43 KPa</td>
<td>59 KPa</td>
</tr>
<tr>
<td>≥85 years</td>
<td>37 KPa</td>
<td>64 KPa</td>
<td>35 KPa</td>
<td>54 KPa</td>
</tr>
</tbody>
</table>

All reference values are valid for the dominant and non-dominant hand using the Martin Vigorimeter. The threshold value corresponds to the p=0.05 level. Adapted from Merkies et al. (60)
Fatigue resistance

• Based on max. grip strength

• Time (seconds) until grip strength ↓ to 50%Max

• Reliability
  – Inter-observer ICC(3,1)= 0.77 – 0.91
  – Intra-observer ICC(3,1)= 0.82 – 0.94

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Table 2. Factors Contributing to Sarcopenia.

<table>
<thead>
<tr>
<th>Type</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Anabolism</td>
<td>↓ Hormonal stimulation (Growth Hormone, IGF-1, Testosterone, Oestrogen)</td>
</tr>
<tr>
<td>Endogenous</td>
<td>Loss of motorneurones, denervation of muscle fibres</td>
</tr>
<tr>
<td></td>
<td>↑ non-contractile tissue in muscle</td>
</tr>
<tr>
<td>Exogenous</td>
<td>↓ Physical activity</td>
</tr>
<tr>
<td></td>
<td>Bed rest, immobilisation</td>
</tr>
<tr>
<td></td>
<td>Malnutrition</td>
</tr>
<tr>
<td>↑ Catabolism</td>
<td>↑ Basal inflammatory profile (IL-6, TNF-α)</td>
</tr>
<tr>
<td>Endogenous</td>
<td></td>
</tr>
<tr>
<td>Exogenous</td>
<td>Stress-induced inflammation: Life events, Depression</td>
</tr>
<tr>
<td></td>
<td>Disease</td>
</tr>
</tbody>
</table>

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Bautmans et al. Acta Clinica Belgica, 2009; 64-4
**Inflammation**

- = immune response upon aggression
- Pathologic situations
  - Trauma, Surgery, Infection
- Cytokine-mediated phenomenon
  - Secreted by monocytes, macrophages
  - ↑ IL-1, IL-6, TNF-α → proteolysis
- Cytoprotective / anti-inflammatory mechanisms
  - Heat shock proteins
  - IL-10
  - IGF-1


*Fig. 5. Hypertrophy and atrophy signalling via Akt, increases in Akt/PI3K/AKT/mTORC1 pathway results in an up-regulation of cellular proliferation in response to IG-1 binding.

**Inflammation + Atrophy**

**Hypertrophy**

Protein Synthetic Hypertrophy

Protein Degradation Atrophy

Proliferation


Increase of 0.016 pg/mL per year in healthy subjects

**Interleukin-6**

- Basal inflammatory profile
  - ↑IL-6, TNF-α, ...
  - Muscle weakness
  - Muscle atrophy

**Cesari ea J Gerontol 2004**

![Graph showing interleukin-6 levels with age](image)

**FIG. 1.** Correlation of interleukin-6 and donor age.

**Hager ea Neurobiol of Ageing 1994**

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**Accelerating factors**

- Serious systemic inflammation
  - Inflammatory conditions (e.g. infection, surgery)
Inflammatory Patients Non-inflammatory Patients

N=63, Age=70-98 yrs
Bautmans ea. J Gerontol 2005

Inflammatory Patients Significantly Weaker than Non-Inflammatory (p<0.05)
‡ Significant difference in evolution (p<0.05)

Fatigue resistance

Grip Strength

Fatigue resistance

Grip Strength

Inhibition IL-6

Adapted from Penglis et al. Intern Med J 2001; 31: 37-41
Hospitalized geriatric patients with acute infection, N=43, aged 84 ± 6 years

Mets, Bautmans ea. Am J Geriatr Pharmacother 2004

* Evolution FR significantly different between 3 groups (p=0.021) and improvement celecoxib group significantly better than acetaminophen group (p<0.05) control group (p<0.05)

+66%

Mets, Bautmans ea. Am J Geriatr Pharmacother 2004

Grip Work = 0.75 x Fatigue resistance = area under the curve

N=291, age 20-93 yrs

Bautmans ea. In Press

$\mathbf{r=0.98}$

Hospitalized geriatric patients, N=91
- Community-dwelling elderly, N=100
- Young controls, N=100
<table>
<thead>
<tr>
<th>Cutoff</th>
<th>Male</th>
<th>Female</th>
<th>Male &amp; Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>3000 KPa*sec</td>
<td></td>
<td></td>
<td>40 KPa*sec/kg</td>
</tr>
<tr>
<td>2500 KPa*sec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 KPa*sec/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>86%</td>
<td>84%</td>
<td>83%</td>
</tr>
<tr>
<td>Sens</td>
<td>90%</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Spec</td>
<td>70%</td>
<td>70%</td>
<td>68%</td>
</tr>
</tbody>
</table>


Community dwelling elderly, N=40, aged 75 ± 5 years

<table>
<thead>
<tr>
<th></th>
<th>Grip Work kg body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grip Work</td>
</tr>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>VAS-Fatigue</td>
<td>-.59*</td>
</tr>
<tr>
<td>Mobility scale</td>
<td>.37</td>
</tr>
<tr>
<td>WHOQOL F2.4</td>
<td>-.51*</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>.50*</td>
</tr>
</tbody>
</table>

Bautmans et al. BMC Geriatrics 2007

Values represent Spearman’s Rho Coefficients; *p<.05, **p<.01, VAS-F = Visual Analogue Scale for Fatigue, Mob-Tiredness = Mobility-Tiredness scale, WHOQOL = WHO Quality of Life Questionnaire (F2.2 = "How easily do you get tired?", F2.4 = "How much are you bothered by fatigue?", both scored on a 1-to-5 scale going from 'not at all' to 'extremely').
NURSING HOME

77 nursing home residents aged 81±8 yrs

Table 3. Relationships Between Handgrip Endurance, Fatigue, and Mobility

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fatigue Resistance</th>
<th>Grip Work</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility-Tiredness scale(^{a})</td>
<td>0.22(^{a})</td>
<td>0.38(^{a})</td>
</tr>
<tr>
<td>Visual Analogue Scale for Fatigue</td>
<td>– 0.15</td>
<td>– 0.29(^{a})</td>
</tr>
<tr>
<td>World Health Organization Quality of Life question</td>
<td>– 0.24(^{a})</td>
<td>– 0.30(^{a})</td>
</tr>
<tr>
<td>F2.2</td>
<td>– 0.10(^{b})</td>
<td>0.27(^{a})</td>
</tr>
<tr>
<td>Treniti test</td>
<td>0.31(^{a})</td>
<td>0.88</td>
</tr>
<tr>
<td>Elderly Mobility Scale</td>
<td>0.20(^{a})</td>
<td>0.35(^{a})</td>
</tr>
</tbody>
</table>

\(^{a}\) \(P < .05\).
\(^{b}\) \(P < .01\).
\(^{a}\) Higher scores reflect less fatigue.
\(0.05 > P > .05\) (trend).

F2.2 = “How easily do you get tired?” F2.4 = “How much are you bothered by fatigue?” both scored on a 1 to 5 scale from 1 (not at all) to 5 (extremely).

Bautmans ea. JAGS 2008
Figure 1. Fatigue resistance in relation to extracellular heat shock protein (Hsp70) and interleukin (IL)-6 in nursing home residents. Bars represent means ± standard errors. Serum Hsp70 and IL-6 values at the 70th percentile and higher were considered as high levels.

(B) Grip work expressed per kg of lean body mass. Subjects with high Hsp70 and high IL-6 serum levels had poorer grip work than those with low Hsp70 and high IL-6 serum levels (P = .045).
N=66, age 24-91 yrs, elective abdominal surgery

Bautmans ea. J Gerontology 2010

Figure 1 - Evolution of post-surgical muscle fatigue resistance according to age. Patients aged >75 years (N=20, dotted line) worsened significantly more and recovered significantly less rapidly for fatigue resistance at day 4 post-surgery compared to the younger (age 60-75 years: N=25, plain line; age <60 yrs: N=29, semi-dotted line) patients (Repeated measures ANOVA, interaction between age and fatigue resistance p<0.05).

Bautmans ea. J Gerontology 2010
Muscle Fatigue

Central or Peripheral origin?
Central or peripheral mechanism?

Age 66-91 yrs, 18 healthy control, 10 hospitalized with acute infection

Methods

12.5 kHz, Butterworth 4th order Band pass 10-5000 Hz filter, notch filter, Preload = 0.2 kg
Methods

Twitch-interpolated method

Voluntary activation ratio
= 100 - [(FtwitchMVC / FtwitchRelaxed) x 100]

RMS (during 2 seconds)
normalized for M-wave ptp

Decreased activation ratio at MVC50 *p<0.05

■ = Hospitalized Patients ■ = Healthy Elderly

Decreased RMS/M-wave PTP ratio at 3/4 and 4/4 of MVC50 in Hospitalized patients (...) compared to Healthy Elderly (...). Repeated Measures ANOVA corrected for age *p<0.05

Bautmans ea. Unpublished data

12.5 kHz, Butterworth 4th order Band pass 10-5000 Hz filter, notch filter, Preload = 0.2 kg
Fig. 4. Single-skinned fiber force-frequency curves. Single skinned fiber force generation for diaphragm muscle fibers from CLP animals (●) was significantly reduced compared with the force generated by single diaphragm fibers from control animals (○) (P < 0.001). Forces generated by single skinned fibers from either CLP plus CII III (▲) or CLP plus OA ID (■) groups were significantly higher than the force generated by fibers from the CLP group (P < 0.001).

Powers ea. JApplPhysiol 2007

Fig. 3. Intact diaphragm force-frequency curves. Intact muscle force generation was significantly lower at stimulation frequencies from 1 to 80 Hz for diaphragms from CLP treated animals (●) than for control animals (○) (P < 0.001). Diaphragms from CLP animals given CII III (▲) generated forces significantly higher than diaphragms from CLP animals for frequencies from 1 to 80 Hz (P < 0.001). Force generation for muscles taken from CLP animals given OA ID (■) was also greater than for CLP animals at frequencies 1–80 Hz, P < 0.001. *Significant statistical difference between CLP and the other groups, P < 0.05.

Supinski ea. JApplPhysiol 2009

Fig. 3. Pathway involved in myocellular apoptosis in streptomyxin skeletal muscle. Apoptosis can be initiated by receptor signaling, sarcolemmaraeticulum (SR), and/or mitochondrial-regulated pathways in skeletal muscle. Lactate receptor (FAS/TNF) binding results in caspase-3-dependent DNA fragmentation and/or myofibril release. Reactive oxygen species (ROS) digestion or sarcolemmareticulum calcium (Ca2+) handling results in caspase-7 and caspase-9 activation. ROS affects the mitochondria to influence the opening of the mitochondrial permeability transition pore to release cytochrome c (Cyt C), independent of caspase activity. Mitochondrial endonuclease G (Endo G), and/or apoptosis inducing factor (m-AIF) are also capable of inducing DNA fragmentation in skeletal muscle. Note the multiple lines of cross-talk between pathways.
Conclusions

• Muscle fatigue resistance
  – Direct measurement of frailty component
  – Reliable and valid outcome measure
  – Easy bedside evaluation
  – Correction for body mass
  – Related to
    • Inflammation & clinical status
    • Self-perceived fatigue
    • Self-perceived physical function
    • Functional mobility

• Fatigue complaint in elderly persons
  – Taken seriously
  – Adequate monitoring

Thank you.

ibautman@vub.ac.be