Is Quadriceps Endurance Reduced in COPD?

A Systematic Review

Rachael A Evans MBChB, PhD 1,2,5, Eric Kaplovitch BSc (H), MD1,2, Marla K Beauchamp PhD1,3,4, Thomas E Dolmage MSc 1, Roger S Goldstein MBChB 1,2,3, Clare L Gillies PhD 6, Dina Brooks PhD 1,3, Sunita Mathur PhD 1,3

1Department of Respiratory Medicine, West Park Healthcare Centre, Toronto, Ontario, Canada,
2Department of Medicine and 3Department of Physical Therapy, University of Toronto, Toronto, Ontario, Canada,
4Department of Physical Medicine and Rehabilitation, Harvard Medical School, Spaulding Rehabilitation Hospital, Cambridge, Massachusetts
5Department of Infection, Immunity and Inflammation and 6Department of Health Sciences, University of Leicester, Leicester, UK

Rachael Evans corresponding author
rachael.evans@uhl-tr.nhs.uk
Department of Respiratory Medicine
Glenfield Hospital
Leicester
UK
LE3 9QP

There are no conflicts of interest for any author. This is a systematic review so no ethical approval was sought for this study.
Abbreviations

ATP Adenine Trinucleotide Phosphate
COPD Chronic Obstructive Pulmonary Disease
FEV1 Forced Expiratory Volume in 1 second
FVC Forced Vital Capacity
MVC Maximum Voluntary Contraction
SD Standard Deviation
SE Standard Error
SMD Standardised Mean Difference
WMD Weighted Mean Difference
Abstract

Background

Although the aerobic profile of the quadriceps muscle is reduced in COPD, there is conflicting evidence whether this leads to reduced quadriceps muscle endurance. We therefore performed a systematic review of studies comparing quadriceps endurance in individuals with COPD to healthy controls.

Methods

Relevant studies were identified by searching six electronic databases (1946-2011). Full text articles were obtained after two researchers independently reviewed the abstracts. The results were combined in a random effects meta-analysis and meta-regression models were fitted to assess the influence of type of measurement.

Results

Data were extracted from 21 studies involving 728 individuals with COPD and 440 healthy controls. Quadriceps endurance was reduced in COPD compared to healthy controls SMD 1.16 (95% CI: 1.02 to 1.30, p<0.001) with a 44.5 (4.5 to 84.5) second (p=0.029) reduction in COPD (large effect size) when measured using a non-volitional technique. The relationship between quadriceps endurance in COPD and controls did not differ when comparing non-volitional and volitional techniques (p = 0.22) or when high or low intensity tasks (p = 0.44) were used.

Conclusion

Quadriceps endurance is reduced in individuals with COPD compared to healthy controls independent of the type of task performed.
Introduction

Skeletal muscle alteration is a recognised extra-pulmonary consequence of Chronic Obstructive Pulmonary Disease (COPD) with particular involvement of the larger muscles of locomotion (1;2). Although the precise causes and mechanisms are still being elucidated, deconditioning from inactivity, systemic inflammation, oxidative stress, hypoxaemia and steroid use have all been implicated (all of which worsen with increasing disease severity) (1;3). Reduced quadriceps muscle mass and strength in COPD (4) have been associated with a higher mortality (5;6) and morbidity, as well as increased hospital admissions (7).

There is also considerable evidence that the oxidative capacity of the skeletal muscle is reduced in COPD with preferential reduction in the type I fibre cross sectional area of the quadriceps muscle and a reduction in oxidative enzyme concentration, mitochondrial density and capillary density (8;9). Collectively, these changes likely contribute to exercise and activity intolerance (10-12). These adaptations are associated with a loss of the aerobic profile of the muscle. This is exemplified during cycling exercise where the muscle energy requirements are unable to be met with a resultant decline in Phosphocreatine and Adenosine Trinucleotide Phosphate (ATP) at very low absolute power (12). Whole body exercise tests such as incremental cycling or treadmill walking do not isolate the contribution of the peripheral muscles to the impaired aerobic capacity since the latter can also be attributed to ventilatory constraints (13) and redistribution of cardiac output to the respiratory muscles (14). Therefore, tasks that specifically target
localised muscle endurance are needed to determine the functional consequences of cellular changes observed in the limb muscles of individuals with COPD.

Muscle endurance and fatigue of the quadriceps (knee extensor muscle group) have been measured using a variety of techniques in individuals with COPD. Muscle endurance has been defined as the ability of muscle to perform repeated work and resist fatigue whereas muscle fatigue has been defined as a decline in the force generating capacity of a muscle (15). Muscle fatigue occurs as a result of impairment at one or more points along the pathway for muscle contraction (Figure 1). As different tasks target different aspects of this pathway, the type of measurement protocol chosen (type, intensity, frequency and duty cycle) can have an important effect on study results (16). Different approaches have been used to measure the two interrelated concepts of muscle endurance and fatigue in individuals with COPD with varying results (17-19). Consequently, it is not definitively known whether quadriceps muscle endurance is reduced in COPD nor how different measurement protocols may influence the interpretation of results.

The primary aim of this study was to resolve the existing uncertainty of whether quadriceps muscle endurance is reduced in individuals with COPD compared to healthy controls and to quantify the difference. The secondary aims were to describe the methodologies reported to measure quadriceps endurance in COPD, investigate whether the type of measurement performed influenced the results, and determine whether disease severity affected the relationship between quadriceps endurance in COPD compared to healthy controls.
Methods

Study design

We performed a systematic review of studies comparing quadriceps endurance in COPD with healthy controls consistent with PRISMA guidelines (20).

Eligibility criteria

We included studies involving individuals with COPD and any measurement of quadriceps/knee extensor endurance. Eligibility required a comparison with a healthy control group. All languages were accepted and if necessary translated to English. Grey literature searches were performed by screening the references from all relevant review articles and international guidelines (2).

Search strategy

Relevant electronic databases were searched from inception to August 2013: PubMed, EMBASE, CINAHL, PEDro, OVID MEDLINE and The Cochrane Library. An example of the search strategy used is:

(COPD OR chronic obstructive pulmonary disease OR chronic obstructive lung disease OR pulmonary emphysema OR chronic airflow limitation OR chronic airflow obstruction OR chronic obstructive airway disease OR COAD) AND (quadriceps OR knee extensor OR lower limb OR leg OR knee OR thigh) AND (endurance OR contractile fatigue OR muscle fatigue OR muscle contraction). The full search strategy is available from the authors.
**Study selection**

After duplicates were removed, the abstracts of all identified citations were reviewed by two assessors independently (RE and EK). The full text citation was reviewed if one of the assessors concluded it was eligible. The full text was then reviewed by RE with the final decision for inclusion taken by SM.

**Data extraction**

Two reviewers performed data extraction (EK and MB) which was checked and, where needed, transformed (see statistical analysis section) by a third reviewer (RE). Baseline demographics, spirometry, details of the study design, measurement properties, and results of the measurement were extracted using a standardised form. Study authors were contacted if additional data were needed.

**Outcome measurements**

The primary outcome measure was quadriceps endurance. The units of measurement varied depending on the type of measurement used. A priori we included any measure of muscle endurance, both sustained and intermittent contractions, isometric or isokinetic movement, as well as intensity (% Maximal Voluntary Contraction [MVC]), measured with either volitional or non-volitional tasks. In studies where both volitional and non-volitional measurements were made, both outcomes were recorded. Studies involving exercise in which a predominant ventilatory limitation was observed were excluded. For example, studies wherein the intent of exercise was to reduce the total active muscle such as single leg cycling or high intensity knee-extensor training, but the limitation to exercise remained predominantly a ventilatory limitation rather than peripheral, were excluded. Practically, the studies excluded were those where the mean peak ventilation
(VE L/min) was greater than 80% of the maximal voluntary ventilation at the end of the test in question.

A high intensity task was defined as a task involving contractions at > 50% MVC (21). The force-time index was used to quantify endurance time over a range of power when different versions of a similar protocol had been used. It provides a way to relate fatigue of the muscle system to the relative energy requirements, power or rate of work, of the exercise. The total energy requirements can be related to the rate of relative force accumulation, the product of the force generated and the duration of force production. The force-time index was plotted against endurance time where the force-time index = (contraction force · maximum voluntary contraction) · duty cycle, and the duty cycle = time of the contraction / total time of the cycle.

Quality assessment

Assessment of the methodological quality of the studies was performed by two independent researchers (EK and RE) based on the relevant components of the checklist by Downs and Black (22). Any disagreements were resolved by consensus with a third reviewer (SM).

Statistical analysis

Standardised mean differences (SMD) and their standard errors were calculated for each study. The SMD is used as a summary statistic for meta-analyses for studies which all assess the same outcome but measure it in a variety of ways. It expresses the size of the
intervention effect in each study relative to the variability observed in that study, and is calculated by taking the difference in the mean outcome measure between the two groups and dividing it by the standard deviation.

Where studies reported results by sub-groups (for example, separated by gender) numbers were combined to give a single result for each study. Standard deviations were calculated if originally presented as standard error using \( SD = SE \cdot \sqrt{n} \) where \( n \) represents the sample size. A random effects meta-analysis was carried out to combine results across all 21 studies. Separate meta-analyses were also carried out for non-volitional studies to explore the effects of heterogeneity between studies in terms of measurement technique and Cohen’s \( d \) was calculated for effect size (23). Meta-regression models were fitted to assess the influence of type of measurement (high vs. low intensity) and disease severity of the population studied on the relationship between quadriceps endurance between COPD and healthy controls.

**Results**

**Identification of studies**

Figure 2 summarises the process of identifying eligible studies. Of 349 studies, knee extensor/quadriceps muscle endurance was compared between individuals with COPD and healthy controls in 25. Two studies (French and Chinese) required translation (the latter was included in the final meta-analysis). Four studies \([n = 88 (15\%) \text{ individuals with COPD and } n = 79 (22\%) \text{ healthy controls}]\) were excluded because of missing data, which was unavailable from the authors (24-27). Data were therefore extracted from 21 studies \((17;18;28-46): 728 \text{ individuals with COPD (71.2}\% \text{ male, mean age 65.1 years,} \)
FEV₁ 41.5% predicted, FEV₁/FVC 41.7 and 440 healthy controls: 67.8.1% male, mean age 63.5 years, FEV₁ 103.2% predicted, FEV₁/FVC 80.0%. The FEV₁/FVC ratio was not reported in 9 studies, and one study did not describe the FEV₁ % predicted. In 18/21 studies, individuals with co-morbidities that could influence quadriceps endurance were excluded: cardiovascular disease (n=18), renal (n=8), endocrine (n=14), liver (n=7), orthopaedic (n=7), neurological (n=3). Quadriceps strength was measured in all 21 studies and was significantly reduced in 16 of the studies.

**Description of the techniques used**

A number of different techniques were used to assess muscle endurance which are described in Table 1. Five studies included non-volitional measurements and 10 of the 16 studies using volitional measurements involved high intensity tasks.

**Quality assessment**

A quality assessment for each study is presented in Table 2. The quality scores tended to be low because of insufficient reporting on recruitment and retention rates, and blinding. Of note, the study participants were not all clearly described; full spirometric data was not reported in the healthy control group in 5 studies. The primary purpose for eight studies was to compare muscle endurance in COPD and healthy controls.

**Quadriceps endurance in COPD compared to healthy controls**
Based on results from 21 studies, quadriceps endurance was reduced in COPD compared to healthy controls (SMD 1.16 (95% CI: 1.02 to 1.30) in favour of the healthy controls, p<0.001) shown in Figure 3. In this meta-analysis, a positive SMD showed that the healthy individuals performed better than the patients with COPD, whilst a negative value indicated the patients with COPD performed better. As the SMD combines outcomes that have been measured on different scales, the magnitude of the SMD cannot be interpreted further than this. There was significant heterogeneity among studies: \( I^2 = 93.8\% \), p<0.001.

**Results of quadriceps endurance depending on the type of measurement made**

Five studies (from the same research group) used a non-volitional approach by applying magnetic stimulation to the femoral nerve (34;37-39;42); (Table 1). For context, the mean duration for individuals with COPD (n=199) was 87 secs and 107 secs for healthy controls (n=110); a combined mean duration of 93 secs. A meta-analysis of these five studies showed a mean difference of 44.5 (4.5 to 84.5) secs (48% of combined duration), p=0.029, (Cohen’s d = -0.68 moderate to large effect size) between healthy controls and individuals with COPD (Figure 4), with considerably less heterogeneity than for the overall meta-analysis: \( I^2 = 0\% \), p=0.913. Using meta-regression analysis, the between group difference (COPD versus controls) was not affected by whether the task was non-volitional or volitional (p=0.223).

The intensity of the tasks was highly variable among the remaining 16 studies, resulting in durations from under one minute to 20 minutes (28;30). Meta-regression demonstrated that the effect sizes were independent of task intensity (p=0.44). No single study investigated the relationship between power (the energy demand) and endurance.
(response) across a range of power to be able to test the ‘normality’ of the response between the critical power, strength and endurance. We therefore plotted endurance time versus force-time index for four studies where the force-time index could be calculated (Figure 5). It was not possible to calculate either the force-time index or power from the information provided for the other studies.

**Results according to the severity of COPD**

There was no significant effect of severity of COPD (based on FEV₁ % predicted) on the effect size between COPD and healthy controls on muscle endurance, p=0.93. However, most of the studies included only patients with moderate to severe COPD.

**Discussion**

This systematic review and meta-analysis confirms a reduction in quadriceps muscle endurance in individuals with COPD compared to healthy controls (large effect size), irrespective of the type of measurement protocol used. To our knowledge, this is the first synthesis of measurements of quadriceps endurance in COPD and highlights the many different approaches that have been reported to examine localised muscle function in this population.

Impairment of any of the steps involved in muscle contraction, from central nervous system activation to the excitation-contraction coupling and energy metabolism to
produce ATP (Figure 1), can reduce the endurance of the muscle. The majority of tasks reported in the literature for COPD required repeated voluntary contractions of the quadriceps to obtain a measure of muscle endurance. Most of these studies reported a reduced endurance time or faster decline in contractile force in individuals with COPD compared with healthy controls. However, as volitional tasks are effort-dependent, they can be criticised on the basis of variable subject motivation. Two studies also included an additional non-volitional measure of muscle fatigue (magnetic twitch force) (32;46). Both of these studies confirmed a significant reduction in twitch force post-exercise indicating that muscle fatigue had occurred even after a shorter endurance time than in the healthy controls. A meta-analysis of the five studies (34;37-39;42) which included only non-volitional measurements of quadriceps endurance using magnetic stimulation of the femoral nerve confirmed reduced quadriceps endurance in COPD compared to healthy controls by 44.5 seconds (large effect size). These data indicate that the reduction in muscle endurance reported in COPD is in part caused by peripheral mechanisms.

There was a large range in the intensity (% MVC) and thus task duration across studies, which likely leads to different substrates and cellular pathways being utilized for energy production and muscular work. Coronell et al. used very low intensity tasks (repeated contractions of 10% MVC) (30) and showed the largest standardised mean difference between groups. This type of low intensity task is more “aerobic” in nature as it allows for adequate blood flow to and from the muscle (47), but it can also be limited by changes in central activation or peripheral factors, distal to the neuromuscular junction (48). As such, the expected curvilinear relationship between the force-time index and
endurance time (Figure 5) was observed in healthy controls but not in COPD (30-32;35;40); this was mainly affected by two studies using very low intensity protocols. Therefore, it is speculated that both impaired aerobic capacity of the quadriceps muscle and central factors contribute to reduced muscle endurance in COPD.

Some of the studies involved a very high intensity task (less than one minute in duration) (17;29;33;36;41;45) or sustained isometric contractions (18;28;46) where blood flow would likely be restricted, relying on anaerobic energy sources such as glycolysis (47;49). Type IIX fibres (fast-twitch, fatigable fibres) are known to be atrophied in COPD (50) which, in part, could account for this observation (51). Overall, the reduction in muscle endurance compared with controls, was noted with both low and high intensity tasks.

**Clinical implications**

Exercise training is a major therapeutic strategy for individuals with COPD and currently a combination of aerobic (either cycling or walking) and strength training is recommended (52). The results of this synthesis show that muscle endurance in COPD is reduced highlighting the need for the inclusion of muscle-specific training. Partitioned training such as one-legged cycling has been shown to be more effective in improving peak oxygen uptake than two-legged cycling in COPD, (53;54) and a recent paper reported restored oxidative enzyme activity of the quadriceps using high intensity knee extensor training (one leg at a time) in COPD (55). There has been interest into the pharmacological manipulation of the oxidative capacity of skeletal muscle in animal
models and our review highlights the potential relevance for individuals with COPD (56;57).

**Limitations**

Four studies (less than 20%) had to be excluded as we were unable to obtain the necessary data from the original authors, but there were no differences in the demographics of the study sample between the excluded studies and those included in the meta-analysis. We included all types of muscle endurance and fatigue measures into the meta-analysis, which led to large heterogeneity ($I^2 = 93.8\%$). However, the main relationship was unchanged in the meta-analysis restricted to the non-volitional studies, where the heterogeneity was substantially reduced. While the reduction in muscle endurance was independent of measured airflow obstruction, our results may be subject to population bias given the lack of individuals with milder reductions in airflow obstruction. This review pertains to the large quadriceps muscle group of the leg only and the results should not be extrapolated to other muscle groups which may have different usage and fatigue properties.

The low quality assessment results of the included studies are also a limitation of the review, but likely did not affect our findings given the large number of studies that were included. Nonetheless, the quality results highlight the need for improved adherence to reporting standards for future work.
Summary

In a large number of individuals with COPD, we have shown that quadriceps endurance is reduced compared to healthy controls independent of type of task and measurement technique. In addition to the cellular changes that have been observed in muscle oxidative capacity, neuromotor changes that may contribute to the early onset of muscle fatigue should be further examined in this population. Our findings have implications for the development of pharmacological and non-pharmacological therapies targeted at improving skeletal muscle endurance.

Acknowledgements

Rachael Evans is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to the published article. Rachael Evans designed the study, reviewed the abstracts for eligibility, identified the eligible full text studies, reviewed the quality assessment, helped with data-analysis, and drafted the manuscript. Eric Kaplovitch conducted the literature search, reviewed the abstracts for eligibility, performed data extraction, quality assessment and contributed to the revision of the manuscript. Marla Beauchamp performed data extraction, quality assessment, and contributed to the revision of the manuscript. Thomas Dolmage contributed to the data-analysis and critically revised the manuscript. Roger Goldstein contributed to the study design and critically revised the manuscript.
Clare Gillies provided statistical support, data-analysis and critically revised the manuscript.

Dina Brooks contributed to study design and critically revised the manuscript.

Sunita Mathur contributed to the study design, made the final consensus decisions, helped draft and critically revised the manuscript.

We are grateful to Erin Hamanishi for designing Figure 1.

We would like to thank Amanda Natanek, Abigail Jackson and Tania Janaudis-Ferreira for the extra data they supplied.
Figure 1. Illustration of the pathways involved in a muscle contraction.

Figure 2. Prisma flow diagram of the literature search

Figure 3. A comparison of quadriceps muscle endurance between COPD and healthy controls.
ES: Effect Size (standardized mean difference), ID: Identification
The size of the square relates to weight of the study and the diamond represents the pooled effect estimate

Figure 4. A comparison of quadriceps endurance between COPD and healthy controls using a non-volitional measurement.
ES: Effect size (mean difference, seconds), ID: Identification
The size of the square relates to weight of the study and the diamond represents the pooled effect estimate

Figure 5. A comparison of endurance time plotted against the force-time integral between COPD and healthy controls.

Relative force-time index of repeated contractions =
(contraction force · maximum voluntary contraction$^{-1}$) · duty cycle
where the duty cycle = time of the contraction · total time of the cycle$^{-1}$.
t limit = endurance time
Table 1. Description of the measurement used for each study and the quality assessment

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>Number</th>
<th>CONTRACTION</th>
<th>MEASUREMENT TASK</th>
<th>PRIMARY OUTCOME</th>
<th>INTENSITY OF TASK*</th>
<th>SECONDARY MEASURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allaire</td>
<td>29</td>
<td>Sustained Isometric</td>
<td>60% MVC</td>
<td>T limit</td>
<td>HIGH</td>
<td>EMG</td>
</tr>
<tr>
<td>Borghi-Silva</td>
<td>24</td>
<td>Repeated Isokinetic</td>
<td>MVCs at 60 deg.s⁻¹ for 1 min</td>
<td>Fatigue Index (over 1 minute)</td>
<td>HIGH</td>
<td>Nil</td>
</tr>
<tr>
<td>Coronell</td>
<td>36</td>
<td>Repeated Dynamic‡</td>
<td>10% MVC, duty cycle: 2s:3s (40%), 12 contractions.min⁻¹ until exhaustion</td>
<td>T limit</td>
<td>LOW</td>
<td>EMG</td>
</tr>
<tr>
<td>Couillard1</td>
<td>11</td>
<td>Repeated Dynamic</td>
<td>40% MVC, duty cycle: 2s:3s (40%) 12 contractions.min⁻¹ until exhaustion</td>
<td>T limit</td>
<td>LOW</td>
<td>EMG</td>
</tr>
<tr>
<td>Couillard2</td>
<td>12</td>
<td>Repeated Dynamic</td>
<td>30% MVC, duty cycle: 3s:7s (30%), 6 contractions.min⁻¹ until exhaustion</td>
<td>T limit</td>
<td>LOW</td>
<td>Twitch Force</td>
</tr>
<tr>
<td>Franssen</td>
<td>87</td>
<td>Repeated Isokinetic</td>
<td>15 MVCs at 90 deg.s⁻¹</td>
<td>Fatigue Index (reduction in torque per contraction)</td>
<td>HIGH</td>
<td>Nil</td>
</tr>
<tr>
<td>Jackson †</td>
<td>36</td>
<td>Repeated Isometric</td>
<td>Magnetic stimulation 20% MVC</td>
<td>Fatigue Index</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Janaudis -Ferreira</td>
<td>41</td>
<td>Repeated Isokinetic</td>
<td>100 MVC or to exhaustion at 90 deg.s⁻¹</td>
<td>Fatigue Index (over the first 30 MVCs)</td>
<td>HIGH</td>
<td>Nil</td>
</tr>
<tr>
<td>Ju</td>
<td>71</td>
<td>Sustained Isometric</td>
<td>60% MVC</td>
<td>T limit</td>
<td>HIGH</td>
<td>Twitch Force</td>
</tr>
<tr>
<td>Koechlin</td>
<td>10</td>
<td>Repeated Dynamic</td>
<td>40% MVC, duty cycle: 2s:3s (40%) 12 contractions.min⁻¹ until exhaustion</td>
<td>T limit</td>
<td>LOW</td>
<td>Nil</td>
</tr>
<tr>
<td>Malaguti</td>
<td>39</td>
<td>Repeated Isokinetic</td>
<td>30 MVCs at 300 deg.s⁻¹</td>
<td>Total Work/muscle mass</td>
<td>HIGH</td>
<td>Nil</td>
</tr>
<tr>
<td>Man †</td>
<td>18</td>
<td>Repeated Isometric</td>
<td>Magnetic stimulation 30% MVC</td>
<td>T limit to 70% reduction in force</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Natanek1 †</td>
<td>99</td>
<td>Repeated Isometric</td>
<td>Magnetic stimulation</td>
<td>T limit to 80% reduction</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Study</td>
<td>Set</td>
<td>Rest</td>
<td>Type</td>
<td>Protocol Description</td>
<td>T limit</td>
<td>Method</td>
</tr>
<tr>
<td>------------------------</td>
<td>------</td>
<td>-------</td>
<td>-----------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>--------</td>
<td>----------------</td>
</tr>
<tr>
<td>Natanek2 †</td>
<td>38</td>
<td>23</td>
<td>Repeated Isometric</td>
<td>Magnetic stimulation 20%MVC</td>
<td>T limit to 80% reduction in force</td>
<td>N/A</td>
</tr>
<tr>
<td>Orozco-Levi</td>
<td>14</td>
<td>7</td>
<td>Repeated Dynamic</td>
<td>10% MVC, duty cycle: 2s:3s (40%) 12 contractions.min⁻¹ until exhaustion</td>
<td>T limit</td>
<td>LOW</td>
</tr>
<tr>
<td>Rabinovich</td>
<td>15</td>
<td>7</td>
<td>Repeated Isokinetic</td>
<td>30 MVCs at 90 deg.s⁻¹</td>
<td>Total Work / muscle mass</td>
<td>HIGH</td>
</tr>
<tr>
<td>Swallow †</td>
<td>8</td>
<td>8</td>
<td>Repeated Isometric</td>
<td>magnetic stimulation 30% MVC</td>
<td>T limit to 70% reduction in force</td>
<td>N/A</td>
</tr>
<tr>
<td>Vilaro</td>
<td>16</td>
<td>6</td>
<td>Repeated Isokinetic</td>
<td>30 MVCs at 90 deg.s⁻¹</td>
<td>Total Work/ muscle mass</td>
<td>HIGH</td>
</tr>
<tr>
<td>Van den Borst</td>
<td>29</td>
<td>15</td>
<td>Repeated Isokinetic</td>
<td>30 MVCs at 90 deg.s⁻¹</td>
<td>Fatigue Index (reduction in torque per contraction)</td>
<td>HIGH</td>
</tr>
<tr>
<td>Van’t hul</td>
<td>89</td>
<td>31</td>
<td>Repeated Isokinetic</td>
<td>20% MVC, 30 reps.min⁻¹ until exhaustion</td>
<td>T limit</td>
<td>LOW</td>
</tr>
<tr>
<td>Zattara-Hartmann</td>
<td>6</td>
<td>6</td>
<td>Sustained Isometric</td>
<td>80% MVC</td>
<td>T limit</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

MVC: maximum voluntary contraction, T limit: endurance time to exhaustion, reps/min: repetitions per minute, degs/s: degrees per second, EMG: Electromyography, MRS: Magnetic Resonance Spectroscopy, *High intensity defined as a task involving contractions at > 50% MVC, † solely used a non-volitional technique, ‡ Repeated dynamic contractions performed on gym equipment, Fatigue Index: loss of force expressed either over a period of time or per contraction.
<table>
<thead>
<tr>
<th>Paper</th>
<th>Are the main outcomes clearly described?</th>
<th>Are the characteristics of the participants clearly described?</th>
<th>Are the distributions of principal confounders in each group of subjects to be compared clearly described?</th>
<th>Are the main findings of the study clearly described?</th>
<th>Does the study provide estimates of the random variability in the data for the main outcomes?</th>
<th>Have the characteristics of patients lost to follow-up been described?</th>
<th>Have actual probability values been reported for the main outcomes?</th>
<th>Were the subjects asked to participate in the study representative of the entire population from which they were recruited?</th>
<th>Were those subjects who were prepared to participate representative of the entire population from which they were recruited?</th>
<th>Were an attempt made to blind those measuring the main outcomes of the intervention?</th>
<th>Were the main outcome measures used accurate (valid and reliable)?</th>
<th>Were losses of patients in follow-up taken into account?</th>
<th>Overall Score (Total 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allaire</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>Borghi-Silva</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>9</td>
</tr>
<tr>
<td>Correia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Coulard1</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>Coulard2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Franssen</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>7</td>
</tr>
<tr>
<td>Jackson</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>Janausdis-Ferreira</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>Ju</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td>Koechlin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>Malaguti</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Man</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Natanek1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>Natanek2</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>Orzano-Levi</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Rabinovich</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Sathyapala</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Swallow</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Vilano</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>Van den Bosst</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td>Van’t Hul</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td>Zattara-Hartiman</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>4</td>
</tr>
</tbody>
</table>
Reference List


