Physical Fatigue, Fitness and Muscle Function in Patients with Anti-neutrophil Cytoplasm Antibody-Associated Vasculitis.

Mcclean, Andrew; Morgan, Matthew; Basu, Neil; Bosch, Jos ; Nightingale, Peter; Jones, David; Harper, Lorraine

DOI:
10.1002/acr.22827

Physical Fatigue, Fitness and Muscle Function in Patients with Anti-neutrophil Cytoplasm Antibody-Associated Vasculitis.

*Andrew McClean MBCHB, MRCP, Centre for Translational Inflammation Research, University of Birmingham, UK

*Matthew D Morgan PhD, MRCP Centre for Translational Inflammation Research, University of Birmingham, UK

Neil Basu PhD, MRCP School of Medicine and Dentistry, University of Aberdeen, UK

Jos A Bosch PhD Department of Clinical Psychology, University of Amsterdam, The Netherlands

Peter Nightingale PhD Statistician, NIHR/Wellcome Trust Birmingham Clinical Research Facility, UHB NHS Foundation Trust, Birmingham UK

David Jones PhD School of Healthcare Science, Manchester Metropolitan University, Manchester, UK

Lorraine Harper PhD, MRCP Centre for Translational Inflammation Research, University of Birmingham, UK

*Contributed equally to the work in the preparation of this manuscript

Corresponding author: Prof L Harper
Centre for Translational Inflammation Research
University of Birmingham Research Laboratories
Queen Elizabeth Hospital Birmingham
Mindelsohn Way
Edgbaston
Birmingham
B15 2WB
UK
Tel 0121 371 3238

Email L.Harper@bham.ac.uk

Abstract - 250 words

Manuscript - 2509

Running title – Fatigue and ANCA-Associated Vasculitis

Disclosure

None of the authors have any conflicts of interest related to this study. The results presented in this paper have not been published previously in whole or part, except in abstract format.

Abstract

Objective

This study investigated differences in cardiorespiratory fitness, muscular function, perceived exertion and anxiety/depression between patients and healthy controls(HC) and assessed which of these variables may account for fatigue experienced by patients.

Measurements

Fatigue was measured in 48 AAV patients and 41 HC using the Multi-Dimensional Fatigue Inventory (MFI-20) focusing on the physical component. Quality of life, anxiety/depression and sleep quality were assessed by validated questionnaires. Muscle mass was measured by DEXA scan, strength as the maximal voluntary contraction (MVC) force and endurance as sustained isometric contraction at 50% MVC of the quadriceps. Voluntary activation was assessed by superimposed electrical stimulation. Cardiorespiratory fitness (VO2max and O2pulse) and perceived exertion (Borg scale) were measured during progressive submaximal exercise.

Results

Patients reported elevated physical fatigue scores compared to HC (patients MFI-20 physical 13 (IQR 8-16), HC MFI-20 physical 5.5 (IQR 4-8); $p<0.001$). Muscle mass was the same in both groups but MVC and time to failure in the endurance test were lower due to reduced voluntary activation in patients. Estimated VO2max and O2pulse were the same in both groups. For the same relative work load, patients reported higher ratings of perceived exertion which correlated with reports of MFI-20 physical fatigue (R2=0.2). Depression (R2=0.6), anxiety (R2=0.3) and sleep disturbance (R2=0.3) all correlated with MFI-20 physical fatigue.

Conclusion

These observations suggest fatigue in patients is of a central rather than peripheral origin, supported by associations of fatigue with heightened perception of exertion, depression, anxiety and sleep disturbance, but normal muscle and cardiorespiratory function.

Significance and Innovations**:**

Fatigue in patients with ANCA-associated vasculitis is due predominantly to a complex mix of psychosocial factors.

This study is the first to suggest that physical fatigue is unrelated to muscle problems or cardiorespiratory fitness in patients with ANCA-associated vasculitis.

Increased perception of effort and other factors such as sleep disturbance, anxiety and depression are important in fatigue and may be amenable to therapy.

Many patients with ANCA-associated vasculitis (AAV) complain of fatigue despite being in disease remission, and this is strongly associated with impaired quality of life(1-3). There are currently no recommended treatments for fatigue in these patients, and a better understanding of the aetiology would be an important first step in developing an effective treatment. Fatigue in patients with AAV is associated with a wide range of other complaints including, pain, sleep disturbance, dysfunctional coping strategies, inflammation(2) and reduced exercise capacity(4). These findings resemble those for other chronic conditions such as rheumatoid arthritis(5), systemic lupus erythematosus(6), multiple sclerosis(7, 8) and fibromyalgia (9-11) where fatigue is acknowledged to be of complex aetiology.

Our previous work has shown a reduced exercise capacity in patients with AAV(4), with patients reporting fatigue as the limiting factor. When considering the mechanisms by which fatigue may arise, it is useful to divide them into 'peripheral' and 'central' mechanisms. Peripheral mechanisms of fatigue are those which result from physiological problems within either the neuromuscular or cardiorespiratory systems which make physical effort more demanding. Treatment of AAV often necessitates the prolonged use of glucocorticoids, which are known to lead to muscle wasting(12, 13) and might therefore be expected to cause peripheral fatigue, although whether patients with AAV in remission have evidence of muscle wasting is unknown. Another cause of peripheral fatigue is cardiorespiratory deconditioning(14), which results in normal everyday tasks being carried out at a higher percentage of maximum heart rate. It is not known whether patients with AAV in remission are significantly deconditioned. Peripheral fatigue may be measured relatively easily by making objective measurements, for example by measuring muscle strength during isometric contractions in a sport science laboratory. Central fatigue describes functional abnormalities of the CNS such as increased perception of exertion, reduced motivation or reduced central motor activation, which are probably caused by alterations in neurotransmitter pathways within the brain.(15) Such alterations in pathways within the brain cannot be easily measured, but surrogates such as central motor

activation may be measured using recognised sport science techniques including the superimposed electrical stimulation of muscles during voluntary isometric contraction.

We have undertaken a systematic evaluation of the possible relationship between various measures of cardiorespiratory and neuromuscular fitness and the severity of self-reported fatigue in a representative sample of AAV patients in disease remission compared with healthy control subjects. In addition we have investigated the participants' perception of effort during exercise testing and their ability to voluntarily contract and maintain contraction in their quadriceps muscles as a measure of central factors associated with fatigue.

Subjects and Methods

Subjects: Patients meeting the European Medicines Agency (EMA) vasculitis classification algorithm(16) for AAV were recruited consecutively from the University Hospitals Birmingham NHS Foundation Trust vasculitis clinic. All patients were in sustained remission (Birmingham Vasculitis Activity Score =0 for >6 months, with stable dose of prednisolone ≤10mg) at the time of the study. Patients with acute illness, significant cardiorespiratory disease, end-stage kidney disease (ESKD), pregnancy or co-morbidities that prevented exercise were excluded from the study. The healthy controls were recruited from friends or relatives of patients, from the wider community through outreach research clinics, or from the hospital. Individuals were included if they were not known to suffer from AAV, chronic kidney disease or from any other major organ disease on questioning. Minor illnesses such as osteoporosis, hypertension or hyperlipidaemia were permissible, provided that there was no known damage to any major organ, and that the illness had not been previously associated with fatigue in the literature. All participants in both groups were screened for eligibility and recruited by one of the authors (AM). Investigations were carried out during an extra visit to the hospital, and although free parking was offered no other compensation was paid to participants.

91 patients with AAV were screened for entry to the study. Of those, 25 were not suitable due to exclusion criteria (7 ESKD, 10 poor mobility, 2 ischaemic heart disease, 2 tracheal stenosis, 4 miscellaneous acute illness) and 18 declined. 75 healthy controls were screened for inclusion; none were ineligible, but 34 declined. Forty eight patients and 41 healthy controls were recruited to the study.

The Birmingham, East, North and Solihull Research Ethics Committee approved the study (REC ref number 09/H1206/113), and written informed consent was obtained from all patients according to the Declaration of Helsinki.

Data Collection: Participants' demographic data, disease duration and characteristics, and duration of prednisolone use and current prednisolone dose were recorded, together with an assessment of disease damage using the vasculitis damage index (VDI; (17)).

***Fatigue, Quality of Life, Anxiety, Depression and Sleep*:** Fatigue was quantified using the Multi-Dimensional Fatigue Inventory (MFI-20)(18), which characterises fatigue into five dimensions (General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Activity and Reduced Motivation), with scores ranging from four (no fatigue) to twenty (maximal fatigue) for each dimension. We used physical fatigue score throughout this study. The SF-36 was used to assess health-related quality of life (HRQOL) and pain (19); this questionnaire comprises eight sections (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional and Mental Health), and raw scores are transformed into a 1-100 scale for each domain, with high scores in each subscale indicating good HRQOL. The Hospital Anxiety and Depression Scale (HADS) was used to generate summary scores for clinically relevant anxiety and depression symptoms, with possible scores ranging from 0-21 for each symptom (20). Sleep quality was assessed with The Pittsburgh Sleep Quality Index (PSQI)(21); seven component scores are summed to yield a Global PSQI Score which ranges from 0 (best possible sleep quality) to 21 (worst possible sleep quality).

***Body composition*:** Body Composition was measured by dual energy x-ray absorptiometry (DEXA; Hologic Discovery A QDR Bone Densitometer, Massachusetts, USA)(22).

***Muscle Strength and Voluntary Activation*:** Quadriceps muscle function was assessed with the subject sitting with the knee flexed at 90^{o} and force measured at the ankle(23). Three to five brief (3 secs) isometric maximal voluntary contractions (MVCs) were performed at one-minute intervals with electrical stimulation immediately before and at the peak of force. Participants could see the force record and received strong verbal encouragement to achieve maximal effort. The extent of voluntary activation was assessed with the twitch interpolation technique(24). An electrical stimulation to the muscle provides an estimate of the force of the muscle contraction if the muscle is fully activated. If a muscle is being voluntarily activated to its fullest possible extent by a participant, then a superimposed electric stimulus will achieve no increase in the force generated by that contraction; the extent of voluntary activation (VMA) can therefore be estimated by the equation 'VMA = [1-(force generated by super-imposed electrical stimulation/force generated by resting electrical stimulation) x100]'. Peak voluntary force and the degree of voluntary activation were recorded, and these variables were further used to calculate the 'true maximum contraction (TMC) force', i.e. the force which that muscle could exert if it were fully activated.

***Muscle Endurance*:** Participants were asked to maintain a quadriceps contraction at 50% of their peak voluntary force for as long as possible. Participants matched the force trace to a target on the computer screen and received verbal encouragement to continue. The end point was either volitional fatigue or when the force fell more than 5% below the target for 5 seconds. The muscles were electrically stimulated before and every 10s during the contraction to monitor the level of voluntary activation using the same principles as previously described. As the motor units of a skeletal muscle exhaust energy stores during a sustained contraction, the brain will normally compensate by recruiting increasing numbers of motor units in order to maintain a constant overall

force.A superimposed electrical stimulus would normally generate no additional force at the point of volitional fatigue therefore any additional force generated by the superimposed electrical stimulus is interpreted as evidence of reduced central volitional activation of the muscle.

Cardiorespiratory Fitness: Participants underwent a 10 minute incremental exercise protocol on a cycle ergometer (Lode, Groningen, the Netherlands), beginning with a 1 minute warm-up at a workload of 10W, followed by 3 periods of three minutes each at 25W, 50W and 75W. Oxygen uptake (VO_2) was recorded continuously with an on-line gas analysis system (MOXUS, AEI Technologies, USA). Maximum oxygen uptake (VO_2max) was estimated by extrapolating the linear relationship between O_2 uptake and heart rate(25) to the estimated age-related heart rate(26) and expressed as ml/min/kg. Oxygen Pulse (O_2Pulse) was determined as the slope of the linear regression of VO_2 against heart rate(27).

Perception of Exertion: During the exercise participants were asked to rate their perception of exertion (RPE) using the Borg 6-20 scale (Borg, 1982) every three minutes, just before the transition to the next work load.

Statistical Analysis

All analyses were carried out using IBM SPSS Statistics 21.0. Categorical data was summarised with percentages, and quantitative data was summarised with median and interquartile range (IQR). Comparisons of results between the groups were assessed using Fisher's exact tests for categorical data and Mann-Whitney tests for quantitative data, and Spearman's rank order correlation was used to assess the strength of associations between variables.

Results

Participant Characteristics and extent of fatigue: Forty eight AAV patients and 41 healthy controls participated in the study. Except for expected clinical features, there were no significant differences between AAV patients and healthy controls (Table 1). AAV patients reported higher levels of physical fatigue compared with healthy controls (Table 1). All fatigue domains of MFI-20 were elevated in AAV patients compared with healthy controls (supplementary figure 1).

There were no significant associations in the AAV patients between MFI-20 physical fatigue and phenotypic disease category, lung or renal involvement, eGFR or Hb, but there was a significant association between MFI-20 physical fatigue and VDI (r_s=0.418, p=0.034).

Body composition: Patients had significantly higher BMI and greater body fat than the controls (Table 2). No evidence was found of muscle wasting in the patients, as lean body mass and lean leg mass were the same as controls. An identical pattern was seen when the data was analysed by sex.

Muscle function: Patients had reduced quadriceps MVC compared to controls (Table 2). This was due to the tendency to reduced voluntary muscle activation in patients compared with controls (Table 2). When the MVC force was corrected for voluntary muscle activation to give the TMC force there was no difference between the two groups. TMC was closely related to the lean leg mass. The ranges of both lean leg mass and strength were the same in the two groups and their muscles functioned equally well in generating force (Fig 1). There was no association of fatigue with vountary activation (r_s=-0.142, p=0.169), MVC (r_s=-0.208, p=0.352) or TMC (r_s=-0.144, p=0.344) in patients with AAV.

During the muscle endurance test, patients sustained a contraction at 50% of their maximum voluntary contraction force for a significantly shorter time than the controls (Table 2). Muscle

activation at the start of the endurance test was not different between the two groups, but at the time of fatigue, voluntary activation was less in the patient group, and thus central fatigue greater (Table 2).

When analysing all study participants together, a strong correlation was seen between MFI-20 physical fatigue and endurance time (r_s=-0.310, p=0.004). However, when the AAV patients were analysed alone these correlations were lost (MFI-20 physical fatigue and endurance time r_s=-0.014, p=0.0.925).

***Cardiorespiratory testing*:** There were no adverse events during the cycle ergometer exercise. Eight females and one male patient stopped the exercise before the final stage, complaining of a combination of dyspnoea and leg pain. Data from four AAV patients were excluded from the analysis due to technical problems.

VO_2max expressed relative to total body mass was lower in the patient group, almost achieving statistical significance (Table 2), but this was largely due to the greater adiposity of the patients, and when VO_2max was expressed relative to lean body mass there was no difference between the groups (Table 2). VO_2max is most often expressed relative to total body mass because it is more difficult to measure lean body mass, but since adipose tissue is not metabolically active during exercise it is physiologically more correct to express oxygen consumption relative to lean body mass. O_2Pulse is another measure of cardiorespiratory fitness which has the advantage that it does not rely on estimated values for maximum heart rate and weight. There were no differences in O_2Pulse between patients and controls (p=0.184; Table 2). There was no association between cardiorespiratory fitness using O_2 pulse and MFI-20 physical fatigue (r_s=0.110, p=0.341)

Subjects were asked to rate their perception of exertion using the Borg scale. Although patients and control subjects finished the exercise at very similar relative work rates, as judged by their heart rates as a percentage of their age predicted maximum, their reported perception of exertion was significantly greater (Fig 3A). To assess whether physical fatigue was related to this increased perception, the Borg score at the end of exercise was expressed as a fraction of the score expected for that heart rate (RPEindex), assuming that a score of 20 would be obtained at maximum heart rate. In the patient group there was a correlation between perception of effort and self-reported physical fatigue on the MFI-20 (Fig 3B). Interestingly, RPEindex also associated with reduced activity (r_s=0.319, p=0.003) and reduced motivation (r_s=-0.451, p<0.001) domains of the SF36 questionnaire.

As previously reported (2), all indices of quality of life, depression, anxiety, pain and sleep disturbance were significantly worse for the patient group than the controls (Table 3). MFI-20 physical fatigue associated with all indices of quality of life as we have previously published (2) (data not shown). Within the patient group there was a strong correlation between MFI-20 physical fatigue and anxiety, depression, pain and sleep quality. In addition, RPE_{index} correlated with anxiety, depression, and sleep quality, although less strongly; the correlation between RPE_{index} and pain was not significant. (Table 4).

Discussion

The present study extends previous observations (2, 3) that fatigue is a major factor determining the quality of life in patients with AAV who are in stable remission. This is the first study that has systematically examined the role of the cardiopulmonary and neuromuscular systems as causes of fatigue in patients with AAV. In this study the patients showed no evidence of deficits in muscle mass or function or of cardiopulmonary fitness. They did however, have an enhanced perception of exertion and reduced ability to sustain a voluntary muscle contraction.

The extent and nature of fatigue experienced by the patients and controls is comparable with that reported in our previous studies and in other diseases where fatigue is common, such as Primary Biliary Cirrhosis and Chronic Fatigue Syndrome(28). Interestingly, this study shows an association between disease damage and fatigue, which differs from our previous study, and may reflect higher levels of disease damage than in the previous study(2).

During the sustained muscle contraction the patients reached the point of volitional fatigue sooner than the control subjects. The superimposed electrical stimulation showed that the two groups were activating their muscles to a similar extent at the start of the contraction but at the point of muscle fatigue patients were voluntarily activating their muscles to a lesser extent than the healthy control subjects. If the loss of force during the sustained contraction was entirely due to peripheral muscle fatigue, it would be expected that superimposed electrical stimulation would not further increase contraction at this point. In fact, additional electrical stimulation showed that voluntary activation at this point was only 68% for the patients and 75% for the control subjects, indicating both groups experienced considerable central fatigue, but that the contribution of central fatigue was significantly greater for the patients. The data showed no differences in lean body mass or lean leg mass between the patients and control subjects, suggesting the corticosteroid treatment had not led to muscle wasting. Across both groups there was a significant association with physical fatigue and endurance time. However this was lost when analysing patients alone suggesting that either the study was underpowered to find such correlations, or that the apparent correlations were simply a reflection of the differences between the two groups.

The perception of effort during the submaximal exercise test, expressed as RPEindex, was significantly greater for patients than controls at the same workload. It has previously been suggested that fatigue maybe due to reduced cardiorespiratory fitness, but in our study VO_2max was not significantly lower in the patient group when corrected for body composition, indicating that the

patient group was no less aerobically fit than the controls. We estimated maximum oxygen uptake by extrapolating to maximum heart rate, calculated from age. It is generally acknowledged that estimating maximum heart rate from age lacks precision and consequently we also report the Oxygen Pulse as a measure of cardiorespiratory function which does not depend on maximum heart rate or body mass. Oxygen Pulse largely reflects stroke volume during exercise(27) and did not differ between the patient and control groups, neither did it correlate with any aspect of fatigue.

This study suggests that the feeling of fatigue experienced by patients with AAV cannot be explained by any deficit in muscle mass or function, or by a lack of cardiopulmonary fitness. Our previous observation of reduced exercise capacity in patients with ANCA-associated vasculitis(4) may be explained by increased perception of exertion, as demonstrated in the present study, which led to early volitional fatigue.

Scores for depression, anxiety, pain and sleep disturbance were all raised in the patient group compared with controls, as has been reported previously (2, 29); all of these measures showed significant correlations with physical fatigue, and all except pain correlated significantly with RPEindex. Our findings of increased perception of effort and reduced voluntary activation of muscles suggest increased central fatigue in patients with AAV, perhaps, in part, due to depression, anxiety, and poor sleep quality. RPEindex associated with reduced activity and motivation supporting this suggestion. Similar findings are reported in other diseases associated with increased fatigue, including fibromyalgia and multiple sclerosis (MS) where there is also evidence of central fatigue (7, 8, 10). Patients with fibromyalgia reach the point of volitional muscle contraction failure more rapidly than healthy controls. Fibromyalgia is associated with hypersensitisation to many stimuli (30) and it has been suggested that these patients may fail to activate endogenous pain inhibitory mechanisms during muscle contraction (31) resulting in central fatigue. Interestingly, patients with AAV exhibit increased pain scores that correlated with fatigue (2), although not with perception of

effort. AAV patients have increased rates of fibromyalgia compared with the general population(29). None of our patients stopped the investigations due to pain in their joints or muscles.

Several limitations of this study require acknowledgement. It is impossible to measure central factors directly, and we have therefore used perception of effort and voluntary muscle activation as surrogate markers. Increased perception of effort and reduced voluntary muscle activation are likely to make physical effort more demanding thus constituting a barrier to physical activity(3, 32). Habitual exercise was only assessed in this study by questionnaire data, and could have been confirmed by the use of accelerometers for a period of time in some or all of the participants. The use of super-imposed electrical stimulus during voluntary isometric muscle contraction (the 'twitch interpolation technique') is a widely used method for assessing voluntary muscle activation, but could possibly have influenced some participants to cease muscle contraction earlier than they would otherwise have done, particularly during the endurance test. The optimum measurement to assess cardio-respiratory fitness is true VO_2max, but the measurement of this involves extreme physical stress and is not safe to measure in this population; the measurements of aerobic fitness made in this study were a necessary compromise. Although of cross-sectional design and relatively small size, the present study is the largest to investigate the complex physiological and central factors associated with fatigue in AAV. This study adds to our understanding of the complexity of fatigue in patients with AAV and is similar to findings in other chronic diseases where fatigue is common. However further studies confirming our results are required.

This raises the question as to how these results should inform the treatment of fatigue in AAV. It is clear that using exercise simply to increase aerobic capacity or muscle strength is unlikely to be effective, since neither differed from healthy controls or contributed to fatigue in this study. It is possible, however, that structured physical activity, along with addressing the individual psychological components, may be beneficial. There is recent evidence showing that both exercise

and cognitive behavioural therapy can help patients with chronic fatigue syndrome(33, 34) and some combination of the two might also be useful in AAV patients. Establishing an integrated care pathway which acknowledges fatigue to be a real and important problem and addresses specific problems such as depression, anxiety and sleep disturbance would be likely to help patients. An example of such a pathway has been reported to provide significant improvements in symptoms of fatigue for patients suffering from primary biliary cirrhosis(35).

Funding

This work was supported by University Hospitals Birmingham Charity (AM 10/2010). The funder had no role in study design, data collection, analysis, interpretation of data, writing the report or the decision to submit the report for publication.

Acknowledgements

The work was carried out at the National Institute for Health Research (NIHR)/Wellcome Trust Birmingham Clinical Research Facility. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR of the Department of Health. All authors have contributed to the study design, data collection, analyses and drafting of the manuscript and agreement of the final version for publication.

Disclosure

None of the authors have any conflicts of interest related to this study. The results presented in this paper have not been published previously in whole or part, except in abstract format.

Author Contributions

research idea and study design, critical analysis of manuscript and approval: all authors; data acquisition: AM; data analysis/interpretation: PN, DJ, MM, AM LH,; statistical analysis: PN, MM AM; supervision or mentorship: LH, JB, DJ. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. LH takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

References

1. Basu N, McClean A, Harper L, Amft EN, Dhaun N, Luqmani RA, et al. The characterisation and determinants of quality of life in ANCA associated vasculitis. Ann Rheum Dis. 2013.
2. Basu N, McClean A, Harper L, Amft EN, Dhaun N, Luqmani RA, et al. Explaining fatigue in ANCA-associated vasculitis. Rheumatology (Oxford). 2013;52(9):1680-5.
3. Herlyn K, Hellmich B, Seo P, Merkel PA**.** Patient-reported outcome assessment in vasculitis may provide important data and a unique perspective. Arthritis Care Res (Hoboken). 2010;62(11):1639-45.
4. Newall C, Schinke S, Savage CO, Hill S, Harper L**.** Impairment of lung function, health status and functional capacity in patients with ANCA-associated vasculitis. Rheumatology. 2005;44:623-8.
5. Hewlett S, Chalder T, Choy E, Cramp F, Davis B, Dures E, et al. Fatigue in rheumatoid arthritis: time for a conceptual model. Rheumatology (Oxford). 2011;50(6):1004-6.
6. Balsamo S, Santos-Neto LD**.** Fatigue in systemic lupus erythematosus: an association with reduced physical fitness. Autoimmun Rev. 2011;10(9):514-8.
7. Andreasen AK, Jakobsen J, Petersen T, Andersen H**.** Fatigued patients with multiple sclerosis have impaired central muscle activation. Mult Scler. 2009;15(7):818-27.
8. Thickbroom GW, Sacco P, Kermode AG, Archer SA, Byrnes ML, Guilfoyle A, et al. Central motor drive and perception of effort during fatigue in multiple sclerosis. J Neurol. 2006;253(8):1048-53.
9. Bachasson D, Guinot M, Wuyam B, Favre-Juvin A, Millet GY, Levy P, et al. Neuromuscular fatigue and exercise capacity in fibromyalgia syndrome. Arthritis Care Res (Hoboken). 2013;65(3):432-40.
10. Bandak E, Amris K, Bliddal H, Danneskiold-Samsoe B, Henriksen M**.** Muscle fatigue in fibromyalgia is in the brain, not in the muscles: a case-control study of perceived versus objective muscle fatigue. Ann Rheum Dis. 2013;72(6):963-6.

11. Jacobsen S, Wildschiodtz G, Danneskiold-Samsoe B**.** Isokinetic and isometric muscle strength combined with transcutaneous electrical muscle stimulation in primary fibromyalgia syndrome. J Rheumatol. 1991;18(9):1390-3.

12. Minetto MA, Lanfranco F, Botter A, Motta G, Mengozzi G, Giordano R, et al. Do muscle fiber conduction slowing and decreased levels of circulating muscle proteins represent sensitive markers of steroid myopathy? A pilot study in Cushing's disease. Eur J Endocrinol;164(6):985-93.

13. Pereira R, Freire de Carvalho J**.** Glucocorticoid-induced myopathy. Joint Bone Spine. 2011;78:41-4.

14. Neil SE, Klika RJ, Garland SJ, McKenzie DC, Campbell KL**.** Cardiorespiratory and neuromuscular deconditioning in fatigued and non-fatigued breast cancer survivors. Support Care Cancer. 2013;21(3):873-81.

15. St Clair Gibson A, Noakes TD**.** Evidence for complex system integration and dynamic neural regulation of skeletal muscle recruitment during exercise in humans. Br J Sports Med. 2004;38(6):797-806.

16. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis. 2007;66(2):222-7.

17. Exley AR, Bacon PA, Luqmani RA, Kitas GD, Gordon C, Savage CO, et al. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum. 1997;40(2):371-80.

18. Smets EM, Garssen B, Bonke B, De Haes JC**.** The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995;39(3):315-25.

19. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993;31(3):247-63.

20. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69-77.

21. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213.

22. Visser M, Fuerst T, Lang T, Salamone L, Harris TB. Validity of fan-beam dual-energy X-ray absorptiometry for measuring fat-free mass and leg muscle mass. Health, Aging, and Body Composition Study--Dual-Energy X-ray Absorptiometry and Body Composition Working Group. J Appl Physiol. 1999;87(4):1513-20.

23. Edwards RH, Hyde S. Methods of measuring muscle strength and fatigue. Physiotherapy. 1977;63(2):51-5.

24. Rutherford OM, Jones DA, Newham DJ. Clinical and experimental application of the percutaneous twitch superimposition technique for the study of human muscle activation. J Neurol Neurosurg Psychiatry. 1986;49(11):1288-91.

25. Astrand PO, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. J Appl Physiol. 1954;7(2):218-21.

26. Gellish RL, Goslin BR, Olson RE, McDonald A, Russi GD, Moudgil VK. Longitudinal modeling of the relationship between age and maximal heart rate. Med Sci Sports Exerc. 2007;39(5):822-9.

27. Whipp BJ, Higgenbotham MB, Cobb FC. Estimating exercise stroke volume from asymptotic oxygen pulse in humans. J Appl Physiol (1985). 1996;81(6):2674-9.

28. Jones DE, Gray JC, Newton J. Perceived fatigue is comparable between different disease groups. Qjm. 2009;102(9):617-24.

29. Hajj-Ali RA, Wilke WS, Calabrese LH, Hoffman GS, Liu X, Bena J, et al. Pilot study to assess the frequency of fibromyalgia, depression, and sleep disorders in patients with granulomatosis with polyangiitis (Wegener's). Arthritis Care Res (Hoboken). 2011;63(6):827-33.

30. Staud R**.** Mechanisms of fibromyalgia pain. CNS Spectr. 2009;14(12 Suppl 16):4-5; discussion 12-4.

31. Lannersten L, Kosek E**.** Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. Pain. 2010;151(1):77-86.

32. Thorpe CT, DeVellis RF, Blalock SJ, Hogan SL, Lewis MA, DeVellis BM**.** Patient perceptions about illness self-management in ANCA-associated small vessel vasculitis. Rheumatology (Oxford). 2008;47(6):881-6.

33. Larun L, Brurberg KG, Odgaard-Jensen J, Price JR**.** Exercise therapy for chronic fatigue syndrome. Cochrane Database Syst Rev. 2015;2:CD003200.

34. White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet. 2011;377(9768):823-36.

35. Jones DE, Sutcliffe K, Pairman J, Wilton K, Newton JL**.** An integrated care pathway improves quality of life in Primary Biliary Cirrhosis. QJM. 2008;101(7):535-43.

Table 1 Characteristics of the study participants.

	AAV	Healthy	p value
N	48	41	-
Age (yrs)	58 (47-65)	58 (49-63)	0.6
Male	26 (54%)	23 (56%)	1.0
White ethnicity	48 (100%)	40 (98%)	0.5
Hb (g/l)	135 (124-146)	140 (131-148)	0.2
MDRD eGFR (ml/min/1.73m^2)	66 (50-78)	82 (74-90)	<0.001
Disease duration (months)	64 (22-98)	N/A	-
VDI	4 (2-5)	N/A	-
Median current prednisolone dose (mg/d)	5 (0-5)	N/A	-
Median duration of prednisolone use (months)	64 (22-98)	N/A	-
GPA	29 (60.4%)	N/A	-

MPA	16 (33.3%)	N/A	-
Renal Involvement	26 (54.2%)	N/A	-
Lung Involvement	17 (35.4%)	N/A	-
> 1 Hr of Sport / Wk	28 (70.0%)	30 (83.3%)	0.172
MFI-20 Physical Fatigue	13 (8-16)	5.5 (4-8)	<0.001

Gender, ethnicity and '> 1 Hr of Sport /Wk' are expressed as number of participants (column percentage of valid data); all other results are expressed as median (Interquartile Range). Abbreviations; Vasculitis Damage Index, VDI; Estimated Glomerular Filtration Rate calculated using Modification of Diet in Renal Disease formula (MDRD eGFR); not applicable N/A.

Table 2. Body composition and functional measures of muscle function and cardiorespiratory fitness in patients and controls

	measure	AAV	Healthy	significance
Body Composition	Lean body mass (kg)	52.4 (42.2-61.9)	51.4 (45.0-59.8)	p=0.979
	fat mass (kg)	25.1 (18.5-35.4)	19.5 (14.5-24.4)	p=0.004
	Body mass index (kg/m2)	28.1 (24.8-32.0)	24.8 (23.6-27.9)	p=0.019
	lean leg mass (Kg)	8.3 (6.7-9.9)	8.8 (7.1-9.8)	p=0.483
isometric strength	MVC (N)	275 (211-337)	322 (240-385)	p=0.050
	activation %	68 (58-81)	76 (67-86)	p=0.074
	TMC (N)	347 (277-441)	395 (315-480)	p=0.315
muscle endurance	initial activation (%)	46 (32-53)	42 (32-52)	p=0.487
	endurance (sec)	70 (50-90)	91 (71-122)	p=0.006
	fatigue activation (%)	68 (58-79)	75 (68-83)	p=0.038
CV fitness	VO2 max (ml/kgBM)	25.1 (21.8-31.8)	30.3 (24.7-35.2)	p=0.056
	VO2 max (ml/kg lean BM)	37.9 (34.1-49.5)	43.4 (38.2-50.5)	p=0.103
	O2 pulse (ml/beat)	17.3 (12.2-24.5)	20.9 (14.3-25.0)	p=0.184

Isometric strength: MVC, maximum voluntary contraction; TMC, True maximum contraction force after correcting MVC for % activation. Muscle endurance: time to hold 50% MVC; Initial Activation, voluntary muscle activation at the start of the contraction, Fatigue activation, voluntary muscle activation at the point of fatigue. CV Fitness: VO_2max, estimated maximum oxygen uptake,

normalised for either total body mass (BM) or lean body mass (LBM). Data given as median (interquartile range).

Table 3 Quality of life, anxiety/depression and sleep disturbance are all worse in AAV patients compared with Healthy controls

	AAV Patients	Healthy Controls	P
Physical functioning	75 (48-93)	100 (90-100)	<0.001
Physical Role Impairment	*25 (0-100)*	100 (100-100)	<0.001
Bodily Pain	*62 (52-84)*	84 (74-100)	<0.001
General Health	50 (25-67)	87 (72-97)	<0.001
Vitality	50 (30-60)	80 (70-85)	<0.001
Social Functioning	88 (56-100)	100 (100-100)	<0.001
Emotional Role Impairment	100 (33-100)	100 (100-100)	<0.001
Mental Health	68 (52-80)	84 (76-88)	0.001
Physical Component Score SF36	42.5 (32.4-50.3)	55.3 (53.0-57.5)	<0.001
Metal Component Score SF36	48.4 (39.2-55.0)	56.3 (54.4-58.4)	<0.001
Anxiety (HADS)	7 (3-9)	3 (1-6)	0.005
Depression (HADS)	5 (2-8)	1 (0-2)	<0.001
Global Sleep Disturbance	7 (4-10)	4 (2-5)	<0.001

Scores for health-related quality of life from the SF-36 questionnaire, depression and anxiety from the HADS questionnaire; sleep disturbance (PSQI) from the Pittsburgh Sleep Quality Index. Data are given as median (Interquartile range)

Abbreviations AAV, ANCA associated vasculitis; PSQI , Pittsburgh Sleep Questionnaire Index; HADS, Hospital Anxiety and Depression Score

Table 4. Physical fatigue and RPE_{index} as a function of psychological variables in patients with ANCA-associated vasculitis.

	Correlation with physical fatigue (r_s)	Correlation with RPEindex (r_s)
Anxiety score	0.32; p<0.001	0.09; p=0.041
Depression score	0.57; p<0.001	0.09; p=0.049
Global PSQI score	0.32; p<0.001	0.11; p=0.026
Pain	0.27; (p<0.001)	0.07; p=0.066

Abbreviation: Global PSQI, Global Sleep Quality Score from the Pittsburgh Sleep Quality Index. Data are from the Patient group only.

Figure Legends

Figure 1. There was no difference in the relationship between lean leg mass and muscle strength when comparing patients and healthy controls (TMC is MVC corrected for activation). Closed symbols and dashed regression line patients, open symbols and solid regression line control subjects. The formula for the Patient group regression line top left, and for the Controls bottom right. p=0.777 for comparison of the slopes, and p=0.681 for comparison of intercepts.

Figure 2

Figure 2A. Perceived exertion as a function of work rate is significantly greater in patients than controls (p=0.006). The Borg scale ratings (RPE) at the end of exercise are shown compared to exercise intensity, expressed as actual heart rate as a percentage of estimated age-related heart rate. Close symbol, patients; open symbol, control. Data given as median and IQR. Figure 2B. Physical fatigue compared to perceived exertion expressed as RPE_{index}, which takes into account the relative workload at which the subjects were working. Data are for the patient group only.

Supplementary

Figure 1: Self-reported fatigue using the Multi Factorial Index (MFI-20) domains. Bars indicate median, boxes indicate the interquartile range and whiskers indicate the range.

Figure 1

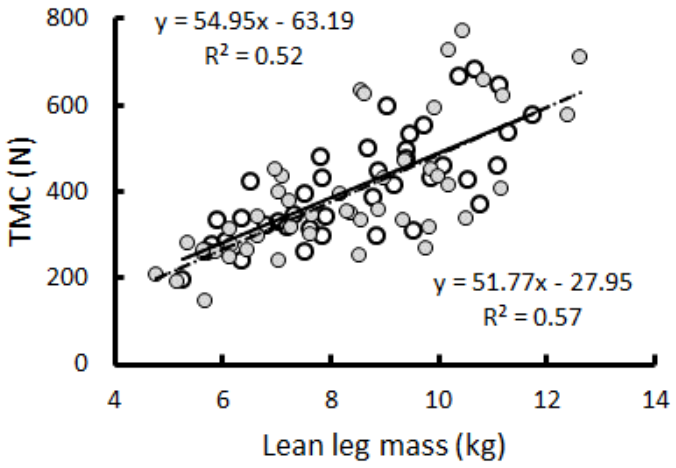
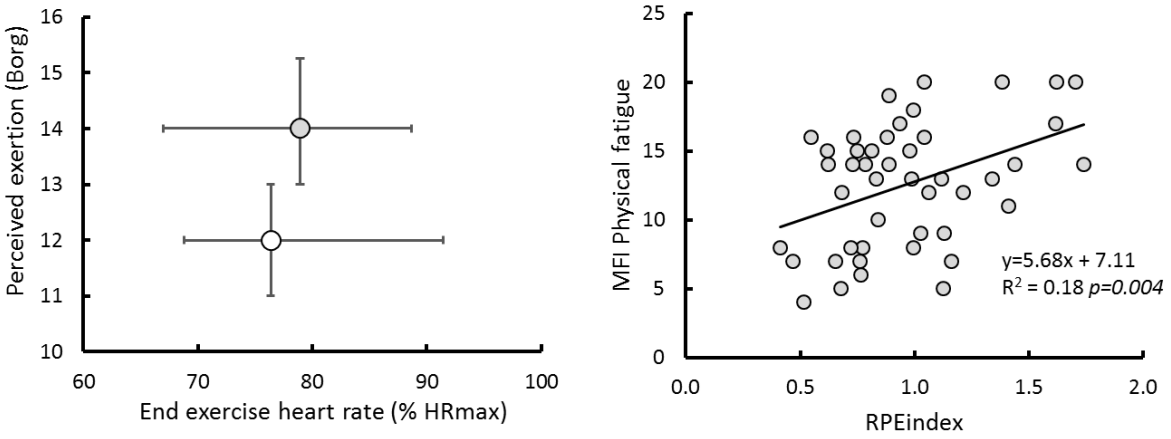

y = 54.95x - 63.19
R² = 0.52
y = 51.77x - 27.95
R² = 0.57
TMC (N)
Lean leg mass (kg)
800
600
400
200
0
4
6
8
10
12
14

Figure 2


Perceived exertion (Borg)
16
15
14
13
12
11
10
60
70
80
90
100
End exercise heart rate (% HRmax)
MFI Physical fatigue
25
20
15
10
5
0
0.0
0.5
1.0
1.5
2.0
RPEindex
y=5.68x + 7.11
R2 = 0.18 p=0.004

Supplementary Figure 1