Br J Sports Med 1999;**33**:352–356

Prediction of peak oxygen uptake in chronic fatigue syndrome

Ricky Mullis, I T Campbell, A J Wearden, R K Morriss, D J Pearson

Abstract

***Objectives*—To establish a simple, valid, and acceptable method of predicting peak oxygen uptake (Vo_{2peak}) in patients with chronic fatigue syndrome (CFS), which could provide a basis for subsequent exercise prescription at an appropriate intensity as part of a clinical rehabilitation programme.**

***Methods*—A total of 130 patients who met UK research criteria for CFS were taken from consecutive referrals for chronic fatigue to the University Department of Medicine at Withington Hospital, Manchester. Vo_{2peak} was determined using an incremental graded exercise test to exhaustion. Respiratory gas exchange, work rate, and heart rate were monitored throughout.**

***Results*—In all patients, Vo_{2peak} was found to correlate strongly and significantly with peak work rate (WR_{peak}) during testing (r^2 = 0.88, p<0.001). In patients who exercised for longer than two minutes (n = 119), regression analysis established the relation as $Vo_{2peak} = 13.1 \times WR_{peak} + 284$, where Vo_2 is given in ml/min and WR in W. The mean error between the measured Vo_{2peak} and the predicted value was 10.7%. The relation between increase in work rate and oxygen uptake across the group was highly significant (r^2 = 0.87, p<0.001), and given as $Vo_{2increase} = 12.0 \times WR_{increase}$, this value being similar to that expected for healthy individuals. Almost all (97%) subjects reported no exacerbation of symptoms after maximal exercise testing.**

***Conclusions*—Using a simple to administer maximal exercise test on a cycle ergometer, it is possible to predict accurately the Vo_{2peak} of a patient with CFS from peak work rate alone. This value can then be used as an aid to setting appropriate exercise intensity for a rehabilitation programme. The increase in Vo_2 per unit increase in workload was consistent with that expected in healthy individuals, suggesting that the physiological response of the patients measured here was not abnormal. Contrary to the belief of many patients, maximal exercise testing to the point of subjective exhaustion proved to be harmless, with no subjects suffering any lasting deterioration in their condition after assessment.**

(*Br J Sports Med* 1999;**33**:352–356)

Keywords: chronic fatigue syndrome; work rate; exercise prescription

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Accepted for publication 3 June 1999

The research criteria produced by Sharpe *et al*[1] describe chronic fatigue syndrome (CFS) as a symptomatically defined illness of definite onset, characterised by fatigue as the principal symptom. The fatigue is severe, disabling, and affects physical and mental functioning, and must have been present for a minimum of six months during which it was evident for more than 50% of the time. Other symptoms may be present, particularly myalgia, arthralgia, and mood and sleep disturbance.[1] Certain patients are excluded from the definition including those with established medical conditions known to produce chronic fatigue.

Investigations into the exercise capacity of CFS sufferers have shown a reduced aerobic work capacity,[2] reduced peak heart rate,[3 4] reduced time to exhaustion on a standardised exercise protocol,[3 5] and higher heart rates at submaximal levels of exertion compared with control subjects.[2] Graded exercise has been recommended as a possible treatment for CFS in a Joint Working Party Report from the Royal Colleges of Physicians, Psychiatrists and General Practitioners.[6] This approach has since been shown to be effective in two independent clinical trials.[7 8]

Any exercise prescription should include specific recommendations for mode of activity, frequency, duration, and most importantly, intensity.[9] The maximal oxygen uptake (Vo_2MAX) of a subject performing gross whole body activity is readily measured in the laboratory by respiratory gas analysis during subjection to gradually increasing workloads to the point of exhaustion.[10] The appropriate training intensity or work rate is then commonly expressed as a percentage of the measured Vo_2MAX, and specific work rates can be prescribed across a variety of common exercise ergometers or modes of activity.

The equipment required to perform respiratory gas analysis and thereby directly measure Vo_2 is rarely available during clinical rehabilitation, although an estimation during either steady state or incremental leg ergometry (cycling) and some other modes of activity (commonly walking or running on a powered treadmill) is possible in normal healthy subjects.[9] Alternatively, the Astrand Rhyming Nomogram[11] provides a simple means of predicting Vo_2MAX from steady state submaximal measures of heart rate and workload, and is widely used within the health and fitness industry. However, the validity of employing an extrapolative technique to obtain a predicted Vo_2MAX is dependent on the assumption that age related predicted maximal heart rate would be achievable during activity. If this is not the case, then any prediction made upon this basis becomes unsound. As has been reported,[3 4] it is evident that many CFS sufferers are unable to achieve age related predicted maximal heart rate during exhaustive exercise. Therefore the application of such predictive techniques is inappropriate within this patient group, and may even be counterproductive if then used as a basis for exercise prescription.

A simple and practical means of predicting Vo_2 in patients with CFS has yet to be described. The aim of this work was to establish a valid and acceptable clinical method of assessing exercise capacity and predicting peak oxygen uptake (Vo_{2peak}) in such patients. This technique would then provide a means of prescribing exercise intensity across a variety of different modes of activity, based upon a predefined percentage of the estimated Vo_{2peak}.

Methods

PATIENT SELECTION

South Manchester Health Authority research ethics committee approval was obtained (Ref:CM/92/048). Subjects were 136 patients who met operational criteria for CFS[1] and who were taking part in a treatment trial for chronic fatigue at the University Department of Medicine at Withington Hospital, Manchester. Inclusion and exclusion criteria for the treatment trial are described elsewhere.[8] Informed written and verbal consent was obtained from patients before their entry into the trial.

EXERCISE TEST PROTOCOL

A graded incremental cycle ergometer test was used by all of the patients reported on here, although an alternative treadmill or step test was offered as an option. Patients were familiarised with the protocol and the equipment to be used. The Bosch ERG 551 electromagnetically braked cycle ergometer (calibrated by the Department of Medical Physics at Manchester University) was set to the appropriate seat height (knee in 5–10° of flexion at the lowest point). Patients were then given the opportunity to pedal against no resistance and with a mouthpiece and noseclip in place, until they felt comfortable with the procedure. They were then instructed to pedal for as long as possible at a constant 60 rpm. The baseline work rate was 20 W. This was increased every 60 seconds by a further 20 W, as recommended by Davis *et al*[12] for people suspected of having poor exercise capacity. Verbal cues detailing the length of time until completion of the next full minute were provided. This continued until volitional exhaustion or symptom limited maximum was reached, whereupon the test was stopped. WR_{peak} was defined as the highest work rate (in W) that the patient was able to sustain for a full minute during testing—that is, the work rate during the last full minute completed by the patient.

Heart rate was monitored throughout the assessment using a PE 3000 Sport Tester with remote receiver (Polar Electro Oy, Kempele, Finland), the accuracy of which has been verified by Seaward *et al*.[13]

Subjects breathed through a one way valve system which was attached to a 6V Fleisch pneumotachograph. This was calibrated using a 3 litre calibration syringe. A gas sample line was connected to a P K Morgan gas analyser (P K Morgan Ltd, Chatham, Kent, UK). This system uses a paramagnetic oxygen analyser which was calibrated to span between 15 and 21% using certified reference gases from CryoService Ltd, Worcester, UK. The infrared carbon dioxide analyser was calibrated to span between 0 and 4%. Calibration was performed each day before testing and between patients. Interface to a Dabs Press microprocessor allowed minute by minute monitoring of respiratory variables including oxygen consumption (Vo_2), carbon dioxide production (Vco_2), and minute volume. The Vo_{2peak} was taken as the highest recorded 60 second average during the course of the exercise test.

Immediately after cessation of the test, patients were asked to rate on the Borg RPE scale[14] their own perception of their overall exertion at the end of the test. Patients had to position themselves on a scale with values ranging from 6 (marked "No exertion at all") at one end to 20 (marked "Maximal exertion") at the other. At a subsequent appointment one week later, they were asked specifically if they had experienced any adverse after effects following testing, including excess fatigue or additional pain.

STATISTICAL ANALYSIS

This was carried out using SPSS for Windows (release 8.0). A Pearson correlation coefficient was calculated to establish the strength of the association between Vo_{2peak} and WR_{peak}. Linear regression was used to determine the relation between variables. Statistical significance was set at $p<0.05$ (two tailed).

Results

Of the 136 patients who were initially screened and found to be eligible to undergo testing, four dropped out during the initial assessment before all physiological measures were taken and two patients chose to do a step test for their exercise assessment. This left 130 patients who

Table 1 Summary of demographic details and selected physiological variables after exhaustive cycle ergometer exercise in 130 patients with chronic fatigue syndrome

Demographic detail/variable	*Value*
Sex	94F/36M
Age (years)	38.9 (10.7)
Weight (kg)	69.6 (14.8)
Illness duration (months)	37.9 (28.7)
Resting Vo_2 (ml/min)	343 (327 to 360)
Vo_{2peak} (litres/min)	1.612 (1.494 to 1.730)
Peak work rate (W)	101 (92 to 109)
Test duration (min)	5.1 (4.6 to 5.5)
Peak heart rate (bpm)	140 (136 to 144)
% Predicted max heart rate	77 (74 to 79)
Peak RER	0.95 (0.93 to 0.97)
RPE	17 (15 to 18)

Values are mean (SD) or mean (95% confidence interval) as applicable. Subjects were seated erect on cycle ergometer to measure resting Vo_2. Predicted max heart rate was calculated as $(210-0.65)\times$age.[11] RER, respiratory exchange ratio (Vco_2/Vo_2); RPE, rating of perceived exertion (median (interquartile range)).

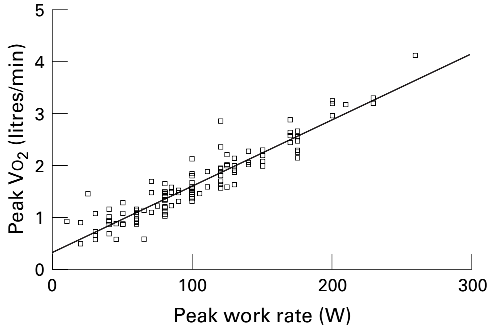

Figure 1 Scatterplot showing peak work rate against peak oxygen uptake.

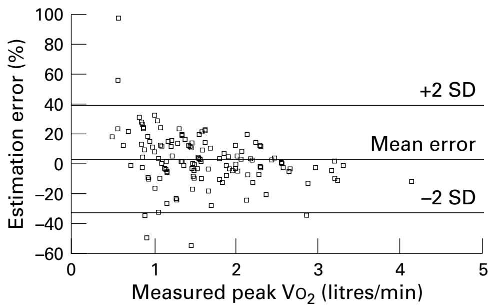

Figure 2 Scatterplot showing peak oxygen uptake against estimation error.

completed the cycling protocol. Table 1 gives a summary of demographic details and data obtained from physiological testing.

Figure 1 shows that Vo_{2peak} and WR_{peak} correlated strongly and significantly ($r^2 = 0.88$, F = 930, Df = 129, $p<0.001$). Linear regression analysis determined the line of best fit to be defined as:

$Vo_{2peak} = 12.73 \times WR_{peak} + 332$

where Vo_{2peak} is in ml/min and WR_{peak} is given in W.

The percentage error encountered when comparing the actual measured Vo_{2peak} with the predicted value (using the regression derived equation) was calculated. These residuals were then plotted against the measured values (fig 2).

In 104 cases out of 130 (80%), the error in the prediction was less than 20% when compared with the measured Vo_{2peak}. The error was less than 35% in 126 cases (97%). It can be seen that in four cases, the error of the predicted value when compared with the measured value was greater than 35%. There were 11 patients who failed to exercise for more than two minutes, and this subgroup included all four cases with high error values. In those patients who exercised for more than two minutes (n = 119), the mean (SD) error between the predicted and measured values was only 10.7 (8.9)%. Figure 3 shows the error plot for all patients who exercised for longer than two minutes.

A linear regression analysis on this subgroup of 119 patients (details given in table 2) determined the corrected line of best fit to be defined as: $Vo_{2peak} = 13.1 \times WR_{peak} + 284$

Vo_2 during exercise may be divided into two separate components: the basal metabolic requirement (resting Vo_2) and the additional

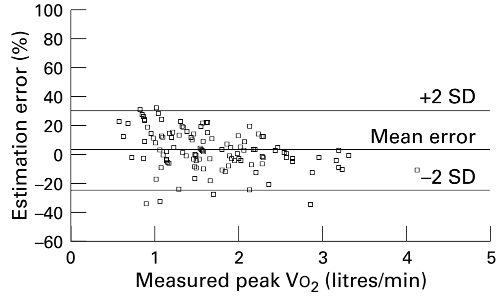

Figure 3 Scatterplot showing peak oxygen uptake against estimation error (test time longer than two minutes).

Table 2 Regression coefficients taking peak oxygen uptake as the predicted variable for patients who exercised >two minutes (n = 119)

	Coefficient	*SE*	*95% CI*
WR_{peak}	13.10	0.42	12.27 to 13.93
Constant	284	48.74	187 to 380

WR_{peak}, peak work rate.

oxygen cost of the actual work involved. The concept of Vo_2 reserve (the additional oxygen utilisation capacity above and beyond basal metabolic requirements) has recently been recommended as a means of describing potential for exercise performance.[9] The slope of the Vo_2 to work rate relation in healthy subjects has previously been reported.[9 15] When resting Vo_2 was subtracted from Vo_{2peak} and the same analysis undertaken, a strong and significant correlation was obtained ($r^2 = 0.87$, F = 845, Df = 129, $p<0.001$). The gradient of the regression line defining increase in Vo_2 (ml/min) against increase in work rate (W) was 12.00 (95% confidence interval 11.18 to 12.82)—that is, $Vo_2 \times 12.00 \times WR$.

When questioned in the clinic one week after the exercise test, 126/130 patients (97%) stated that they had not been aware of any relapse in their condition. Two patients said that they had experienced leg pain (one for four days, one for seven days), which they felt was due to the exercise protocol. A further two patients experienced an increase in general tiredness, which they attributed as much to the stress of their lengthy journey to the hospital clinic as to the exercise test.

Discussion

The main findings of this study suggest that CFS sufferers can safely undergo maximal exercise testing on a cycle ergometer, and that the work rate/oxygen uptake relation is sufficiently strong to allow prediction of Vo_{2peak} from WR_{peak} alone. However, a cautious approach should be taken where patients are unable to exercise for more than two minutes. In four out of the 11 cases where this occurred in this trial, the predicted Vo_{2peak} was subject to an error of greater than 35%. Where the exercise test lasted for more than 2 minutes, the error in the prediction was always less than 35% and the mean difference was reduced to 10.7%.

The physiological measurements taken in this trial showed a similar pattern of intolerance to exercise by patients with CFS to that observed by other workers.[2–4 16] Peak heart rate attained during exhaustive exercise reached a mean of only 77% of age related predicted maximum.[11] This confirms the findings of Montague *et al*[3] and Gibson *et al*[4] both of whom used a similar cycle ergometer protocol to that used in this study. The onset of disabling exhaustion coincided with a mean peak respiratory exchange ratio ($V\text{CO}_2/V\text{O}_2$) of only 0.95, suggesting that patients were suffering the feeling of gross fatigue before the onset of a significant level of anaerobiosis had occurred. Combined, these findings suggest that oxygen transport was not the limiting factor to exercise performance in this trial group, further supporting the argument that extrapolative methods of predicting $V\text{O}_{2\text{peak}}$ are inappropriate for patients with CFS.

Many patients initially expressed a concern that excessive activity would be detrimental to their condition. However, the patients' own perception of the level of effort that they had exerted during testing equated to "Very Hard" on the Borg scale (a median score of 17). This would suggest that many were at least partially prepared to put aside any predetermined convictions they may have had about the negative effect of higher levels of activity. It is also known that leg fatigue is commonly cited as the cause of test cessation in cycle ergometry.[17] It is still possible that these factors may have influenced the amount of exercise induced discomfort that patients were prepared to tolerate, before fear of a subsequent exacerbation of their symptoms caused them to discontinue cycling.

The protocol described here requires maximal effort from the patient (exhaustive or symptom limited), and therefore does not rely upon extrapolation to obtain a theoretical age related predicted value. The strong relation shown ($r^2 = 0.88$) provides a means of predicting $V\text{O}_{2\text{peak}}$ from WR_{peak} alone. In clinical rehabilitation, where direct measurement of expired gas content is rarely an option, the therapist can obtain a close estimate of $V\text{O}_{2\text{peak}}$ of a patient with CFS by following the simple method described above, armed solely with an accurately calibrated cycle ergometer. The value calculated, as well as providing an additional outcome measure, can serve as a basis for the prescription of rehabilitation exercise. Patients can be instructed to work at a specified percentage of their estimated $V\text{O}_{2\text{peak}}$[7 8] from work rate guidelines based upon the known oxygen cost of standard modes of activity.[9 11 17 18] The estimate of absolute $V\text{O}_{2\text{peak}}$ (ml/min) can readily be converted into a bodyweight specific value (ml/kg/min) if appropriate—that is, for prescribing intensity in weightbearing activities. Although it is known that $V\text{O}_{2\text{peak}}$ can vary depending on the exercise modality used, this method has been succesfully employed in the prescription of both walking and overland cycling exercise for CFS suffferers.[8]

The $V\text{O}_2$ reserve (the additional oxygen utilisation capacity above and beyond basal metabolic requirements) has recently been recommended as a means of describing potential for exercise performance.[9] Subtraction of the resting $V\text{O}_2$ value from the $V\text{O}_{2\text{peak}}$ provides a measure of the extra oxygen demand attributable to the work rate alone. Across the group, the increase in $V\text{O}_2$ for each 100 W increase in workload was 1200 ml/min. This value is consistent with that given in the ACSM guidelines for healthy individuals,[9] although higher than other reported data.[15] This would suggest that the physiological response to increasing work rate of the patients measured here was not abnormal (at least up until the point that symptom limited maximum was reached).

A cycle ergometer protocol was chosen for two reasons in this study, despite the potentially confounding issue of localised leg muscle fatigue which can occur with this mode of activity. Firstly, a reliable measurement of work rate is more easily obtained than with other modes of activity, because the resistance to pedalling is easily controlled and the effect of body weight is largely negated when seated. Secondly, unpublished pilot work showed that CFS sufferers are often unpredictable in their fatigue onset and prone to sudden exhaustion, making the use of a motorised treadmill for exhaustive testing potentially more hazardous. However, other studies[2 7] have successfully used a treadmill protocol with patients with CFS.

Many patients initially expressed a fear that excessive activity would be detrimental to their condition. Contrary to this belief, maximal exercise testing to subjective exhaustion proved to be harmless, with no subjects suffering any lasting deterioration in their condition after assessment. It also provided a sound basis upon which exercise of an appropriate intensity could be prescribed as part of an individual rehabilitation programme.

This work was funded by a grant from the Linbury Trust. Contributors: R M (guarantor) designed the testing protocol, formulated the primary aim of the study, participated in the data collection, analysis and writing of the paper. I C discussed core ideas, assisted in the formulation of the primary aim of the study, the data collection, and writing of the paper. A W discussed core ideas, assisted in the data collection and analysis, and substantially contributed to the writing of the paper. R M assisted in the selection of the patients who took part in the study, data collection, and contributed to the writing of the paper. D P was a principle investigator in the University of Manchester chronic fatigue syndrome study, initiated the research, participated in the original design of the study, and contributed to the paper.

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Take home message

Prediction of peak oxygen uptake for the prescription of exercise at an appropriate intensity for chronic fatigue syndrome sufferers can be achieved within the clinical environment by following the protocol outlined above, and requires no more than an accurately calibrated cycle ergometer.