

## RELIABILITY OF INDICES OF NEUROMUSCULAR LEG PERFORMANCE IN END-STAGE RENAL FAILURE

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The purpose of this study was to examine the day-to-day reproducibility and single measurement reliability of peak force, time to half peak force and rate of force development indices of knee extension neuromuscular performance in patients with end-stage renal failure. Eleven self-selected patients (6 men, 5 women) receiving maintenance dialysis (dialysis history  $67 \pm 42.8$  month) completed 3 inter-day assessment sessions. Each comprised a standardized warm-up and 3 intermittent static maximal voluntary actions of the knee extensors of the preferred limb ( $45^\circ$  knee flexion angle [ $0^\circ$  = full knee extension]) using a specially-constructed dynamometer. Repeated measures ANOVA of coefficient of variation scores revealed significant differences between indices in their reproducibility across day-to-day trials. *Post-hoc* comparisons of group mean scores suggested that peak force ( $6.6 \pm 3.0\%$ ) offers significantly greater measurement reproducibility than time to half peak force ( $16.8 \pm 9.5\%$ ) or rate of force development ( $20.3 \pm 12.1\%$ ). Intraclass correlation coefficients and standard error of measurement scores showed that single-trial assessments of peak force, time to half peak force and rate of force development would demonstrate limited precision and capability to discriminate subtle intra-subject or inter-subject changes in neuromuscular performance.

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### INTRODUCTION

The term “uraemic myopathy” is frequently used to describe a collection of symptoms, clinical findings and muscle pathology associated with chronic renal failure (CRF) and end-stage renal failure (ESRF) such as tiredness, ease of fatigability and impaired physical functioning (1). In addition, the muscle wasting consequent on malnutrition in these patients is associated both with weakness and with impaired aerobic power (2). Most previous studies investigating the physical function of patients with ESRF have almost exclusively focused on peak aerobic power ( $VO_{2peak}$ ) as the key index of exercise tolerance

(3) with no real consideration given to the capacity of the patient to accommodate functional stresses more characteristic of the demands of daily living. Indeed, it has recently been reported that reliance on  $VO_{2peak}$  alone to characterize exercise tolerance would lead to an significant underestimation of the prevailing degree of physical dysfunction in patients with ESRF (4).

Although many activities of daily living require muscle forces and associated joint torques which would be expected to be within the capability of patients with CRF and ESRF (5), it is probable that neuromuscular performance expressed in terms of absolute strength alone may also inadequately describe the prevailing degree of physical dysfunction. For example there is evidence to suggest that available rate of force development rather than absolute strength is critical to successful restoration of perturbed balance (6). In addition, the identification of a pre-clinical or subclinical level of disability that is characterized by the development of a mild functional limitation may be important since impairment in this pre-clinical status may indicate high risk of subsequent overt disability (7, 8).

Physical inactivity may contribute to the pathogenesis of physical dysfunction and myopathy in renal failure (1, 3, 9). In previous cross-sectional and prospective research, relatively small decreases in physical performance have been associated with a high prevalence of dependence in activities of daily living (ADL) (10, 11). Loss of strength performance (12) and impaired walking performance has been associated with ESRF (13).

The literature documents an importance of lower extremity function to selected ADL as measured by tests of performance such as chair rise time, gait and balance (11). The latter assessments are dependent on aspects of neuromuscular and musculoskeletal function. The measurement of the physiological functions underpinning the latter performance tests may serve as an important proxy for subtle but important impairments to real or perceived normal function and cascade of sequelae towards disability and loss of social independence.

The fundamental purpose of an index of leg muscle neuromuscular function is to provide a reliable estimate of performance capacity. Within a given measurement setting, suitable reliability characteristics should ensure that the index is sensitive to small changes in performance capacity (14). The practicality of achieving such levels of reliability may be described as measurement utility (15). Discrimination of subtle levels of muscle dysfunction and/or insufficiency in this clinical

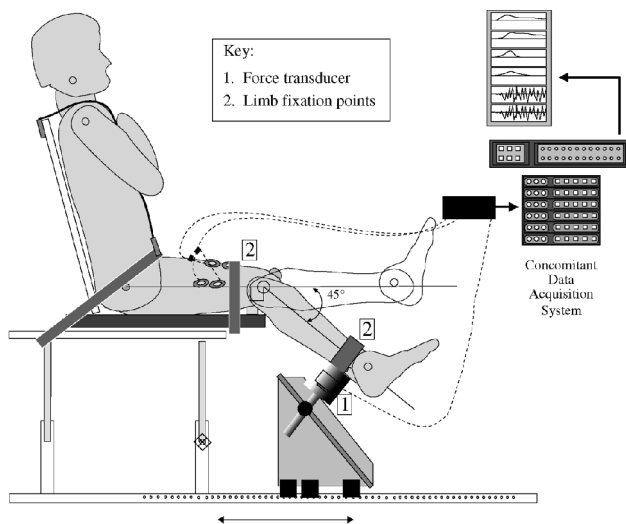


Fig. 1. Participant and dynamometer orientation.

setting may facilitate the proper diagnosis of impending impairment at an early stage, identify elements which are critical to those impairments and optimize physical therapies to focus on the critical elements.

There is a high degree of heterogeneity of physical functioning in patients with CRF and ESRF on dialysis related to differences in the illness, co-existent cardiovascular disease, age, physical inactivity, nutritional status and the degree of anaemia. The interactions of these factors associated with ESRF and CRF, variability in disease severity, both within and between diseases, and anthropometric and physiological differences would be expected to influence the level of physiological impairment, physical performance and ultimately, the degree of disability (16, 17). Furthermore, such factors may result in heterogeneous and idiosyncratic responses to neuromuscular assessments and to the effects of training interventions.

No studies have investigated either the time-course of accommodation to optimum neuromuscular performance in patients with ESRF or the number of day-to-day trials necessary to attain a level of parameter stability and reliability commensurate with a given assessment setting. Inter-day variability in neuromuscular performance has been reported to be greater than intra-day variability (18–20). This suggests that the calculation of reliability based solely on intra-day measures may be an overestimate that fails to account fully for the biological variability inherent in leg strength test performance. The primary purpose of this study was to examine the day-to-day reproducibility and single measurement reliability of peak force (PF), time to half peak force (T1/2) and rate of force development (RFD) indices of knee extension neuromuscular performance in ESRF patients. A subsidiary aim of this study was to investigate the accommodation response of neuromuscular performance to testing.

## METHODS

### Participants

Following approval by the local Scientific Merit and Ethical committees volunteers were solicited from the maintenance haemodialysis patient population of a large renal unit (a population of 102 patients) to participate in the study. Patients with evidence of recent myocardial infarction (within 6 weeks), uncontrolled arrhythmias, uncontrolled hypertension, unstable angina, symptomatic left ventricular dysfunction, uncontrollable diabetes and neurological disorder with functional deficit were excluded from participating. Study participants were recruited from those patients regularly receiving dialysis treatment in the morning (~08.00–12.00 h; a total of 34 patients, 25 of whom were eligible to participate). Eleven self-selected patients (6 men, 5 women; [mean  $\pm$  SD], age  $51.5 \pm 13.8$  years, range 33–79 years; height  $1.64 \pm 0.06$  metres; weight  $69.9 \pm 18.3$  kg) receiving maintenance haemodialysis (dialysis history  $67 \pm 42.8$  months) gave written informed consent to participate in this study.

### Procedures

Following habituation to procedures in which participants had visited the renal rehabilitation gymnasium used for testing and had practised the procedures of assessment, each participant completed 3 assessment sessions at the same time of day ( $\pm 1$  hour), separated by 4 days. All assessments were conducted approximately 1 hour prior to the start of the haemodialysis session and before the consumption of breakfast.

Within each session, participants performed a standardized warm-up consisting of 3 minutes of unloaded exercise on a cycle ergometer and 2 minutes of static stretching of the involved musculature. This was followed by a specific warm-up involving 3 sub-maximal voluntary actions of the knee extensors of the preferred limb (at self-perceived exercise intensities of 50%, 75% and 90% of maximum effort, respectively) after fixing the participant to a specially-constructed dynamometer interfaced to a computerized data acquisition system (Fig. 1). Two further sub-maximal practice trials and a 60-second recovery period preceded the completion of 3 static maximal voluntary actions of the involved musculature by the participant. The 3 static maximal voluntary actions were separated by a recovery period of 120 seconds.

The participant was situated in an upright seated position on the dynamometer with the knee flexed passively to 45° (0° = full knee extension). The lower leg was supported at a position 0.1 metres proximal to the lateral malleolus by a rigid adjustable system. The latter system incorporated a load cell (RDP Electronics Ltd, Wolverhampton, UK; range 0–1000 N) interfaced to a voltage signal recording system that provided analogue to digital conversion of muscle force (Cambridge Electronic Design Ltd, UK; 1902 medically isolated programmable amplifier/filter [zero amplification; no filtering]; 1401plus laboratory I/O interface [12-bit ADC; sampling at 4 kHz]). Participants were seated with the angle between the back and seat of the dynamometer chair set at 120° and the angle between the chair and horizontal frame set at 10° to the horizontal. To localize the action to the proper muscle groups, participants were securely strapped at the hip, waist, chest and shoulders with an additional restraint applied to the thigh proximal to the involved joint. The lever length between the rigid adjustable system at the lateral malleolus and the axis of rotation of the dynamometer was standardized for each participant during the day-to-day trials. The axis of rotation of the dynamometer was aligned midway between the lateral condyle of the tibia and the lateral epicondyle of the femur consistent with the anatomical axis of the knee joint.

### Indices of peak force (PF), time to half peak force (T1/2) and rate of force development (RFD)

After a verbal warning, an auditory signal was delivered to the subject randomly within a 1–4-second period. On receipt of the signal the subject attempted to extend the knee joint as forcefully and rapidly as possible against the immovable restraint offered by the apparatus. After a suitable period of maximal voluntary muscle activation (~3 seconds) to identify PF, another auditory signal was delivered to the subject to cue the conscious withdrawal of muscle activation and associated neuromuscular relaxation by the subject as rapidly as possible. Data was archived to magnetic media for later analysis.

The index of PF was selected as a marker of physiological capability associated with voluntary forceful activation of the knee joint extensors inherent in many activities of daily living. The PF was identified from data records associated with each of the 3 intra-session maximal voluntary muscle actions of the knee extensors using software (Spike2, version, 2.01, Cambridge Electronic Design Ltd, UK) as the highest gravity-corrected force observed during the single muscle activation.

T1/2 and RFD were selected as indices of the rate at which muscle activation can be initiated and the rapidity with which physiologically meaningful levels of force can be mustered. The index of T1/2 was identified as the time interval in milliseconds between the observed development of muscle force (defined as the point in time at which muscle force was observed to first exceed the technical error associated with the electrical noise of the force transducer [99% confidence limits, or  $\pm 1.1$  N]) and the point on the time-history at which 50% PF was observed. The index of RFD was determined as the average rate of force increase associated with the force-time response between 25% and 75% of PF and calculated for each of the 3 intra-session maximal voluntary muscle actions of the knee extensors. The best of the 3 intra-session scores for PF, T1/2 and RFD were used for subsequent statistical analyses.

Potential distractions to the participants were minimized and only 2 investigators were present in the laboratory in addition to the participants during data capture. The same test administrator performed all measurements. Participants were not given feedback of results until after the completion of the prescribed number of day-to-day trials.

#### Gravity moment correction

Compensation procedures for gravitational errors in recorded forces during maximal voluntary muscle actions in the vertical plane were undertaken just prior to testing. Angle-specific torque data generated by the effect of gravity acting on the mass of the involved lower extremity of each participant and the weight of the input accessories at the prescribed knee flexion angles of  $45^\circ$  were recorded with the participant resting passively. These scores were used to correct all subsequent force measurements.

#### Test apparatus calibration

Prior to and repeatedly during testing the technical error performance of the measurement instrument was subjected to a limited validity assessment using inert gravitational loading. Experimentally recorded force transducer responses were compared with those expected during the application of standard known masses through a biologically valid range (0–600 N). Recorded forces demonstrated an overall mean technical error ( $\pm$  standard error of the estimate) of  $0.2 \pm 0.03$  N across a total of 11 calibrations.

#### Statistical analyses

The selected muscle function indices were described using ordinary statistical procedures (mean  $\pm$  SD). Coefficient of variation (V%) corrected for small sample bias (21) was used to assess variability of indices across 3 inter-day trials. V% was calculated according to the expression  $(SD/mean) \cdot (1 + [1/4N])$  where N is the number of trials. Intra-class correlation coefficients ( $R_1$ ) were computed to describe single-measurement reliability. Standard error of a single measurement (SEM%) (95% confidence limits, computed as a percentage of the group mean score) was calculated for each index (22). Absolute scores for PF, T1/2 and RFD across 3 trials were compared using one-way ANOVA with repeated measures (test occasion [time 1, time 2, time 3]). Variability (V%) associated with the neuromuscular performance indices was compared using one-way ANOVA with repeated measures (performance index [PF, T1/2, RFD]). Tukey's honestly significant difference tests were used for *post hoc* comparisons of group mean scores, where appropriate. An *a priori* alpha level of 0.05 was applied in all statistical procedures. The experimental design offered an approximate 0.80 power of avoiding a Type-II error when employing a least detectable difference of 10 N, 10 ms,  $30 \text{ N}\cdot\text{s}^{-1}$  and 2% during comparisons of absolute PF, T1/2, RFD and V% scores, respective (23). All statistical analyses were programmed using SPSS/PC+ (V5.0) software (SPSS Inc., 1992).

## RESULTS

Table I shows group mean changes in absolute scores over 3 day-to-day trials for PF, T1/2 and RFD, respectively. One-way repeated measures ANOVA revealed no significant differences in absolute scores across the 3 trials for the tested indices.

Group mean coefficient of variation (V%) scores associated with PF, T1/2 and RFD and the 3 day-to-day test occasions were  $6.6 \pm 3.0\%$  (mean  $\pm$  SD),  $16.8 \pm 9.5\%$  and  $20.3 \pm 12.1\%$ , respectively. Intra-class correlation coefficients ( $R_1$ ) associated with PF, T1/2 and RFD were 0.99, 0.92 and 0.91, respectively. Corresponding scores for standard error of a single measurement (SEM%: 95% confidence levels, expressed as a percentage of the mean group score) were computed as 9.5%, 30.7% and 42.2%, respectively.

Repeated measures ANOVA of V% scores revealed significant differences between indices in their reproducibility and stability across day-to-day trials ( $F[2,20] = 11.2$ ;  $p < 0.001$ ). Tukey HSD *post-hoc* tests showed that PF ( $6.6 \pm 3.0\%$ ) offers significantly greater measurement reproducibility compared with T1/2 ( $16.8 \pm 9.5\%$ ) or RFD ( $20.3 \pm 12.1\%$ ) ( $p < 0.05$ ).

## DISCUSSION

The statistical equivalence between performance scores for PF, T1/2 and RFD across the 3 day-to-day trials in this study suggest that inter-day changes in performance can be attributed to biological and technological error sources rather than to systematic learning effects. This finding suggests further that the assessment of the number of inter-day trials to achieve stable base-line measures can be made on reproducibility and reliability criteria alone. The accommodation response to neuromuscular testing in this sample of patients with ESRF was achieved rapidly.

The coefficient of variation for PF in this study is similar to that reported during day-to-day assessments of static leg strength (6.9% (24)). This index offers significantly greater measurement reproducibility compared with both T1/2 and RFD ( $p < 0.05$ ). All the latter indices of neuromuscular performance demonstrate a compromised capability to properly discriminate subtle changes in performance during intra-individual comparisons (15). Since T1/2 shows greater stability than RFD across day-to-day assessments, it should be preferred based on this criterion as a general marker of the rate at which physiologically meaningful levels of force can be generated.

The  $R_1$  for PF, T1/2 and RFD exceeds a clinically acceptable reliability coefficient threshold of greater than 0.80 (25). However, overall group mean SEM% scores for these indices, which compensate for potential overestimation of reliability based on  $R_1$  scores alone by taking account of the group heterogeneity, indicate a limited capability to discriminate physiological change or difference based on single-trial assessments associated with intra-group comparisons (15).

No studies have assessed performance capacity scores for T1/2 and RFD in ESRF populations. It would be expected that

Table I. Group mean peak force (PF), time to half peak force (T1/2) and rate of force development (RFD) associated with static knee extensor activity at 45° of knee flexion over 3 trials (mean ± SD)

Test occasion	Time		
	Time 1	Time 2	Time 3
PF (N)	227 ± 108	234 ± 114	217 ± 101
T1/2 (ms)	243 ± 136	237 ± 105	241 ± 109
RFD (N·s <sup>-1</sup> )	718 ± 563	657 ± 585	678 ± 488

observed performance in these indices (Table I) would be markedly inferior to that in normal age-matched populations. This would be congruent with both the observed inferior physiological performance ceiling and potential for peripheral neuropathy (26). It is also noteworthy that results from this study show a significant and relatively large heterogeneity of response on the selected indices of performance (PF, T1/2 and RFD: intra-population V% >30%; F[1,10] >11.0;  $p < 0.005$ ). The PF scores from populations undergoing long-term maintenance dialysis (24, 27) share this characteristic and this may impact considerably on the interpretation of the expected reliability of indices of performance (15, 28).

The overall group mean PF score (226 ± 108 N) was lower than that reported for younger patients (~44 years; 5 men, 2 women) undergoing long-term (55.2 ± 49.2 months) maintenance dialysis (271 ± 102 N [right leg], 296 ± 129 N [left leg]; knee flexion angle 1.05 rad (27)). It was inferior also to the strength performance observed by Fahal et al. (24) in patients who had undergone a similar duration of maintenance dialysis (30.9 ± 22 months; ~42 years; 13 men, 6 women) (330 ± 116 N; knee flexion angle 1.57 rad). While such comparisons are complicated by methodological differences (notably the potential differences in the muscle fibre length), all the latter recorded performance scores are substantively lower than those from normal age-matched populations (~400–640 N; 60–80 years) (24, 29) and suggest a marked inferior volitional strength performance capacity in these patients with ESRF.

There is accumulating evidence that resistance exercise may delay or reverse the disturbance to protein homeostasis and loss of muscle mass in elderly or frail people and may enhance their ability to perform activities of daily living (30–32). The general efficacy of such resistance training interventions to improve neuromuscular performance may be evaluated properly using single-trial performance assessments and appropriate experimental design sensitivity for inter-group comparisons. However, the findings from this study suggest that in many important applications that require high levels of measurement sensitivity, for example during intra-individual comparisons to optimize exercise treatments, it would be imperative to use a mean score of multiple trials as the basis for estimating performance capability in order to reduce measurement error (variability) and to enhance precision. Figure 2 illustrates the potential reduction in measurement error (V% and SEM% [95% confidence limits]) associated with the use of the mean score of multiple trials (1 to 25) for the indices of PF and RFD. Estimated error of the mean score of multiple trials would be expected to vary inversely with the square root of the number of intra-subject replicates, assuming a normal distribution of the replicates (33). Using this criterion, the mean score of 10 and >25 intra-subject replicates would be needed to achieve an arbitrarily acceptable error of better than ±5% (95% confidence limits) for PF and RFD, respectively.

Similarly, the Spearman-Brown prophecy formula (33) used in conjunction with the calculation of SEM% suggests that at least 5 and >25 replicates would be needed to discriminate properly between scores from different individuals with the same level of measurement precision, respectively. Equivalent threshold numbers of trials for T1/2 would be >25 in both measurement scenarios.

These findings raise concern about the effectiveness of even the most reproducible indices of neuromuscular performance to provide sufficient precision and sensitivity to evaluate correctly small changes in physiological capacity in both inter-subject and intra-subject comparisons. Such limitations may be unacceptable when attempting to discriminate subtle but important pre-clinical impairments to patient function that may lead to subsequent disability. They may be unacceptable also in the interpretation the effects of intervention conditioning in a single patient with ESRF or in the effective targeting of limited clinical resources to appropriate recipient patients. Furthermore, these estimates relate to the average group response that does not reflect fully the performance heterogeneity of some patients with ESRF within this sample.

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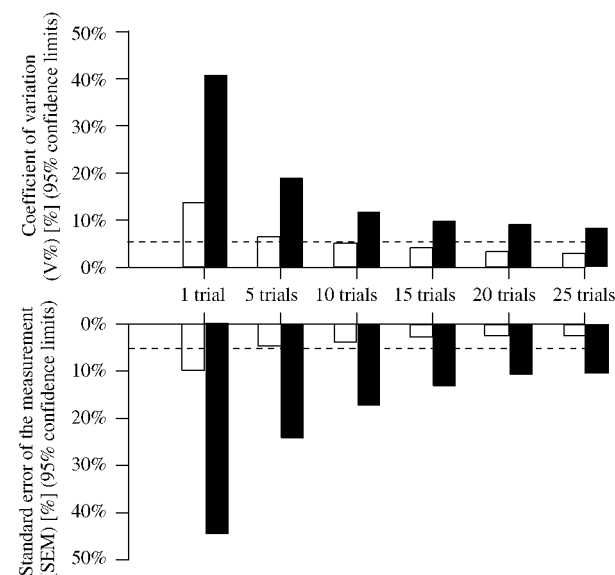


Fig. 2. Error associated with the assessment of peak force (N) [open bars] and rate of force development (N·s<sup>-1</sup>) [closed bars] using 1 to 25 interday trials (coefficient of variation (V%) and standard error of the measurement (SEM) [95% confidence limits]) during static knee extensor activity at 0.78 rad knee flexion. Horizontal dashed lines indicate ±5% error limits.

The measurement sensitivity concerns that have been identified provide a basis from which to question seriously the rationale for the unreserved application of neuromuscular assessments. Having taken due consideration of the likely measurement errors, the trade-off between measurement sensitivity and utility means that in clinical settings such as in the physiological monitoring of the patient with ESRF, the detection of potentially subtle and important differences in neuromuscular performance may be possible only where relatively large differences in performance can be expected.

In conclusion, results do not support the use of PF, T1/2 and RFD unreservedly in the estimation of the true performance capacity given the extent of variability of performance observed over 3 day-to-day trials and corresponding scores for single measurement reliability and standard error of the measurement. For clinical purposes in patients with ESRF, the latter indices must be assessed using multiple inter-day trial protocols to adequately describe neuromuscular performance. In this respect, performance information from T1/2 and RFD may not provide necessary measurement utility. The accommodation response to neuromuscular testing in this sample of patients with ESRF was achieved rapidly.

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