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Exercise Assessment for People with End-stage Renal Failure

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Introduction

Progressive loss of kidney function is often described as chronic kidney disease (CKD). Chronic kidney disease may progress to end stage renal failure (ESRF), at which point the kidneys are not able to perform their regulatory and excretory functions. The transition into end-stage renal failure, with the concomitant derangement of normal biochemical, metabolic and endocrine functions, is almost always accompanied by the clinical syndrome of uraemia. Symptoms such as anorexia, generalised lethargy and fatigue, sleep disorder, neurological dysfunction, nausea and vomiting are frequently evident. The appearance of these symptoms is remarkably consistent and appears to coincide with abnormal plasma levels of many substances including urea, creatinine, phosphate, and parathyroid hormone, which have been identified as potential uraemic toxins. Accompanying clinical signs of ESRF include fluid retention (peripheral and pulmonary oedema), raised blood pressure, diminishing haemoglobin levels and abnormal biochemistry (creatinine, serum urea and potassium) (Bommer 1992, Moore 2000).

The partial or complete loss of kidney function requires that some form of renal replacement therapy be initiated to maintain life. Renal replacement therapy refers to treatments that aim to remove excess fluid and waste products from the body (dialysis or kidney transplantation) and administration of drugs to supplement residual kidney functions, or manage the effects of lack of kidney functions (UK Renal Registry 2002). Haemodialysis (HD) and continuous ambulatory peritoneal dialysis (PD) are the principal dialysis techniques commonly used. The former involves the removal of excess fluid and toxic solutes from the blood through a dialysis machine (artificial kidney). Peritoneal dialysis utilises the peritoneal cavity, and a permanently implanted catheter, as the means by which the exchange of toxic metabolic by products and removal of excess waste is achieved. For details on the differences between dialysis techniques the interested reader may refer to the *Oxford Handbook of Dialysis* (Levy et al, 2004). The guidelines discussed in this chapter refer only to patients undergoing dialysis therapy.

Pathophysiology and Physical Dysfunction in End-stage Renal failure

Kidney disease is associated with multi-systemic dysfunction including abnormalities of the cardiovascular, endocrine-metabolic and musculoskeletal systems, electrolyte and acid base imbalances, neurological, haematological and psychosocial disorders (Moore 2000). Renal failure may result as a consequence of underlying and/or pre-existing conditions such as diabetes, arteriosclerotic renovascular disease, genetic defects or kidney infections. Conversely, established renal failure itself may precipitate the development of co-existing conditions including ischaemic heart disease, peripheral vascular disease and heart failure. This produces a complex pathophysiology for each individual patient with ESRF that will influence the choice of dialysis mode, may reduce the effectiveness of dialysis therapy and ultimately will dictate clinical outcome.

In addition, to the restrictions imposed by the multi-systemic dysfunction and the dialysis treatment itself, patients with ESRF are commonly physical inactive and characterised by limited levels of physical functioning (Deligiannis et al. 1999, Johansen et al. 2000). As a result, patients with ESRF have significantly reduced levels of exercise capacity. Typically, mean VO_2 peak is around 19 ml•kg^{-1}•min^{-1} and ranges from 13 – 28 ml•kg^{-1}•min^{-1}. This corresponds to ~65% of values reported for age, gender and physical activity-matched healthy controls (Moore et al. 1993, Kouidi et al. 1998, Deligiannis et al. 1999, Koufaki et al. 2002). Objective measurement of functional capacity, using reliable and validated tests, reveals an even greater degree of impairment of ESRF patients in relation to activities of daily living. Deficits ranging from 20-120% have been observed, especially in the older dialysis population, indicating that the extent of functional impairment may be greatly underestimated if one relies only on physiological measures of peak exercise capacity (Naish et al. 2000, Painter et al 2000).

Correlates and "predictors" of physical function in ESRF include: sedentary life style, cardiovascular comorbidity, number of additional comorbidities, age, serum albumin, serum creatinine, dialysis dose, nutritional status, muscle atrophy, muscle strength, dialysis age, functional capacity, systemic inflammation (Moore et al. 1993, Johansen et al. 2001, Sietesema et al. 2002, Johansen et al. 2003). Whilst these observations confirm the multi-systemic effects of renal disease they also highlight the difficulties of establishing a single best approach to characterise physical dysfunction in these patients. Nonetheless, it is imperative that any safe and accurate assessment of physical function must be conducted within the context of appropriate risk factor stratification. This must take into account the patient's medical history, the prevailing clinical picture and their life style. The choice of the most informative and feasible method of functional assessment should then be reviewed on an individual basis, bearing in mind that for some patients exercise assessment will be contraindicated (see Table 1).

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Exercise Tolerance assessment

The specific choice and type of protocol for physical function assessment will mainly depend on the primary purpose of the assessment (diagnostic, exercise training prescription, risk stratification etc). The execution of comprehensive physiological exercise testing that includes measures of gas exchange, cardiac function, systemic blood pressure monitoring and patients' subjective responses to general and specific discomfort (Ratings of perceived exertion, angina and breathlessness scales) is considered to be the "gold standard" of exercise capacity assessment for ambulatory patients on dialysis. Measures of VO_2 peak and VO_2 at lactate threshold (LT) obtained during this type of test can be used to:

- Establish physiological impairment and determine prognosis
- Categorise patients to different risk factor groups
- Evaluate the presence and severity of symptoms
- Identify potential life threatening situations
- Determine safe and effective exercise rehabilitation intensities
- Evaluate responses to interventions

It is vital that patients fully understand the procedures, reasons and possible "side effects" associated with all tests and agree to execute them. It is also essential that patients are given adequate opportunity to be habituated to all protocols and equipment. Although all conventional guidelines for the conduct of graded exercise testing of people with chronic disease need to be applied some additional ESRF condition-specific pre-testing considerations are highlighted in table 2. In particular patients should always be tested "on" their usual regime of medication unless indicated otherwise by their physician.

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Peak exercise capacity: The most commonly reported measures of integrated cardiorespiratory exercise capacity in patients with ESRF are peak $VO_{2,}$ peak heart rate, peak power output and time to exhaustion, obtained during incremental treadmill or cycle ergometer protocols (Moore et al. 1993, Deligiannis et al. 1999, Koufaki et al. 2001). The clinical value of peak exercise capacity assessment for patients with ESRF is underscored by a recent report indicating that VO_2 peak (>17.5 $ml{\bullet}kg^{-1}{\bullet}min^{-1}$) was ~~a~~ in fact a stronger predictor of survival than many traditional prognostic variables, some of which are subject to ceiling effects (Seitsema et al, 2004).

Exercise test mode: Cycle ergometers are the most frequently used mode of exercise testing in patients with ESRF. The main advantage of cycle ergometry is that the monitoring of ECG and BP responses are more easily achieved. Moreover, patients with orthopaedic limitations and impaired balance or orthostatic intolerance may feel more confident exercising in a seated position. On the other hand, treadmill-walking protocols more closely mimic activities of daily living that are familiar to patients and may also prevent earlier termination of the test because of localised leg fatigue, a frequently reported cause of patient discomfort and test termination.

Typically, a period of at least 2-3 min of unloaded exercise is required as a warm up, after which small increments of about 10-15 $watts.min^{-1}$ should be applied to ensure that peak performance capacity is reached after a total of 12-15 minutes of exercise. The increase in exercise intensity (or power output) can be applied either in a step or ramp fashion. In contrast, Kouidi (2001) advocates a longer duration protocol for the assessment of peak exercise capacity and has described a peak exercise capacity treadmill assessment protocol (*Nephron* - a modification of the Bruce treadmill protocol) that they have developed successfully used for over 10 years with patients with ESRF. Regardless of the protocol employed careful and continuous monitoring of all physiological responses is essential in order that adverse events be avoided and/or minimised during exercise assessment. Table 3 outlines abnormal responses that would indicate termination of the exercise test. Following the cessation of the peak exercise test patients should be encouraged to complete a gradual, active return to the non-exercising state (of at least 3 minutes duration), during which monitoring of all assessed variables is continued. Patients should remain supervised in the assessment area until all indices of cardiovascular function have stabilised to pre-exercise or resting levels.

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Reproducibility information on exercise tolerance assessment and outcome measures in patients with ESRF is scarce in the literature. The only published study (Koufaki et al. 2001) that has evaluated the reproducibility of peak exercise parameters during incremental cycle ergometry, on a representative sample of contemporary dialysis patients, reported coefficients of variation of 4.7 % for VO_2 peak, 9% for peak power output, 5.9% for peak HR and 13% for exercise test duration. These observations were based on repeated assessments, on non-dialysis days, for a group of maintenance dialysis patients characterised by stable fluid status and resting haemodynamics. There is no published information available regarding the estimation of VO_2 peak values from incremental exercise tests where gas exchange data has not been recorded.

***Submaximal exercise capacity**:* Peak exercise capacity measures provide valuable information on the upper limits of integrated cardio-respiratory physiology. However, that information may not necessarily reflect the ability of patients to perform activities of daily living. Functional independence is also associated with the ability to sustain tasks without experiencing fatigue and this information may be more easily and safely derived from sub-maximal exercise tests (Basset and Howley 2000).

Measurement and/or estimation of lactate threshold (LT) using gas exchange data (GET/VT) during the execution of an incremental test is feasible and exhibits good reproducibility in patients undergoing dialysis. An important pre-test requirement for accurate and reliable measurement of these parameters is that standard clinical chemistry values are within the normal range for dialysis patients (for normal ranges see *Oxford Handbook of Dialysis*, 2004). Indicative CV% for VO_2 at VT, time at VT, power output at VT and HR at VT are 6.6%, 11.7%, 9.7% and 4.9% respectively (Koufaki et al. 2001). The use of sub-maximal indices associated with physiological anchor points, such as VT or LT are also less likely to be influenced by discomfort, tolerance and motivation and therefore may reflect more meaningful physiological changes in follow up studies

An additional sub-maximal index of exercise capacity/tolerance that has been described in patients with ESRF is the rate of adjustment of VO_2 (VO_2–on kinetics) in response to constant load exercise (Koufaki et al. 2002a). The rate at which VO_2 reaches steady state is believed to reflect an integrated physiological ability to meet sudden increased demands of energy production. If the oxygen supply at the beginning of a task is insufficient to meet O_2 demand then there is a delay in reaching steady state and the development of early fatigue is more prominent (Grassi 2000).

In the clinical context constant load exercise tests are usually designed to allow patients to reach a steady state for VO_2 and as a result most tests are conducted at an exercise intensity level below the directly determined LT or GET (VT). The test typically comprises a two minute period of "loadless" cycling followed by a "loaded" exercise period of ~ six minutes with a subsequent "loadless" pedalling recovery period of a further two minutes. Reproducibility data on VO_2 kinetics for patients with ESRF indicate that there is a substantial variability/error associated with this measure based on the average values from 2 transitions performed twice within a week. The reported CV% associated with the mean response time kinetics for exercise intensity corresponding to 90% of GET (VT) was 19.8% (Koufaki et al. 2002b). Non-clinical approaches to this type of assessment advocate the use of several "rest-to-work" transitions (at least 4) to reduce problems with "signal to noise ratio" (and thus intra-subject variability). However, in our experience this is rather impractical with ESRF patients as their fatigue tolerance threshold is very low and in most cases they can only tolerate a maximum of 2-3 transitions in a single assessment day.

Neuromuscular exercise function: Muscle mass and muscle function related measures have been also been implicated in predicting disease progress and survival in patients on dialysis (Diesel et al. 1990, Beddhu et al 2003, Johansen et al. 2003, Sietsema et al.

2004). Accurate and reliable assessment of these parameters is essential therefore for the clinically meaningful interpretation of results.

Muscle function in the dialysis population has been assessed by means of measuring absolute dynamic muscle strength (1, 5 or 10 repetition maximums), peak force, rate of force development, rate of muscle relaxation, during both isokinetic and isometric contractions with or without superimposed electrical stimulation, of nearly all main muscle groups (leg extensors, hamstrings, leg abductors and adductors, dorsiflexors, forearm muscles, back extensors) (Diesel et al. 1990, Kouidi et al 1998, Gleeson et al. 2002, Johansen et al. 2003). Investigators have used a wide variety of assessment protocols involving a range of joint angles and/or limb movement speeds. However, published information regarding the reliability of muscle performance assessment protocols in patients with ESRF is only provided by one research group (Gleeson et al. 2002). Day-to-day variability expressed as CV% for peak force and rate of force development indices during maximal voluntary isometric force production of the knee extensor (45 degrees knee flexion angle [0 degrees = full knee extension]) was found to be 6.6% and 20.3% respectively. Although it is evident from the literature that the application of many muscle performance assessment protocols is feasible in patients with renal failure, extra caution still needs to be applied as these people are more prone to muscle and tendon ruptures in response to sudden changes in forces. As a result, extensive whole body and muscle group-specific warm up exercise and stretches are mandated before the execution of any strength assessment protocols.

Functional Capacity Assessment

Performance based functional capacity assessment is an alternative and/or complementary way to fully describe physical function in patients with ESRF. Recent reports have stressed the observation that functional impairment of patients on dialysis is often underestimated by measures of physiological exercise capacity alone (Naish et al. 2000). Moreover, it has recently been suggested that the utility of established clinical assessments of the nutritional status of patients on dialysis may be enhanced by the inclusion of simple and inexpensive measures of functional capacity, that reflect muscle mass and muscle function (Mercer et al, 2004).

Several investigators have reported patients' functional capacity using the 6 minute walk test, gait speed tests, stair climb and descent, sit to stand tests (STS), and sit and reach test (Mercer et al. 1998, Painter et al. 2000, Johansen et al. 2001, Koufaki et al. 2002a). Although many of these tests have been fully validated in the general rehabilitation and exercise gerontology literature (refer to Aging chapter in this book), information about the validity and reproducibility of these tests in the ESRF population is available only for STS tests and stair climb and descent (Mercer et al, 1998, Koufaki 2001). Therefore, subsequent discussion will be restricted to those functional capacity tests that have been evaluated in the dialysis population.

North Staffordshire Royal Infirmary Walk (NSRI walk): This test is composed of 4 distinctive parts. A walk of 50 metres on flat ground, a stair climb (2 flights; 22 stairs of 15cm height; total elevation 3.3m), a stair descent, and another 50 m walk back to the start point. Total time and split time for constituent elements should be recorded. The patients should be instructed to perform the test as fast as they can. This test has been shown to significantly correlate with VO_2 peak (r = -0.83) with a prediction error of 11% (Mercer et al. 1998) Therefore, it seems to be a very useful overall assessment of functional capacity and in particular the ability to complete ambulatory tasks often required in daily living. Reproducibility analysis has shown that the overall CV% for the NSRI walk is 8.2% and the CV% separately for the stair climb and stair descent is 11.1% and 11.4% respectively (Koufaki 2001)

Sit-to-Stands: These tests involves rising unassisted from a standard height chair (.42 - .46m) and sitting back on the chair as fast as possible. The patients should be instructed to keep their hands crossed over their chest so they don't use them to push themselves up and feet should remain on the ground at all times. The patients should also be instructed to squat over and touch the chair on the sitting down phase and fully extend their knees on the standing up phase. Several variations of the test exist such as STS-5 and STS-10 which is the fastest time (in seconds) at which patients can complete 5 or 10 STS cycles (Painter 2000, Johansen 2001) These tests have been interpreted as indicators of muscle power. The reported CV% for STS-5 based on contemporary dialysis patients is 15%. STS-60, on the other hand, has been used as an indicator of muscular endurance and fatiguability as it requires patients to perform as many STS as they can in 60 seconds. The CV% for this version of STS has been reported to be 12.8% (Koufaki 2001). It is not unusual that some of the patients may need to take resting breaks especially during the STS-60 test. The number of STS-cycles at the exact time of break should be recorded, without stopping the timer. Also the time at which the patients resume the test should be noted.

Summary

Measures of peak exercise tolerance and/or functional capacity have been shown to be related to clinically important outcomes (survival, morbidity and quality of life) in patients receiving dialysis-based renal replacement therapy. Given the prognostic potential of these factors it is recommended that their measurement should form part of the routine assessment (and management) of patients receiving maintenance dialysis therapy. If good practice is followed the available literature suggests that exercise tolerance and functional capacity assessment of the patient with ESRF is both safe and feasible.

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Table 1: Absolute and Relative contraindications to exercise testing in patients with ESRF

ABSOLUTE	*RELATIVE*
• *Hyper/hypokalaemia*	• *History of angina*
• *Excess inter-dialytic weight gain*	• *Resting BP >180/100 or < 100/60mm Hg*
• *Unstable on dialysis treatment and medication regime*	• *Tachyarrhythmias or bradyarrhythmias*
• *Unstable BP*	• *Orthostatic BP drop of >20 mmHg with symptoms*
• *Pulmonary congestion*	• *Resting blood glucose of <5 or > 10 mmol.l^{-1}*
• *Peripheral oedema*	
• *Unstable cardiac condition*	
• *Suspected or known aneurysm*	
• *Uncontrolled diabetes*	
• *Recent cerebrovascular event*	
• *Acute infections*	

- *Patients that present with relative contraindications may be exercise tested only after the risk/benefit ratio has been evaluated and close monitoring of vital signs is in place*

- *The presence of qualified clinical staff is also required.*

Table 2. Special considerations for exercise testing of patients with ESRF

- *Assessments are recommended to be performed on non-dialysis days and preferably not immediately after a weekend for haemodialysis patients, as this will be the longest interval without dialysis*
- *Peritoneal dialysis patients may find it easier to perform tests with their abdominal cavity empty of the dialysing fluid, as this may increase pressure on the diaphragm and result in more symptoms of breathlessness and chest discomfort.*
- *The arm with the arterio-venous fistula should not be used for BP monitoring or strength assessment, as that will give erroneous readings, and may possibly damage the fistula*
- *A complete list of medication regime and doses should be obtained and reviewed before each test to ensure informed decisions in case of adverse medication-exercise interaction effects*

Table 3. Reasons to terminate the exercise test

- *Sustained cardiac arrhythmias*
- *No increases in BP with increasing workload*
- *Evidence of cardiac ischaemia*
- *When BP exceeds 220/110 mmHg*
- *When there is a sudden drop in BP by more than 20mmHg*
- *Symptoms such angina, dizziness, severe breathlessness, lack of responsiveness or cooperation to oral and/or visual signs*
- *Equipment failure*
- *Patient's request*