

A New Trend in Clinical Exercise Physiology – Exercise in End Stage Renal Disease 臨床運動生理新趨勢 – 運動與末期腎病

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Abstract

Research in exercise physiology achieved significant progresses in the past two decades. Clinical exercise physiology is a branch of exercise physiology in its proliferation phase. Research in clinical exercise physiology requires the collaboration between exercise physiologists and physicians, thus imposing newer challenges in this field. The present article will shed light on the potential research issues regarding clinical exercise physiology particularly in the renal area.

摘要

過去的二十年，運動生理的研究有重大的進展。臨床運動生理的研究替運動生理學開拓了新的領域。它需要運動生理學者與臨床醫生的緊密合作，本文嘗試綜合報道運動與腎病在臨床運動生理方面的突破性發展。

Introduction

End stage renal disease (ESRD) was defined by Guyton and Hall (1996) as “an initial insult to the kidney [that] leads to progressive deterioration of kidney function and further loss of nephrons to a point at which the person must be placed on dialysis treatment or transplanted with a functional kidney to survive” (p. 413). Hemodialysis is a process that diverts blood from the patient through a hemodialysis machine in which uremic substances and excess fluid are removed, and electrolyte balance is restored (Hanson, Ward, & Painter, 1986). The patients with ESRD are required to hemodialyze for an average of 4 hr per treatment, 3 days per week (Goldberg, Hagberg, Delmez, Folrman, & Harter, 1979; Hanson et al., 1986). Most ESRD patients are hypertensive and diabetic. They characteristically show elevated serum creatinine, elevated blood urea nitrogen, abnormal hormonal and lipid profiles, and severe anemia (Goldberg et al., 1979; Hanson et al., 1986).

Most patients are physically inactive and suffer from the consequences of sedentary lifestyles (Painter & Zimmerman, 1986). Endurance exercise training is effective in improving exercise tolerance in ESRD patients (Painter & Zimmerman, 1986).

Hemodialysis adequacy and urea kinetics are issues impacting on exercising ESRD patients. In this article, the benefits of exercise on ESRD patients are discussed; secondly and more specifically, the hemodialysis adequacy and urea kinetic issues are addressed. The article has been presented in the following two sections: exercise in end stage renal disease; and hemodialysis adequacy and urea kinetics.

Exercise in End Stage Renal Disease

Exercise tolerance, as measured by maximal oxygen consumption and physical work capacity (PWC) tests, is extremely low in ESRD patients (Hanson et al., 1986; Painter & Zimmerman, 1986). Painter, Messer, Hanson, Zimmerman, and Glass (1986a) reported that the mean maximal oxygen consumption of ESRD patients was only 63% of age-predicted sedentary normal values. Barnea et al. (1980) indicated that PWC in 22 ESRD patients was only 51% of normal. Zabetakis et al. (1982) revealed that ventilatory threshold in patients with ESRD occurred at 40% of maximal oxygen consumption, and suggested that early onset of anaerobic metabolism and elevated lactate production resulted in early muscle fatigue.

Shalom, Blumenthal, Williams, McMurray, and Dennis (1984) indicated that age-predicted maximal heart rates could not be achieved in ESRD patients due possibly to a decreased adrenergic stimulation sensitivity. The ESRD patients therefore showed a lower heart rate at a given oxygen consumption when compared with normal healthy people (Shalom et al., 1984). Painter and Zimmerman (1986) claimed that conditions limiting exercise tolerance in ESRD patients was multisystemic; including anemia, abnormal peripheral metabolism, abnormal hormonal control, ventricular dysfunction, and physical deconditioning.

To improve exercise tolerance, endurance exercise training is an effective therapeutic modality (Harter & Goldberg, 1985). Effects of exercise after hemodialysis (off-dialysis exercise) and during hemodialysis (on-dialysis/intradialytic exercise) have been extensively studied and are described in the following two subsections: off-dialysis exercise training and intradialytic (on-dialysis) exercise training.

Off-dialysis Exercise Training

Research in the early 1980s primarily focused on exercise training after hemodialysis treatment (off-dialysis training). Most studies used walking, jogging, or stationary cycling, two to three days per week, at intensities 60% to 80% of maximal oxygen consumption for 20 to 50 min. ESRD patients on off-dialysis training increased maximal oxygen consumption by 22% to 42% over a period of 10 weeks to 12 months in off-dialysis training studies (Goldberg et al., 1983; Shalom et al., 1984; Zabetakis et al., 1982).

Accompanying increases in exercise tolerance, other clinical benefits of exercise training included decreased triglycerides, increased high density lipoprotein (HDL) concentrations, improved glucose tolerance, increased hemoglobin and hematocrit counts, and improved blood pressure control with a reduction or discontinuation of antihypertensive medication (Goldberg et al., 1983; Hagberg et al., 1983). However, low compliance to off-dialysis exercise training is a problem. Time commitments to hemodialysis treatment in addition to exercise training imposed serious psychological burdens to patients, who were characterized with depression and anxiety (Painter & Zimmerman, 1986). Shalom et al. (1984) stated that only 14 of 50 patients were medically able to participate in exercise training and only 7 patients attended more than 50% of exercise sessions.

Intradialytic (On-dialysis) Exercise Training

Recently, exercise during hemodialysis treatment (intradialytic/on-dialysis training) has been found to be feasible and safe for

ESRD patients. Painter et al. (1986b) indicated a high compliance rate of 91% in a 6-month intradialytic exercise training study. A total of 14 patients exercised on a stationary bicycle during hemodialysis for 30 to 45 min at 75% to 80% of their maximal heart rate. The maximal oxygen consumption increased by 23% and blood pressure control was improved. In addition, patients reported positive subjective ratings of higher exercise enjoyment. All patients revealed that they enjoyed the intradialytic exercise program and would recommend it to other patients. Eight of the 14 patients reported that intradialytic exercise positively helped pass time, decreased cramping, and decreased hypotensive episodes (Painter et al., 1986b).

The acute responses to on-dialysis exercise and the physiological effects of exercise on-dialysis versus after-dialysis were studied (Burke, Germain, Braden, & Fitzgibbons, 1984; Burke, Germain, Fitzgibbons, Braden, & Hartzog, 1987). Burke et al. (1984) found that performing exercises during hemodialysis reversed the adverse effects of hemodialysis such as decreased arterial oxygen tension and hypotension. Burke et al. (1987) demonstrated that abnormally high potassium responses to off-dialysis exercise leading to cardiac arrhythmia and sudden death could be prevented when exercise was performed during hemodialysis, suggesting that on-dialysis exercise was safer.

Moore, Painter, Brinker, Stray-Gundersen, and Mitchell (1998) examined the cardiovascular responses to intradialytic exercise in ESRD patients. Patients ($N = 8$) performed stationary cycling exercise for 5 min, at 60% maximal oxygen consumption, at 0, 1, 2, and 3 hr of a hemodialysis treatment. During the first two hours, no unstable cardiovascular effects were observed. At three hours, cardiac output, stroke volume, and mean arterial pressure decreased, and 5 of 8 patients could not exercise. The researchers concluded that exercise should be performed during the first two hours of treatment as patients were more susceptible to cardiovascular instability during the later stage of hemodialysis (Moore et al., 1998).

To briefly conclude, exercise intolerance is a problem in ESRD patients. Significant improvements in exercise tolerance by performing mild endurance exercises have been extensively reported (Goldberg et al., 1983; Shalom et al., 1984; Zabetakis et al., 1982). Intradialytic (on-dialysis) exercise appears to be safer and more practical than off-dialysis exercise with an additional benefit of improving exercise adherence, thus facilitating consistent improvements (Burke et al., 1984; 1987; Painter et al., 1986b). Concerning the timing of intradialytic exercise, exercise performed during the early stage of a hemodialysis treatment seems to be safer in terms of maintaining a stable cardiovascular condition (Moore et al., 1998).

Hemodialysis Adequacy and Urea Kinetics

Hemodialysis adequacy refers to the delivery of adequate and optimal quantity of hemodialysis (Parker, 1994). Since the 1960s, the question of "What is adequate dialysis?" has been a major concern in the nephrology community (Parker, 1994). In the mid-1970s, the National Cooperative Dialysis Study (NCDS) informed the dialyzing community that the quantification of hemodialysis was a fundamental and absolute principle that should be of primary importance in hemodialysis (Lowrie, Laird, Parker, & Sargent, 1981). With further mechanistic analysis of the NCDS data, Gotch and Sargent (1985) developed Kt/V, an index of hemodialysis adequacy. The Kt/V is an expression to quantify the amount or dose of hemodialysis; where K is the urea clearance (ml/min), t is the duration of dialysis (min), and V is the urea distribution volume (the body water volume) (ml) (Gotch & Sargent, 1985).

Kt is the volume of blood cleared of urea (Parker, 1994). V is included to allow normalization among patients of different size (Depner, 1996). Kt divided by V is therefore the fraction of total body water which is cleared of urea during a hemodialysis treatment (Parker, 1994). Simply phrased, Kt is the dose of hemodialysis and Kt/V is therefore the hemodialysis dose normalized to body size (Keshaviah & Star, 1994). Kt/V is a dimensionless number and in effect the fractional urea clearance per hemodialysis (Depner, 1996; Parker, 1994; Tattersall, DeTakats, Chamney, Greenwood, & Farrington, 1996). The dose of hemodialysis (Kt/V) has been shown to be negatively associated with the morbidity and mortality of the ESRD patients (Ikizler & Schulman, 1997). Researchers indicated that the morbidity and mortality rates are high for a Kt/V value between .4 and .8; and the rates decrease significantly when the Kt/V value increases to a range of .9 to 1.5 (Gotch & Sargent, 1985; Keshaviah, 1993; Keshaviah & Collins, 1988; Smye, Dunderdale, Brownridge, & Will, 1994).

Urea kinetic modeling is an approach to address the problem of estimating hemodialysis adequacy (Smye, Lindley, & Will, 1998). The Kt/V, the dose of hemodialysis, can be precisely measured with the aid of the urea kinetic models (Depner, 1996). The following two urea kinetic models are classified and discussed: single-compartment model, and multiple-compartment model.

Single-compartment Model

The single-compartment/one-compartment/single-pool/one-pool model assumes that urea is distributed uniformly in the body in a single well-mixed pool of volume whose concentration is the same as the blood concentration and the postdialysis urea rebound is considered negligible (Depner, 1994, 1996; Keshaviah & Star, 1994; Pedrini, Zereik, & Rasmy, 1988). Postdialysis

urea rebound was defined by Pedrini et al. (1988) as "the rapid increase in end-dialysis urea concentration immediately after the end of dialysis, which greatly exceeds that expected as an effect of urea generation" (p. 817). The mechanism and implication of postdialysis urea rebound are discussed in the following subsection. The Kt/V is derived with the assumption that residual clearance is zero, that no weight change occurs during or between hemodialysis, and that no urea is generated during hemodialysis (Depner, 1994; 1996). Since K and V cannot be easily measured accurately, Kt/V is usually measured directly from pre- and post-dialysis blood urea nitrogen (BUN) concentrations using the following equation: $Kt/V = \ln(\text{pre-BUN}/\text{post-BUN})$. The Kt/V index is therefore the natural logarithm of the ratio of the pre- to postdialysis BUN (Depner, 1996; Keshaviah & Star, 1994; Tattersall et al., 1996).

Owing to the multiple pool nature of the human body and the mass transfer resistance of the biological membranes, rapid solute removal during hemodialysis creates intercompartmental imbalances and the postdialysis urea rebound is an indication of the interpool re-equilibrium (Pedrini et al., 1988; Keshaviah & Star, 1994). The major component of the urea rebound is due to solute transfer between compartments, such as cells, intestinal tract, and regions of the body where there are relatively low blood flows (Pedrini et al., 1988; Tattersall et al., 1996). The mechanism of solute transfer between compartments may be diffusion (across cell membranes) or flow (from poorly-perfused areas into the main circulation) (Pedrini et al., 1988; Tattersall et al., 1996).

Regarding the limitations of the single-compartment model, the assumptions of single pool distribution and an absence of postdialysis urea rebound do not hold true for real hemodialysis (Depner, 1994; 1996). The actual BUN is frequently lower than predicted by the single-compartment model and physicians may prescribe a higher hemodialysis dosage than is required. The single-compartment model overestimates blood urea concentrations during hemodialysis and fails to predict the postdialysis urea rebound following hemodialysis (Depner, 1994; 1996).

Other equations for Kt/V with the effects of residual renal function, urea generation, and ultrafiltration corrected for have been developed (Keshaviah & Star, 1994; Tattersall et al., 1996). A recent comparison of these equations indicated a calculated Kt/V range of 1.04 to 1.52 based on the same pre- and postdialysis BUN measurements (Bosticardo et al., 1993). With this wide range of Kt/V, one has to be careful in comparing Kt/Vs in different studies regarding their assumptions in computing Kt/V. Keshaviah and Star (1994) commented that the use of Kt/V was diminished by the variability in the methods of calculation and underlying assumptions.

Multiple-compartment Model

With increased uses of high efficiency/flux and short duration hemodialysis, solute gradient is susceptible to occur (Depner, 1994; 1996). Formation of gradients where solute concentrations differ among body compartments is termed solute disequilibrium. The slow movement of solute from tissues during hemodialysis creates solute disequilibrium among tissue compartments that dissipate after hemodialysis ceases, thus causing urea rebound over a period of 30 to 60 min after hemodialysis (Depner, 1994; 1996; Pedrini et al., 1988). The postdialysis urea rebound is indicative of disequilibrium induced by the dialytic process between body compartments and represents a re-establishment of equilibrium after hemodialysis as urea diffuses from central pools into the vascular pool because of concentration gradients (Keshaviah & Star, 1994). Daugirdas et al. (1997) claimed that "rebound is due to the non-uniform distribution of urea and other solutes among various body compartments that develops during dialysis and reflects diminished solute removal during dialysis" (p. 1395). Immediately after hemodialysis, the urea concentration rebounds upward as urea continues to be transferred from peripheral body compartments into the arterial circulation (Tattersall et al., 1996). The effect of this internal transfer is to reduce the effective clearance. The rebound takes at least 30 min to complete. Unless the postdialysis sample is taken 30 min after hemodialysis, the Kt/V computed will be overestimated. This overestimation will be relatively greater in short-duration high-efficiency hemodialysis (Tattersall et al., 1996).

The magnitude of solute disequilibrium depends on the diffusibility of the solute, barriers to diffusion, and blood flow to the peripheral compartments (Depner, 1994; 1996). Some researchers (Frost & Kerr, 1977; Gotch, 1989) explained the urea rebound phenomenon as a re-establishment of equilibrium between intra- and extracellular compartments (diffusion-limited disequilibrium); whereas others (Schneditz, Fariyike, Osheroff, & Levin, 1995; Schneditz, Van Stone, & Daugirdas, 1993) suggested the variations of blood flow to various body organs as the cause (flow-limited disequilibrium). The model describing diffusion-limited disequilibrium is termed the intracellular-extracellular model (Depner, 1994; 1996; Pedrini et al., 1988) and the model describing the flow-limited disequilibrium is called the regional blood flow model (Depner, 1994; 1996; Schneditz et al., 1993; 1995).

Regarding the intracellular-extracellular model, urea is assumed to be distributed in two well-mixed compartments identified as intracellular and extracellular compartments, between which urea transport occurs by diffusion (Pedrini et al., 1988; Smye et al., 1998). The two compartments are separated by a resistance to diffusion that limits urea flux (Depner, 1994; 1996). The resistance is represented as the intercompartment mass-transfer-area coefficient

(KC). The magnitude of KC correlates positively with membrane surface area between compartments and negatively with resistance to diffusion (Depner, 1994; 1996). The delayed transfer of urea from intracellular to extracellular compartment is attributed to limited membrane permeability. The assumption of this model is that urea is generated only in the proximal dialyzed compartment (extracellular compartment) whereas the remote compartment (intracellular compartment) has a fixed volume (Depner, 1994; 1996; Frost & Kerr, 1977; Gotch 1989; Schneditz et al., 1992).

In the regional blood flow model, the two-compartment distribution arises from two tissue compartments perfused by either low or high blood flows (Schneditz et al., 1993; 1995). The organ systems with a blood flow to water volume ratio of greater than .2/min are defined as the high flow systems such as kidneys, small organs, heart, brain, portal system, lungs, and blood. The remaining organ systems with a blood flow to water volume ratio of less than .2/min represent the low flow systems such as muscles, bones, skin, and fat (Daugirdas & Schneditz, 1995; Schneditz et al., 1993; 1995).

The high flow systems receive a relatively large proportion of total cardiac output and contain a relatively small proportion of the total body water (Daugirdas & Schneditz, 1995; Schneditz et al., 1993; 1995). At the end of hemodialysis, it is hypothesized that the urea concentration in the low flow system is higher than in the high flow systems, and that flow related equilibration of blood with different urea concentrations between these compartments leads to postdialysis urea rebound (Daugirdas & Schneditz, 1995; Schneditz et al., 1993; 1995). The regional blood flow model addresses the significance of the differential perfusion of different regions and organs of the body relative to their water volume, thereby leading to different urea clearance from these regions and organs (Schneditz et al., 1993; 1995; Sherman, 1995).

Implication of the Regional Blood Flow Model

Based upon the theory of the regional blood flow model, Smye et al. (1998) developed a mathematical model to assess the effect of changing regional blood flows on urea clearance during hemodialysis. The objective of manipulating the regional blood flow was to simulate the effect of exercise. The model was based upon a theoretical framework that, during the early stage of hemodialysis, urea clearance from the high-flow compartment perfused by relatively high blood flows occurred rapidly whereas urea clearance from the low-flow compartment, particularly skeletal muscles, occurred relatively slowly. During the later stage of hemodialysis, the transport of urea from the well-perfused high-flow compartment to the blood level of urea became negligible and the dominant factor would be the poorly-perfused skeletal muscles. The rate of urea clearance during the later stage of

hemodialysis therefore reflected the muscle perfusion rate; hence, the perfusion of skeletal muscle became the rate-limiting step towards the end of hemodialysis. As a result, the researchers postulated that exercise would produce an increase in the perfusion rate of the low-flow compartments due to changes in cardiac output, thus resulting in an increase in the muscle perfusion rate, a facilitation of urea clearance in the low-flow compartment, and a reduction of postdialysis urea rebound (Smye et al., 1998).

The model developed by Smye et al. (1998) simulated a 150-min hemodialysis session with dialyzer urea clearance ranging from .15 to .35 L/min. From the analysis of the model, exercise during hemodialysis would increase the rate of skeletal muscle, bone, and skin compartment urea clearance and reduce the concentration gradient of urea between the high-flow and low-flow compartments. The postdialysis urea rebound could be eliminated by sustaining an increased blood flow to the low-flow compartment for at least the last 30 min of a hemodialysis session. As theoretical benefits of exercise during hemodialysis were found, experimental studies are warranted to examine the effect of exercise on urea kinetics (Smye et al., 1998).

Conclusion

To conclude, exercise tolerance is extremely low in ESRD patients. Endurance exercise training is found to be effective in improving exercise tolerance in ESRD population. Exercise during hemodialysis (intradialytic exercise) appears to be safer and more practical than exercise after hemodialysis (off-dialysis exercise) with an additional benefit of enhancing exercise adherence. Regarding the timing of intradialytic exercise, Smye et al. (1998), using a mathematical model, demonstrated a theoretical benefit of exercise in improving urea clearance efficiency. According to the model, exercise during the last 30 min of a hemodialysis treatment facilitates urea clearance and reduces postdialysis urea rebound. Experimental studies are warranted to examine the validity of this model. On the other hand, Moore et al. (1998) reported that the cardiovascular conditions are unstable during the later stage of hemodialysis. Hence, comprehensive studies examining the timing of exercise on urea kinetics and cardiovascular stability are crucial cutting edge investigations in clinical exercise physiology regarding the renal area.

Figure 1. Patients Using the Bicycle Ergometer for Exercise.



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