

What Maintains the Metabolic Cost at Peak Aerobic Exercise in End Stage Renal Disease Patients?

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Abstract

Background: End-stage renal disease (ESRD) reduces performance of cardiopulmonary function and peak oxygen uptake (VO_2 peak). The possible roles of oxygen delivery and oxygen extraction as limiting factors of exercise tolerance in ESRD patients were assessed.

Methods: A cross-sectional study was conducted with twenty-two ESRD patients who underwent a peak cardiopulmonary and echocardiograph exercise test *via* leg cycle ergometry.

Results: During exercise, elevated lactic acid occurred at a mean workload of 68.6 ± 5.7 Watts, corresponding to 78% of their respective peak work capacity. At peak exercise, in all measured variables except for systolic blood pressure, ESRD patients did not achieve normally predicted values. Heart rate, left ventricular end diastolic and systolic volumes, stroke volume, cardiac output, VO_2 peak, arteriovenous oxygen difference, and workload were below normal values, while diastolic blood pressure, mean blood pressure and total peripheral resistance were above normal values.

Conclusions: In ESRD patients, values for both oxygen delivery and extraction were far below the recorded values in normal. This suggests diminished central cardiopulmonary responses as well as reduced peripheral capacity to extract oxygen at the muscle level. Findings support the concept and possible importance of exercise rehabilitation programs in the approach for treatment of ESRD patients.

Keywords: End-stage renal disease; Hemodynamics; Hemodialysis; Left ventricular function

Introduction

Functional capacity of end-stage renal disease (ESRD) patients is dramatically impaired, with changes occurring mainly in the cardiopulmonary and skeletal muscles, thus reducing maximum exercise tolerance [1,2]. Maximal oxygen uptake according to the Fick equation depends on the differential relationship between oxygen delivery (cardiac output and hemoglobin) and arteriovenous oxygen ($a-v$) O_2 . Therefore, an imbalance between oxygen demand-supply during exercise may expose ESRD patients to a low pH, which may alter left ventricular contractility and function [3,4] and in turn, reduce oxygen delivery to the working muscles [2].

Previous studies have not clarified which factors are responsible for the diminished maximal oxygen uptake in ESRD patients [5,6]. Data on $(a-v) O_2$ at maximal effort in ESRD patients, as well as information concerning the functional capacity of their peripheral musculature are limited. In addition, little evidence is available on the relationship between oxygen delivery and extraction at peak oxygen uptake determined *via* maximal graded dynamic exercise test in ESRD patients. In a clinical setting, knowing the factors affecting maximal oxygen uptake in ESRD patients will facilitate determination of training heart rate and outcomes associated with exercise treatment.

In the current study we hypothesized that ESRD patients compared to normal, may manifest differences in the oxygen delivery and extraction relationship during maximal graded dynamic exercise testing. Therefore, the present study was designed to assess the possible roles of both the oxygen delivery and oxygen extraction as factors limiting the exercise tolerance of ESRD patients.

Methods

Subjects

Twenty-two ESRD patients (6 females, 16 males: age 33 ± 5 years) completed this study. Subjects averaged 61.7 ± 7.2 kg in weight, 170 ± 8 cm in height, and $14.1 \pm 3\%$ body fat. All but four were on maintenance hemodialysis for 34 ± 29 months (range 13-90). Three were on continuous ambulatory peritoneal dialysis and two were in the pre-dialysis stage. All patients had arterial-venous fistula performed by a single vascular surgeon. The subjects' hematological profiles are given in Table 1. All were on a stable regimen of medications, three of them on the beta-adrenergic blocking agent propranolol for stable angina due to coronary artery disease. Medications were not adjusted for in this study and propranolol was continued during testing. None of the patients was on recombinant erythropoietin. Patients were excluded from this study if they suffered from unstable anginal syndrome, cerebrovascular accident, clinical bone damage, severe anemia or uncontrolled hypertension. After being fully informed of the details and possible discomforts associated with the experimental protocol, written informed consent was obtained

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Variable	Values
Hemoglobin (g•dL ⁻¹)	9.9 ± 1.5
Urea (mg•dL ⁻¹)	151.0 ± 17.0
Creatinine (mg•dL ⁻¹)	9.8 ± 1.2
Glucose (mg•dL ⁻¹)	106.4 ± 14.0
Phosphate (mg•dL ⁻¹)	4.6 ± 0.7
Calcium (mg•dL ⁻¹)	8.6 ± 0.7
Potassium (mEq•dL ⁻¹)	4.6 ± 0.5

Values shown are means ± SD.

Table 1: Blood chemistry values (n=22).

from each subject, which was approved by the Clinical Science Center Committee on Human Subjects that complies with the Declaration of Helsinki.

Procedure and measurements

Each subject reported to the laboratory two times. The first session was devoted to accustoming subjects to study procedures and general scope of the study. In addition, subjects were weighed on an electronic scale (± 0.05 kg), and measured for height, using a stadiometer (± 0.5 cm). Adipose fat assessment included measurement of total body weight (± 0.05 kg), skin fold thicknesses at 8 sites (± 1 mm) using the Lange Caliper (chest, axilla, triceps, sub-scapula, abdomen, suprailium, front thigh and circumferences at the shoulder). Anthropometric procedures followed the recommendations of Behnke and Wilmore [7]. During the second session subjects underwent a maximal graded exercise test on a mechanical weight-adjusted Monark leg cycle-ergometer (Model 818). Subjects were tied by torso-straps to the wall while cycling, to minimize movement of the upper body and help facilitate auscultation of blood pressure and echocardiographic measurements during sub-maximal and maximal exercise [4].

Maximal tests were terminated by one or more of the following criteria: a) leveling off or no further increase in VO₂ with increasing work rate, b) attainment of the age-predicted maximum heart rate, c) respiratory exchange ratio >1.1, and d) when the subject could not keep up with the load or voluntary withdrawal, according to the guidelines of the American College of Sports Medicine [8]. Oxygen uptake was determined breath-by-breath utilizing the Medical Graphics (St. Paul, MN) metabolic cart. The metabolic cart was calibrated before each test with known primary standard quality gases [9].

Heart rate and electrocardiogram were monitored continuously, using a Burdick Eclipse 400 3-channel, 12-lead ECG recorder system, and oscilloscope. Five-second recordings were obtained at rest and at peak exercise. Following warm-up, subjects peddled against an initial work rate of 25 watts, which was increased by 15 watts every minute until the subject could no longer continue at the predetermined pace. Blood pressure was taken using a standard sphygmomanometer cuff and mercury manometer mounted at eye level, in the sitting position at rest and at peak exercise.

Echocardiographic data processing

2-D, echocardiographic and M-mode images were performed at rest and at peak exercise utilizing Vingmed 725 Sonotron and Sony recorders equipped with 2 and 3 MHz transducers. The diameters of the aorta were determined by two-dimensionally directed M-mode. The left atrium was measured from the parasternal long-axis view. At rest, left ventricular end-diastolic and end-systolic diameters, and intraventricular septum and left ventricular posterior wall thicknesses were measured from the parasternal long- and short-axis views,

as well as from 4 and 5 chamber views, just below the mitral valve level, according to the recommendations of the American Society of Echocardiography [10]. At peak exercise, due to the short time available for measurements, left ventricular volumes and ejection fraction were determined using Simpson's rule from the apical 4 chamber view.

All echocardiographic studies were performed with the subjects in the sitting position at rest, and at peak aerobic effort. The probe was hand-held and directed to a marked point from which the resting data was obtained. The beam was directed to the aortic valve outflow tract in the 5-chamber view, or from the suprasternal approach for those subjects in whom adequate imaging of 5-chamber or parasternal long axis views was not obtained. To assess the objectivity of the echocardiographic readings, all recordings were evaluated by two independent experts. A high correlation (r=0.94) was found for inter-observer reliability.

Calculations

At rest and during exercise, variables were computed as follows:

Stroke volume was the difference between left ventricular end diastolic volume and end systolic volume.

Cardiac output was determined as the product of heart rate and stroke volume.

Venous oxygen content (mlO₂•dl⁻¹) was calculated from the measured O₂ saturation, and Hb concentration multiplied by 1.34 mlO₂ [11].

Oxygen saturation and Hb concentration were measured independently in each blood sample (IOSM3 hemoximeter, Radiometer).

Arterial O₂ content was calculated utilizing the Fick equation, in which:

$$VO_2 = HR \times SV (a-v) O_2$$

Therefore, the arteriovenous O₂ difference (a-v) O₂ was calculated by using the measured VO₂, cardiac output and venous O₂ content.

Total Peripheral resistance was calculated as follow [12]:

$$TPR = (MABP \cdot 80) / Q$$

Whereas TPR: Total Peripheral Resistance; 80: a constant number; Q: Cardiac output

Lactate measurements

A 25 µl fingertip blood sample was taken at rest and at the end of the third minute post peak exercise test for determination of lactate response. The sample was immediately transferred to a micro-tube containing 100 µl of 7% perchloric acid. The tubes were centrifuged after standing at least 1 h. Twenty microliter aliquots of the supernatant were subsequently used for blood lactate analysis on the Analox LM3 analyzer (Analox Instruments, England; Reagent Kit # GMRD-071).

Statistical methods consisted of a descriptive analysis (mean ± SD).

Results

All subjects completed the testing with no medical complications or electrocardiographic irregularities. All measurements were compared to norms for young adults [13,14]. The subjects' hematological profiles are given in Table 1. Hemodynamic and echocardiographic variables at rest and in response to aerobic exercise are summarized in Table 2. At rest, heart rate, systolic, diastolic and mean blood pressures, end

Variable	Rest	Exercise	Range Rest	Range Exe.
	(mean ± SD)	(mean ± SD)	(min/max)	(min/max)
HR (beats·min ⁻¹)	81.3 ± 8.2	156.2 ± 6.3*	69/93	132/178
SBP (mmHg)	136.7 ± 15.3	198.3 ± 13.5	104/148	172/236
DBP (mmHg)	87.2 ± 9.3	94.5 ± 4.2**	70/97	82 / 116
MABP (mmHg)	103.7 ± 11.2	129.1 ± 9.1**	81/110	112/156
EDV (ml)	98.7 ± 6.2	110.1 ± 7.6*	89/108	99/136
ESV (ml)	47.4 ± 5.0**	42.1 ± 5.3*	42/54	38/48
SV (ml)	51.3 ± 8.6*	68.0 ± 9.8*	45/55	57/74
Q (l·min ⁻¹)	4.2 ± 0.6	10.6 ± 1.3*	3.8/4.5	8.9/12.1
TPR (dynes·s ⁻¹ ·cm ⁵)·10 ⁻¹	19.8 ± 3.1**	9.7 ± 2.41**	17.4/20.3	7.7/12.6
(a-v)O ₂ (O ₂ ml·l ⁻¹)	60.2 ± 5.6**	146.1 ± 11.6*	54.8/66.2	132.6/152.9
VO ₂ (ml·kg ⁻¹ ·min ⁻¹)	4.1 ± 0.7	25.1 ± 4.4*	3.7/4.5	21.0/29.4
Blood lactate (mmol·l ⁻¹)	2.6 ± 0.2**	6.6 ± 0.8	2.4/2.9	6.1/7.3
Workload (Watts)	-----	88.5 ± 12.1*	-----	70/100

*: significantly below normally predicted values.
 **: significantly above normally predicted values.
 HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MABP: Mean Arterial Blood Pressure; EDV: End Diastolic Volume; ESV: End Systolic Volume; SV: Stroke Volume; Q: Cardiac output; TPR: Total Peripheral Resistance; (a-v) O₂: oxygen extraction; VO₂: Oxygen uptake.

Table 2: Cardiopulmonary and hemodynamic measurements at rest and in response to exercise.

diastolic volume, cardiac output and oxygen uptake were within normal limits. Conversely, values of end systolic volume, oxygen extraction, (a-v) O₂, total peripheral resistance, and lactate were above those reported for normal individuals, 5 while stroke volume was lower (Table 2).

During exercise (Table 2), onset of blood lactate determination was feasible in all subjects and occurred at a mean workload of 68.6 ± 5.7 watts, corresponding to 78% of mean respective peak work capacity. At peak exercise, for all measured variables except systolic blood pressure, the ESRD patients did not attain the normally predicted values. Heart rate, left ventricular end diastolic and systolic volumes, stroke volume, cardiac output, (a-v)O₂, oxygen uptake and workload were below the normal values, while diastolic and mean blood pressures and total peripheral resistance were above the normal values.

Discussion

The current study revealed that in ESRD patients, both oxygen delivery and oxygen extraction in response to the aerobic exercise challenge were far below the normal values reported in healthy matched sedentary individuals [10]. These findings suggest that ESRD patients had impaired cardiac function as well as reduced capacity to extract oxygen at the muscle level. Thus, the limited maximal oxygen uptake in these patients is a complex interaction of central and peripheral factors [5]. Patients' extremely lower aerobic capacity may be attributable to poor functioning of both central and peripheral factors. These findings are different from those found by Moore and colleagues, [5] suggesting that the limited VO_{2peak} in ESRD patients is due mainly to the oxygen delivery factor. Their cardiovascular response to peak exercise was slightly decreased, i.e. stroke volume was similar to that of normal subjects but peak heart rate reached only 77% compared to values achieved by normal subjects.

Values for cardiac output at peak aerobic exercise were low in our ESRD patients compared to normal individuals and even to patients with coronary artery disease [15]. The lower values of cardiac output may be related to small changes in left ventricular volumes [16], limited reserve in heart rate and contractility, and inappropriate adjustment of

circulation [4,6,17] to the increase in the pressure opposing ejection, i.e., total peripheral resistance. The integrated mechanism involving changes in contractility and total peripheral resistance resulted in the small changes of left ventricular volumes at maximal exercise that were seen in our ESRD patients. Accordingly, the maximal oxygen uptake augmentation in the present study was mainly due to moderate increases in arteriovenous oxygen content difference at peak exercise and to a lesser extent to increases in cardiac output [4]. These findings suggest that ESRD patients can partially compensate for their lower cardiac output by moderately increasing their oxygen extraction.

In healthy subjects, when oxygen transport is gradually decreased, oxygen consumption is maintained as tissue oxygen extraction is increased. When delivery is decreased further, there is a critical level below which tissue extraction cannot increase in proportion to the reduced delivery, and oxygen consumption falls. Blood lactate levels then rise, a sign of tissue hypoxia, despite further increases in oxygen extraction as delivery drops below this critical level.

Explanation for the low oxygen uptake in the present study may be attributable to premature termination of the test due to shortness of breath and/or ECG irregularities. However, in the present study, all patients performed efforts without shortness of breath and/or ECG irregularities. Therefore, it is suggested that oxygen extraction, in addition to low oxygen delivery, may be one factor that limits maximal oxygen uptake.

In the present study, the patients' reduced ability to extract oxygen corresponds to previously reported findings [18-20].

One possible mechanism that could be responsible for the reduced oxygen extraction could be mitochondrial dysfunction [21,22]. Oxygen exchange capacity appeared to be unmatched or perhaps intrinsic mitochondrial function and regulation (abnormal mitochondrial function) were altered significantly in our ESRD patients due to physical inactivity or pathological status. In addition, it is possible that the inability of skeletal muscles to extract oxygen from the arterial blood was due to considerably below-normal oxygen conductance from the muscle capillary to the mitochondria [19]. The latter is most likely associated with poor muscle microcirculatory network and capillary-myofiber dissociation due to uremic myopathy [20]. Uremic myopathy provokes cytosolic dysfunction so that mitochondrial oxidative capacity is reduced, but not abnormal [20].

Metabolic myopathies are the result of changes in intermediate muscle metabolism triggered either by exercise intolerance or by progressive muscle weakness. The molecular defect in patients with mitochondrial myopathies commonly involves the mitochondrial genome, with either single, large-scale deletions or point mutations detected [23]. Since there are multiple copies of the mitochondrial genome in individual muscle fibers, these defects can be either homoplasmic (all copies of the genome mutated) or heteroplasmic (with a mixture of wild-type and mutated copies in the same muscle fiber). In the presence of heteroplasmy a threshold level of mutated mitochondrial DNA (mtDNA) is typically required before a biochemical defect is observed [24].

Patients with mitochondrial myopathies characteristically exhibit exercise intolerance, undue fatigue, lactic acidosis, and muscle pain during low- to moderate-intensity work [25,26]. These symptoms are thought to result from impaired mitochondrial oxidative phosphorylation, which limits the capacity of mitochondria to generate the adenosine triphosphate needed for muscle work.

In many chronic diseases, physical deconditioning limits exercise tolerance [27-29]. It has been hypothesized that patients with mitochondrial myopathies in particular suffer from chronic inactivity [30,31] further aggravating their exercise intolerance. Secondary deconditioning could make a potentially reversible contribution to the disability of mitochondrial diseases and could be more responsive to therapeutic intervention than is the primary biochemical defect.

The second possible mechanism for the inability to increase oxygen extraction could be mild arterial hypoxemia at maximum exercise. This is related to a misdistribution of the cardiac output, i.e., over-perfusion of some organs rather than those where perfusion and diffusion limitation are rapidly compromised [32]. This suggests the existence of perfusion/oxidative metabolism mismatch and arteriovenous blood shunt, bringing about an impaired systemic oxygen extraction in ESRD [33,34].

Study Limitations

We did not put the expected normal ranges for healthy subjects. Instead we cited references no. 13 and 14 for normal values and comparisons and controls.

Conclusions

In ESRD patients, both oxygen delivery and oxygen extraction at peak exercise were far below the normal values recorded in healthy individuals, implying that patients' limited exercise tolerance may be attributable to impaired response of central cardiopulmonary factors and reduced peripheral ability to extract oxygen at the muscle level. These findings further support the concept that ESRD patients may benefit from exercise rehabilitation programs by improving both their left ventricular function as well as skeletal muscle metabolic capacity.

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