Goda et al. Int J Clin Cardiol 2015, 2:2
ISSN: 2378-2951

International Journal of Clinical Cardiology

Research Article: Open Access

Erythropoietin Treatment Improves Peak VO_2 and Oxygen Uptake Efficiency Slope without Changing VE vs. VCO_2 Slope in Anemic Patients

Ayumi Goda[1], Haruki Itoh[2]*, Yoshiko Ebi[3], Kumiko Kondo[2], Tomoko Maeda[2] and Toshitsune Shimada[4]

[1]*Department of Cardiology, Kyorin University Hospital, Tokyo, Japan*

[2]*Sakakibara Heart Institute, Tokyo, Japan*

[3]*Daiyukai General Hospital, Aichi, Japan*

[4]*Chiba Social Insurance Hospital, Chiba, Japan*

***Corresponding author:** *Haruki Itoh, MD, Sakakibara Heart Institute, Asahi-cho 3-16-11, Fuchu-city, Tokyo 183-0003, Japan, Tel: +81-42-314-3111, Fax: +81-42-314-3199, E-mail: itoh@cepp.ne.jp*

Abstract

Background: While the improvement of anemia with erythropoietin (EPO) treatment increases peak VO_2 in anemic patients, the effects of EPO on minute ventilation (VE), VO_2, and VCO_2 kinetics are not well described.

Objectives: The aim of this study was to evaluate the improvement in hemodynamic, metabolic, and ventilatory response during exercise along with the improvement of anemia with EPO treatment in anemic hemodialysis patients.

Methods: Thirty-seven hemodialysis patients with anemia (48.8 ± 13.6 years) received EPO (1500 or 3000 unit, 3 times a week). Parameters measured prospectively before and after EPO treatment included hemoglobin, cardiac output by dye dilution method, echocardiography, and cardiopulmonary exercise parameters.

Results: With EPO treatment, hemoglobin increased from 6.4 ± 0.9 to 10.3 ± 0.9g/dl ($p<0.001$), with concomitant improvements of O_2 delivery at rest (from 663.8 ± 161.1 to 793.4 ± 188.5ml/min, $p=0.004$) and high output state (from 8.0 ± 1.6 to 5.6 ± 1.2l/min, $p<0.001$). Peak heart rate, peak systolic blood pressure, and peak VE did not change. Peak VO_2 increased from 15.7 ± 5.3 to 18.8 ± 5.3ml/min/kg ($p=0.017$), and oxygen uptake efficiency slope (OUES) improved from 1,255 ± 375 to 1,517 ± 357 ($p<0.001$). However, VE vs. VCO_2 slope (from 34.3 ± 7.3 to 31.8 ± 7.2, $p=0.86$) and VE-VCO_2 curve did not change.

Conclusion: The treatment of anemia improved peak VO_2 and OUES without affecting VE vs. VCO_2 slope significantly. In evaluating the efficacy of treatment for patients with renal failure and anemia, the VE vs. VO_2 relation rather than the VE vs. VCO_2 should be used.

Keywords

Anemia, Exercise tolerance, Ventilation, Chronic renal failure

Introduction

Exercise tolerance in anemic patients is markedly reduced, and shortness of breath is a common symptom in these patients. The mechanism of shortness of breath is thought that reduction of hemoglobin concentration may result in exercise intolerance by decreasing oxygen (O_2) delivery. It has been reported that erythropoietin (EPO) treatment for anemia improves exercise tolerance (i.e. peak oxygen uptake (peak VO_2)) [1-6]. In chronic renal failure (CRF) patients with anemia and reduced cardiac function, treatment of the anemia with EPO has improved many of abnormalities seen in chronic heart failure (CHF), reducing left ventricular hypertrophy, preventing left ventricular dilatation, and increasing the left ventricular ejection fraction (LVEF) [7-10].

Minute ventilation (VE) vs. CO_2 output (VCO_2) slope, which reflects a ventilatory efficiency during exercise, has been emphasized an importance in patients with CHF [11,12]. Recently, the oxygen uptake efficiency slope (OUES), a new expression of the relationship between VE and VO_2 during exercise has been described [13,14]. Peak VO_2 [15], OUES and VE vs. VCO_2 slope are not only indexes of exercise tolerance but also powerful predictors of mortality. Although EPO treatment improves peak VO_2, the effects of EPO on VE, VO_2, and VCO_2 kinetics, OUES and VE vs. VCO_2 slope are not well recognized in anemic patients. The aim of this study was to evaluate the improvement in hemodynamic, metabolic, and ventilatory response during exercise along with the improvement of anemia with EPO treatment in anemic hemodialysis patients.

Methods

Study patients

Thirty-seven (14 males, 23 females; 48.8 ± 13.6 years) ambulatory anemic patients with CRF on regular hemodialysis (3 times a week) without apparent heart disease were eligible for study. Patients were excluded if they had exercise limitation by peripheral vascular or lung disease, moderate to severe valvular heart disease, left ventricular

ClinMed International Library

Citation: Goda A, Itoh H, Ebi Y, Kondo K, Maeda T, et al. (2015) Erythropoietin Treatment Improves Peak VO_2 and Oxygen Uptake Efficiency Slope without Changing VE vs. VCO_2 Slope in Anemic Patients. Int J Clin Cardiol 2:023

Received: February 16, 2015: **Accepted:** March 17, 2015: **Published:** March 20, 2015

dysfunction, ischemic heart disease who stopped exercise testing due to chest pain or significant ST depression in exercise electrocardiogram (ECG), or a history of EPO treatment within the past 6 months. The underlying renal diseases included chronic glomerulonephritis in 26 patients, diabetic nephropathy in 6 patients, and other chronic renal disease in 5 patients. All the patients were on the 4 hours, 3 times a week regular hemodialysis. The averaged hemodialysis period was 6.6 ± 5.2 years.

This study was approved by the committee on clinical study and ethics. The purposes and risks of the study were explained to the patients, and informed consent was obtained from each patient.

Study protocol

EPO (1500 or 3000 unit) was administrated intravenously 3 times per week, after each dialysis session. For the patients whose serum ferritin was less than 1000ng/ml, oral or intravenous iron was supplied. Hemoglobin and hematocrit were measured before dialysis once a week. The patients were evaluated measurement before treatment and after the hematocrit reached the target range of 30% to 35%. Serum EPO was measured before and after treatment.

Echocardiography

M-mode and 2-dimensional echocardiographic studies were performed before and after EPO treatment in all patients. We used an ultrasound system with a 2-dimensional mechanical sector scanner (SSD-2000; Aloka; Tokyo, Japan). Left ventricular end-diastolic dimension (LVDd) and end-systolic dimension (LVDs) were obtained from the apical 4- and 2-chamber views from which LVEF was automatically calculated by a modified Simpson's method [16].

Blood gas analysis and memodynamic measurements

Arterial blood gases were measured before and after EPO treatment in all patients at rest before hemodialysis. The partial pressure of arterial O_2 (PaO_2), arterial CO_2 ($PaCO_2$), and the pH were measured with a blood gas analyzer (ABL 300, Radiometer, Copenhagen, Denmark). Cardiac output was measured by the dye dilution method using an earpiece with a dye densitometer (MCL-4200, Nihon Coden, Tokyo, Japan) [17]. A 19G cannula was placed in the artecubital vein, and 5 mg of indocyanine green dissolved in 5 ml distilled water was injected through this cannula at rest. O_2 delivery was calculated using the formula as follows; hemoglobin X 1.36 X O_2 saturation in arterial blood X cardiac output.

Cardiopulmonary exercise test

Cardiopulmonary exercise test was performed before and after EPO treatment on the next day to the first hemodialysis of the week. An incremental symptom-limited exercise test using to ramp protocol was performed with a treadmill. After 4-min standing on the treadmill, exercise began with a 4-min warm-up at the speed of 1.0km/h, followed by an increase in grade and speed according to treadmill-ramp protocol. Treadmill-ramp protocol was developed in Japan which was designed to increase VO_2 linearly at the rate of 3/min/kg based on the formula as follows; VO_2=0.15S*2 + 0.14 SG + 0.45 S + 0.4 G + 0.423, where S is speed (km/hr) and G is grade (%) [18]. Heart rate and ECG were monitored continuously during the test with a Stress System ML-5000 (Fukuda Denshi Co. Ltd.; Tokyo, Japan). Cuff blood pressure was measured at rest, and every minute during the test.

Respiratory gas analysis

VO_2, VCO_2, VE, respiratory rate (R-R), and tidal-volume (TV) were measured throughout the test using an Aeromonitor AE-280S (Minato Medical Science; Osaka, Japan). Prior to calculating the parameters from respiratory gas analysis, an eight-point moving average of the breath-by-breath data was obtained. Peak VO_2 was defined as the average value obtained during the last 30 seconds. The anaerobic threshold (AT) was determined by the V-slope method [19]. VE vs. VCO_2 slope was calculated from the start of incremental exercise to the respiratory compensation point by least squares linear regression, as previously described [20]. The oxygen uptake efficiency slope (OUES) describes as the gradient of the linear relationship between VO_2 and VE during incremental exercise via a single-segment logarithmic expression of VE and is defined as the regression slope "a" in VO_2 = a log10 VE + b [13].

Table 1: Laboratory data, echocardiography, blood gas analysis and hemodynamic measurements between Pre and Post EPO treatment

	Pre	Post	P value
Body weight (kg)	53.0 ± 8.4	53.1 ± 8.6	0.976
Hct, (%)	19.0 ± 2.5	32.9 ± 3.1	<0.001
Hb, (g/dl)	6.4 ± 0.9	10.8 ± 1.0	<0.001
Serum Epo, (mIU/ml)	17.3 ± 4.5	19.3 ± 5.7	0.128
pH	7.353 ± 0.036	7.339 ± 0.039	0.125
PaO_2, (Torr)	90.9 ± 14.8	90.9 ± 12.7	0.979
$PaCO_2$, (Torr)	35.7 ± 3.7	37.5 ± 3.6	0.046
HCO_3^-, (mmol/l)	20.2 ± 2.4	20.2 ± 2.4	0.963
LVDd, (mm)	51.3 ± 5.0	47.7 ± 5.4	0.006
LVDs, (mm)	30.9 ± 4.6	29.5 ± 4.5	0.219
LVEF, (%)	77.6 ± 6.7	75.8 ± 7.4	0.299
Cardiac Output, (L/min)	7.97 ± 1.59	5.61 ± 1.21	<0.001
O_2 delivery, (ml/min)	663.8 ± 161.1	793.4 ± 188.5	<0.001

Data presented are the mean value ± SD. Hct: Hematocrit; Hb: Hemoglobin, Epo: Erythropoietin, PaO_2: Arterial O_2, $PaCO_2$: Arterial CO_2, HCO_3^-: Bicarbonate ion, LVDd: Left Ventricular End-Diastolic Dimension, LVDs: Left Ventricular End-Systolic Dimension, LVEF: Left Ventricular Ejection Fraction.

Statistics

Clinical and exercise variables for before and after treatment were compared through the use of and paired t tests. Statistical comparisons were considered significant for probability value <0.05.

Results

Laboratory data

All thirty-seven patients responded to the treatment with EPO without apparent side effect. Duration of therapy averaged 160 ± 49 days (between 86 and 275 days). Mean values of hemoglobin and hematocrit increased significantly during the study period from 6.4 ± 0.9 to 10.8 ± 1.0g/dl (p<0.001) and from 19.0 ± 2.5 to 32.9 ± 3.1 % (p<0.001), respectively (Table 1). Serum EPO did not change significantly by during the treatment (from 17.3 ± 4.5 to 19.3 ± 5.7mIU/ml, p=0.128). Among 37 patients, 31 patients prescribed elemental oral or intravenous iron.

Echocardiography

By the treatment with EPO, LVDd significantly decreased from 51.3 ± 5.0 to 47.7 ± 5.4mm (p=0.006), while LVDs unchanged from 30.9 ± 4.6 to 29.5 ± 4.5mm (p=0.219), and LVEF unchanged from 77.6 ± 6.7 to 75.8 ± 7.4 % (p=0.299).

Blood gas analysis and hemodynamic measurements

$PaCO_2$ at rest increased significantly from 35.7 ± 3.7 to 37.5 ± 3.6 Torr (p=0.046). PO_2 unchanged from 90.9 ± 14.8 to 90.9 ± 12.7 Torr (p=0.979), and pH unchanged from 7.353 ± 0.036 to 7.339 ± 0.039 (p=0.125). Before treatment, resting cardiac output was 8.0 ± 1.6l/min, which is high output state caused by anemia. It significantly decreased to 5.6 ± 1.2l/min (p<0.001) in accordance with the increase in hemoglobin, but it still is upper limit of normal range. O_2 delivery at rest increased from 663.8 ± 161.1 to 793.4 ± 188.5ml/min (p=0.004). O_2 delivery increased significantly with improving anemia, even though cardiac output at rest decreased.

Exercise testing

Exercise measurements are shown in Table 2. Heart rate and systolic blood pressure at both of rest and peak exercise did not change by the treatment. However, at given exercise time, heart rate and systolic blood pressure decreased after the treatment, and heart rate at AT decreased significantly from 113.4 ± 23.9 to 102.5 ±19.0bpm (p=0.034). Exercise time and time at AT after starting ramp exercise also prolonged

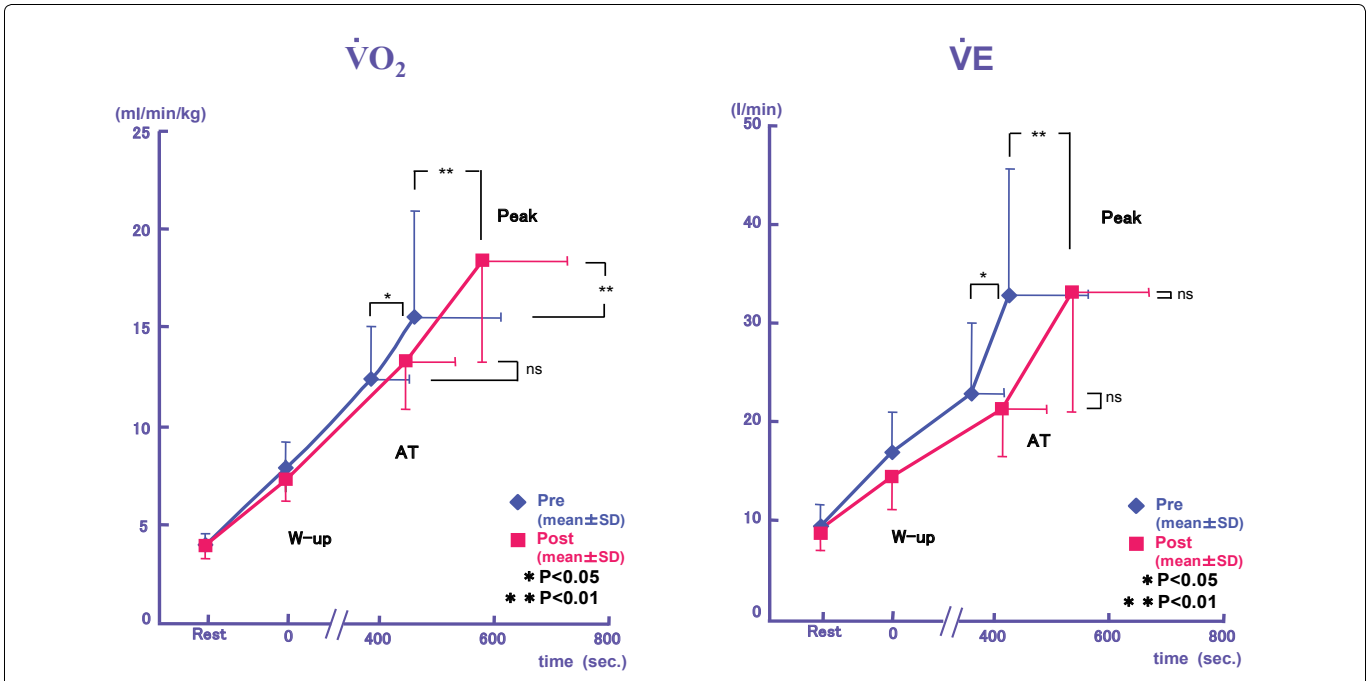

Figure 1: Changes in Oxygen Uptake and Minute Ventilation during Exercise

Table 2: Cardiopulmonary exercise testing parameters at rest and exercise between Pre and Post EPO treatment

	Pre	Post	P value
At Rest			
Rest HR, (bpm)	88.2 ± 18.2	84.8 ± 13.1	0.362
Rest SBP, (mmHg)	148.5 ± 24.7	141.0 ± 18.9	0.147
Rest VE, (l/min)	9.4 ± 2.2	8.7 ± 1.7	0.110
Rest R-R, (n/min)	16.3 ± 4.0	16.9 ± 4.2	0.510
Rest TV, (ml)	617.1 ± 228.4	566.8 ± 187.6	0.304
Rest VO_2, (ml/min)	202.9 ± 42.1	207.7 ± 36.2	0.604
Rest VCO_2, (ml/min)	172.2 ± 41.5	165.5 ± 31.4	0.436
Rest VE/VO_2, (ml/ml)	46.9 ± 6.4	43.8 ± 5.5	0.028
Rest VE/VCO_2 , (ml/ml)	55.6 ± 8.1	55.2 ± 8.1	0.824
Rest VCO_2/VO_2	0.85 ± 0.05	0.80 ± 0.05	<0.001
During Exercise			
Exercise time, (sec.)	467.8 ± 154.4	584.5 ± 145.6	<0.001
Peak HR, (bpm)	125.5 ± 27.7	121.6 ± 27.5	0.548
Peak SBP, (mmHg)	186.1 ± 29.7	183.9 ± 29.4	0.755
Peak VE, (l/min)	32.8 ± 12.8	33.1 ± 12.2	0.919
Peak R-R, (n/min)	27.8 ± 7.1	28.9 ± 7.1	0.492
Peak TV, (ml)	1181.2 ± 362.5	1148.7 ± 335.6	0.690
AT, (mL/min/kg)	12.3 ± 2.8	13.3 ± 2.5	0.153
AT time, (sec.)	393.1 ± 66.0	449.4 ± 86.8	<0.05
ΔVO_2/time, (mL/min/sec)	1.91 ± 1.03	1.67 ± 0.31	0.178
Peak O_2 pulse, (mL/min/beat)	6.5 ± 2.1	8.1 ± 2.1	0.001
Peak VO_2, (ml/min/kg)	15.7 ± 5.3	18.8 ± 5.3	0.017
OUES	1,255 ± 375	1,517 ± 357	<0.001
VE vs. VCO_2 slope	34.3 ± 7.3	31.8 ± 7.2	0.861
Peak VCO_2/VO_2	0.97 ± 0.12	0.90 ± 0.13	0.026

Data presented are the mean value ± SD. HR: Heart Rate, SBP: Systolic Blood Pressure, VE: Ventilation, R-R: Respiratory Rate, TV: Tidal Volume, VO_2: O_2 uptake, VCO_2: CO_2 output, AT: Anaerobic Threshold, AT time: Time at AT after starting ramp exercise, OUES: Oxygen Uptake Efficiency Slope.

significantly from 393.1 ± 66.0 sec to 449.4 ± 86.8 sec (p<0.05) and from 467.8 ± 154.4 sec to 584.5 ± 145.6 sec (p<0.001). Peak VO_2 increased significantly from 15.7 ± 5.3 to 18.8 ± 5.3ml/min/kg (p=0.017) (Figure 1), which represented a mean increase of 20% over the baseline measurements. There was weak correlations between change in Hb and change in peak VO_2 (r=0.330, p=0.046). AT VO_2 and ΔVO_2/time did not change between before and after treatment.

TV and R-R both at rest and peak exercise did not change (Table 2). VE decreased at given exercise time after the treatment (Figure 1). Therefore, VE/VO_2 curve shifted downward after the treatment and OUES improved significantly from 1,255 ± 375 to 1,517 ± 357 (p<0.001) (Figure 2). There was weak correlations between change in Hb and change in OUES (r=0.395, p=0.017). In contrast, VE/VCO_2 curve and VE vs. VCO_2 slope (from 34.3 ± 7.3 to 31.8 ± 7.2, p=0.86) did not change (Figure 3).

Discussion

In the present study, treatment for anemia resulted in 1) increasing O_2 delivery at rest, Peak VO_2, and OUES, 2) decreasing cardiac output at rest, VE, and VE vs. VO_2 relationship, and an 3) unchanging VE vs. VCO_2 relationship. The result of the present study has revealed that anemia affected VE vs. VO_2 but not VE vs. VCO_2 relationship in CRF patients.

Anemia and exercise tolerance

The treatment of anemia with EPO improves exercise tolerance, which has previously been described in many studies [1-6]. In our present study, peak VO_2 represented a mean increase of 20% over the baseline measurements in agreement with the other reports. The mechanism by which EPO improves exercise tolerance has been presumed to be increased hemoglobin concentration leading to increased O_2 delivery. In CRF patients, EPO has been shown to improve skeletal muscle function and O_2 use, as well as endothelial function [21]. In our present study, instead of skeletal muscle function and O_2 use, cardiac output was actually measured by the dye dilution method, and O_2 delivery was calculated. We demonstrated that O_2 delivery increased along with the improvement of anemia.

OUES

A non-linear measure of the ventilatory response to exercise (i.e. OUES) has been described, initially in young patients with cardiac disease [13]. The OUES is derived from the single-segment logarithmic relation between VO_2 and VE during incremental exercise. OUES incorporates in a single index not only cardiovascular and peripheral factors that determine VO_2 but also pulmonary factors that influence the ventilatory response to exercise. It has been showed that OUES is significantly correlated to peak VO_2 in patients with CHF [22] and is not influenced by the duration of the exercise test, or by achieved exercise intensity. However, the effect of anemia on OUES hasn't been well known. In our present study, OUES improved along with improvement of anemia. Its mechanism might be similar in peak VO_2, due to increasing O_2 delivery and VO_2 and decreasing VE.

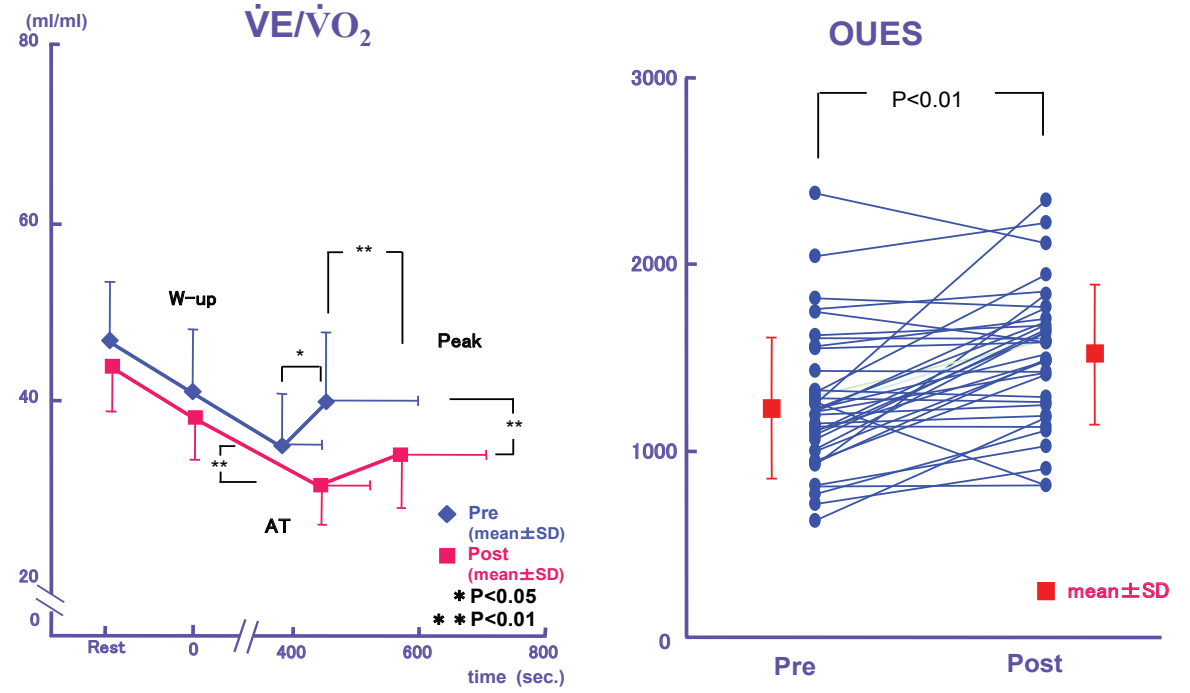

Figure 2: Changes in VE/VO_2 and oxygen uptake efficiency slope (OUES) during Exercise

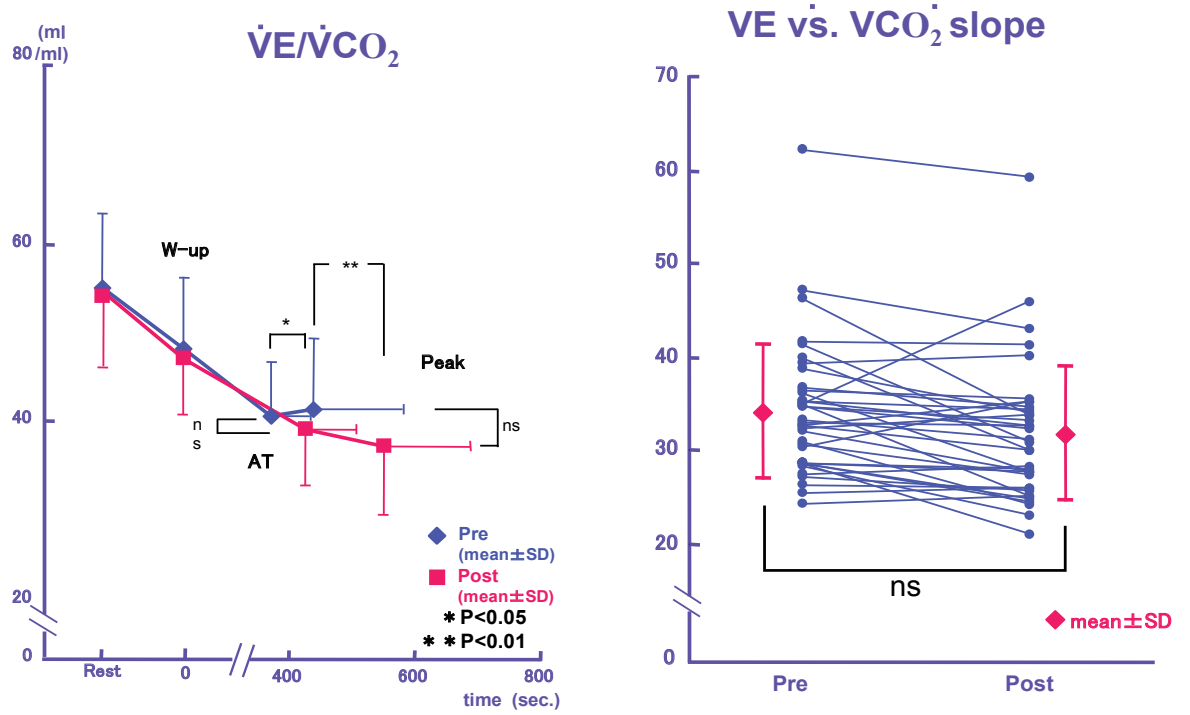

Figure 3: Changes in the VE/VCO_2 and VE vs. VCO_2 slope during Exercise

Anemia and VE vs. VCO_2 relationship

VE vs. VCO_2 slope, which reflects a ventilatory efficiency during exercise, has been emphasized a powerful predictors of prognosis and severity of CHF [11,12]. Ventilatory efficiency depends on pulmonary hemodynamics and related parameters such as ventilation-perfusion mismatch, skeletal muscle ergoreceptor and peripheral chemoreceptor sensitivity, and heightened sympathetic activity. Until now, the effects of EPO on VE, VO_2, and VCO_2 kinetics and VE vs. VCO_2 slope are not well recognized in anemic patients.

On the patients of iron deficiency anemia, Davies et al. [23] revealed that improvement of anemia decreased VE at the same exercise stage. Robertson et al. [1] reported that correction of anemia significant by decreased VE in CRF patients. But they did not mention about the physiologic mechanism of this changing. On the patients of HbSC sickle cell patients, Oyono-Enguelle et al. [24] reported VE in anemic patients (HbSC patients) drifted upward than that in normal patients (HbAA patients). They expected that caused by changes of the body temperature, epinephrine and norepinephrine, acidosis, and lactate metabolism.

Similarly, in our present study, VE decreased by improving anemia. Treatment for anemia might improve tissue O_2 supply and muscle function in terms of lactate production and/or utilization, then improvement of acidosis in the tissue during exercise lead the decreasing the VE in the given exercise intensity. That would be

explained by the delay of AT appearance after treatment and decrease of heart rate at AT. VE is mainly determined by the rate of CO_2 production, the physiologic and anatomic dead space, and the level at which $PaCO_2$ during exercise. VE vs. VCO_2 slope was steeper in CHF patients than normal subjects, because it is considered to be derived from the ventilation-perfusion mismatch and the increased ratio of physiologic dead space to TV, which was due mainly to the inappropriate increase in cardiac output during exercise [25]. However, in case of anemia without CHF, VE vs. VCO_2 relationship are parallel, because dead space ventilation doesn't increase.

Ventilatory efficacy for VO_2 and VCO_2

Improvement of anemia decreases VE at the same exercise stage, which results in improvement in OUES. In contrast, the kinetics of VE and VCO_2 are parallel, which results in unchanging VE vs. VCO_2 slope. In the point of O_2 transport capacity during exercise, anemic state is similar with the state of decreased pulmonary blood flow with normal hemoglobin concentration. In contrast, in the point of the CO_2 kinetics, differ from O_2 kinetics, CO_2 is transported across alveolar membrane by diffusion mechanism, which means CO_2 excretion is not disturbed when pulmonary blood flow is maintained even in anemic state. In summary, hemoglobin affects O_2 but not CO_2 transport. The improvement of CHF results in the improvement of both VE vs. VCO_2 slope and OUES, however, the improvement of anemia results in unchanging of the VE vs. VCO_2 slope and changing of the OUES. That is the difference between ventilatory efficacy for VO_2 and VCO_2 in the treatment of anemia.

Limitation

In the interpretation of our study results, some limitations should be considered. The major limitations of this study were the small number of patients and the lack of a control group. In case of CRF patients, improvement of anemia induces improvement of hyperdynamic state. However, the physiological mechanism at the pulmonary alveolar membrane level is similar with CHF patients, so it was worth in considering about VE, VO_2 and VCO_2 kinetics in anemia in this model.

Conclusions

The treatment of anemia improved peak VO_2 and OUES without affecting VE vs. VCO_2 slope significantly. In evaluating the efficacy of treatment for CRF patients with anemia the VE vs. VO_2 relation rather than the VE vs. VCO_2 should be used.

Acknowledgment

The authors thank Donna Mancini, MD, for her advice in this manuscript.

References

1. Robertson HT, Haley NR, Guthrie M, Cardenas D, Eschbach JW, et al. (1990) Recombinant erythropoietin improves exercise capacity in anemic hemodialysis patients. Am J Kidney Dis 15: 325-332.
2. Metra M, Cannella G, La Canna G, Guaini T, Sandrini M, et al. (1991) Improvement in exercise capacity after correction of anemia in patients with end-stage renal failure. Am J Cardiol 68: 1060-1066.
3. Lundin AP, Akerman MJ, Chesler RM, Delano BG, Goldberg N, et al. (1991) Exercise in hemodialysis patients after treatment with recombinant human erythropoietin. Nephron 58: 315-319.
4. Baraldi E, Montini G, Zanconato S, Zacchello G, Zacchello F (1990) Exercise tolerance after anemia correction with recombinant human erythropoietin in end-stage renal disease. Pediatr Nephrol 4: 623-626.
5. Lewis NP, Macdougall IC, Willis N, Coles GA, Williams JD, et al. (1993) Effects of the correction of renal anaemia by erythropoietin on physiological changes during exercise. Eur J Clin Invest 23: 423-427.
6. Mancini DM, Katz SD, Lang CC, LaManca J, Hudaihed A, et al. (2003) Effect of erythropoietin on exercise capacity in patients with moderate to severe chronic heart failure. Circulation 107: 294-299.
7. Löw I, Grützmacher P, Bergmann M, Schoeppe W (1989) Echocardiographic findings in patients on maintenance hemodialysis substituted with recombinant human erythropoietin. Clin Nephrol 31: 26-30.
8. Low-Friedrich I, Grutzmacher P, Marz W, Bergmann M, Schoeppe W (1991) Therapy with recombinant human erythropoietin reduces cardiac size and improves heart function in chronic hemodialysis patients. Am J Nephrol 11: 54-60.
9. Goldberg N, Lundin AP, Delano B, Friedman EA, Stein RA (1992) Changes in left ventricular size, wall thickness, and function in anemic patients treated with recombinant human erythropoietin. Am Heart J 124: 424-427.
10. Foley RN, Parfrey PS, Morgan J, Barré PE, Campbell P, et al. (2000) Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. Kidney Int 58: 1325-1335.
11. Chua TP, Ponikowski P, Harrington D, Anker SD, Webb-Peploe K, et al. (1997) Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. J Am Coll Cardiol 29: 1585-1590.
12. Tabet JY, Beauvais F, Thabut G, Tartière JM, Logeart D, et al. (2003) A critical appraisal of the prognostic value of the VE/VCO2 slope in chronic heart failure. Eur J Cardiovasc Prev Rehabil 10: 267-272.
13. Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, et al. (1996) Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. J Am Coll Cardiol 28: 1567-1572.
14. Hollenberg M, Tager IB (2000) Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. J Am Coll Cardiol 36: 194-201.
15. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, et al. (1991) Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 83: 778-786.
16. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, et al. (1989) Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 2: 358-367.
17. Yamanaka H, Akutsu Y, Watanabe T, Okazaki O, Michihata T, et al. (1995) Relation between cardiac index and regional myocardial blood flow in the non-infarcted wall using PET with 13NH3 in healed myocardial infarction. Jpn Heart J 36: 283-292.
18. Yamamoto M, Tanabe K, Ohmiya K, Iwasaki T, Ito H, et al. (1992) [Development of computer software in ramp slope controller for treadmill ergometer]. J Cardiol 22: 687-693.
19. Sue DY, Wasserman K, Moricca RB, Casaburi R (1988) Metabolic acidosis during exercise in patients with chronic obstructive pulmonary disease. Use of the V-slope method for anaerobic threshold determination. Chest 94: 931-938.
20. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ (2005) Principles of Exercise Testing and Interpretation. Baltimore, Maryland: Lippincott Williams & Wilkins: 93-98.
21. Marrades RM, Alonso J, Roca J, Gonzalez de Suso JM, Campistol JM, et al. (1996) Effects of erythropoietin on muscle O2 transport during exercise in patients with chronic renal failure. J Clin Invest 97: 2092-2100.
22. Van Laethem C, Bartunek J, Goethals M, Nellens P, Andries E, et al. (2005) Oxygen uptake efficiency slope, a new submaximal parameter in evaluating exercise capacity in chronic heart failure patients. Am Heart J 149: 175-180.
23. Davies CT, Van Haaren JP (1973) Effect of treatment on physiological responses to exercise in East African industrial workers with iron deficiency anaemia. Br J Ind Med 30: 335-340.
24. Oyono-Enguéllé S, Le Gallais D, Lonsdorfer A, Dah C, Freund H, et al. (2000) Cardiorespiratory and metabolic responses to exercise in HbSC sickle cell patients. Med Sci Sports Exerc 32: 725-731.
25. Wasserman K, Zhang YY, Gitt A, Belardinelli R, Koike A, et al. (1997) Lung function and exercise gas exchange in chronic heart failure. Circulation 96: 2221-2227.