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Abstract

This study examined the effects of physical training on exercise hyperpnea (EH) in patients on hemodialysis (HD). In baseline, 17 (trained group) and 12 (control group) patients on HD performed symptom limited exercise test using a treadmill. Trained group, but not control group, exercised 2 to 3 times weekly on non-dialysis days under medical supervision. Exercise testing was repeated 20 weeks after the baseline. Ventilatory response to exercise was evaluated using the regression slope relating minute ventilation ($\dot{V}E$) to carbon dioxide output ($\dot{V}CO_2$) during incremental exercise ($\dot{V}E/\dot{V}CO_2$ slope) below the point of respiratory compensation. In trained group, $\dot{V}E$, oxygen uptake ($\dot{V}O_2$) and $\dot{V}CO_2$ at peak exercise increased and $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ decreased after physical training, respectively. No change was observed in control group. $\dot{V}O_2$ at the anaerobic threshold increased in trained group, but not in control group. The post training $\dot{V}E/\dot{V}CO_2$ slope (33.9±5.0) was significantly ($p<0.05$) lower than the pre-training slope (38.0±4.8) and remained constant in control group. In trained group, changes in the $\dot{V}E/\dot{V}CO_2$ slope correlated with those in peak $\dot{V}O_2$ ($p<0.05$). These results suggest that physical training decreases EH in patients on HD and that it correlates with changes in exercise tolerance.

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key word：hemodialysis, physical training, exercise hyperpnea, $\dot{V}E/\dot{V}CO_2$ slope

Introduction

It is well established that exercise hyperpnea (EH) occurs during physical exertion in patients on chronic hemodialysis (HD). It is believed that EH restricts daily life activities and maximal physical activity ; it also critically limits a person's quality of life (QOL)[1]. We had previously evaluated EH in patients on HD using the regression slope relating minute ventilation ($\dot{V}E$) to carbon dioxide output ($\dot{V}CO_2$) during incremental exercise ($\dot{V}E/\dot{V}CO_2$ slope)[2]. In this earlier study, we showed that $\dot{V}E/\dot{V}CO_2$ slope was steeper in patients on HD than in normal subjects and that it correlated linearly with exercise tolerance[2]. However, randomized trials to investigate the relation between EH and changes in exercise tolerance in patients on HD have not been conducted yet. We hypothesized that an increase in exercise tolerance decrease EH in patients on HD. The purpose of this study was to determine the effect of physical training on EH in patients on HD.

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Methods

Subjects

The study population consisted of 29 patients (mean age 40.0±11.2 years) who had regular HD for 2.4±2.5 years. The underlying disease in all patients was chronic glomerulonephritis. Exclusion criteria included presence of heart diseases, diabetes mellitus and liver dysfunction. Heart diseases were diagnosed based on signs, symptoms, chest x-ray, 12-lead electrocardiogram, results of exercise test and echocardiographic evidence. Diabetes mellitus and liver dysfunction were diagnosed based on results of blood examination. The patients were randomly divided into 2 groups of trained (n=17) and control (n=12) groups (Table 1). Medication was prescribed as clinically indicated throughout the study period. No patient received beta blockers, antiarrhythmics or digitalis. We received the written informed consent from each patient.

Exercise testing

Both the groups received symptom limited exercise tests at the baseline and 20 weeks later. Exercise testing was performed on non-dialysis days using a Marquette CASE 2 computerized treadmill system (Milwaukee, WI, USA) according to a modified Bruce protocol (Sheffield). Throughout the test, we monitored heart rate and a 12-lead electrocardiogram. Cuff blood pressure (BP) in the right arm was measured by a skilled medical technician every minute using a manual sphygmomanometer. For safety, the patients lightly touched a rail with the left hand throughout the BP measurement. The subjects were encouraged to continue the exercise until they felt exhausted. Once testing was discontinued, the patients were asked about the primary reason for terminating the exercise test (e. g., leg fatigue and dyspnea). A supervising physician was in attendance to stop the exercise if any of the following occurred : 1) development of potentially dangerous symptoms including chest pain and dizziness ; 2) not less

Table 1. Demographics and clinical characteristics of patients on hemodialysis.

	Trained Group	Control Group
No. of Patients	17	12
Age (years)	40.1± 11.9	39.7 ±10.7
Gender (M/F)	9/8	5/7
Body Height (cm)	160.4±6.7	160.6±8.3
Body Weight (kg)	52.4±7.7	52.6±8.6
HD Duration (years)	2.1±2.5	2.7±2.6
Hematocrit (%)	23.0±5.4	22.8±3.4
SBP (mmHg)	143.2±19.8	138.5±20.5
DBP (mmHg)	83.6±11.2	83.0±14.0
Peak $\dot{V}O_2$ (ml/kg/min)	21.5±3.0	22.2±6.7
$\dot{V}O_2$ at AT (ml/kg/min)	15.6±3.4	15.0±3.7
$\dot{V}E/\dot{V}CO_2$ Slope	38.0±4.8	36.4±2.9
Antihypertensive Drugs (%)	41.2	41.7

SBP : systolic blood pressure, DBP : diastolic blood pressure, $\dot{V}O_2$: oxygen uptake, AT : anaerobic threshold, $\dot{V}E$: minute ventilation, $\dot{V}CO_2$: carbon dioxide output.

than 250/120 mmHg of BP or the decrease of systolic BP or heart rate as workload increased ; 3) development of a serious or potentially serious arrhythmia ; and 4) horizontal or downsloping ST segment depression of not less than 0.1 mV at 80 msec after the J point.

Analysis of expired gas

$\dot{V}E$ (l/min, BTPS), $\dot{V}CO_2$ (ml/min, STPD) and oxygen uptake ($\dot{V}O_2$, ml/min, STPD) were continuously measured on a mixing chamber basis using a System-5 respiratory gas analyzer (AIC, Tokyo, Japan) equipped with Fleish pneumotachometer, a polarograph-type oxygen sensor (RAS-31) and an infrared sensor for carbon dioxide detection (RAS-41)[3]. Gas was sampled through a Rudolph's mask. The flow, oxygen and carbon dioxide sensors were calibrated before each test.

The $\dot{V}E/\dot{V}CO_2$ slope was calculated by linear regression analysis using the $\dot{V}E$ and $\dot{V}CO_2$ measured during incremental exercise before the point of respiratory compensation[4]. The following equation was used to determine the relation between $\dot{V}E$ (ml/kg/min) and $\dot{V}CO_2$ (ml/kg/min) during the exercise test :

$$\dot{V}E = a \times \dot{V}CO_2 + b$$

where constant "a" was defined as $\dot{V}E/\dot{V}CO_2$ slope[4]. Peak $\dot{V}O_2$ was determined in the subjects who had reached exhaustion during exercise. The anaerobic threshold (AT) was defined as $\dot{V}O_2$ at which either one of the following was observed[5,6] : 1) the increase in $\dot{V}E/\dot{V}O_2$ without a simultaneous increase in the $\dot{V}E/\dot{V}CO_2$ and 2) changes in the slope of the linear relation between $\dot{V}O_2$ and $\dot{V}CO_2$ in response to incremental exercise (the V-slope method).

Physical training

Seventeen patients exercised 2 to 3 times per week for 20 weeks at the intervals between the exercise tests. On non-dialysis days, the patients underwent a combination training of stationary bicycle ergometry, walking and jogging for 30-min duration under medical supervision. The intensity of physical training was adjusted to maintain the exercising heart rate at between 50% and 60% of the peak heart rate using a heart rate monitor (CAT EYE, Osaka, Japan). Before and after physical training the patients were interviewed and their BP, electrocardiogram and heart rate at rest were measured.

Statistical analysis

The results were expressed as the mean ± SD. The differences in clinical characteristics between the trained and control groups were determined by the Mann-Whitney test and the chi-square test for independent variables. Using the Wilcoxon test, we determined the differences in gas analysis data that was obtained baseline and 20 weeks later. Using Spearman's correlation coefficient, we determined the relation between changes in $\dot{V}E/\dot{V}CO_2$ slope and those in each parameter. P values of less than 0.05 were considered to be statistically significant.

Results

Body height and weight showed no difference between the baseline and after 20 weeks in either group. Reasons for terminating the exercise test in trained group were as follows : leg fatigue in 11 patients (64.7%) and breathlessness in 6 patients (35.3%) at the baseline ; and leg fatigue in 12 patients (70.6%) and breathlessness in 5 patients (29.4%) after 20 weeks. The reasons in control group were as follows : leg fatigue in 8 patients (66.7%) and breathlessness in 4 patients (33.3%) at the baseline ; and leg fatigue in 8 patients (66.7%) and breathlessness in 4 patients (33.3%) after 20 weeks.

In trained group, exercise did not affect the ventilatory parameters at rest. At exhaustion, physical training increased $\dot{V}E$, $\dot{V}O_2$, $\dot{V}CO_2$ and tidal volume, and decreased $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$. Additionally, $\dot{V}O_2$ at AT increased in trained group. These parameters did not change in control group (Table 2).

In trained group, exercise did not affect hemodynamic parameters at rest. At exhaustion, physical training increased heart rate. Peak heart

Table 2. Effects of physical training on respiratory parameters at rest, AT and exhaustion during symptom limited treadmill exercise test in patients on hemodialysis.

	Baseline	20 Weeks Later
Trained Group		
Rest		
$\dot{V}O_2$ (ml/kg/min)	3.5±0.3	3.7±0.3
$\dot{V}E$ (ml/kg/min)	138.3±22.6	144.3±39.7
$\dot{V}CO_2$ (ml/kg/min)	2.8±0.4	3.0±0.5
$\dot{V}CO_2/\dot{V}O_2$	0.80±0.09	0.81±0.12
$\dot{V}E/\dot{V}O_2$	39.5±6.1	39.4±8.8
$\dot{V}E/\dot{V}CO_2$	49.6±4.9	48.3±6.1
RR (breaths/min)	15.0±4.7	14.7±5.1
V_T (ml)	529.9±217.9	540.5±219.3
AT		
$\dot{V}O_2$ (ml/kg/min)	15.6±3.4	17.9±3.4 †
Peak		
$\dot{V}O_2$ (ml/kg/min)	21.5±3.0	27.0±5.6 ††
$\dot{V}E$ (ml/kg/min)	902.8±236.1	1011.5±266.0 *
$\dot{V}CO_2$ (ml/kg/min)	21.6±6.0	27.3±6.7 †
$\dot{V}CO_2/\dot{V}O_2$	1.00±0.11	1.01±0.12
$\dot{V}E/\dot{V}O_2$	42.2±6.2	37.4±6.1 *
$\dot{V}E/\dot{V}CO_2$	42.5±5.6	37.1±4.1 †
RR (breaths/min)	37.3±9.2	36.1±8.9
V_T (ml)	1288.8±349.0	1433.1±441.7 *
Control Group		
Rest		
$\dot{V}O_2$ (ml/kg/min)	3.5±0.3	3.4±0.2
$\dot{V}E$ (ml/kg/min)	141.7±22.4	135.1±21.5
$\dot{V}CO_2$ (ml/kg/min)	2.8±0.5	2.8±0.4
$\dot{V}CO_2/\dot{V}O_2$	0.81±0.1	0.82±0.12
$\dot{V}E/\dot{V}O_2$	40.4±7.2	39.6±6.8
$\dot{V}E/\dot{V}CO_2$	50.1±3.3	48.5±4.3
RR (breaths/min)	15.4±3.6	15.3±4.7
V_T (ml)	494.7±127.7	501.1±187.0
AT		
$\dot{V}O_2$ (ml/kg/min)	15.0±3.7	14.9±3.2
Peak		
$\dot{V}O_2$ (ml/kg/min)	22.2±6.7	21.7±4.9
$\dot{V}E$ (ml/kg/min)	867.0±241.9	884.6±179.9
$\dot{V}CO_2$ (ml/kg/min)	21.7±6.7	21.9±6.0
$\dot{V}CO_2/\dot{V}O_2$	0.98±0.10	1.00±0.09
$\dot{V}E/\dot{V}O_2$	39.6±5.5	40.7±4.4
$\dot{V}E/\dot{V}CO_2$	40.5±3.1	41.3±4.0
RR (breaths/min)	35.8±11.5	36.8±9.4
V_T (ml)	1336.1±481.1	1293.2±328.8

$\dot{V}E$: minute ventilation, $\dot{V}O_2$: oxygen uptake, $\dot{V}CO_2$: carbon dioxide output, RR : respiratory rate, V_T : Tidal volume, AT : anaerobic threshold. * : $p<0.05$, † : $p<0.005$, †† : $p<0.001$

Table 3. Effects of physical training on hemodynamic parameters at rest and exhaustion during symptom limited treadmill exercise test in patients on hemodialysis.

	Baseline	20 Weeks Later
Trained Group		
Rest		
HR (beats/min)	86.9±10.1	81.9±8.7
SBP (mmHg)	143.2±19.8	141.5±16.4
DBP (mmHg)	83.6±11.2	85.8±12.3
Peak		
HR (beats/min)	157.8±10.0	164.2±10.2 *
SBP (mmHg)	198.7±21.5	202.4±24.8
DBP (mmHg)	89.1±13.3	84.7±19.7
Control Group		
Rest		
HR (beats/min)	76.9±7.1	84.3±13.6
SBP (mmHg)	138.5±20.5	130.8±23.3
DBP (mmHg)	83.0±14.0	79.0±13.5
Peak		
HR (beats/min)	153.5±20.3	155.8±20.7
SBP (mmHg)	182.8±17.2	176.8±28.3
DBP (mmHg)	79.5±14.3	80.8±13.8

HR : heart rate, SBP : systolic blood pressure, DBP : diastolic blood pressure, * : $p < 0.05$.

rate did not change in control group (Table 3).

There was a linear correlation between the $\dot{V}E$ and $\dot{V}CO_2$ during exercise below the point of respiratory compensation at the baseline ($r = 0.994 \pm 0.004$ in trained group and $r = 0.995 \pm 0.003$ in control group) and after 20 weeks ($r = 0.994 \pm 0.005$ in trained group and $r = 0.995 \pm 0.004$ in control group).

$\dot{V}E/\dot{V}CO_2$ slope after 20 weeks (33.9 ± 5.0) was significantly ($p < 0.05$) lower than that at the baseline (38.0 ± 4.8) in trained group. $\dot{V}E/\dot{V}CO_2$ slope in control group did not change (Fig. 1).

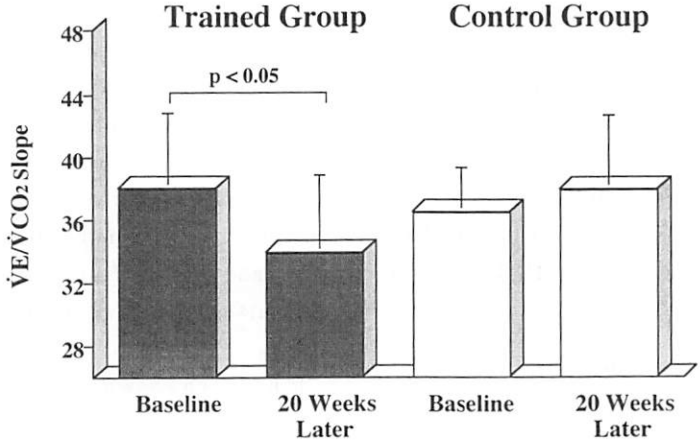

Fig. 1. Effects of physical training on the regression slope relating minute ventilation to carbon dioxide output ($\dot{V}E/\dot{V}CO_2$ slope) during exercise in patients on hemodialysis.

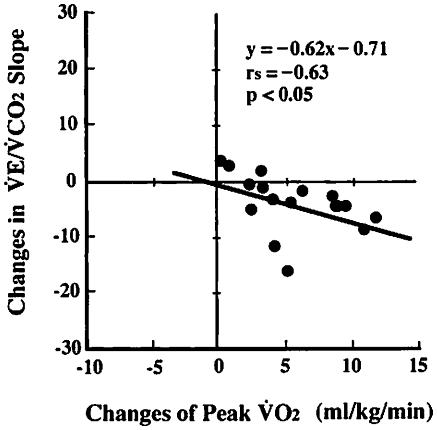

Fig. 2. Relation between changes of peak $\dot{V}O_2$ and changes in $\dot{V}E/\dot{V}CO_2$ slope in trained patients on hemodialysis.

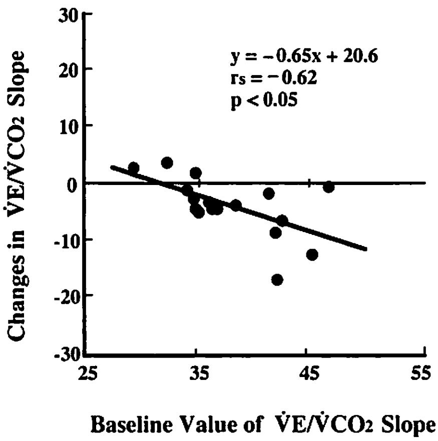

Fig. 3. Relation between value of $\dot{V}E/\dot{V}CO_2$ slope before physical training and changes in $\dot{V}E/\dot{V}CO_2$ slope in trained patients on hemodialysis.

In trained group, changes in $\dot{V}E/\dot{V}CO_2$ slope correlated with those in peak $\dot{V}O_2$ ($p<0.05$) (Fig. 2). In trained group, changes in $\dot{V}E/\dot{V}CO_2$ slope also correlated with the baseline value ($p<0.05$) (Fig. 3). On the other hand, changes in slope $\dot{V}E/\dot{V}CO_2$ did not correlate with age, HD duration or hematocrit.

Discussion

A number of reports have found that peak $\dot{V}O_2$ in patients on HD can be increased by physical training[7~9]. This study also confirmed that physical training increases peak $\dot{V}O_2$. We did not perform a preliminary exercise test before this study. This omission might have influenced the change in peak $\dot{V}O_2$, but because the control group's peak $\dot{V}O_2$ did not change between the baseline and after 20 weeks it probably had no effect.

In our previous report, we showed that the $\dot{V}E/\dot{V}CO_2$ slope was steeper in patients on HD than in normal subjects. $\dot{V}E/\dot{V}CO_2$ slope, however, decreased with physical training. In trained group, the post-training slope was below the upper limit of normal, as reported by Chua et al.[10] and by Reindl and Kieber[11] (34.0 and 35.0, respectively) and this was "normalized". This finding shows that physical training can decrease EH and suggests that regular exercise improves QOL. Additionally, Our report's finding that exercise tolerance is related to EH in patients on HD[2] was also supported.

Before this study, we had believed that the pathophysiology of EH in patients on HD was primarily due to an increase in physiologic dead space ventilation which was caused by decreased pulmonary diffusing capacity[12] and decreased pulmonary perfusion because of calcification[13], as well as due to metabolic acidosis developing early in exercise[14] and the anemia associated with renal failure. Unfortunately, the effects of physical training on pulmonary perfusion and diffusing capacities in patients on HD have been poorly understood. In healthy subjects, those capacities are increased by physical training[15], and it is possible that the training effects contribute to the decrease of EH. Pulmonary calcification in patients on HD, however, might obstruct such effects.

It has been shown that physical training improves anemia in patients on HD[16,17] and it is possible that improved anemia decreases the $\dot{V}E/\dot{V}CO_2$ slope. Lewis et al.[18], however, have shown that when anemia is improved by the administration of erythropoietin, the $\dot{V}E/\dot{V}CO_2$ slope does not change. Thus, improvement in anemia in patients on HD who exercise is not likely to be the principal cause of decreased EH.

One plausible cause of the decrease of EH is reduced stimulation of peripheral chemoreceptors, secondary to a smaller increase in lactate production. It has been established in healthy subjects that the acceleration of metabolic acidosis that occurs during exercise is inhibited by physical training[19], and a similar result has been reported in patients with chronic heart failure[20,21]. Probably, a similar phenomenon occurred in patients on HD.

We believe that there are other causes of EH in patients on HD, such as reduced sensitivity of the peripheral chemoreceptors[22] and the reduction of central command[23]. Additional information, however, is needed before it would be appropriate to propose them as EH's mechanism of action.

The changes in the $\dot{V}E/\dot{V}CO_2$ slope correlated with those in peak $\dot{V}O_2$ in period of physical training. This supports the idea that a close relation exists between EH and exercise tolerance[2].

There is also a correlation between the improvement of the $\dot{V}E/\dot{V}CO_2$ slope achieved by physical training and the pre-training slope, this suggests that increased EH brings a greater probability of improvement from physical training. This data agrees with the findings of the Sato et al.'s study[24] which evaluated EH during the recovery phase in patients who suffered from acute myocardial infarction.

In the present study, the results suggest that physical training decreases EH in patients on HD and that it correlates with changes in exercise tolerance.

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