Clinical Correlates and Prognostic Significance of Six-minute Walk Test in Patients with Primary Pulmonary Hypertension

Comparison with Cardiopulmonary Exercise Testing

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The six-minute walk test is a submaximal exercise test that can be performed even by a patient with heart failure not tolerating maximal exercise testing. To elucidate the clinical significance and prognostic value of the six-minute walk test in patients with primary pulmonary hypertension (PPH), we sought (*1*) to assess the relation between distance walked during the six-minute walk test and exercise capacity determined by maximal cardiopulmonary exercise testing, and (*2*) to investigate the prognostic value of the six-minute walk test in comparison with other noninvasive parameters. The six-minute walk test was performed in 43 patients with PPH, together with echocardiography, right heart catheterization, and measurement of plasma epinephrine and norepinephrine. Symptom-limited cardiopulmonary exercise testing was performed in a subsample of patients ($n = 27$). Distance walked in 6 min was significantly shorter in patients with PPH than in age- and sex-matched healthy subjects (297 $\pm$ 188 versus 655 $\pm$ 91 m, $p < 0.001$). The distance significantly decreased in proportion to the severity of New York Heart Association functional class. The distance walked correlated modestly with baseline cardiac output ($r = 0.48$, $p < 0.05$) and total pulmonary resistance ($r = -0.49$, $p < 0.05$), but not significantly with mean pulmonary arterial pressure. In contrast, the distance walked correlated strongly with peak $\dot{V}O_2$ ($r = 0.70$, $p < 0.001$), oxygen pulse ($r = 0.57$, $p < 0.01$), and $\dot{V}E$-$\dot{V}CO_2$ slope ($r = -0.66$, $p < 0.001$) determined by cardiopulmonary exercise testing. During a mean follow-up period of 21 $\pm$ 16 mo, 12 patients died of cardiopulmonary causes. Among noninvasive parameters including clinical, echocardiographic, and neurohumoral parameters, only the distance walked in 6 min was independently related to mortality in PPH by multivariate analysis. Patients walking < 332 m had a significantly lower survival rate than those walking farther, assessed by Kaplan-Meier survival curves (log-rank test, $p < 0.01$). These results suggest that the six-minute walk test, a submaximal exercise test, reflects exercise capacity determined by maximal cardiopulmonary exercise testing in patients with PPH, and it is the distance walked in 6 min that has a strong, independent association with mortality. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, Nakanishi N, Miyatake K. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension: comparison with cardiopulmonary exercise testing. AM J RESPIR CRIT CARE MED 2000;161:487–492.

Primary pulmonary hypertension (PPH) is a rare, but life-threatening disease characterized by progressive pulmonary hypertension (1). Most patients with PPH have severe exertional limitation owing to cardiopulmonary factors from an early phase of this disease, which ultimately leads to right ventricular (RV) failure and death. Indeed, D'Alonzo and coworkers have demonstarted a decrease in peak exercise oxygen consumption (peak $\dot{V}O_2$) and an increase in the regression slope relating minute ventilation to carbon dioxide output ($\dot{V}E$-$\dot{V}CO_2$ slope) in patients with PPH, using cardiopulmonary exercise testing (2). Rhodes and coworkers have shown that the ability of cardiopulmonary exercise testing to identify PPH patients at high risk for cardiac catheterization is superior to that of other noninvasive variables (3). Interestingly, peak $\dot{V}O_2$ and $\dot{V}E$-$\dot{V}CO_2$ slope obtained from cardiopulmonary exercise testing have been shown to be related to mortality in patients with chronic heart failure (4, 5). These results raise the possibility that exercise testing can be used as a prognostic indicator in patients with PPH. However, maximal stress testing may be difficult in some patients with severe PPH (3).

(*Received in original form June 3, 1999 and in revised form July 30, 1999*)

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Am J Respir Crit Care Med Vol 161. pp 487–492, 2000
Internet address: www.atsjournals.org

The six-minute walk test is a submaximal exercise test that can be performed by a patient not tolerating maximal exercise tests (6). The test is very simple, requires inexpensive equipment, and is reproducible. In addition, it is considered safe because patients are self-limited during exercise. Recently, the distance walked in 6 min has been shown to correlate significantly with peak $\dot{V}O_2$ and $\dot{V}E$-$\dot{V}CO_2$ slope in patients with advanced heart failure, and thereby serves as a prognostic indicator in this disease (7, 8). In patients with PPH, the six-minute walk test has been used as a relative parameter to assess changes in functional capacity during vasodilator therapy (9, 10). However, few data exist regarding clinical significance and prognostic value of the six-minute walk test in patients with PPH.

In the present study, we sought (*1*) to assess the relation between the distance walked during the six-minute walk test and exercise capacity determined by cardiopulmonary exercise testing in patients with PPH and (*2*) to investigate the prognostic value of the six-minute walk test in comparison with clinical parameters, echocardiographic findings, and plasma catecholamine levels, which had been reported to be related to mortality in patients with PPH (3, 11, 12).

METHODS

Study Subjects

This study included 43 patients with PPH (13 men and 30 women; mean age, 37 yr; range, 14 to 67 yr) who were referred to our institute between December 1994 and January 1999. PPH was defined as pulmonary hypertension unexplained by any secondary cause, based on the criteria of the National Institutes of Health registry on PPH (1). Six patients were classified as New York Heart Association (NYHA) functional class II, 29 patients as class III, and eight patients as class IV. Thirty-eight patients (88%) received prostacyclin therapy: intravenous prostacyclin (n = 13) (9, 10, 13) or an oral prostacyclin analogue (n = 25) (14, 15). The remaining five patients did not receive prostacyclin therapy because four patients could not tolerate it due to hypotension resulting from uncompensated right heart failure and one patient developed hypoxia during prostacyclin therapy. All subjects gave informed consent.

Hemodynamic Studies

Diagnostic right heart catheterization was performed in all patients while they were in a stable condition during hospitalization. Baseline hemodynamic variables including mean pulmonary arterial pressure, mean right atrial pressure, pulmonary capillary wedge pressure, and mean systemic arterial pressure were measured in all patients. Cardiac output was measured by Fick's method (16). Total pulmonary resistance was calculated by dividing mean pulmonary arterial pressure by cardiac output.

Six-minute Walk Test

The six-minute walk test was performed in all patients with PPH and 16 age- and sex-matched healthy volunteers according to a standardized protocol (6, 17). They walked along an enclosed, level, measured corridor. Technicians escorted and encouraged subjects with the standardized statements, "You are doing well" or "Keep up the good work," but were asked not to use other phrases. Subjects were instructed to walk at their own pace but to cover as much ground as possible in 6 min. They tolerated the six-minute walk test without any adverse effects. Patients with PPH were divided into two groups according to the median value of the distance walked in 6 min: long distance group ($\geqslant$ 332 m, n = 21 and short distance group ($<$ 332 m, n = 22).

Cardiopulmonary Exercise Testing

Symptom-limited cardiopulmonary exercise testing was performed in 27 patients with PPH and 16 age- and sex-matched healthy volunteers. The remaining 16 patients with PPH were excluded from the protocol because they could not tolerate the maximal exercise test. Patients first pedaled at 55 rpm without any added load for 1 min. The work rate was then increased by 15 watts/min up until their symptom-limited maximum. Heart rate was monitored with standard electrocardio-

TABLE 1

COMPARISON OF PATIENT CHARACTERISTICS ACCORDING TO MEDIAN VALUE OF DISTANCE WALKED DURING THE SIX-MINUTE WALK TEST IN PATIENTS WITH PPH*

Variables	Short Distance Group[†] (*n = 22*)	Long Distance Group[‡] (*n = 21*)	p Value
Demographics			
Age, yr	39 ± 15	35 ± 13	NS
Sex, male/female	6/16	7/14	NS
Body surface area, m^2	1.5 ± 0.2	1.6 ± 0.2	NS
Hemodynamic variables			
Heart rate, beats/min	81 ± 15	75 ± 11	NS
$\overline{Psa}$, mm Hg	82 ± 8	85 ± 10	NS
$\overline{Ppa}$, mm Hg	61 ± 11	54 ± 12	NS
$\dot{Q}$, L/min	2.6 ± 0.7	3.9 ± 1.3	$<$ 0.001
TPR, Wood units	24 ± 6	16 ± 7	$<$ 0.001
$\overline{Pra}$, mm Hg	9 ± 4	6 ± 4	$<$ 0.001
Ppcw, mm Hg	8 ± 4	7 ± 3	NS
Blood gas variables			
Sa_{O_2}, %	93 ± 4	95 ± 3	NS
$S\bar{v}_{O_2}$, %	55 ± 8	66 ± 6	$<$ 0.001
Neurohumoral factors			
Plasma NE, pg/ml	534 ± 500	315 ± 196	NS
Plasma EPI, pg/ml	57 ± 63	39 ± 27	NS
Medication use, n			
Intravenous prostacyclin	8	5	NS
Oral prostacyclin analogue	11	14	NS
Anticoagulant agents	16	15	NS

Definition of abbreviations: EPI = epinephrine; NE = norepinephrine; NS = not significant; $\overline{Ppa}$ = mean pulmonary arterial pressure; Ppcw = pulmonary capillary wedge pressure; Pra = mean right atrial pressure; $\overline{Psa}$ = mean systemic arterial pressure; $\dot{Q}$ = cardiac output; Sa_{O_2} = arterial oxygen saturation; $S\bar{v}_{O_2}$ = mixed venous oxygen saturation; TPR = total pulmonary resistance.

* Values are expressed as mean ± SD unless otherwise indicated.

[†] Short distance group = patients walking $<$ 332 m in 6 min.

[‡] Long distance group = patients walking $\geqslant$ 332 m in 6 min.

graphic leads, and blood pressure was measured at the brachial artery with a sphygmomanometer. Breath-by-breath gas analysis was performed using an AE280 (Minato Medical Science, Osaka, Japan) connected to a personal computer running analyzing software (18).

The anaerobic threshold (AT) was chosen as the $\dot{V}O_2$ at which the $\dot{V}E/\dot{V}O_2$ increased while the $\dot{V}E/\dot{V}CO_2$ decreased or remained constant. Peak $\dot{V}O_2$ was defined as the value of averaged data during the final 15 s of exercise. The oxygen pulse was calculated by dividing $\dot{V}O_2$ by heart rate, an index of stroke volume during exercise. The $\dot{V}E$-$\dot{V}CO_2$ slope was determined as the linear regression slope of $\dot{V}E$ and $\dot{V}CO_2$ from the start of exercise until the RC point (the time up until which ventilation is stimulated by CO_2 output and end-tidal CO_2 tension begins to decrease) (19).

Blood Sampling and Assay for Neurohormones

Blood samples were drawn from a peripheral vein at diagnostic catheterization while the patient was in a stable hemodynamic state and not receiving vasodilator drugs. Blood was immediately transferred into a chilled glass tube containing disodium ethylenediaminetetraacetic acid (EDTA) (1 mg/ml), and plasma epinephrine and norepinephrine were measured as reported previously (20).

Echocardiographic Assessment

Echocardiography was performed with a Toshiba SSH-120A (Tokyo, Japan). Parasternal short-axis views were obtained at the papillary muscle level of the left ventricle (LV) using a 3.5-MHz sector transducer. The longest (L) and the shortest (S) diameters of the LV cavity were measured at the point of maximal deformity in early diastole. The LV deformity index was calculated as L/S (21). Pericardial effusions were also evaluated in the parasternal short-axis views in early diastole and graded as absent, small (separation less than 1 cm), or large (separation more than 1 cm).

Survival Estimates

Survival was estimated from the date of initial diagnosis to February 28, 1999, or the death of the patient. No patient received lung or heart–lung transplantation during the follow-up period. No patient died of noncardiopulmonary causes. The follow-up rate was 100%.

Statistical Analysis

All data were expressed as mean values ± SD. Comparisons between two groups were made by Fisher exact test or unpaired Student's *t* test. Comparisons of parameters among the four groups were made using one-way analysis of variance, followed by Scheffe's multiple comparison test. Correlation coefficients between distance walked in 6 min and other variables were determined by linear regression analysis. To determine whether the six-minute walk test has independent prognostic significance, the following eight variables were entered into a multivariate Cox proportional hazards regression analysis: age, sex, plasma norepinephrine, heart rate, arterial oxygen saturation, presence of pericardial effusion, LV deformity index, and the distance walked in 6 min. Survival curves according to the median value (332 m) of the distance walked in 6 min were derived using the Kaplan-Meier method and were compared using log-rank test. A p value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Demographic, hemodynamic, and neurohumoral data of the patients grouped according to the median value (332 m) of the distance walked in 6 min are summarized in Table 1. There were no significant differences in demographics between the long distance group and the short distance group. Cardiac output and mixed venous oxygen saturation were significantly lower in the short distance group than in the long distance group. Total pulmonary resistance and mean right atrial pressure were significantly higher in the short distance group than

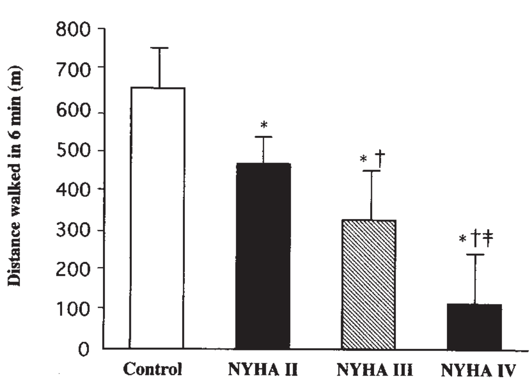

Figure 1. Relation between distance walked during six-minute walk test and NYHA functional class in patients with PPH. *p $<$ 0.05 versus control subjects; †p $<$ 0.05 versus NYHA functional class II; ‡p $<$ 0.05 versus NYHA functional class III.

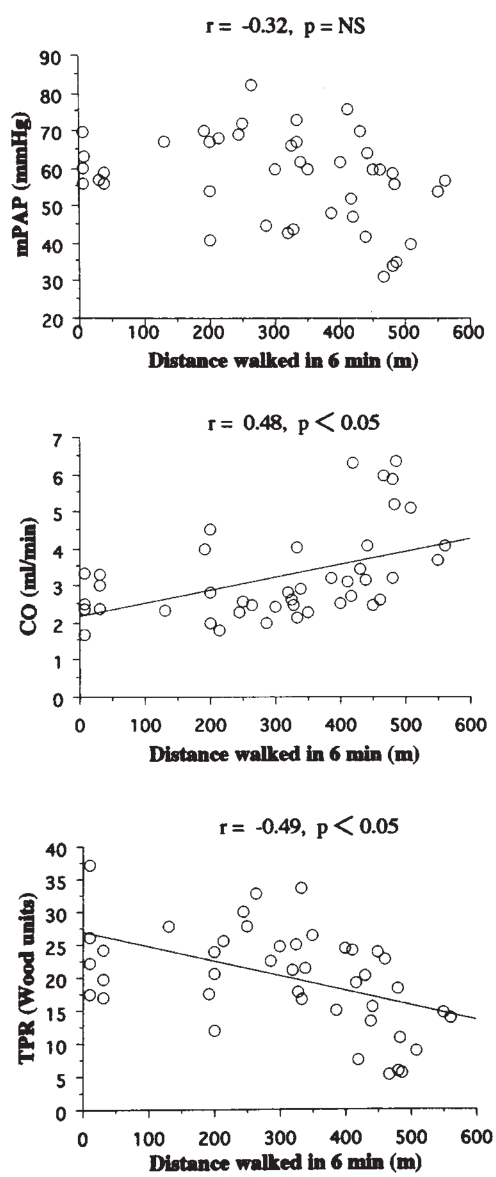

Figure 2. Relations between distance walked during six-minute walk test and hemodynamic variables at rest in patients with PPH. mPAP = mean pulmonary arterial pressure; CO = cardiac output; TPR = total pulmonary resistance.

in the long distance group. Neither plasma epinephrine nor norepinephrine level significantly differed between the two groups. There was no significant difference in medication use between the two groups.

Relations between Six-minute Walk Test and Clinical, Hemodynamic, and Neurohumoral Parameters

Distance walked in 6 min was significantly lower in patients with PPH than in healthy subjects (297 ± 188 versus 655 ± 91 m, $p < 0.001$). The distance significantly decreased in proportion to the severity of NYHA functional class (Figure 1). The distance walked in 6 min did not significantly correlate with mean pulmonary arterial pressure at baseline (Figure 2). In contrast, the distance walked was modestly, but significantly, correlated with cardiac output and total pulmonary resistance at baseline values. The distance walked in 6 min was not significantly correlated with plasma epinephrine or norepinephrine at baseline values.

Relations between the Six-minute Walk Test and Maximal Cardiopulmonary Exercise Testing

AT, peak $\dot{V}O_2$, and oxygen pulse were markedly lower in patients with PPH than in healthy subjects (AT, 8.0 ± 2.1 versus 17.9 ± 4.5 ml/kg/min; peak $\dot{V}O_2$, 13.4 ± 4.3 versus 36.4 ± 7.8 ml/kg/min; oxygen pulse, 0.09 ± 0.03 versus 0.21 ± 0.06 ml/kg, $p < 0.001$, respectively). The $\dot{V}E$-$\dot{V}CO_2$ slope was significantly higher in patients with PPH than in healthy subjects (42.5 ± 8.6 versus 24.5 ± 2.4, $p < 0.001$). Distance walked in 6 min showed strong positive correlations with peak $\dot{V}O_2$ and oxygen pulse determined by maximal cardiopulmonary exercise testing (Figure 3). The distance walked showed a strong negative correlation with $\dot{V}E$-$\dot{V}CO_2$ slope. The distance walked was modestly, but significantly, correlated with AT.

Six-minute Walk Test and Mortality in PPH

During a mean follow-up period of 21 ± 16 mo, 12 patients died of cardiopulmonary causes: seven patients died of progressive RV failure and five patients died suddenly. Among noninvasive variables, i.e., distance walked in 6 min, age, sex, plasma norepinephrine, heart rate, arterial oxygen saturation, presence of pericardial effusion, and LV deformity index, only the distance walked was independently related to mortality in PPH by multivariate Cox proportional hazards analysis (Table 2).

The Kaplan-Meier survival curves grouped according to the median value of the distance walked in 6 min demonstrated that patients walking < 332 m had a significantly lower survival rate than those walking farther (log-rank test, $p < 0.01$, Figure 4).

DISCUSSION

In this study, we demonstrated that distance walked during the six-minute walk test significantly decreased in proportion to the severity of NYHA functional class in patients with PPH, and that distance walked in 6 min was significantly correlated with baseline cardiac output, total pulmonary resistance, and mean right atrial pressure. We also demonstrated that the distance walked in 6 min was strongly correlated with peak $\dot{V}O_2$,

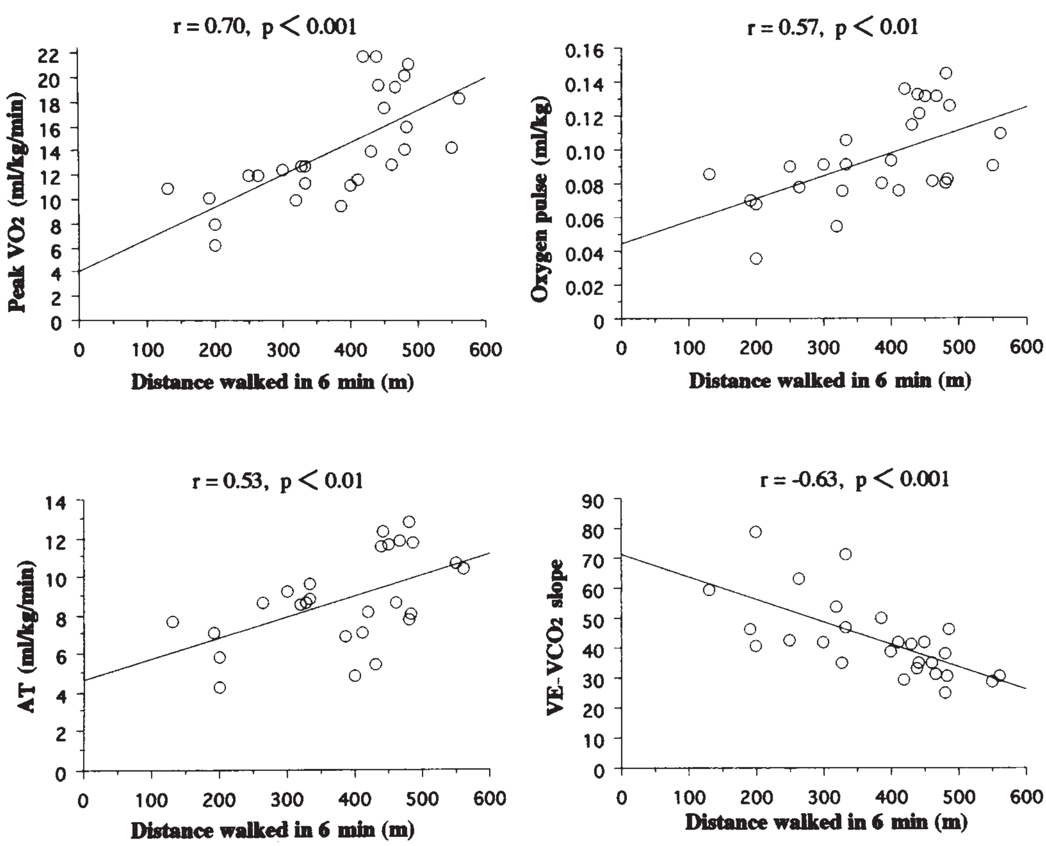

Figure 3. Relations between distance walked during six-minute walk test and exercise capacity determined by cardiopulmonary exercise testing in patients with PPH. Peak $\dot{V}O_2$ = peak exercise oxygen consumption; AT = anaerobic threshold; $\dot{V}E$-$\dot{V}CO_2$ slope = regression slope relating minute ventilation to carbon dioxide output.

TABLE 2

MULTIVARIATE ANALYSIS OF NONINVASIVE VARIABLES ASSOCIATED WITH MORTALITY IN PPH

Variable	Risk Ratio Estimate	95% CI	p Value
Age	1.024	0.940–1.115	0.5935
Sex	0.085	0.002–3.598	0.1970
Heart rate	1.044	0.917–1.189	0.5173
Sa_{O_2}	0.979	0.498–1.924	0.9503
Pericardial effusion	0.367	0.024–5.530	0.4687
LV deformity index	1.602	0.317–8.100	0.5689
Plasma NE	1.000	0.998–1.003	0.7467
Distance walked in 6 min	0.986	0.973–0.999	0.0381

Definition of abbreviatons: CI = confidence interval; LV = left ventricular; NE = norepinephrine; Sa_{O_2} = arterial oxygen saturation.

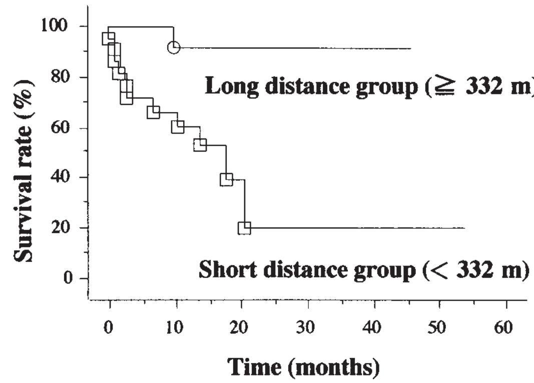

Figure 4. Kaplan-Meier survival curves according to median value of distance walked during six-minute walk test in patients with PPH. Patients walking < 332 m had a significantly lower survival rate than those walking farther (log-rank test, p < 0.001).

oxygen pulse, and $\dot{V}E$-$V CO_2$ slope determined by maximal exercise testing. Finally, we demonstrated that, among noninvasive variables, the distance walked in 6 min was independently related to mortality in PPH, and that patients walking < 332 m had a significantly lower survival rate than those walking farther as assessed by the Kaplan-Meier survival curves.

Six-minute Walk Test and Maximal Cardiopulmonary Exercise Testing

Maximal cardiopulmonary exercise testing has been shown to be a useful noninvasive tool to assess physiological changes associated with exercise (3, 22). Peak $\dot{V}O_2$ has been used as a marker for exercise capacity in a variety of cardiopulmonary diseases because it is determined by the maximal cardiac output during exercise, the potential for O_2 extraction by the exercising muscle, and the ventilatory capacity (23). Earlier studies have shown that peak $\dot{V}O_2$ was markedly decreased in patients with PPH, indicating an impaired cardiac reserve during exercise in this disease (2, 3). Unfortunately, however, cardiopulmonary exercise testing could not be performed in the most severe forms of PPH in this study, consistent with an earlier study (3). In contrast, the six-minute walk test, a submaximal exercise test, could be performed in all patients with PPH. Thus, this submaximal test may be applicable for evaluation of exercise capacity in patients with PPH. In fact, the six-minute walk test has been used as a relative parameter to assess changes in functional capacity during vasodilator therapy (9, 10). However, little information is available regarding clinical significance of the six-minute walk test in patients with PPH.

In the present study, we first demonstrated that distance walked in 6 min decreased in proportion to the decrease in peak $\dot{V}O_2$ and oxygen pulse determined by maximal cardiopulmonary exercise testing. On the other hand, the distance walked correlated modestly with baseline hemodynamic parameters. Considering that oxygen pulse is representative of changes in stroke volume during exercise (24), these results suggest that the distance walked during the six-minute walk test may reflect insufficient oxygen delivery to the body during exercise at least due to an inadequate increase in stroke volume during exercise. Unlike our study, Guyatt and coworkers failed to define a close association of the six-minute walk test with the results of maximal exercise testing in all patients with heart failure (25). Like our study, however, Cahalin and coworkers concluded that the six-minute walk test was useful in predicting peak $\dot{V}O_2$ in patients with severe heart failure who were referred for heart transplantation (7). The discrepancy may be explained in part by the difference in the severity of heart failure. The PPH patients in our study had severely limited daily activity (mean NYHA functional class, 3.0 ± 0.6). These results raise the possibility that there is a close association between submaximal exercise and maximal exercise in patients with severely reduced functional capacity. Thus, distance walked during the six-minute walk test may be related to exercise capacity determined by maximal exercise testing in patients with PPH.

In the present study, distance walked in 6 min was negatively correlated with $\dot{V}E$-$V CO_2$ slope in patients with PPH. This steeper slope is considered to be associated with increased physiologic dead space resulting from an impaired increase in pulmonary perfusion during exercise (5, 26). Thus, the six-minute walk test may also reflect pulmonary circulation reserve during exercise.

Six-minute Walk Test and Mortality in PPH

Previous studies have shown that mortality in PPH correlates with RV hemodynamic variables obtained invasively, such as mean pulmonary arterial pressure, cardiac output, and mean right atrial pressure (27, 28). However, a simple, noninvasive, and repeatedly available assessment of the mortality would be more desirable. Interestingly, distance walked during the six-minute walk test has been shown to have a strong, independent association with short-term mortality in patients with severe left-sided heart failure (7, 8). However, whether the six-minute walk test can predict mortality in PPH has remained unknown. Earlier studies have shown that pericardial effusion determined by echocardiography is associated with severe pulmonary hypertension and high right atrial pressure, and therefore may serve as a prognostic indicator (11). Sympathetic nervous system activation, indicated by a high plasma noreprinephrine level, has recently been shown to be associated with mortality in patients with PPH (12). Thus, in the present study, these parameters were included in multivariate Cox proportional hazards regression analysis. Among these noninvasive variables, however, only the distance walked in 6 min was the best predictor of mortality. It is interesting to speculate that a decreased cardiac reserve during exercise indicated by a short distance walked in 6 min may be associated with poor outcome in patients with PPH. Furthermore, the Kaplan-Meier survival curves according to the median value of distance walked demonstrated that patients walking < 332 m had a significantly lower survival rate than those walking farther. Thus, distance walked during the six-minute walk may serve as a prognostic indicator of PPH, which may complement invasive standard prognostic markers, such as RV hemodynamic variables.

Study Limitations

First, patients with the most severe forms of PPH were excluded from the cardiopulmonary exercise study. However, the conclusions drawn from the data would not have been different even if these patients had been included, because they had markedly poor exercise capacity (distance walked in 6 min = 170 ± 168 m).

Second, it appears to be important to show the relation of peak $\dot{V}O_2$ to survival. In the present study, however, this kind of analysis was impossible to perform, because the prognosis of patients completing maximal cardiopulmonary exercise testing was so good.

Third, subsequent therapy, which included vasodilators and anticoagulant agents, was not controlled in this study. Nevertheless, 38 patients (88%) received prostacyclin therapy: intravenous prostacyclin or an oral prostacyclin analogue, both of which have beneficial effects on survival in PPH (9, 10, 13–15). In addition, there was no significant difference regarding the medication use in the long distance group and the short distance group. Furthermore, this high rate of medication use in the present study may explain, at least in part, that plasma catecholamine levels were not an independent predictor of mortality by multivariate analysis.

Finally, our results may apply to the only patients receiving medical therapy, and it may be uncertain that the six-minute walk test would be as good a prognostic indicator in untreated patients.

Conclusions

The six-minute walk test, a submaximal exercise test, reflects exercise capacity determined by maximal cardiopulmonary exercise testing in patients with PPH, and it is the distance walked in 6 min that has a strong, independent association with mortality.

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