Six-minute walk distance as parameter of functional outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension

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Objectives: In chronic thromboembolic pulmonary hypertension, objective data to assess the functional outcome after pulmonary endarterectomy are lacking. We studied the 6-minute walk distance in relation to the clinical and hemodynamic severity of disease, and assessed the effect of pulmonary endarterectomy on the 6-minute walk distance.

Methods: A total of 50 consecutive patients with chronic thromboembolic pulmonary hypertension were studied. Subsequently, pulmonary endarterectomy was performed in 42 patients, 35 of whom underwent a 6-minute walk distance 1 year after surgery.

Results: The mean $\pm$ standard error of the mean 6-minute walk distance was 391 ± 19 m. The 6-minute walk distance decreased in proportion to New York Heart Association functional class and correlated (all $P < .0001$) with mean pulmonary artery pressure ($r = -0.62$), cardiac output ($r = 0.76$), total pulmonary resistance ($r = -0.75$), mixed venous oxygen saturation ($r = 0.77$), and brain natriuretic peptide ($r = -0.65$). One year after pulmonary endarterectomy, the 6-minute walk distance increased from 417 ± 19 m to 517 ± 16 m ($P < .0001$). The change from baseline in 6-minute walk distance correlated with the changes after 1 year in New York Heart Association functional class ($P < .01$) and brain natriuretic peptide ($r = 0.57$, $P < .002$), and with the observed hemodynamic changes directly after pulmonary endarterectomy (change in mean pulmonary artery pressure: $r = 0.52$; change in cardiac output: $r = 0.70$; change in total pulmonary resistance $r = 0.70$; all $P < .001$). In patients with residual pulmonary hypertension after pulmonary endarterectomy, the 6-minute walk distance was significantly lower than in hemodynamically normalized patients. However, the absolute increase in the 6-minute walk distance was higher in patients with residual pulmonary hypertension (137 ± 26 m and 82 ± 20 m, respectively; $P = .03$).

Conclusions: The 6-minute walk distance was demonstrated to reflect the clinical and hemodynamic severity of disease in patients with chronic thromboembolic pulmonary hypertension. One year after pulmonary endarterectomy, the 6-minute walk distance had increased significantly, and the change in the 6-minute walk distance correlated with the observed clinical and hemodynamic improvement.

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H. J. R. and M. N. vdP were supported by a nonrestricted grant from Actelion Pharmaceuticals, The Netherlands bv, Woerden, The Netherlands. P. B. received honoraria from Actelion Pharmaceuticals for lecturing at conferences. The other authors state that no conflict of interest exists.

Received for publication June 13, 2006; revisions received Oct 2, 2006; accepted for publication Oct 9, 2006.

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J Thorac Cardiovasc Surg 2007;133:510-6
0022-5223/\$32.00

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doi:10.1016/j.jtcvs.2006.10.020

The 6-minute walk test (6-MWT) is a reproducible, safe, and simple submaximal exercise test that can be used to evaluate exercise limitation in patients with cardiac and pulmonary diseases.¹ The 6-minute walk distance (6-MWD) was shown to correlate with peak oxygen consumption (peak VO_2) in patients with advanced heart failure^{2,3} or idiopathic pulmonary arterial hypertension (iPAH).⁴ In iPAH, the 6-MWD was also correlated with hemodynamic severity of disease and independently associated with mortality.⁴ Moreover, in

Abbreviations and Acronyms

BNP	= brain natriuretic peptide
CO	= cardiac output
CTEPH	= chronic thromboembolic pulmonary hypertension
iPAH	= idiopathic pulmonary arterial hypertension
mPAP	= mean pulmonary artery pressure
PEA	= pulmonary endarterectomy
SvO ₂	= venous oxygen saturation
TPR	= total pulmonary resistance
WSR	= Wilcoxon signed-ranks

iPAH, the 6-MWT was repeatedly used to assess changes in functional capacity in studies on the effectiveness of medical treatment.⁵⁻⁷

Chronic thromboembolic pulmonary hypertension (CTEPH) results from incomplete resolution of the vascular obstruction associated with pulmonary embolism.⁸ CTEPH is a life-threatening⁹ but potentially correctable form of pulmonary hypertension by means of pulmonary endarterectomy (PEA).⁸ After surgery, most patients experience a significant hemodynamic improvement, which is associated with improvements in reported New York Heart Association (NYHA) functional class and long-term survival.¹⁰ However, as the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for Surgical Treatments for Pulmonary Arterial Hypertension stated, objective data (eg, the 6-MWD) to assess the postoperative functional status are still lacking in patients with CTEPH after PEA.¹¹ In fact, data on the correlation of the 6-MWD with parameters reflecting clinical and hemodynamic severity of disease in CTEPH were not studied before.

Therefore, we studied the 6-MWD in relation to the clinical and hemodynamic severity of disease in patients with CTEPH. Moreover, we assessed the level of improvement of the 6-MWD 1 year after PEA and studied its relation to the postoperative clinical and hemodynamic outcome.

Methods**Study Subjects**

Fifty consecutive patients (29 females, mean age 53 ± 2 years, range 16–85 years) with a diagnosis of CTEPH, who were referred to the Academic Medical Center of the University of Amsterdam between July 2003 and July 2005, were studied. The diagnosis of CTEPH was established on the basis of previously reported procedures.¹² Diagnosis and cardiopulmonary hemodynamics were determined by pulmonary angiography and right-sided heart catheterization. Pulmonary hypertension was defined as mean pulmonary artery pressure (mPAP) greater than 25 mm Hg at rest ($n = 42$) or greater than 30 mm Hg during a standardized exercise test on a cycle ergometer ($n = 8$).¹³ In all patients, normal left ventricular function was documented by echocardiography. In

addition, coronary angiography was routinely performed in all patients aged more than 40 years. Postoperative hemodynamics were determined on the first or second day after PEA, before removal of the Swan-Ganz catheter. All patients received oral anticoagulation therapy for at least 3 months before referral to our hospital. All investigations were approved by the local institutional review board.

Six-minute Walk Test

The 6-MWT was routinely performed in all patients according to the guidelines of the American Thoracic Society.¹ At least 1 practice walk test was performed. All tests were supervised by a respiratory function technologist encouraging subjects with standard phrases as stated in the American Thoracic Society protocol. Patients were instructed to walk at their own pace along a 40-m corridor and to cover as much ground as possible in 6 minutes.

For each patient, the predicted 6-MWD was estimated by use of the regression equation described by Enright and Sherill.¹⁴

New York Heart Association

Each patient was functionally classified according to the NYHA classification of the World Health Organization before enrollment in the study and, if applicable, 1 year after PEA.¹⁵

Blood Sampling and Assay

Blood samples were analyzed at baseline ($n = 47$) and 1 year after PEA ($n = 33$) for brain natriuretic peptide (BNP) as a marker of right ventricular function.¹⁶ Samples were obtained from the brachial vein for plasma (ethylenediamine-tetra-acetic acid), centrifuged at 3000 rpm for 10 min at 4°C, and subsequently stored at –80°C until analysis. The patients were in a horizontal position for at least 15 minutes before the blood samples were obtained. BNP levels were determined by an immunoradiometric assay (Shionoria, Osaka, Japan), as previously described.¹⁷

Statistical Analysis

All data are expressed as mean $\pm$ standard error of the mean. All analyses were performed using the statistical package SPSS 11.5 (SPSS Inc, Chicago, Ill). The Jonckheere–Terpstra test was used to analyze the trend between the 6-MWD (continuous variable) and NYHA functional class (discontinuous variable).¹⁸ The differences between groups were tested with a parametric 1-way analysis of variance. In case of an overall statistical difference, the differences between 2 groups were further analyzed with the Student *t* test with Bonferroni's correction for multiple comparisons. Pearson's correlation test was used to assess correlations between the 6-MWD and the hemodynamic parameters, and was tested for 2-sided significance. Stepwise linear regression analysis was performed to calculate the predictive value of the individual parameters in relation to the 6-MWD. The Wilcoxon signed-ranks (WSR) test was used to analyze the effect of PEA on the 6-MWD. Spearman's rank correlation test was used to assess correlations between the change on PEA in the 6-MWD and the observed changes in the hemodynamic parameters, and was tested for 2-sided significance. The Mann-Whitney *U* test was used to analyze the difference between patients with normalized pulmonary

TABLE 1. Baseline characteristics

	mPAP > 25 mm Hg	mPAP ≤ 25 mm Hg
Subjects, n	42	8
Demographics		
Age, y	54 ± 2	52 ± 5
Female/male, n	23/19	6/2
Weight, kg	82 ± 2	82 ± 7
Height, cm	173 ± 2	169 ± 7
BSA, m ²	2.03 ± 0.05	1.93 ± 0.07
NYHA, n		
II	1	8
III	35	
IV	6	
Resting hemodynamics		
mPAP, mm Hg	48 ± 2	22 ± 1
CO, L/min ⁻¹	4.1 ± 0.2	6.5 ± 0.5
TPR, dynes/sec/cm ⁻⁵	1038 ± 71	277 ± 23
mRAP, mm Hg	11 ± 1	6 ± 1
PCWP, mm Hg	13 ± 1 (n = 35)	9 ± 1 (n = 7)
SvO ₂ , %	57 ± 2 (n = 38)	72 ± 1
Neurohormones		
BNP, pg/L	51 ± 9 (n = 40)	3 ± 1 (n = 7)

BNP, Brain natriuretic peptide; BSA, body surface area; CO, cardiac output; NYHA, New York Heart Association; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; PCWP, pulmonary capillary wedge pressure; SvO₂, venous oxygen saturation; TPR, total pulmonary resistance. All values are expressed as mean ± standard error of the mean.

hemodynamics (mPAP ≤ 25 mm Hg) and patients with residual pulmonary hypertension (mPAP > 25 mm Hg).

Results

All 50 patients underwent a full preoperative evaluation. Subsequently, 42 patients underwent a PEA procedure, that is, 37 patients with pulmonary hypertension at rest and 5 patients with exercise-induced pulmonary hypertension. The latter patients were selected for surgery on the basis of previously described criteria.^{8,19} They all had disabling impairment of exercise tolerance and angiographic evidence for proximal chronic thromboembolic occlusion of at least 2 lobes. Five patients were considered to have distal, inoperable CTEPH. In 3 of the 8 patients with exercise-induced pulmonary hypertension, a PEA was postponed.

The characteristics of the patients are summarized in Table 1. Most patients with pulmonary arterial hypertension at rest (n = 42) had moderate to severe pulmonary hypertension, with a median mPAP of 48 mm Hg (range 26–75 mm Hg) and a median total pulmonary resistance (TPR) of 976 dynes/sec/cm⁻⁵ (range 301–2064 dynes/sec/cm⁻⁵). Asymptomatic coronary artery disease was present in 2 patients with a significant stenosis in the left anterior descending coronary artery and the right coronary artery, respectively.

Figure 1. The 6-MWD in relation to NYHA functional class in patients with CTEPH (Student *t* test with Bonferroni's correction for multiple comparisons). NYHA, New York Heart Association; 6-MWD, 6-minute walk distance.

Correlates of 6-Minute Walk Distance in Patients With Chronic Thromboembolic Pulmonary Hypertension

The mean ± standard error of the mean of the 6-MWD was 391 ± 19 m. The 6-MWD decreased significantly in proportion to the severity of NYHA functional class (Figure 1), and a statistically significant negative trend was demonstrated ($P < .0001$; Jonckheere–Terpstra test). The 6-MWD correlated significantly with mPAP, cardiac output (CO), TPR, and mixed venous oxygen saturation (SvO₂) (Figure 2, A–D). The mean right atrial pressure ($r = -0.52$, $P < .0001$; Pearson's test) and levels of plasma BNP ($n = 47$; $r = -0.53$, $P < .0001$; Pearson's test) showed significant correlations with the 6-MWD. In contrast, pulmonary capillary wedge pressure ($n = 42$) did not correlate with the 6-MWD ($P = .8$).

After exclusion of the 8 patients with exercise-induced pulmonary arterial hypertension, significant correlations between the 6-MWD and the hemodynamic parameters were demonstrated (Pearson's test): mPAP: $r = -0.46$, $P < .005$; CO: $r = 0.65$, TPR: $r = -0.65$, SvO₂: $r = 0.69$ (all $P < .0001$); mean right atrial pressure $r = -0.44$ ($P < .005$); BNP $r = -0.46$ ($P < .005$).

By multivariate linear regression analysis of all individual parameters that correlated significantly with the 6-MWD, only SvO₂ and CO were shown to be independently associated with the 6-MWD (model: $r^2 = 0.63$, $P < .0001$; SvO₂: $\beta = 0.49$, $P = .001$; CO: $\beta = 0.36$, $P < .02$).

Effect of Pulmonary Endarterectomy

In 35 of the 42 patients in whom a PEA was performed, a 6-MWT was obtained 1 year postoperatively. Four patients

Figure 2. Correlations between the 6-MWD and the pulmonary hemodynamic parameters. **A,** mPAP; Pearson $r = -0.62$; $P < .0001$. **B,** CO; Pearson $r = 0.76$; $P < .0001$. **C,** TPR; Pearson $r = -0.75$; $P < .0001$. **D,** Mixed SvO_2 ; $n = 46$; Pearson $r = 0.77$; $P < .0001$. mPAP, Mean pulmonary artery pressure; 6-MWD, 6-minute walk distance; TPR, total pulmonary resistance; CO, cardiac output; SvO_2 , venous oxygen saturation.

died postoperatively, 2 of progressive right heart failure caused by persistent pulmonary hypertension and 2 of post-operative massive alveolar hemorrhage. In addition, 3 patients were excluded from the analysis after 1 year because they were already treated medically for symptomatic (NYHA III/IV) residual pulmonary hypertension.

In the 35 patients, PEA was associated with significant hemodynamic improvement (WSR test): mPAP decreased from 44 ± 3 mm Hg to 25 ± 1 mm Hg ($P < .0001$); CO increased from 4.6 ± 0.2 L/min⁻¹ to 5.0 ± 0.2 L/min⁻¹ ($P = .5$); and TPR decreased from 878 ± 88 dynes/sec/cm⁻⁵ to 444 ± 33 dynes/sec/cm⁻⁵ ($P < .0001$).

Directly after PEA, 12 patients had (by definition) residual pulmonary hypertension (mPAP > 25 mm Hg; range 26–48 mm Hg), 4 of whom had an mPAP greater than 30 mm Hg. Hemodynamically, the patients with residual pulmonary hypertension represented the more severely affected patients; preoperative mPAP was significantly higher in patients with residual pulmonary hypertension compared

with patients with normalized pulmonary hemodynamics (55 ± 9 mm Hg vs 36 ± 10 mm Hg, $P < .0001$; WSR test).

One year after PEA, NYHA functional class had improved in all but 2 patients (Figure 3), and the 6-MWD had increased from 417 ± 19 m to 517 ± 16 m ($P < .0001$; WSR test). The change in NYHA functional class correlated significantly with the change in the 6-MWD ($P < .02$; Jonckheere Terpstra test). In addition, the observed change (Δ) in the 6-MWD correlated with the change from baseline 1 year after PEA in plasma BNP levels (Δ BNP: $r = 0.57$, $P < .002$; Spearman's rank correlation test). In addition, the change from baseline in the 6-MWD 1 year after PEA correlated significantly with the change from baseline observed in the hemodynamic parameters directly after PEA (Δ mPAP: $r = 0.52$; Δ CO: $r = 0.70$; Δ TPR: $r = 0.70$; all $P < .001$; Spearman's rank correlation test).

The 6-MWD in patients with and without residual pulmonary hypertension differed significantly both before and after PEA (Figure 4, A). In patients with residual pulmonary

Figure 3. NYHA functional class in individual patients ($n = 35$) before and 1 year after PEA (WSR test). NYHA, New York Heart Association; PEA, pulmonary endarterectomy.

hypertension, the 6-MWD, expressed as percentage of predicted, was significantly lower than in hemodynamically normalized patients. The absolute increase in the 6-MWD, however, was significantly higher in patients with residual pulmonary hypertension (mPAP > 25 mm Hg: 137 ± 26 m, and mPAP ≤ 25 mm Hg: 82 ± 20 m, respectively; $P = .03$; Mann-Whitney U test).

One year after PEA, the 6-MWD expressed as the percentage of predicted had increased from $69\% \pm 4\%$ to $87\% \pm 3\%$ ($P < .0001$; WSR test). The 6-MWD 1 year after PEA particularly tended to normalize in the patients with normalized pulmonary hemodynamics after PEA (Figure 4, B).

Discussion

In the present study, we demonstrated that the 6-MWD correlated with parameters reflecting clinical and hemodynamic severity of disease in CTEPH. PEA resulted in a significant increase in the 6-MWD 1 year after surgery. Moreover, the change in the 6-MWD correlated with the observed clinical and hemodynamic improvement.

Previously, in patients with iPAH, the 6-MWD was shown to correlate significantly with hemodynamic severity of disease.⁴ Compared with the data reported in these patients, however, the correlations observed between the 6-MWD and pulmonary hemodynamics in the present study seem more robust. In fact, the mean PAP did not correlate with the 6-MWD in patients with iPAH. This difference

Figure 4. The 6-MWD before and 1 year after PEA in 35 patients in relation to postoperative hemodynamic outcome (Mann-Whitney U test). Patients with residual pulmonary hypertension (open bars) (mPAP > 25 mm Hg; $n = 12$); patients with normalized pulmonary hemodynamics (solid bars) ($n = 23$). A, 6-MWD expressed as the absolute distance walked (m). B, 6-MWD expressed as percentage of predicted values. PEA, Pulmonary endarterectomy; 6-MWD, 6-minute walk distance.

may be explained, at least in part, by the inclusion of patients with exercise-induced pulmonary hypertension in the current study. By inclusion of these patients, we were able to study the whole spectrum of disease severity. Inclusion of these patients in the correlations between the 6-MWD and the hemodynamic parameters at rest, however, may have affected the statistical significance of these correlations. Exclusion of these patients from the analyses, however, only modestly affected the statistical significance of the observed correlations.

In the present study, parameters reflecting (impairment of) cardiac function (ie, CO, SvO₂, and plasma BNP levels) strongly correlated with the distance walked in the 6-MWT,

even without apparent loss of correlation in the most severely affected patients. By multivariate linear regression analysis, SvO₂ and CO were demonstrated to be independently associated with the 6-MWD. The current data in patients with CTEPH are consistent with previous observations in patients with iPAH, that is, the 6-MWD is in major part related to the parameters reflecting the (right-sided) heart function.^{4,20}

In the patients who performed a 6-MWT 1 year after PEA, a significant improvement of the 6-MWD was observed. Moreover, the change in the 6-MWD correlated with the observed changes in the hemodynamic parameters directly after PEA. In fact, the 6-MWD 1 year after PEA differed between patients with and without residual pulmonary hypertension. Although pulmonary hemodynamics may improve up to 2 years after PEA,²¹ evidence of residual pulmonary hypertension directly after PEA seemed to discriminate and was associated with a significantly lower 6-MWD 1 year after PEA. Preoperatively, the group with residual pulmonary hypertension represented, clinically and hemodynamically, the more severely affected patients. The observed improvement in the 6-MWD in the patients with residual pulmonary hypertension, however, was even higher than in the patients with normalized pulmonary hemodynamics. Thus, although these patients were not fully normalized hemodynamically after PEA, functionally, they truly benefited from surgical treatment. Moreover, it should be emphasized that these patients (who are likely to have more distally localized chronic thromboembolic disease) may benefit more from PEA in highly experienced centers.

To estimate the extent of normalization of functional capacity after PEA, we calculated predicted values for the 6-MWD according to the regression equation of Enright and Sherill.¹⁴ One year after a hemodynamically successful PEA, the 6-MWD expressed as the percentage of the predicted value appeared within the normal range. Normalization of functional capacity in these patients was consistent with the fact that the (more subjective) NYHA functional class was I/IV in all patients. Interpretation of this observation, however, should be done with some care. The algorithm was validated in individuals between 40 and 80 years of age, whereas, in this series, 9 patients with normalized pulmonary hemodynamics were aged less than 40 years. By assuming that younger people can walk a longer distance than predicted by the algorithm, this may lead to an apparent normalization of the functional capacity expressed as the percentage of predicted. This may have a positive effect on the observed outcome in the entire group. However, because neither the absolute 6-MWD nor the 6-MWD expressed as the percentage of predicted value differed between both groups 1 year after PEA, this seems unlikely.

Although the subgroup of patients with CTEPH in whom a 6-MWT was performed 1 year after PEA repre-

sented those who underwent operation consecutively, some selection bias may have occurred. Four patients died postoperatively, and 3 patients were excluded from the analysis after 1 year because they were already treated medically for symptomatic (NYHA III/IV) residual pulmonary hypertension.

Conclusions

The 6-MWT is a safe, easy-to-perform, noninvasive, sub-maximal exercise test that was demonstrated in this study to reflect the clinical and hemodynamic severity of disease in patients with CTEPH. One year after PEA, the 6-MWD increased significantly, and the change correlated with the observed clinical and hemodynamic improvement. Moreover, in patients with normalized pulmonary hemodynamics after PEA, the 6-MWD, expressed as the percentage of the predicted value, tended to normalize.

The authors thank Dr Jaring S. van der Zee for his constructive comments on the article.

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