



Pulmonary arterial compliance and exercise capacity after pulmonary endarterectomy

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ABSTRACT Patients with chronic thromboembolic pulmonary hypertension (CTEPH), despite successful pulmonary endarterectomy (PEA), can continue to suffer from a limitation in exercise capacity. The objective of this study was to assess whether pulmonary arterial compliance is a predictor of exercise capacity after PEA.

Right heart haemodynamics, treadmill incremental exercise test, spirometry, carbon monoxide transfer factor, arterial blood gas and echocardiographic examinations were retrospectively analysed in a population of CTEPH patients who underwent PEA at a single centre. Baseline and 3-month haemodynamic data were available in 296 patients; 5-year follow-up data were available in 68 patients.

In a multivariable model the following parameters were found to be independent predictors of exercise capacity after surgery: age, sex, pulmonary arterial compliance, tricuspid annular plane excursion, arterial oxygen tension and carbon monoxide transfer factor ($p < 0.0001$); the model showed good discrimination (Harrell's $c = 0.84$) and calibration (shrinkage coefficient = 0.91). Poor exercise capacity at 3 months was loosely associated with higher death rate during subsequent survival (Harrell's $c = 0.61$).

In conclusion, after successful PEA, reduced pulmonary arterial compliance is an important determinant of exercise capacity in association with the age and sex of the patients, and the extent of recovery of both cardiac and respiratory function. However, exercise capacity does not explain a large proportion of the effect of surgery on subsequent survival.



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Introduction

Pulmonary endarterectomy (PEA) is the treatment of choice to relieve pulmonary artery obstruction in patients with chronic thromboembolic pulmonary hypertension (CTEPH) [1–3]. In expert centres PEA is associated with low mortality even in patients with distal segmental chronic thromboembolic disease [4]. However, the information on long-term effects of PEA on exercise capacity is scant. In a long-term follow-up study, functional capacity slowly recovered over time and was still impaired in a substantial proportion of patients 4 years after PEA, despite the fact that right heart haemodynamics improved rapidly and steadily [5]. However, from a pathophysiological point of view, standard right heart haemodynamic parameters cannot provide a complete and correct description of right ventricular afterload in patients with pulmonary hypertension. In fact, right ventricular afterload is usually underestimated from single determinations of pulmonary vascular resistance (PVR), which assume a steady flow and completely ignore the pulsatile load imposed by the cardiac cycle. It has recently been shown that the relationship between PVR and pulmonary compliance is hyperbolic, with a proportionally more important decrease in pulmonary compliance at close to normal PVR and little further decrease of pulmonary compliance in severe pulmonary hypertension [6, 7]. Pulmonary compliance is a pathophysiologically and clinically relevant descriptor of the arterial load on the right ventricle [8–10]. In 13 successfully operated patients with CTEPH and persistent dyspnoea, a decreased pulmonary compliance under exercise was shown to be a predictor of limited exercise capacity [11]. A limitation of previous series is that, due to the small number of patients, the independent role of pulmonary compliance was not tested in a multivariable model.

Accordingly, the objective of this study was to determine whether pulmonary compliance at rest is an independent determinant of exercise capacity after PEA. In addition, we aimed to assess the prognostic significance of exercise capacity after PEA; this information might be useful considering the increasing number of trials with pharmacological interventions, which include patients with persistent pulmonary hypertension after surgery and include exercise tolerance as an end-point to test drug efficacy.

Methods

Patients

From April 1994 to October 2012, 433 patients diagnosed with CTEPH, according to published standardised protocols [1, 2], underwent PEA at our institution (Fondazione IRCCS Policlinico San Matteo, Pavia, Italy). The present study is a retrospective evaluation of the cohort of 296 patients in whom at least one control right heart haemodynamic evaluation was performed in the follow-up after PEA (at 3 months). The anaesthesiological and surgical methods used have been extensively reported and discussed elsewhere [12]. Of note, the operability rate improved over the years, increasing from 74% in 2004 to 91% in 2011, mainly after the indication for surgery was extended to patients with more distal (Jamieson type III) disease. All patients signed an informed consent agreement, approved by the institutional review board of Fondazione IRCCS Policlinico San Matteo (Pavia, Italy) for longitudinal, nonpharmacological, non-sponsored studies, which complies with the Italian legislation (Codex on Privacy, D. Lgs. 30 giugno 2003, n. 196).

Follow-up

Patients underwent haemodynamic, echocardiographic, respiratory and functional evaluations preoperatively and after surgery at hospital discharge, at 3 months and then every year for the next 5 years. On the basis of the haemodynamic evaluation performed at hospital discharge, patients were considered to have residual pulmonary hypertension if PVR at discharge was $>500 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ or if the reduction in PVR from the preoperative evaluation was $<50\%$ [13]. Good exercise tolerance during follow-up was primarily defined as the ability to cover at least 400 m, as described in a previous paper [5], or as the ability to reach a metabolic equivalents (METs) value above the median value of $5 \text{ kcal}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$. During follow-up, some patients with persistent pulmonary hypertension after surgery were enrolled in clinical trials to test the effects of drugs on this condition; however, the data reported in the present study do not include those obtained during the active phases of the clinical trials.

Right heart catheterisation was performed through the right internal jugular vein using a flow-directed, balloon-tipped Swan–Ganz catheter (7.5F; Edwards Lifesciences, Irvine, CA, USA). The following parameters were measured or calculated: cardiac output, cardiac index, right atrial pressure, pulmonary artery pressure, capillary wedge pressure, PVR and pulmonary compliance (calculated as stroke volume/pulse pressure).

A standard M-mode, two-dimensional and Doppler echocardiographic study was performed using commercially available equipment. The examination included several parameters describing right ventricular geometry and function: the right ventricular end-diastolic diameter determined in parasternal long axis view; the right ventricular end-diastolic (RVEDA) and end-systolic (RVESA) areas measured in an

apical view; the right ventricular fractional area change calculated as $(RVEDA-RVESA/RVEDA) \times 100$; the systolic displacement of the tricuspid annular plane (TAPSE); the tricuspid regurgitation graded using the jet area method; and the diameter of the inferior vena cava and its inspiratory collapse.

The treadmill exercise was performed according to the modified Bruce protocol, the distance (in metres) walked and the METS during the test were measured to describe functional capacity. The respiratory evaluation included spirometry, single breath transfer factor of the lung for carbon monoxide ($TLCO$) and arterial blood gas analyses. $TLCO$ was considered moderately to severely impaired when $<60\%$ predicted and severely impaired when $<40\%$ pred. Patients were defined as hypoxaemic when arterial oxygen tension (PaO_2) was <80 mmHg and to have respiratory failure when PaO_2 was <60 mmHg; to evaluate changes over time, the measured PaO_2 was standardised to an arterial carbon dioxide tension of 40 mmHg.

Statistical Analysis

Data were described as mean \pm SD or median (25th–75th percentiles) if continuous and as counts (%) if categorical. Changes over time for the studied parameters were assessed by means of a generalised linear model. At each time point during follow-up (from 3 months to 5 years) the determinants of functional capacity were assessed with a logistic regression model, with calculation of robust Huber–White standard errors to account for intra-patient correlation. Two analyses were performed: in the first good functional capacity was defined as Bruce protocol ≥ 400 m and in the second as a value of METS greater than the median; in both cases noncollinear variables with $p < 0.1$ in univariable analysis were included in a multivariable model. A Cox regression model was used to verify whether functional capacity at 3 months could be considered a surrogate end-point for long-term survival after PEA (with start of follow-up at 3 months). In this analysis those patients who did not perform the Bruce test, because of respiratory failure or for any other reason, were treated statistically as a separate group. The end-point of survival analysis was cardiovascular mortality; lung transplant was considered a censoring event. Median (25th–75th percentiles) survival was computed with the inverse Kaplan–Meier method. Mortality rates per 100 person-years and hazard ratios were computed with 95% confidence intervals. Model validation was performed in all cases.

Stata 13 (StataCorp LP, College Station, TX, USA) was used for computation, a two-sided p -value < 0.05 was considered statistically significant.

Results

Clinical characteristics of the patients and changes occurring over a 5-year follow-up

The baseline characteristics of the 296 patients enrolled in the present study are shown in table 1. No patient started an off-label therapy with pulmonary arterial hypertension drugs as a bridge to PEA, patients who were referred on vasodilator therapy discontinued this therapy after surgery. Additional cardiac surgical procedures were performed in few patients during PEA: coronary artery grafting was performed in 26 patients, valve replacement in four patients and closure of an atrial septal defect in one patient. The pulmonary capillary wedge pressure was elevated (>15 mmHg) in nine patients.

Long-term clinical changes after PEA are summarised in online supplementary table S1. Preoperatively, the majority of patients were in World Health Organization functional class III/IV and, on average, the functional capacity evaluated in the modified Bruce test was poor. Postoperatively, most patients were in functional class I/II and the distance walked during the exercise test gradually increased during the follow-up period (online supplementary fig. S1). All haemodynamic parameters normalised after surgery and the improvement was steadily maintained over time (online supplementary table S2). The changes over time for pulmonary compliance are shown in figure 1. Residual pulmonary hypertension (as defined above) was present in 35 out of the 296 patients at the 3-month evaluation. At different times during the follow-up, 20 patients with residual pulmonary hypertension were enrolled in randomised clinical trials testing the efficacy of pulmonary arterial hypertension drugs.

Among the echocardiographic measures (online supplementary table S3), TAPSE decreased, when compared to baseline, in the first few months after surgery; restoration of baseline preoperative values for TAPSE were observed at the 3-year visit. Online supplementary figure S2 includes the data for TAPSE 1 month after surgery, to better clarify the substantial early decrease in TAPSE after surgery.

Among the respiratory measures (online supplementary table S4), $TLCO$ slowly improved over the 5-year follow-up period (online supplementary fig. S3), whereas PaO_2 and vital capacity improved soon after surgery and the improvement was maintained over time.

19 patients died during the follow-up period after the third month. Death was considered to be due to irreversible heart failure in four patients, pulmonary embolism in one patient, myocardial infarction in two

TABLE 1 Baseline preoperative characteristics of the population

Age years	57.0 ± 15.3
Male	143
Jamieson type 1/2/3/4	135/76/80/5
WHO class II/III/IV	40/136/120
Previous deep venous thrombosis	186
Oxygen therapy	137
Months in WHO class III/IV before surgery	19.1 [5.1–22.2]
COPD	29
Systemic hypertension	73
Diabetes mellitus	11
Ischaemic heart disease	21

Data are presented as mean ± SD, n or median (25th–75th percentile). n=296. WHO: World Health Organization; COPD: chronic obstructive pulmonary disease.

patients and sudden in two patients. The cause of death was major bleeding in seven patients, stroke in two patients and respiratory failure in one patient.

Compliance as a determinant of the improvement in functional capacity

At univariable analysis, the following parameters were found to be associated with good functional capacity (defined as Bruce test ≥ 400 m): younger age (analysed as continuous variable), male sex, higher pulmonary compliance (analysed as continuous variable), preserved TAPSE (analysed both as a continuous variable and dichotomised as >14 mm or ≤ 14 mm), higher P_{aO_2} and $TLCO$ (analysed as continuous variables) and absence of residual pulmonary hypertension (defined as above). At multivariable analysis, pulmonary compliance was shown to independently predict functional capacity at any time (OR 1.91, 95% CI 1.06–3.42; $p=0.030$), while adjusting for potential confounders, other independent predictors were age, sex, TAPSE (dichotomised as >14 mm or ≤ 14 mm), P_{aO_2} and $TLCO$ % pred (table 2). Overall, the model showed good discrimination ($c=0.84$) and calibration (shrinkage coefficient=0.91).

At univariable analysis, the following parameters were found to be associated with good functional capacity (defined as a METS value greater than the general median of $5 \text{ kcal}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$): younger age (analysed as continuous variable), male sex, higher pulmonary compliance (analysed as continuous variable), preserved TAPSE (analysed both as a continuous variable and dichotomised as >14 mm or ≤ 14 mm), higher P_{aO_2} and $TLCO$ (analysed as continuous variables) and absence of residual pulmonary hypertension (defined as above). At multivariable analysis pulmonary compliance was shown to independently predict functional capacity at any time (OR 2.13, 95% CI 1.14–3.97; $p=0.030$), while adjusting for potential confounders (table 3), other independent predictors were age, sex, P_{aO_2} and $TLCO$ % pred. Overall, the model showed good discrimination ($c=0.85$) and calibration (shrinkage coefficient 0.92).

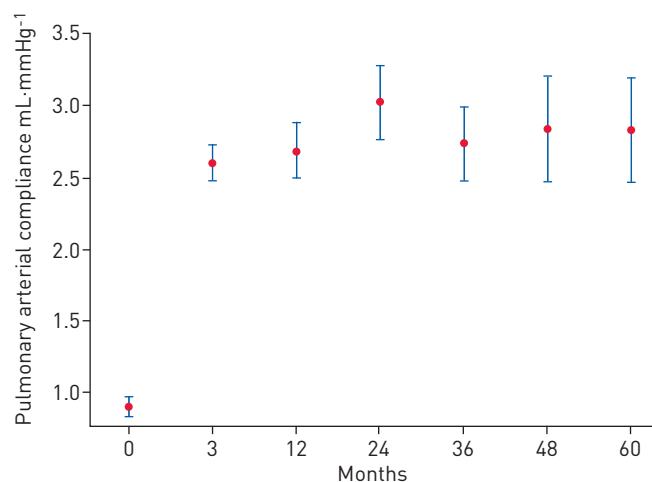


FIGURE 1 Changes in pulmonary compliance over time. Data are displayed on the log scale. Bars indicate 95% confidence intervals.

TABLE 2 Multivariable logistic regression model for predicting good functional capacity (definition based on distance walked) after pulmonary endarterectomy

Variables	OR (95% CI)	p-value
Pulmonary compliance mL·mmHg⁻¹	1.91 (1.06–3.42)	0.030
Age[#]	0.96 (0.93–0.98)	<0.001
Female sex	2.04 (1.13–3.68)	0.018
PaO₂[‡]	1.07 (1.05–1.10)	<0.001
TLCO % predicted[‡]	1.03 (1.01–1.06)	0.003
TAPSE⁺	0.56 (0.34–0.95)	0.030

PaO₂: arterial oxygen tension; TLCO: transfer factor of the lung for carbon monoxide; TAPSE: systolic displacement of the tricuspid annular plane. Global p-value of the model <0.001; c statistic 0.84; shrinkage 0.91. [#]: per year; [‡]: per unit; ⁺: ≥14 mm versus <14 mm.

Relationship between exercise capacity at 3-months and long-term survival after PEA

At the 3-month follow-up evaluation, the Bruce test was performed in 244 out of the 296 patients: 12 patients were unable to perform a maximal exercise test due to respiratory insufficiency (PaO₂ <60 mmHg), 34 patients because of orthopaedic problems and for six patients it was considered too early to perform a symptom-limited test after major surgery.

During the subsequent follow-up period, 19 patients died and no patients underwent lung transplant; no patient was lost to follow-up. In particular, two patients died in the group of 121 patients walking ≥400 m, 12 patients died in the group of 123 patients walking <400 m, and five patients died in the group of 52 patients who could not perform the test (fig. 2). In Cox regression analysis the hazard ratio was 0.18 (95% CI 0.04–0.79) for walking ≥400 m versus <400 m (p=0.023), 1.01 (95% CI 0.40–2.58) for not performed versus walking <400 m (p=0.978), and 0.18 (95% CI 0.04–0.85) for walking ≥400 m versus not performed (p=0.031). Despite statistical significance, the association between the distance walked at 3 months and subsequent survival was loose, the discrimination (Harrell's c) and the Royston explained variation were 0.63 and 0.26, respectively.

Discussion

The present study shows that in CTEPH patients who have undergone PEA: 1) exercise tolerance has a multifactorial aetiology, as it is strongly associated with pulmonary arterial compliance together with the age and sex of the patient and with the extent of recovery of both cardiac and respiratory function after surgery; 2) functional capacity assessed 3 months after surgery does not appear to explain a large proportion of the effects of PEA on subsequent survival.

Determinants of exercise capacity after PEA

The improvement of conventional haemodynamic parameters after PEA is known to be rapid and sustained over time. However, the study of pulmonary compliance under exercise uncovered an abnormal pulmonary haemodynamic response to exercise as a strong predictor of limited exercise capacity after PEA [11]. In addition, the study of the relationship between PVR and pulmonary compliance (*i.e.* the time constant of the pulmonary circulation) revealed that persistent alterations may be observed in CTEPH patients undergoing PEA, possibly because of persistent structural changes even after the removal of obstructions [14].

The present study expands previous observations showing, in a large unselected population of patients who underwent PEA, that pulmonary compliance at rest is an independent predictor of functional capacity. Importantly, the role of pulmonary compliance remained statistically significant in a multivariable model taking into account demographics, and the recovery of respiratory and of right ventricular function. Female sex and old age were found to be significant determinants of functional outcome after PEA; old age may be associated with skeletal muscle deconditioning and might delay recovery or need a long time to be restored. In fact, a relatively old age was considered important to explain the discrepancy between positive haemodynamic changes and poor exercise capacity improvements in CTEPH patients treated with bosentan in the BENEFIT (bosentan effects in inoperable forms of chronic thromboembolic pulmonary hypertension) trial [15, 16].

In addition, muscle strength may be reduced in patients with pulmonary hypertension compared with control subjects [17]. A delayed recovery in TLCO could be considered the consequence of major surgery in the early period after PEA and of the vessels remodelling before surgery in the nonobstructed segments of

TABLE 3 Multivariable logistic regression model for predicting good functional capacity (definition based on metabolic equivalents) after pulmonary endarterectomy

Variables	OR (95% CI)	p-value
Pulmonary compliance mL·mmHg⁻¹	2.13 (1.14–3.97)	0.018
Age[#]	0.96 (0.94–0.98)	<0.001
Female sex	2.29 (1.3–4.0)	0.003
PaO₂[†]	1.08 (1.05–1.11)	<0.001
TLCO % predicted[‡]	1.04 (1.01–1.06)	0.001
TAPSE⁺	0.64 (0.37–1.08)	0.096

PaO₂: arterial oxygen tension; TLCO: transfer factor of the lung for carbon monoxide; TAPSE: systolic displacement of the tricuspid annular plane. Global p-value of the model <0.001; c statistic 0.85; shrinkage 0.92. #: per year; †: per unit; +: ≥14 mm versus <14 mm.

the lungs in the later follow-up. At baseline TLCO may not necessarily be profoundly reduced in CTEPH patients because of back-perfusion of the capillary bed by the extensive bronchial arterial collateral blood flow [18]. TAPSE was the echocardiographic index of longitudinal right ventricular function included in the final multivariable predictive model. Noticeably, TAPSE was substantially impaired immediately after surgery and baseline values were restored only at the 3-year follow-up evaluation. Such an abnormality of longitudinal function of the right ventricle is neither related to the type of intervention (PEA) nor to the disease treated (CTEPH), since it has already been described in patients undergoing surgery for ischaemic or valvular heart disease. The most likely responsible mechanism is tethering of the right ventricular wall due to adhesions between the heart and surrounding tissues [19, 20]. An incomplete recovery of right ventricular function after PEA may be more relevant in the presence of decreased pulmonary compliance to explain the imperfect recovery of exercise capacity; thus, the present data are in agreement with the previous hypothesis of a cardiac, rather than a ventilatory, limitation of exercise capacity after PEA [11].

Prognostic significance of reduced functional capacity

The present data add to a growing body of literature on the use of exercise capacity as an outcome measure in another form of pulmonary hypertension, pulmonary arterial hypertension, where the data suggests that the distance walked during the 6-min walking test does not explain much of the pharmacological effect, has only modest validity as a surrogate end-point for clinical events and, therefore, may not be a reliable marker of disease in clinical trials [21–24]. The results presented in this article suggest that poor exercise capacity after PEA is related to poorer subsequent survival; however, the effects of surgery on survival were to a large extent unexplained by exercise capacity data. Therefore, caution is necessary when considering functional capacity as an outcome measure in trials including operated CTEPH patients.

Limitations

As this is a retrospective analysis of data obtained in a single centre, the findings should be validated in a larger multicentre setting. However, the use of a prospective dedicated database since the PEA programme was started, the inclusion of consecutive patients who underwent PEA and the long follow-up period after

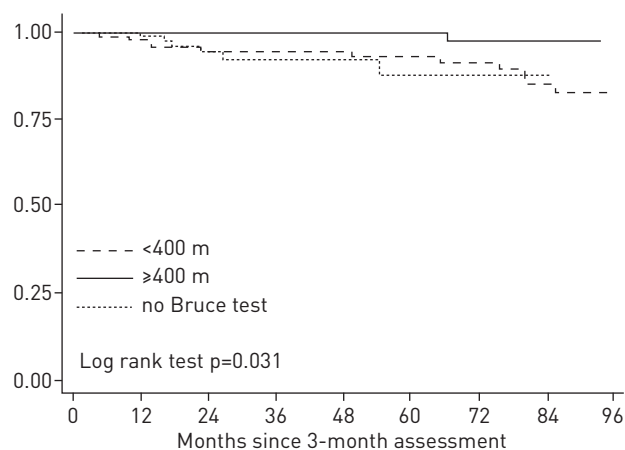


FIGURE 2 Survival rates after the 3-month follow-up evaluation. Three groups of patients are considered: patients who walked ≥400 m at the Bruce test; patients who walked <400 m at the Bruce test; and patients who could not perform the test.

surgery gives strength to the assessment of the prognostic significance of reduced functional capacity. The inescapable selection of the best patients over time is a feature of any registry. However, the study did not aim to evaluate the changes in any parameter after PEA; the objective of the study was to assess the determinants of exercise capacity, correlating the results of the Bruce test with other parameters at any time after surgery. Although both the medical management of patients (including the use of pulmonary arterial hypertension specific vasodilator therapy in clinical trials) and the operative techniques have necessarily evolved with time and experience over the study period, this does not challenge the intra-patient correlations between clinical, surgical, haemodynamic and functional characteristics.

Conclusion

After successful PEA, reduced pulmonary arterial compliance is an important determinant of exercise capacity, in association with the age and sex of the patient and the extent of recovery of both cardiac and respiratory function. However, exercise capacity does not explain a large proportion of the effect of surgery on subsequent survival and this issue should be taken into account when planning pharmacological studies in CTEPH.

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