

Point-of-Care Oxygen Titration Predicts Survival in Diffuse Parenchymal Lung Disease

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BACKGROUND

As defined by the American Thoracic Society (ATS), the diffuse parenchymal lung diseases (DPLD) are a heterogeneous group of pulmonary disorders characterized by inflammation and fibrosis, leading to parenchymal injury.¹ They include granulomatous diseases (e.g. sarcoidosis), idiopathic interstitial pneumonias (e.g. idiopathic pulmonary fibrosis [IPF], non-specific interstitial pneumonia [NSIP], cryptogenic organizing pneumonia [COP], desquamative interstitial pneumonia [DIP]), pulmonary diseases secondary to exposure to drugs or systemic disease (e.g. connective tissue diseases, bleomycin, radiation), and other unique pulmonary disorders including lymphangiomyomatosis (LAM) and histiocytosis X. This heterogeneous group has high intrinsic variability in clinical course, both within and between disorders,^{1,2} making prognostication difficult.

The availability of validated, objective tests can improve physician-patient communication by providing a basis for counseling regarding appropriate therapy, including transplant listing and end-of-life care. The six-minute walk test (6MWT) is a reproducible, relatively simple assessment of functional capacity that has been multiply shown to predict clinical outcomes in a variety of pulmonary disease settings,³ making it useful in patients with DPLD. Despite its advantages, however, there are drawbacks; the need for a dedicated location and trained technologist, in addition to the cost of testing, need for referral and separate appointment, and risk of exercise-induced adverse events, leave room for improvement in non-invasive prognostic testing in DPLD.

A potential alternative to the 6MWT is point-of-care oxygen titration (POCOT), a novel method for measuring oxygen requirement in DPLD, thereby determining a proxy for degree of compromise of pulmonary oxygenation and disease severity. Advantages to POCOT include facility of testing, yielding low-cost, immediate results to the clinician in the office, and lower risk of adverse events. Because of the proposed pathophysiologic link between POCOT and disease severity, we hypothesize POCOT can be used to predict medium-term mortality in DPLD, providing an attractive alternative to the 6MWT.

PURPOSE AND SPECIFIC AIMS

Purpose: to identify point-of-care alternatives to 6MWT for predicting survival in DPLD

Aim 1: to determine if POCOT predicts survival in DPLD

Aim 2: to compare the predictive value of POCOT versus other measures of disease severity for one-year (primary) and six-month survival in DPLD

METHODS

Study design: retrospective analysis of a prospective, observational cohort study

Primary endpoint: time from date of testing to date of death (one year, six months)

Independent variables: oxygen flow (L/min), 6MWD (m)

Dependent variable: time to death

Study Population

The study population includes adults with DPLD followed in the Columbia Center for Interstitial Lung Diseases and NewYork-Presbyterian Lung Transplant Program. Recruitment takes place from February 2007 to December 2010 and is projected to enroll approximately 300 participants. Patients are initially approached by study personnel, and those interested are referred to consultation with a study investigator for information and consent. Participants are then scheduled to complete the baseline questionnaire, oxygen titration and 6MWT protocol, and pulmonary function tests (PFTs) at the General Clinical Research Center (GCRC). Throughout enrollment, testing, and data analysis, every effort is made to maintain patient confidentiality.

Because of the heterogeneous nature of the DPLD population, an important consideration is method of diagnosis. The majority of our study group is given a “clinico-radiologic-pathologic” diagnosis based on history and physical exam, chest xray, high-resolution CT, and PFTs. When findings are typical, this method has been shown to yield high-probability diagnoses, foregoing the need for pulmonary biopsy.¹ When the diagnosis is unclear or definitive information might change management, however, pulmonary biopsy is warranted; biopsy was undertaken in approximately 30-40% of our study patients.

Exclusion criteria are few, as we want to build a broad DPLD study population. Applicable criteria are diagnoses that fall outside the DPLD umbrella, i.e. COPD, emphysema, cystic fibrosis, pulmonary arterial hypertension, etc.

The “PASS – Power and Sample Size Calculation”⁴ program was used for power analysis. Power was calculated for Specific Aim 1, using alpha level of 0.05 and beta level of 0.20.

		Total sample size (# in highest flow quartile)		
		200 (50)	240 (60)	300 (75)
Effect size Event rate in control group	1.5-fold increase			
	0.15	25	28	34
	0.20	32	37	44
	0.25	20	46	55
	2.0-fold increase			
	0.15	64	71	80
	0.20	79	85	92
	0.25	90	94	98
	2.5-fold increase			
0.15	90	94	98	
0.20	98	99	100	
0.25	100	100	100	

Specific aim 1 seeks to detect a difference in one-year mortality between patients requiring low-flow oxygen (controls) and those requiring high flow to achieve normalization of oxygenation, as detailed in the protocol below. Across the top of the table is sample size, both total and “highest flow quartile.” The highest flow quartile, or experimental group, is the 25% of patients requiring the highest oxygen flow to normalize oxygenation. The vertical entries are control event rate and effect size. Control event rate is the one-year risk of mortality in the control group, the 75% of the study population requiring lower oxygen flow; control event rate is estimated to be 15-25%. Effect size is the mortality risk ratio, or

relative risk of death in the high (experimental) versus low (control) groups; effect size is estimated to be 1.5-2.5. Central table entries are statistical power achieved with the given parameters. The basis for our power calculation is a Z test with pooled variance, therefore assuming a normal distribution.

Based on this power calculation, the study population is likely to be sufficiently large. For example, if N=200 and control event rate is 20%, then 40% one-year mortality in the high flow group, reflecting a mortality risk ratio of 2.0, would not be statistically significant; however, a population of 240 or 300 with the same parameters or the initial population with only slightly higher baseline mortality of 25% *would* be significant.

Oxygen Titration and 6MWT Protocols

Guidelines for the 6MWT protocol have been recommended by the ATS³ but not standardized. Our novel oxygen titration protocol, performed just before the patient begins the 6MWT, is designed to correct oxygenation to a uniform SpO₂ of 96-98%.

The titration instructions are the following, taken directly from the study protocol.⁵

1. Room air resting saturation should be recorded.
2. The patient should have been at rest for 5 minutes.
3. The entire oxygen titration should be performed while standing.
4. If patient does not use oxygen at all AND room air SpO₂ is 96% or greater: perform room air test
5. If patient does not use oxygen at all AND room air SpO₂ ≤95%, then begin oxygen by NC at 1 liter/min and titrate up by 1 step increments until SpO₂ is 96 to 98% for 1 minute.
6. If patient uses nasal cannula oxygen with activity, begin titration at their usual oxygen flow and then titrate liter flow up or down by 1 step increments until SpO₂ is 96 to 98% for 1 minute.
7. If SpO₂ does not settle between 96 and 98% (i.e., SpO₂ changes from 95% to 99% with 1 liter change in oxygen flow), increase oxygen flow to keep SpO₂ ≥98%.
8. If SpO₂ is ≤85% despite non-rebreather, consider canceling test.
9. Clinical judgment may dictate the need for a resting SpO₂ > 98%.

Steps: nasal cannula: 0L, 1L, 2L, 3L, 4L, 5L, 6L → facemask: 10L, 15L → non-rebreather: 15L

Comparing with 6MWT guidelines, departures in our protocol include oxygen titration, continuous monitoring of heart rate and pulse oximetry, measurement of nadir and rest stop pulse oximetry, and recording of number of rest stops.

Statistical Analysis

Our primary endpoint is time to death, specifically considering one-year and, secondarily, six-month mortality from date of testing. Death will be determined by hospital and public records. Missing data will be inserted using multiple imputations, using conservative estimates to minimize introducing bias in favor of our hypothesis. We expect missing data to be minimal given the high degree of compliance with follow-up in this population.

Table 1: Baseline characteristics, grouped by oxygen flow quartile

- demographics, anthropomorphic measures
- underlying lung disease, comorbidities, smoking history

Table 2: Mortality rate ratio, grouped by oxygen flow quartile

- construct using Cox proportional hazards model, a type of logistic regression well-suited to analysis of survival data; unadjusted and adjusted for clinically important covariates

Figure 1: Kaplan-Meier survival estimates by quartile

- construct using Cox data, compare using log-rank test for statistical significance

Figure 2: ROC curves for six-month and one-year mortality predictions

- construct curves for oxygen flow, 6MWT, DLCO, SOB score, etc.
- compare curves, analyze flow curve to identify optimal predictive flow for mortality

Table 3: Sensitivity, specificity, and PPV for six-month and one-year predictions

- construct using points on oxygen flow ROC curve

STRENGTHS AND LIMITATIONS OF DESIGN

Strengths of the design are its prospective nature, allowing for standardized protocol and measures to minimize misclassification, adequate power for the primary outcome, and mortality as the endpoint, yielding an unbiased and clinically meaningful result.

Limitations include bias, study group heterogeneity, and the unproven value of the titration protocol. Selection bias may be present in the population (referral center slanting toward more advanced disease, patients given the option to participate, losses to follow-up), and information bias is present in the imperfect method of diagnosis. Although we plan to control for confounding variables, it may be difficult to identify patients who die of non-cardiopulmonary causes. With regard to study group heterogeneity, what is lost in specific application may be gained in generalizability. Finally, this novel protocol lacks validity and reproducibility, limiting our ability to compare our results with existing studies.

NEXT STEPS

1. Complete data collection: projected 12/2010, may have interim data set fall 2009
2. Perform statistical analysis: fall 2009, winter 2010
3. Evaluate protocol for reproducibility in small sample, N = 10-20 (?)

REFERENCES

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