CHEST

Original Research

PRIMARY CILIARY DYSKINESIA

Pulmonary Radioaerosol Mucociliary Clearance in Diagnosis of Primary Ciliary Dyskinesia*

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Background: **Methods relying on nasal ciliary motility for the diagnosis of primary ciliary dyskinesia (PCD) are often hampered by secondary ciliary dyskinesia. A functional test for pulmonary mucociliary clearance, which is not influenced by secondary nasal ciliary defects, would be a valuable tool in a PCD workup.**

Methods: **The diagnostic validity and repeatability of a pulmonary radioaerosol mucociliary clearance (PRMC) test for the diagnosis of PCD was assessed in the following three sequentially performed substudies: (1) a preliminary cross-sectional study of PRMC in patients with known PCD; (2) a prospective blinded trial of patients referred for suspicion of PCD; and (3) an implementation study of PRMC as a routine method used in a PCD workup. PRMC was studied after ^{99m}Tc-albumin colloid aerosol inhalation, and the results were compared to (1) the results of nasal ciliary motility studies, (2) ciliary ultrastructure, and (3) the final clinical diagnosis. The repeatability of PRMC was assessed in 14 patients.**

Results: **A total of 95 patients, 5 to 74 years of age, were included in the study (57 patients in whom PCD was diagnosed, 26 non-PCD patients, and 12 patients referred for PCD workup without a conclusive workup result). In substudy 1, 14 of 15 patients with known PCD showed impaired PRMC; the results were inconclusive in 1 patient. In substudy 2, among 59 patients referred for PCD workup PRMC test results, compared to nasal ciliary motility, showed a sensitivity of 88% and a specificity of 100%. In substudy 3, among 21 patients referred for PCD investigation who were included in a routine PCD workup after PRMC implementation, 71% of PRMC test results were in alignment with nasal ciliary motility. Repeatability of interpretation was seen in 13 of 14 cases. A conclusive PRMC after only one test was found in 81 of 95 patients (85%).**

Conclusion: **PRMC is a noninvasive functional test for total tracheobronchial mucociliary clearance with a high sensitivity and specificity for PCD, a high rate of conclusive results after only one test and a further ability to separate PCD from focal pulmonary mucociliary defects.**

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Key words: mucociliary clearance; primary ciliary dyskinesia; secondary ciliary dyskinesia; ^{99m}Tc-albumin colloid; tracheobronchial transport

Abbreviations: CI = confidence interval; EM = electron microscopy; HRCT = high-resolution CT; LR1 = lung retention after 1 h; LR2 = lung retention after 2 h; PCD = primary ciliary dyskinesia; PI = penetration index; PRMC = pulmonary radioaerosol mucociliary clearance; RSD = residual SD

A single test for the definitive diagnosis of primary ciliary dyskinesia (PCD) has yet to come. Until then, the workup of patients with PCD has relied on the combination of ciliary function analysis and electron microscopic (EM) examination of the ultrastructure, preferably after *in vitro* regeneration. Nasal nitric oxide measurement is a promising tool in PCD workup for screening and excluding PCD.[1] However, further investigations will still be needed when low nasal nitric oxide values indicate the presence of PCD in order to confirm or exclude PCD.

Hence, at present the diagnosis of PCD is complex

and time consuming, yet not always exact, and the true incidence is most likely underreported.[2] The early diagnosis of PCD is important since early and aggressive management of lower airway infection is crucial in preventing bronchiectasis and reduced lung capacity.[3]

In patients with PCD, mucociliary transport is impaired as a result of abnormal ciliary motion. In this study, we applied a method based on clearance patterns after the inhalation of a radioaerosol tracer as a whole-lung functional test for pulmonary radioaerosol mucociliary clearance (PRMC) used as an adjunctive test in the workup of patients with proven and suspected PCD. PRMC is noninvasive and applicable to children older than approximately 5 years of age.

Aim

The aim of this three-part study was as follows: (1) to describe PRMC in a preliminary study by testing it on a population of patients with known PCD; (2) following that, to assess the diagnostic validity (*ie*, sensitivity, specificity, and positive and negative predictive values) in patients referred for a PCD workup in a blinded trial by testing PRMC against nasal ciliary motility studies; and (3) after acceptance of PRMC as a valid method based on the results of substudies 1 and 2, to implement PRMC in a routine PCD workup of a group of referred patients to evaluate the value of PRMC as a supplementary diagnostic test for PCD.

Furthermore, a comparative study of high-resolution CT (HRCT) scanning and PRMC was performed in patients from substudies 2 and 3 in whom PRMC showed regional lung clearance defects in order to evaluate whether a regional abnormal PRMC could predict the localization of bronchiectasis that had been demonstrated on an HRCT scan. Finally, a study of the repeatability of PRMC interpretation for the diagnosis of PCD was performed.

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Methods and Materials

Patients

We studied 95 patients, all of whom were referred to the National PCD Centre in Copenhagen for workup due to a clinical suspicion of PCD. Prior to study inclusion, cystic fibrosis was ruled out. Tests were performed at least 4 to 6 weeks after the occurrence of an acute upper or lower respiratory tract infection. In case of inconclusive tests, repeated testing was performed after treatment with antibiotics for 6 weeks. PRMC was allowed to be performed up to three times and a ciliary motility test was allowed to be performed up to five times in cases of inconclusive initial results. In cases of abnormal ciliary motility, the test would always be repeated at least once to exclude the possibility of secondary ciliary dysfunction, and only in cases of normal nasal ciliary motility would one test be considered acceptable. The study was designed as a three-part study:

Preliminary Cross-Sectional Study To Validate PRMC: In 1998, patients with known PCD were included for PRMC. PCD had been previously diagnosed in all patients as the result of an abnormal ciliary ultrastructural and an abnormal ciliary function test finding. The PCD diagnosis was known to the PRMC reader in this substudy.

Prospective Blinded Trial of Referred Patients With Suspected PCD: During a 3-year period (from 1999 to 2001), we consecutively included patients who had been referred and were suspected to have PCD and were > 5 years of age for evaluation by PRMC. All patients were additionally investigated routinely by nasal ciliary motility test for ciliary beat frequency and motion pattern analysis. Throughout this 3-year period, the PRMC reader was blinded to the results of nasal ciliary motility investigation, and the evaluation of PRMC results was not performed before all included patients were finally diagnosed. PRMC results were then compared to the results of (1) nasal ciliary motility, (2) EM ultrastructure, and (3) final clinical diagnosis.

A 1-Year Implementation Study of PRMC as a Routine Method in PCD Workup: In 2002, new patients who were > 5 years of age and had been referred for a PCD workup underwent PRMC as part of the investigation. The PRMC reader was blinded to the results of the nasal ciliary motility investigation. The results of a PRMC test were passed on to the pediatric department where the interpretation of those results was used equally to ciliary motility studies and EM studies when coming to a final clinical diagnosis of a referred patient.

Regional Lung Clearance Defects

Subjects from substudies 2 and 3 with a regional abnormal clearance pattern were further investigated by HRCT scan. The site for regional abnormal clearance on the PRMC test was then compared to the localization of structural defects on HRCT scans. The radiologists interpreting the HRCT scans were blinded to the PRMC test result. The PRMC reader was blinded to the HRCT scan in cases in which the HRCT scan was performed before the PRMC test.

Repeatability of PRMC Test Interpretation

From a randomly selected sample of subjects participating in substudies 1 and 2, an intraobserver repeatability test of inter-