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Pre-procedural Sars-CoV-2 testing and pulmonary function testing

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Background: CF Foundation guidelines encourage quarterly pulmonary function testing (PFTs) for all patients as part of routine care. The COVID-19 pandemic significantly affected our ability to obtain PFTs at recommended intervals, as patients were reluctant to come to the hospital and being advised to shelter in place to avoid unnecessary exposure to the Sars-CoV-2 virus. To obtain PFTs at our center during this time, we required negative Sars-CoV-2 testing for asymptomatic patients in the preceding 48–72 hours. We hypothesized that the extra trip away from home for viral testing affected our ability to adhere to the recommended PFT testing intervals. We sought to analyze the number of patients who did not have any PFTs completed since the start of the testing requirement. We also sought to analyze the positivity rate for Sars-CoV-2 associated with PFTs.
Methods: All charts of CF patients ordered for PFTs and Sars-CoV-2 PCR testing from July 2020 to March 2021 were retrospectively queried for viral test results and either the subsequent completion or cancelation of a PFT appointment. Charts were abstracted for patient age, number of PFTs completed, and Sars-CoV-2 status.
Results: Patient ages ranged from 6 years to 55 years. Of the 110 patients, 37 (34%) were under 18 years old. PFTs were ordered 134 times on 110 patients during the 9-month period, along with antecedent viral testing. Thirty-five patients (32%) did not have any PFTs completed in that time frame. None of the viral testing for Sars-CoV-2 prior to each PFT returned positive (0%). Nine patients (9%) tested positive independent of their PFT appointments and were tested due to symptoms, only 1 of whom was a pediatric patient.
Conclusion: At our single center of 121 patients, we found a 0% positivity rate of Sars-CoV-2 PCR in asymptomatic CF patients preparing for PFTs. We also found that since the implementation of this extra testing requirement, nearly one-third of our patients did not have any PFTs during the pandemic. With vaccination rates steadily increasing among both hospital staff and CF patients, we believe this low positivity rate argues for the removal of pre-procedural viral testing in this population when asymptomatic, provided that we continue to utilize symptom screening questions, appropriate PPE, and appropriate room cleaning procedures as outlined by the American Thoracic Society. The removal of the pre-procedural viral testing would eliminate a significant barrier to obtaining routine care for our CF patients.

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C-reactive protein (CRP) as a biomarker of exacerbation presentation and treatment response

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Background: C-reactive protein (CRP), a systemic marker of inflammation, has been proposed as a biomarker for pulmonary exacerbation (PEx) diagnosis and treatment response. CRP >75 mg/mL ($\log_{10}$CRP >1.875) has been associated with increased risk of PEx treatment failure. We interrogated CRP measures collected during the STOP2 PEx study (NCT02781610) of clinical response to different intravenous (IV) antimicrobial treatment durations as a PEx presentation and treatment response biomarker.
Methods: The STOP2 study design has been reported in detail [1]. CRP measures were collected at IV antimicrobial treatment start (V1), randomization (V2, 7 to 10 days after treatment start), and 2 weeks post-treatment end (V3) and converted to $\log_{10}$ values. Correlations between V1 $\log_{10}$CRP, $\log_{10}$CRP change from V1 to V3, and clinical responses (change in lung function as $ppFEV_1$ and Chronic Respiratory Infection Symptom Score [CRISS] from V1 to V3) were assessed by least squares regression. Clinical responses associated with V1 $\log_{10}$CRP >1.875 versus ≤ 1.875 mg/L were compared by *t* test. Subjects with covariate data missing at a given visit were excluded only from analyses that included those specific covariates at those visits, without imputation.
Results: In all, 951 (92.7%) of 982 STOP2 subjects had CRP measures at V1. Mean V1 $\log_{10}$CRP varied significantly by lung function subgroup ($ppFEV_1$ < 40, 1.4 [95%CI 1.4, 1.5] vs ≥70, 0.8 [0.7, 0.9]), CRISS quartile (≥59, 1.4 [1.3, 1.5] vs < 44, 0.9 [0.8, 1.0]), and sex (females 1.1 [1.1, 1.2] vs males 1.2 [1.2, 1.3]), but not by age subgroup. V1 $\log_{10}$CRP correlated somewhat with $\log_{10}$CRP change from V1 to V3 ($r^2 = 0.255$) but less so with V1 to V3 changes in ppFEV1 ($r^2 = 0.016$) or CRISS ($r^2 = 0.031$). Correlations of $\log_{10}$CRP changes from V1 to V3 with ppFEV1 and CRISS changes from V1 to V3 were modest (r^2 of 0.061 and 0.066, respectively). In all, 109/951 subjects (11.5%) had a V1 $\log_{10}$CRP >1.875 mg/L; mean V1 to V3 ppFEV1 and CRISS changes were significantly better for this group than those with $\log_{10}$CRP ≤1.875 mg/L ($ppFEV_1$ response of 9.1 [7.0, 11.3] vs 6.1 [5.5, 6.8]; CRISS response of −24.6 [−26.6, −21.6] vs −17.6 [−18.6, −16.6]).
Conclusion: V1 $\log_{10}$CRP concentrations varied widely at PEx diagnosis in the STOP2 study cohort. Correlations between $\log_{10}$CRP concentration changes from V1 to V3 and ppFEV1 and CRISS changes over the same period were very modest, suggesting that CRP change will have limited utility as a biomarker of PEx treatment response. A $\log_{10}$CRP of >75 mg/L at PEx diagnosis did not predict a worse lung function or symptom change from V1 to V3 (in fact, these subjects had significantly better mean treatment responses).

Reference

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Late diagnosis of cystic fibrosis after first decade of life: Clinical observations of a milder phenotype in India

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Background: There is paucity of data on the prevalence, phenotype, and clinical outcome of patients with cystic fibrosis (CF) from the Indian subcontinent, specifically among those who were diagnosed after the first decade of life. In general, late diagnosis results in severe pulmonary and nutritional morbidity. We report data from a cohort of patients with CF (PwCF) focusing on those with a milder phenotype of CF disease despite late diagnosis.
Methods: Retrospective chart review of PwCF followed at a tertiary medical center in India was conducted. Of the 63 newly diagnosed PwCF between May 2018 and December 2020, 18 were diagnosed after 10 years of age. Patient demographics, clinical outcomes, spirometry, nutritional parameters, and diagnostic data were reviewed.
Results: Of the 18 patients, 11 were from India and 7 from Bangladesh. Median age was 16 years (range 10.5 – 23.4 years) and 10 (56%) were male. Overall, median age at which earliest symptom was reported was 1.9 years (range 0.1–15 years); however median age of diagnosis was 12 years (range 10.25–21.75). In the first decade, the majority did not report any recurrent CF-specific symptoms, and 3 patients reported only fatigue in summer. Sweat chloride levels were diagnostic in 9/18 (50%), in the indeterminate zone in 8, and normal in 1 patient. Family history of CF was noted in 27% of patients. CFTR sequencing with deletion/duplication was completed in 16 patients. None had homozygous F508del mutations; 4 patients were heterozygous for F508del and of these patients, 3 were pancreatic insufficient. Three patients were heterozygous for the intronic variant 3718–2477C >T (previously reported from India); all 3 had normal or indeterminate sweat chloride levels and 2 were pancreatic sufficient. From a pulmonary perspective, 83% had respiratory symptoms with a mean

FEV1% predicted of 61% (range 18–101%). Extensive bronchiectasis was noted in 77.8%. Three patients had no respiratory symptoms. Microbiologic cultures from sputum isolated *Pseudomonas aeruginosa* and *Staphylococcus aureus* in 66.7% and 55.6% respectively. Three patients had documented pulmonary tuberculosis, and atypical mycobacterium was isolated from 1 patient. Nasal polyps were noted in 16.7%. From a nutritional perspective, fecal elastase data was available in 16 patients, and 69% were pancreatic sufficient, 31% were pancreatic insufficient. Median body mass index (BMI) was 14.8 kg/m2 (range 11–25 kg/m^2), and at time of diagnosis 27% had BMI above the 25thpercentile. Four patients had CF-related diabetes.

Conclusion: In the Indian subcontinent, PwCF diagnosed after 10 years of age had mild clinical phenotype in early childhood, often related to uncommon mutations. However, there is a trend toward significant decline in pulmonary disease in a few patients in the second decade. Proactive efforts to identify PwCF with milder phenotypes, including surveillance of siblings, would be important to prevent worsening pulmonary morbidity even though disease progression is gradual in the first decade.

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Lung function changes following Sars-CoV-2 infection in cystic fibrosis

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Background: Individuals infected with Sars-CoV-2 commonly have pulmonary manifestations as part of their disease process. There are increasing reports of pulmonary function changes in individuals post Sars-CoV-2 infection. Very little is known about the impact of Sars-CoV-2 infection on lung function in patients with cystic fibrosis. We report on 4 patients with cystic fibrosis who were infected with Sars-CoV-2 and the changes in FVC and FEV1.

Methods: We retrospectively reviewed charts of CF patients at our center since the onset of the COVID pandemic to determine who had been infected with Sars-CoV-2. We then determined which patients had PFTs performed prior to and post infection. We assessed changes in FVC and FEV1 for these patients.

Results: There were 9 patients (age 10 to 42 years) at our center identified as having been infected with Sars-CoV-2 from March 2020 to April 2021. Of these, 4 patients (age 21–40 years) had PFTs prior to and following Sars-CoV-2 infection. There were 3 of these patients being treated with elexacaftor/tezacaftor/ivacaftor as part of their routine care. One patient did receive monoclonal antibody therapy for his infection. Baseline FVC pp ranged from 78 to 97% predicted and baseline FEV1 pp ranged from 59 to 89% predicted. Sars-CoV-2 infection severity for all patients was mild, and no patients were hospitalized as a result of this infection. The percent change in FVC (pre- to post-Sars-CoV-2) for all 4 patients was 1.5%, 10.5%, –7.7% and 0.9%. The percent change in FEV1 (pre- and post-Sars-CoV-2) for all 4 patients was 0.8%, 5%, –2.4% and –0.4%. There was no significant change in the FVC and FEV1 from baseline values following Sars-CoV-2 infection for these 4 patients with mild infection (Table 1).

	Pre FVC (L)	Pre FVC pp	Post FVC (L)	Post FVC pp	Pre FEV1 (L)	Pre FEV1 pp	Post FEV1 (L)	Post FEV1 pp	% Change FVC	% Change FEV1
Patient 1 (31yo)	4.78	97	4.85	98	3.6	89	3.63	89	1.50%	0.80%
Patient 2 (40yo)	2.87	78	3.17	86	1.99	66	2.09	70	10.50%	5.00%
Patient 3 (38yo)	3.39	78	3.13	71	2.07	59	2.02	57	-7.70%	-2.40%
Patient 4 (21yo)	3.23	84	3.26	84	2.85	84	2.84	84	0.90%	-0.40%

Table 1. Sars-CoV-2 pre- and post-spirometry

Conclusion: This small case series of 4 adult patients with CF infected with Sars-CoV-2 noted no significant change in lung function following infection. The range in Sars-CoV-2 infection severity can vary between mild disease with no change in lung function to death. Based on CFF reports, it is recognized that outcomes may depend on baseline lung function and severity of lung disease, as well as if post-lung transplant. Other factors may play a role in COVID-19 outcomes, including use of routine airway clearance, possible treatment with highly effective CFTR modulators, and outpatient therapies for Sars-CoV-2.

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Using dynamic chest radiography to assess response to treatment in acute pulmonary exacerbations of adult people with cystic fibrosis

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Background: Using dynamic chest radiography (DCR), a unique real-time X-ray imaging system [1], we have shown variation in diaphragm movement following pulmonary exacerbations (PEx) in adult people with CF (PwCF). Now, to assess the impact of PEx on tidal and deep breathing phases of respiratory physiology, we have utilized DCR to look at their effect on lung area changes.

Methods: Twenty PwCF ([mean ± SD] age 25.2 ± 6.6 years, average ppFEV1 59.5 ± 17.1, BMI 21.1 ± 3.6kgm^{-2}, 14 female) underwent spirometry and DCR before and after inpatient treatment for PEx. Hemidiaphragm speed and change in vertical hemidiaphragm position were measured by DCR during tidal and deep breathing, to assess the impact of PEx on respiratory muscle function, with the posteroanterior projected lung area (PLA) measured as a surrogate for lung volume.

Results: Treatment improved maximum excursion during tidal breathing of both left (12.9 ± 5.1 to 15.9 ± 6.6 mm, $P = 0.01$) and right (11.2 ± 5.2 to 14.5 ± 7.1 mm, $P = 0.02$) hemidiaphragms, as well as maximum tidal inspiratory speed (left 15.8 ± 5.0 to 18.6 ± 6.6 mm/s, $P = 0.04$; right 13.9 ± 5.1 to 16.5 ± 6.9 mm/s, $P = 0.07$). Hemidiaphragm excursion on deep breathing improved on the right (13.4 ± 6.7 to 18.3 ± 8.9 mm, $P < 0.001$) and left (18.2 ± 8.4 to 23.9 ± 9.5 mm, $P = 0.01$), as did maximum passive expiratory speed for right (12.0 ± 4.4 to 19.5 ± 10.4 mm/s, $P = 0.003$) and left (15.6 ± 8.4 to 22.6 ± 11.9 mm/s, $P = 0.008$) hemidiaphragms. The ratio between maximum inspiratory/expiratory PLA correlated with ppFEV1 (r = 0.753, $P < 0.001$). PLA at maximum expiration correlated with the FEV1/FVC ratio (left, r = –0.800, $P < 0.001$; right, r = –0.672, $P < 0.001$; Figure 1). Maximum hemidiaphragm excursion correlated with FVC (left, r = 0.6340, $P < 0.001$; right, r = 0.6927, $P < 0.001$).

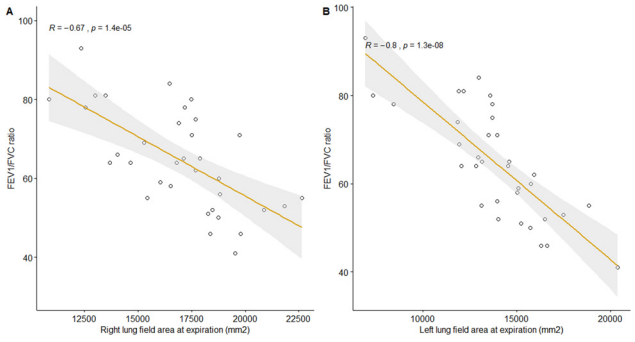

Figure 1. Relationship between FEV1/FVC ratio, and right (A) and left (B) lung field area at end expiration

Conclusion: We have demonstrated improvement in diaphragm excursion and speed during tidal breathing, suggesting individuals are able to take deeper and faster tidal breaths as a result of treatment for PEx. The increase in passive expiratory speed following a deep breath matches our previous work and suggests improvement in the elastic recoil of the lungs. The correlation between spirometric and DCR parameters suggest DCR may be a complementary investigation in measuring lung function changes during PEx, especially in individuals in whom reproducible spirometry is difficult.

Reference

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