

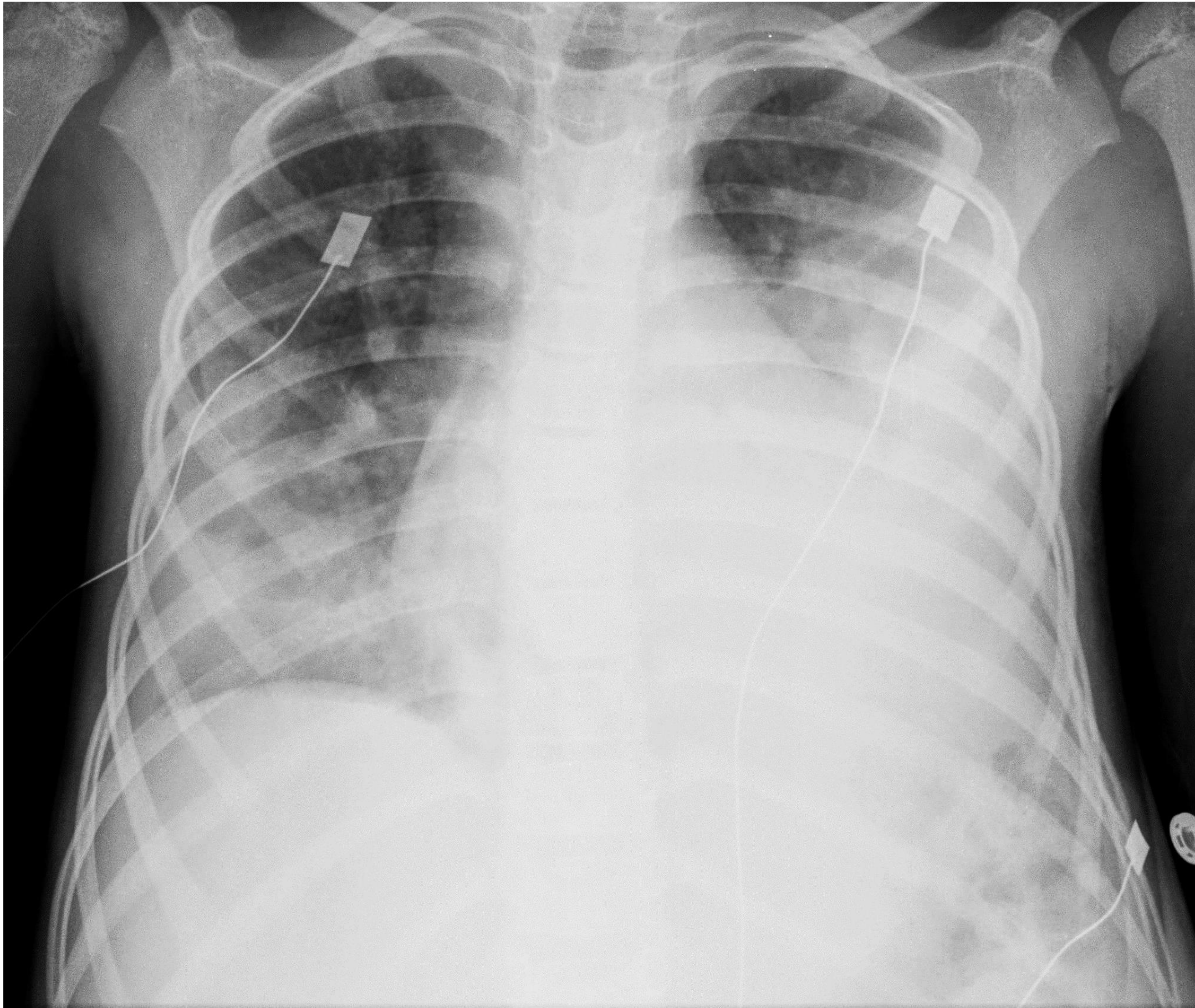
The Effects of Hydroxyurea on Pulmonary Complications in the Pediatric Sickle Cell Population

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BACKGROUND

Acute Chest Syndrome (ACS) is a common complication in the Sickle Cell Disease (SCD) population. It is the leading cause of death in the adult SCD population.¹ The mechanism of ACS has not been fully delineated but there are several proposed mechanisms. An infectious etiology involving *C. pneumoniae* is the most prevalent pathogen and responsible for significant morbidity.² Also, sickled erythrocytes interact with the vascular endothelium, recruiting activated white cells and platelets causing injury to the endothelium with resultant leakage of fluid into the pulmonary parenchyma.³ ACS has been associated with vaso-occlusive crises (VOC) and Morphine therapy.^{4,5} Patients with concurrent asthma have an increased risk of ACS suggesting airway hypersensitivity as another possible component.⁶ ACS can be an aggressive pneumonitis and repeated episodes may lead to chronic lung disease.



Acute Chest Syndrome in a 6 yo female with HbSS

Prevention of ACS is the best method of treatment. Inhaled corticosteroids and short acting β 2-agonists are commonly used for prevention. However, Hydroxyurea (HU) may provide the best preventive treatment. HU increases fetal hemoglobin (HbF), decreases sickled hemoglobin (HbS), and has been shown to decrease the expression of cellular adhesion molecules on the endothelium which are involved in endothelial damage by sickled erythrocytes.⁷

Special thanks to Dr. Fengxia Yan MD, our biostatistician

SIGNIFICANCE

Hydroxyurea has been shown to decrease all SCD complications (VOC, ACS, Splenic Sequestration, etc) in the adult population.⁸ One local study demonstrated a positive effect on pulmonary function test (PFT) results in pediatric SCD patients.⁹ However, there are few studies outlining the effect of HU on the pulmonary complications in the pediatric SCD population.

Pediatric ACS patients display an obstructive lung pattern ($\uparrow$ FEV1 and $\downarrow$ FEV1/FVC ratio). While adult patients display restrictive lung disease ($\downarrow$ FVC, FEV1). Therefore, it is possible that there is a progression from childhood obstructive lung disease to adult restrictive lung disease with repeated ACS events. Therefore, decreasing ACS episodes in pediatrics could preserve the lung parenchyma and improve adult outcomes.

HYPOTHESIS

Addition of Hydroxyurea will provide an advantage over standard therapy of inhaled steroids and beta agonist in preventing repeated episodes of Acute Chest Syndrome

SPECIFIC AIMS

- ◆ To compare the rate of admissions for Acute Chest Syndrome in the Hydroxyurea versus Non-Hydroxyurea subjects with ACS risk
- ◆ To compare the difference, if any, in pulmonary function testing between the two groups
- ◆ To assess compliance with Hydroxyurea therapy

METHODOLOGY

Retrospective Case-Control Study:

- ◆ Subjects drawn from the Hughes Spalding Sickle cell / Pulmonary Clinic
- ◆ HbSS or HbS- β^o thal
- ◆ 4-18 years old
- ◆ History of ACS prior to 2013

Cases n=29: Prescribed HU and standard therapy prior to 2013
Controls n=29: Age, gender, and severity matched, on standard therapy, having never taken hydroxyurea
Groups were compared for number of patients with ACS admissions in 2013 and 2014

PFT Evaluation: PFTs pre and post HU therapy compared with the control group

Hydroxyurea Compliance: Verification of the number of refills of HU in 12 months during the study period

Statistical analysis: Student t-test was used for age comparison and χ^2 analysis was used for Hb type, gender, and number of patients admitted with ACS between the two years

RESULTS

	Hydroxyurea # (%)	Control # (%)	p-value
Gender			
Male	18 (62.1)	18 (62.1)	1
Female	11 (37.9)	11 (37.9)	
Age			
Range (y)	6 to 16.0	4.6 to 16.7	0.939
Age mean (SD)	9.97 (2.78)	9.99 (3.15)	
Hgb type			
HbS- β^o thal	3 (10.3)	0 (0)	0.2368
HbSS	26 (89.7)	29 (100)	
Preliminary Severity Comparison*			
Patients with ACS	17 (58.6)	11 (37.9)	0.1149
Patients without ACS	12 (41.4)	18 (62.1)	
2013			
Patients with ACS	5 (17.2)	11 (37.9)	0.0779
Patients without ACS	24 (82.8)	18 (62.1)	
2014			
Patients with ACS	3 (10.34)	9 (31.0)	0.0518
Patients without ACS	26 (89.66)	20 (69.0)	
2013 and 2014			
Patients with ACS	7 (24.1)	13 (44.8)	0.0157
Patients without ACS	22 (75.9)	16 (55.2)	

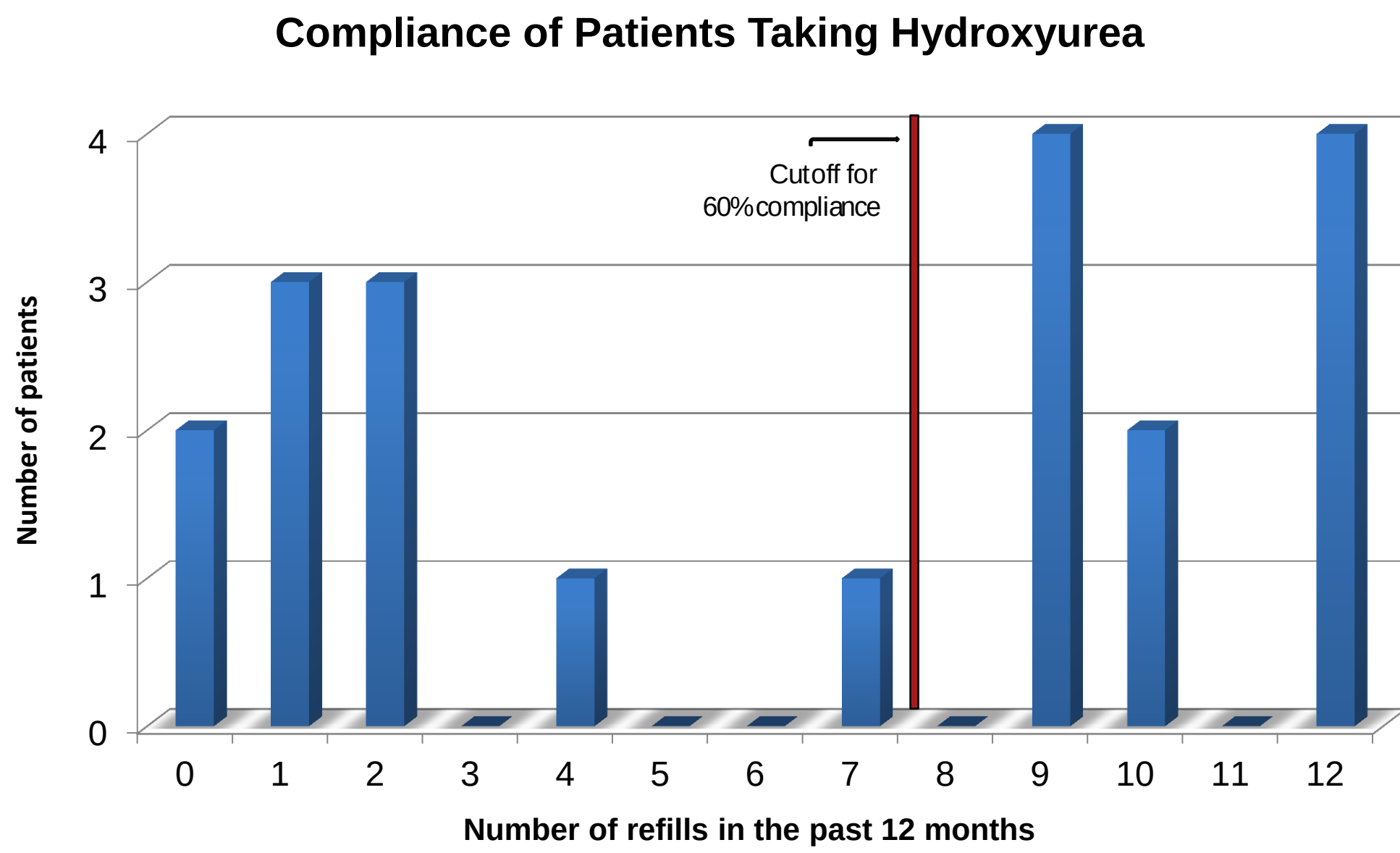
* Measure of patients in HU group who had an ACS admission in the 12 months prior to starting HU compared to the same period for the control group

Over the study period (two years) there was a statistically significant difference in the number of subjects admitted for ACS between the groups (P-value 0.015)

There was no significant difference in age, gender, Hgb type, and pre-HU therapy severity of illness.

PFT data: available records were insufficient for analysis

Hydroxyurea compliance: data was available for 20 of 29 HU patients. 50% were 75-100% complaint with ≥ 9 refills in 12 months. 50% were non-compliant with ≤ 7 refills in 12 months (majority getting only 2-3 refills).



DISCUSSION/CONCLUSION

Overall Hydroxyurea was advantageous in preventing repeated ACS events. Patients who were non-compliant seemingly were still provided an advantage in reduction of ACS events. PFT results pre and post HU could provide a more objective assessment of lung disease reversibility and the impact of Hydroxyurea on the progression of lung disease in pediatric SCD patients.

One of the limitations of the study was the lack of consistent PFT data for the both cases and controls. Additionally, Hemoglobin SC patients were excluded from assessment because they are not generally prescribed HU. The poor compliance of HU brings into question the true effect of HU. HU patients are seen monthly and perhaps this frequent follow-up improves their overall health. Finally, this study was limited to a small number of patients from one institution which limits its generalizability.

Future research could analyze barriers to compliance with HU. Once these barriers are identified, an interventional initiative may have a positive impact on HU daily use, leading to preservation of pulmonary function.

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