

# Albuterol Improves Impaired Mucociliary Clearance After Lung Transplantation

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- Background:** Previous studies have shown that mucociliary clearance (MCC) is diminished after lung transplantation. However, it is unknown how early this deficit occurs after transplantation, or whether the abnormality can be improved by pharmacologic means. We hypothesized that impairment of MCC is evident soon after lung transplantation and that the defect in MCC can be improved by inhaled  $\beta_2$ -adrenergic receptor agonists.
- Methods:** MCC and cough clearance (CC) were quantified in seven patients at  $76 \pm 48$  days (mean  $\pm$  standard deviation) after lung transplantation (baseline visit) and again 1 week later after an acute inhalation of albuterol. MCC was also determined once in four healthy subjects. To measure MCC, volunteers inhaled 99m-technetium-sulfur colloid aerosol, followed by gamma-camera imaging of their lungs for 76 minutes.
- Results:** Baseline MCC was significantly reduced in transplant patients, compared with healthy subjects, averaging  $8.9 \pm 7.3\%$  and  $20.9 \pm 15.1\%$ , respectively ( $p = 0.05$ ). CC was not affected by transplantation. Acute inhalation of albuterol significantly improved MCC in transplant patients ( $31.9 \pm 21.9\%$ ) compared with baseline values ( $p < 0.05$ ).
- Conclusions:** MCC is diminished within a few months after transplantation. However, the response to albuterol suggests that the deficit is not static and can be improved with inhalation of a  $\beta_2$ -adrenergic receptor agonist. *J Heart Lung Transplant* 2007;26:138–44. Copyright © 2007 by the International Society for Heart and Lung Transplantation.

Lung transplantation is the last therapeutic option for several end-stage lung diseases, including chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, cystic fibrosis (CF), primary pulmonary hypertension, sarcoidosis and bronchiectasis. Graft survival immediately post-surgery has improved dramatically in the last decade and is now approaching 95% at 1 month. However, graft survival decreases to 82% at 1 year post-surgery and to 62% at 3 years post-surgery for adult patients ([www.ustransplant.org](http://www.ustransplant.org)). Infection and obliterative bronchiolitis (OB), which is considered to be synonymous with chronic rejection,<sup>1,2</sup> are the two major determinants of long-term graft survival in lung transplant patients. Infections are the major cause of

mortality in the first year after surgery, although OB accounts for the majority of deaths thereafter.<sup>3,4</sup>

Transplant patients are clearly at risk for the development of infections because of the immunosuppression needed to sustain the allograft. However, pulmonary transplantation is unique compared with other solid-organ transplants because there is direct communication between the allograft and the atmosphere, thereby increasing its exposure to bacteria, viruses and toxins and increasing its susceptibility to infections.

In healthy lungs, inhaled bacteria, viruses, antigens and toxins deposit on the tracheobronchial airway surface and are removed from the lung in a matter of hours by mucociliary clearance (MCC). In patients with CF and asthma, MCC is impaired, taking many more hours for removal of mucus compared with normal individuals.<sup>5–7</sup> In patients with ciliary dyskinesia, MCC is absent altogether because of the uncoordinated beating of cilia.<sup>8</sup> When MCC is overwhelmed or impaired some mucus can be removed by mechanical or cough clearance (CC). Nevertheless, impairment of MCC typically leads to the accumulation of mucus in the airways, and this in turn is associated with acute infections, chronic bacterial colonization and chronic inflammation.<sup>8</sup>

Two groups of investigators have shown that MCC is impaired in lung transplant patients. Dolovich et al<sup>9</sup> reported 11% clearance from the transplanted lung of

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single-lung transplant (SLT) patients, compared with 24% from the native lung, at 6 to 12 months after surgery. Herve et al<sup>10</sup> found that MCC was 49% lower in bilateral-lung transplant patients and 56% lower in heart-lung transplant patients, compared with healthy subjects, at an average of 19 months after surgery.

We hypothesized that impairment of MCC is evident soon after lung transplantation. We further hypothesized that the defect in MCC is not static and that it can be improved by pharmacologic therapy. To test this hypothesis we quantified MCC in 7 patients 1 to 5 months after lung transplantation. Cough clearance was also quantified. We also measured MCC and CC after an acute inhalation of albuterol to determine its effectiveness in stimulating MCC in this population.

## METHODS

### Transplant Patients

This study was approved by The Johns Hopkins Institutional Review Board. Between July 2001 and March 2003, 30 patients were transplanted at The Johns Hopkins Hospital for standard indications. Seven patients agreed to participate in the study by giving their informed consent.

### Healthy Volunteers

MCC was also measured in four healthy volunteers who had no symptoms or history of respiratory disease. MCC in this population was compared with MCC measured in the lung transplant patients. We chose to make this comparison instead of comparing MCC in the transplanted lung to that of the native lung in the same patient because MCC values obtained from the native lung would reflect a lung that was diseased and poorly ventilated.

### Medications

Subjects received post-transplant care as previously described.<sup>11</sup> All subjects were maintained on triple-drug immunosuppression, including cyclosporine or tacrolimus, prednisone and either mycophenolate or azathioprine. Five patients received induction therapy with daclizumab, one received thymoglobulin, and one received no induction therapy. Subjects discontinued inhalation of short- and long-acting bronchodilators 12 and 24 hours before each study visit, respectively.

### Pulmonary Function Testing

Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV<sub>1</sub>) were measured by a computerized 10-liter spirometer (Survey III; Warren E. Collins, Inc.; Braintree, MA) at each visit, in accordance with American Thoracic Society/European Respiratory Society guidelines.<sup>12</sup>

### Ventilation Imaging Procedure

At the baseline visit, a ventilation image of the lung was obtained to define the borders of the transplanted lung. Patients inhaled 133-xenon (<sup>133</sup>Xe) gas, using a Xe system (Pulmonex; Biodex Medical, Shirley, NY), while sitting with their back to the gamma camera. They subsequently rebreathed the gas for 90 seconds to promote penetration throughout the lung. The resulting ventilation image was later used to identify the lung borders of the transplanted lung after radio-aerosol inhalation.<sup>14-16</sup> In this way, the ventilation image served as the reference image for all radio-aerosol images.

### Protocol for Measuring MCC and CC

MCC and CC were quantified an average of 76 ± 48 days (range 27 to 151 days) after lung transplantation (baseline visit) and again 1 week later after an acute inhalation of albuterol. Studies were performed when patients had no evidence of acute respiratory infection. To measure MCC and CC, subjects inhaled saline containing the radio-isotope marker 99m-technetium (<sup>99m</sup>Tc)-sulfur colloid (radio-aerosol) and underwent gamma-camera imaging of their lungs for 76 minutes thereafter, as described previously.<sup>13</sup>

### Radio-aerosol Generation and Inhalation

To quantify MCC and CC, the <sup>99m</sup>Tc-sulfur colloid radio-aerosol was deposited onto the subject's airway mucus at each study visit by inhalation of a saline solution containing the radio-isotope. <sup>99m</sup>Tc-sulfur colloid was chosen as the radio-isotope for these experiments because it is a non-diffusible agent that either remains in the lungs and decays to undetectable levels over 1 to 2 days, or is removed from the lungs through MCC and swallowed. There is no removal of this label by absorption into the systemic circulation.

Radio-aerosol (mass median aerodynamic diameter = 3.7 μm; geometric standard deviation = 3.0) was generated by an LC Plus nebulizer and ProNeb Turbo compressor (PARI Respiratory Equipment, Midlothian, VA), while patients breathed tidally for 30 seconds from functional residual capacity. Peak inspiratory flow rate during inhalation was regulated by means of a biofeedback technique, which has been described previously.<sup>16</sup> After inhalation, participants rinsed their mouth with water, expectorated the rinse, and drank water to wash any remaining radioactivity into the stomach.

### Lung Imaging and Image Analysis

After inhalation of the radio-aerosol, participants underwent 19 posterior lung scans, lasting 4 minutes each, over 76 minutes, with a large field-of-view ZLC gamma

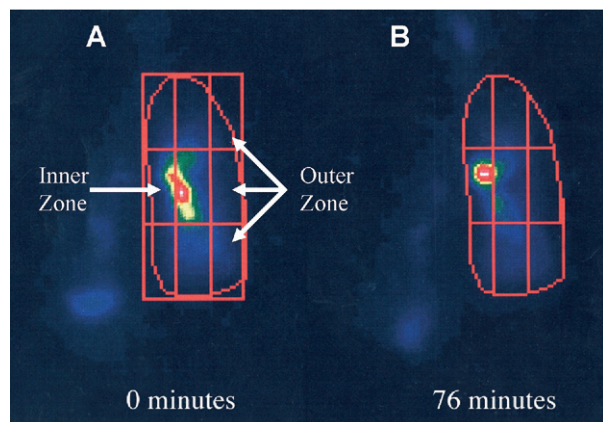
camera (Siemens, Munich, Germany). These lung images were stored on a computer (GE Health Care, Waukesha, WI) for later processing and analysis. Careful attention was paid to positioning the volunteer in front of the camera on all study visits so that the acquired lung images were appropriately superimposed with the  $^{133}\text{Xe}$  ventilation image obtained before radio-aerosol inhalation.

### Quantifying Deposition Pattern

To assure that the deposition pattern was similar at each study visit, we quantified deposition of the radio-aerosol in an inner and outer zone of the transplanted lung image immediately after aerosol inhalation (Time 0). Inner and outer zones were determined as described previously.<sup>14,15,17</sup> Briefly, the width of the ventilation lung image was divided into three vertical regions. Similarly, the height of the image was divided into three horizontal regions. This procedure resulted in the ventilation lung image being divided into a total of nine smaller regions. These regions and the ventilation lung border were superimposed on the radio-aerosol image (Figure 1A). This nine-region grid was used to quantify and compare the initial deposition pattern of the radio-aerosol on each study visit.

Mean counts per picture element in the inner and outer regions of the ventilation scan and the radio-aerosol scan were calculated and inner:outer (I:O) ratios derived. Ratios for the aerosol scan were divided by that of the ventilation scan to correct for lung volume differences. The deposition pattern for the radio-aerosol was then reported in terms of the corrected I:O ratio.

Anatomically, it was assumed that the inner zone was comprised predominantly of larger, central airways and the outer zone was composed of peripheral airways.



**Figure 1.** Deposition of the isotopic marker on the baseline visit at Time 0 (i.e., immediately after aerosol inhalation) in a patient who had undergone SLT (A). Radioactivity remaining in the lung after 76 minutes is shown in (B).

Thus, lower I:O ratios indicated enhanced deposition in the peripheral airways, whereas higher I:O ratios indicated enhanced deposition of aerosol in the larger, central airways. Because these images were a 2-dimensional representation of deposition in a 3-dimensional organ, deposition in some smaller airways and alveoli also appeared in the inner zone region of the image. However, because of the lung's anatomy, we assumed that the number of smaller airways and alveoli comprising our inner region was significantly less than that found in our outer region, and that the two zones provided us with substantially different regional deposition information.<sup>14,15,17</sup>

### Percent MCC Calculation

To quantify MCC, we first measured the total counts of radioactivity ( $^{99\text{m}}\text{Tc}$ ) that were detected in the participant's transplanted lung at Time 0 (Figure 1A) and the amount of radio-isotope that was retained in the lung over the 76-minute acquisition period (Figure 1B). The total number of counts detected in the lung at each time-point was corrected for background and decay-corrected to Time 0.

Counts detected at Time 0 were considered to reflect 100% retention of the initially deposited radioactivity. Decay- and background-corrected counts for the later time-points were expressed as a percentage of the Time 0 activity. Percent retention values were then plotted vs time and a best-fit line, determined through appropriate regression analysis, was calculated. Percent retention at 76 minutes (Y) was then recalculated, based on the regression equation for the best-fit line. MCC at 76 minutes was expressed on a continuous scale from 0 to 100 as the complement of percent retention and calculated from the equation: % MCC at 76 minutes = 100% - Y. Based on anatomy, it was assumed that percent clearance after 76 minutes represented a measure of MCC for the large and smaller airways combined.

### Percent CC Calculation

Cough clearance was measured on each of the study visits, after the 76 minutes of imaging for MCC. After imaging for MCC, subjects were asked to cough gently 60 times in 10-cough intervals. CC was calculated as the difference in the amount of  $^{99\text{m}}\text{Tc}$  that was measured in the lung image before coughing (i.e., at 76 minutes) and after coughing (i.e., at 85 to 90 minutes).

### Albuterol Treatment

Approximately 1 week after the baseline visit, subjects underwent repeat imaging of their lungs after albuterol administration. During this visit, subjects first inhaled the radio-aerosol and then inhaled four separate actuations of albuterol (Proventil HFA; GlaxoSmithKline,

Philadelphia, PA), using a small volume spacer device (Aerochamber; Forest Pharmaceuticals, St. Louis, MO).

### Data Analysis

All data are presented as mean  $\pm$  standard deviation. All paired comparisons of I:O ratio, MCC and CC were performed using a Wilcoxon signed-rank test. Unpaired comparisons were performed using a Wilcoxon-Mann-Whitney test. Correlation coefficients were derived from regression analyses.  $p \leq 0.05$  (2-tailed) was considered statistically significant.

## RESULTS

### Demographics

The demographics of the seven transplant patients studied are shown in Table 1. There were four male and three female patients, ranging in age from 29 to 61 years at the time of transplant. The average age was  $53 \pm 11$  years.

Single-lung transplantation (SLT) was performed in five patients with chronic obstructive pulmonary disease and in one patient with  $\alpha_1$ -anti-trypsin deficiency. Three patients received a right lung at transplantation and three patients received a left lung. One subject underwent bilateral-lung transplantation for end-stage CF. Mean FVC and FEV<sub>1</sub> were  $55 \pm 14\%$  and  $50 \pm 12\%$  of predicted values, respectively, at baseline.

Mean donor age was  $35 \pm 11$  years for the six males and one female. Four of the seven donor/recipient pairs had mismatched cytomegalovirus (CMV) serology. Mean ischemic time was  $203 \pm 62$  minutes.

Measurements were also obtained in four healthy male volunteers without pulmonary disease, ranging in age from 23 to 43 years, with an average age of  $32 \pm 10$  years. Although the average age of the healthy subjects was considerably lower than that of the lung transplant patients, the mean ages of the donors and the healthy subjects were similar; therefore, the age of the lungs were similar when compared in terms of MCC. Mean

FVC and FEV<sub>1</sub> values were  $98 \pm 10\%$  and  $106 \pm 13\%$  of predicted values, respectively.

### Distribution of Radio-isotopic Marker Quantified as I:O Ratio

At baseline visit, mean inner:outer (I:O) zone ratio was  $2.7 \pm 2.2$  in the transplanted lungs. Mean I:O ratio in the transplant patients was not statistically different from that observed in the lungs of the healthy volunteers ( $1.8 \pm 0.3$ ). Nevertheless, the higher I:O values indicated that the initial distribution of the radio-isotopic marker in the allografts of the transplant patients was more central compared with the healthy subjects. Normally, deposition in the larger central airways should lead to faster MCC values as a result of an increase in the number of cilia on epithelial cells in these airways and a shorter distance to travel in terms of removal. However, MCC values measured in the lung transplant patients were statistically significantly slower than in the healthy subjects (see subsequent text and Figure 2).

I:O ratios quantified on the albuterol treatment visit for the transplant patients averaged  $1.8 \pm 1.2$ , which was not statistically different from the baseline visit.

### MCC and CC After Lung Transplantation

Deposition of the radio-isotopic marker on the baseline visit at Time 0 (i.e., immediately after aerosol inhalation) in a patient who had undergone SLT is shown in Figure 1A. Radioactivity remaining in the lung after 76 minutes is shown in Figure 1B. For this patient, MCC after 76 minutes was 20.2%. MCC for all seven patients at the baseline visit averaged  $8.9 \pm 7.3\%$  and ranged from 0% to 20.2% (Figure 2A). This represented a >50% reduction in MCC, compared with normal volunteers, whose MCC values ranged from 8.1% to 42.8% and averaged  $20.9 \pm 15.1\%$  ( $p = 0.05$ ).

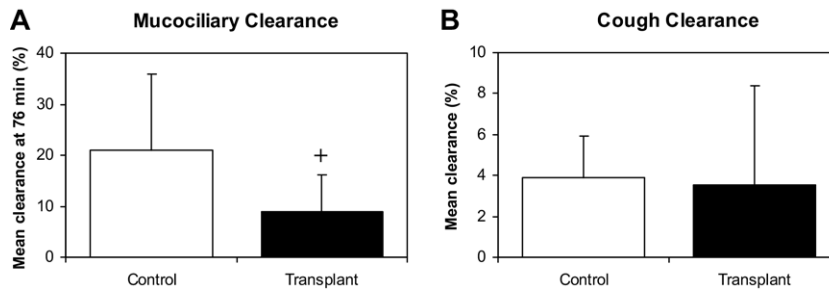
CC in the transplant patients ranged from 0% to 12.4%. However, mean CC in these patients was not significantly

**Table 1.** Demographics of Seven Lung Transplant Patients at Baseline

Patient number	Reason for transplant	Recipient			Donor			Ischemic time (min)	Post-operative baseline	
		Gender	Age (y)	CMV	Gender	Age (y)	CMV		FEV <sub>1</sub> <sup>a</sup>	FVC <sup>a</sup>
1	COPD	M	52	Neg	M	27	Pos	140	36	43
2	COPD	M	61	Pos	M	27	Neg	240	38	35
3	COPD	F	55	Neg	M	49	Neg	155	52	71
4	CF	F	29	Neg	M	29	Pos	243	72	64
5	COPD	F	59	Pos	F	33	Neg	173	58	70
6	$\alpha_1$ -anti-trypsin deficiency	M	54	Pos	M	53	Pos	162	47	57
7	COPD	M	61	Pos	M	26	Pos	309	45	45

CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity.

<sup>a</sup>FEV<sub>1</sub> and FVC are expressed as percent predicted.



**Figure 2.** Baseline mucociliary clearance (MCC) and cough clearance (CC) at the initial study visit. Mean and standard deviation MCC for normal subjects ( $n = 4$ ) and lung transplant patients ( $n = 7$ ) is shown in (A) ( $^+p = 0.05$ ). CC for normal subjects ( $n = 4$ ) and lung transplant patients ( $n = 7$ ) is shown in (B).

different from the healthy volunteers,  $3.5 \pm 4.9\%$  vs  $3.9 \pm 2.0\%$ , respectively (Figure 2B). Transplant patients with higher MCC values tended to have higher CC values as well ( $r = 0.831$ ;  $p < 0.02$ ; Figure 3).

### Relationship Between Mucociliary Clearance and Ischemic Time

Linear regression analysis showed no significant relationship between MCC and ischemic time ( $r = 0.383$ ).

### Effect of Acute Inhalation of Albuterol on Mucociliary Clearance

Because decreased MCC may place lung transplant patients at greater risk for developing pulmonary infections, we explored whether the MCC impairment was fixed, or if it could be pharmacologically modulated by treatment with albuterol aerosol. All patients had a substantial increase in MCC, ranging from 230% to 580%, after albuterol administration. The mean MCC of  $8.9 \pm 7.3\%$  measured on the baseline visit, rose 2.5-fold to  $31.9 \pm 21.9\%$  after inhalation of albuterol ( $p = 0.016$ ; Figure 4A). These data indicate that impaired MCC after lung transplantation can be stimulated and enhanced by acute inhalation of a  $\beta_2$ -adrenergic receptor agonist.

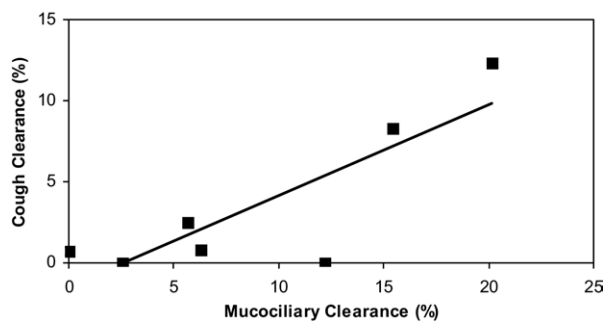
The response of CC to albuterol was more variable. In fact, CC decreased in three patients after albuterol

administration (Figure 4B). Although mean CC increased from  $3.5 \pm 4.9\%$  to  $7.3 \pm 10.6\%$  after albuterol, this increase was not statistically significant.

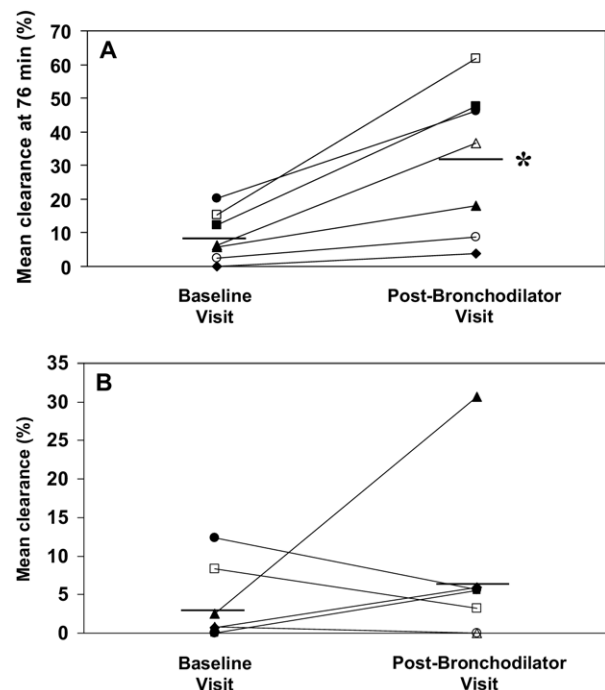
### DISCUSSION

Results from this study go beyond previous studies, which reported decreased MCC in lung transplant patients at 6 to 19 months after surgery.<sup>9,10</sup> Our study demonstrates that MCC is most likely impaired within 3 months after lung transplantation in the majority of patients. Although MCC was impaired in the allograft, we found that the secondary lung defense mechanism of CC was not affected by transplantation.

The etiology of the diminished MCC observed after lung transplantation is unknown, but it is likely to be



**Figure 3.** Relationship between mucociliary clearance (MCC) and cough clearance (CC) at the initial study visit for seven lung transplant patients ( $r = 0.831$ ;  $p < 0.02$ ).



**Figure 4.** Effect of inhaled albuterol on mucociliary clearance (A) and cough clearance (B) for each patient ( $*p = 0.016$ ). The mean is indicated by a horizontal line.

multifactorial. Several factors, including immunosuppression, ischemic injury and/or denervation, could play a role in the observed changes in MCC. Clearly, immunosuppression increases susceptibility to infection, primarily through an effect on lymphocytes. However, it is unknown if these drugs also directly affect MCC. Further studies are needed to address this issue.

Lung ischemia created by interrupting bronchial artery blood flow in sheep has been shown to decrease MCC.<sup>18</sup> However, systemic blood flow typically returns to the allograft within 1 month after transplant in animal models.<sup>19</sup> This finding suggests that long-term MCC impairment is most likely not due to peri-operative changes in blood flow. In addition, the degree of MCC impairment did not correlate with transplant ischemic time in the present study.

Another explanation for the decreased MCC may involve the denervation that occurs during lung transplantation and the subsequent changes in mucus rheology. MCC is dependent on an optimal ratio between mucus viscosity and mucus elasticity.<sup>20</sup> Traditionally, the mucus blanket in the airways is thought to consist of a low-viscosity, aqueous layer called the sol or peri-ciliary layer, which bathes the cilia, and a gel layer that is more dense and lies on top of the sol layer. Mucins are the principal structural components of mucus.<sup>21</sup> These macromolecules are secreted by goblet cells and the sub-mucosal glands. Mucin concentration is related in part to mucus hydration, which depends on the salt concentration and pH of the peri-ciliary fluid and is regulated by active ion transport across the epithelial cells with concomitant passive water transfer.<sup>22</sup> The sub-mucosal glands are thought to be under the control of the cholinergic nervous system.<sup>23</sup> It is not known if lung transplantation affects the peri-ciliary fluid composition or depth. However, we do know that pulmonary nerves that regulate the sub-mucosal glands are severed and are not reconnected during lung transplantation. In dogs, this denervation has been associated with atrophy of the sub-mucosal glands and diminished gland-secreting capacity after pharmacologic post-ganglionic stimulation.<sup>24</sup> The effects of denervation have been shown to persist for up to 36 months after heart-lung transplant.<sup>25</sup>

The MCC apparatus is comprised of ciliated epithelial cells, airway surface fluid, secretory granule-containing goblet cells and sub-mucosal glands. Insoluble material that deposits on the mucus layer is propelled toward the oropharynx by the coordinated action of the beating cilia.<sup>20</sup> The effectiveness of the cilia depends on the number of ciliated cells, length of the cilia and frequency of ciliary movements. The inability of cilia to beat properly leads to slower or impaired MCC such as in patients with ciliary dyskinesia.<sup>8</sup> Although a decrease in ciliary beat frequency (CBF) could explain MCC

impairment after lung transplantation, results from several studies that quantified CBF after transplantation are conflicting. For example, Read et al<sup>26</sup> and Veale et al<sup>27</sup> found that CBF was reduced in transplanted lungs compared to healthy controls or the native lung, respectively. In contrast, Dolovich et al<sup>9</sup> reported that CBF appeared normal in patients after SLT or heart-lung transplant.

It is well documented that lung transplant patients are at risk for developing significant pulmonary infections.<sup>3</sup> Because MCC is a key lung defense mechanism, responsible for the removal of insoluble material such as bacteria, viruses, antigens and toxins that deposit on the tracheobronchial airway surface during respiration, impaired MCC could place some lung transplant patients at greater risk for acute and chronic infections than others, and stimulating MCC could protect lung transplant patients from infection.

Although MCC appears to be impaired soon after lung transplantation, its back-up lung-defense mechanism, cough clearance, is not impaired. This means that one way to offset the loss of MCC after transplantation and decrease exposure of the allograft to viruses, bacteria and toxins would be to encourage patients to cough at regular intervals throughout the day as part of their routine standard of care. Patients should be instructed to cough moderately (not strenuously) 30 to 60 times over a 3- to 5-minute period several times per day. This should provide removal of some of the mucus from the airways that normally would be removed by MCC. However, because CC and MCC are correlated, voluntary coughing will be least efficient in patients with the lowest MCC.

Another approach to improve removal of mucus from the allograft would be to stimulate MCC pharmacologically. Because  $\beta_2$ -adrenergic receptor agonists have been shown to acutely stimulate MCC in other patient populations,<sup>28</sup> we tested the acute effect of albuterol in terms of improving MCC in lung transplant patients in this study. We found that a single administration of albuterol led to a marked increase in MCC in these patients, suggesting that the impairment is not fixed. To our knowledge, this is the first time that anyone has examined whether a drug could improve MCC in lung transplant patients.

The fact that the MCC impairment can be reversed by acute treatment with albuterol suggests that this intervention may also be useful in decreasing pulmonary infections after lung transplantation. Additional studies are needed to determine if long-term use of albuterol, or another  $\beta_2$ -adrenergic receptor agonist, can decrease the incidence of infections after lung transplantation.

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