Automatic Event Detection in Lung Transplant Recipients Based on Home Monitoring of Spirometry and Symptoms

Wayne Wang, PhD,¹ Stanley M. Finkelstein, PhD,²
and Marshall I. Hertz, MD³

¹Department of Biomedical Engineering, ²Department of Laboratory Medicine and Pathology, and ³Pulmonary/Critical Care Medicine, University of Minnesota, Minneapolis, Minnesota.

Abstract

Objective: The goal of this study was to develop, implement, and test an automated decision system to provide early detection of clinically important bronchopulmonary events in a population of lung transplant recipients following a home monitoring protocol. **Subjects and Methods:** Spirometry and other clinical data were collected daily at home by lung transplant recipients and transmitted weekly to the study data center. Decision rules were developed using wavelet analysis of declines in spirometry and increases in respiratory symptoms from a learning set of patient home data and validated with an independent patient set. **Results:** Using forced expiratory volume in 1 s or symptoms, the detection captured the majority of events (sensitivity, 80–90%) at an acceptable level of false alarms. On average, detections occurred 6.6–10.8 days earlier than the known event records. **Conclusions:** This approach is useful for early discovery of pulmonary events and has the potential to decrease the time required for humans to review large amount of home monitoring data to discover relatively infrequent but clinically important events.

Key words: lung transplant, home monitoring, pulmonary function test, spirometry, wavelet analysis, cumulative sum

Introduction

Lung transplant recipients are at high risk of post-transplant complications such as infection and rejection, which gradually erode lung function and are the two leading contributors to morbidity and mortality.¹ Survival after lung transplantation remains inferior to other solid organs such as heart and liver transplants,^{2,3} mostly because of pulmonary complications. Many transplant centers recommend that lung recipients perform daily pulmonary function tests (spirometry) and report respiratory symptoms, which may allow early diagnosis and treatment of transplant complications^{4–7} and thus help toward increasing long-term survival.³ Early intervention may also reduce cost and improve quality of life.⁸

Spirometry provides mechanistic insight into the physiologic impairment of the lungs and is routinely used to aid diagnosis of lung disease.⁹ Reliable and valid spirometry can be obtained by patients at

home and is comparable to the measurements obtained in the clinic.¹⁰ Spirometry measurements include lung volumes and air flows at specific times during a forced expiratory breathing maneuver to assess lung function. The forced expiratory volume in 1 s (FEV₁), the ratio of FEV₁ to the forced vital capacity, the mid-expiratory flow rate, and the peak expiratory flow rate are the most frequently used indices for assessing airway obstruction and airflow limitations. Respiratory symptoms have been the common reasons that trigger a clinic visit, and they are the least invasive type of surveillance available to capture clinical events.¹¹

Recent technological advancements have made home monitoring more convenient and more reliable, which may facilitate the detection of clinically important pulmonary events. However, as the number of monitored patients grows, increased time is required of transplant clinic nurses for screening the large amounts of data. Event detection is limited by considerable noise observed as inter- and intra-subject variability in clinical data. Therefore, we are exploring new, computer-based approaches to analyzing data, which will facilitate efficient and accurate early detection of pulmonary events.

Subjects and Methods

DATASETS

The Lung Transplant Home Monitoring Program (LTHMP) at the University of Minnesota provided the home monitoring datasets used in this study. In LTHMP, patients were trained to use an electronic spirometer/diary device at home to record and transmit daily respiratory measurements of FEV₁, forced vital capacity, mid-expiratory flow rate, and peak expiratory flow rate and symptoms including the frequency and intensity of dyspnea, wheeze, sputum, and cough.¹² The home monitoring protocol instructed subjects to maintain consistency and perform tests at the same time each day to control for diurnal variation. A learning set consisting of 28 transplant recipients had a minimum home monitoring period of 60 days. Data were recorded daily except for occasional gaps where subjects did not record or transmit data.

Events of interest were acute bronchopulmonary-related clinical complications (e.g., bronchitis, pneumonitis, and acute rejection), which were captured through typical post-lung transplant surveillance including routine examination, clinic measured spirometry, and patient complaint of symptoms.¹³ Case definitions required that the event be a newly diagnosed or treated episode of an acute, primary bronchopulmonary infection or rejection that was accompanied by the start of a new treatment or the change of a chronic medication, as determined by a qualified health science professional, who retrospectively reviewed the medical records of each subject.¹⁴

Records of transbronchial lung biopsies with graded acute rejection and infections¹⁵ were combined into the event list. The absence of events was determined by the lack of evidence of event occurrence.

A validation set compiled from a subsequent LTHMP investigation consisted of 30 subjects not included in the learning dataset, with a minimum home monitoring period of 24 days. Event diaries for the validation data set were actively maintained by a dedicated research nurse as the basis of event determination. *Table 1* summarizes the datasets.

All subjects in the LTHMP studies provided informed written consent, following the guidelines of the University of Minnesota Institutional Review Board.

EVENT DETECTION BASED ON SPIROMETRY

According to the American Standardization of Spirometry guidelines to diagnose pulmonary diseases,¹⁶ spirometric readings are compared with the previous readings, denoted as baseline. To automatically identify a decline from baseline, wavelet analysis,^{17–21} consisting of fitting dynamic data with translation and dilation of the same basis function wavelets, was used. This provided an adaptive approach to analyzing the home monitoring datasets, which included nonconventional data characteristics such as the abrupt jumps observed in the spirometry series in this study. Wavelet analysis decomposed spirometry series variation and compared data representations based on two moving time frames: a “high-resolution” representation, which contained acute response to an event, and a low-resolution baseline, which when crossed below resulted in trending crossovers. The time frames of 8 and 64 days were determined experimentally under the learning set. Furthermore, a cumulative sum (CUSUM),²² which added up the area past crossover at daily increments, was compared with a preset threshold to classify events. These steps are illustrated in *Figure 1*.

EVENT DETECTION BASED ON SYMPTOMS

Symptom data consisted of ordinal scales of frequency and intensity of dyspnea, wheeze, sputum production and color, and cough. A symptom index (symptom) was derived from the rules formulated by lung transplant triage nurses in an earlier home monitoring study.²³ Thus, the multiple series of symptom scores were converted to one composite index series for each subject. The same concept of trending crossover except for an increase in symptom was used to detect events.

	LEARNING SET	VALIDATION SET
Subjects (<i>n</i>)	28	30
Female [<i>n</i> (%)]	10 (36%)	12 (40%)
Male [<i>n</i> (%)]	18 (64%)	18 (60%)
Age at transplant [years (range)]	50.8 ± 12.5 (23–67)	55.5 ± 9.8 (20–68)
Monitoring records (<i>n</i>)	9,653	2,426
Monitored days	469 ± 228	148 ± 66
Range	60 days–2.8 years	24–269 days
Events (<i>n</i>)	101	40
Events/subject-year (range)	2.3 ± 2.7 (0–8)	4.2 ± 6.5 (0–7)
Subjects with events (<i>n</i>)	26	14
Events/subject [median (range)]	2 (1–8)	2 (1–7)
Subjects without events (<i>n</i>)	2	16

Fig. 1. Illustration of wavelet analysis of a forced expiratory volume in 1 s (FEV1) series with events. CUSUM, cumulative sum.

PERFORMANCE EVALUATION

Event detection occurred and alarms were issued when the CUSUM passed a predetermined threshold. This threshold could be set by the monitoring staff (user) to adjust for acceptable sensitivity and false alarm rates. The timing of detection was compared with the time of actual event occurrence within a timing window around the known event. An event window was defined based on clinical judgment as 3 weeks preceding and 1 week trailing the date of the event record, where a true positive detection that occurs prior to or after the event represents an early or a delayed detection, respectively. The remaining time intervals were considered free of events. The absence of an alarm within an event window indicates a missed detection. Conversely, alarms generated outside the event windows are false alarms. Figure 2 illustrates how alarms were classified according to the CUSUM.

The collective performance of event detection is characterized using an operating characteristics curve of sensitivity versus false alarm rate as a function of threshold cutoff values. Sensitivity is the number of correctly detected events divided by the total number of events. The false alarm rate is the total number of alarms when events were absent divided by the total duration of monitoring, denoted as number/subject-year. A paired Student's *t* test was used to compare the timing between detections using FEV₁ and symptom data.

WAVELET AND STATISTICAL ANALYSIS

Wavelet analyses were based on Daubechies' wavelets^{17,18} "db3" and "db4" for the high- and the low-resolution signal smoothing, respectively. All analyses were performed in the MATLAB 7 (The Mathworks, Natick, MA) computing environment with Wavelets Toolbox.²⁴ Statistical analysis used SAS version 9.2 software (SAS Institute, Cary, NC). Operating characteristics plots were produced in Microsoft® (Redmond, WA) Office EXCEL 2007.

Results

Figure 3 illustrates a representative clinical case with well-documented event diaries: a male single lung transplant subject who experienced two infection events within 250 days after transplantation. Three detections were made, of which both infection events were correctly predicted by home spirometry 2 weeks before their detection by routine clinical methods. The false detection was determined to be due to lack of qualifying event documentation. Although formally listed as a false alarm, it was clearly related to a declining condition that prompted the patient to visit the emergency department, at which time it was decided that no further treatment was necessary.

The operating characteristics curves (Figs. 4 and 5) depict performance of each variable. The

Fig. 2. Illustration of alarm classification. CUSUM, cumulative sum.

Fig. 3. Real case application of event detection. (A) Data points for forced expiratory volume in 1s (FEV₁), high- (H) and low- (L) resolution trends. (B) Subtraction (H - L) and trend crossover(s). (C) Cumulative sum (CUSUM) and event detection. Explanation of time points: Spirometry decline was observed. Lab report (Day 123): "bronchoscopy-cultures showed moderate *Pseudomonas* growth." The subject visited the emergency room for a sore throat (Day 161). No surgical or medical treatment was given. Nurse's note (Day 212): "Upper respiratory sinusitis—amoxicillin provided and no other treatment."

Fig. 4. The operating characteristics of the learning set. FA, false alarm; FEV₁, forced expiratory volume in 1 s; FFR, ratio of FEV₁/FVC; MEFR, mid-expiratory flow rate; PEFR, peak expiratory flow rate.

Fig. 5. The operating characteristics (OC) of the validation set. FA, false alarm; FEV₁, forced expiratory volume in 1 s; FFR, ratio of FEV₁/FVC; MEFR, mid-expiratory flow rate; PEFR, peak expiratory flow rate.

top tier detection performance was FEV₁ and symptom as shown in Table 2, of which FEV₁ correctly detected 81 of 101 events with a sensitivity of 80% at 3.8 false alarms per subject-year in the learning set and detected 34 of 40 events with a sensitivity of 86% per subject at 2.8 false alarms per subject-year in the validation set. The symptom correctly detected 82 of 101 events with a sensitivity of 82% at 4.3 false alarms per subject-year in the learning set and detected 33 of 40 events with a sensitivity of 83% per subject at 4.4 false alarms per subject-year in the validation set.

The timing of detection is compared in Figure 6. In the learning set, FEV₁ and symptom provided an early warning at 10.8 ± 9.6 and 10.0 ± 13.5 days, respectively, in which FEV₁ led symptoms by 1.9 days (paired $p=0.04$). In the validation set, FEV₁ and symptom provided an early warning of 7.7 ± 6.6 and 6.6 ± 6.7 days, respectively; there was no significant difference in timing of detected events between the FEV₁ and symptom analyses.

Discussion

This study defines rules for automated data screening and detection of clinical events in a population of lung transplant recipients following a home monitoring protocol. This approach has the potential to decrease the time required for humans to review large amounts of data to discover relatively infrequent but clinically important events. For example, using manual methods, a nurse following 100 lung transplant recipients would be required to review all 100 weekly monitoring reports even though most would be negative. Assuming 10% of monitoring reports indicate potential problems, the nurse would have to review all 100 to find the 10 with potential problems. In contrast, the automated detection system would review all 100 cases and find, for example, 20% that the system determines to be potential problems, which would be directed to the nurse for closer review. So instead of reviewing all 100 cases to find the 10 with potential problems, the nurse would have to look at only 20 cases to find the 10 with problems—reducing workload by 80%.

Table 2. Operating Characteristics Summary

	FEV ₁	FEV ₁ /FVC	MEFR	PEFR	SYMPTOM
Learning set					
Sensitivity (%) ^a	80.002	80.1	72.1	78.1	82.3
FAR	3.81	4.81	4.40	4.72	4.26
Validation set					
Sensitivity (%) ^a	85.7	62.3	85.7	51.3	82.5
FAR	2.83	2.51	4.82	2.78	4.42
Threshold T	0.5	0.25	0.5	1.0	1.0

^aSensitivity is the percentage of events detected.

FAR, false alarm rate (number of events/subject-year); FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; MEFR, mid-expiratory flow rate; PEFR, peak expiratory flow rate.

Fig. 6. Timing of detection (days). Note the cutoff threshold at $|T|=0.5$ for forced expiratory volume at 1s (FEV₁) and $|T|=1$ for symptom.

In the current study, the best overall performance was consistently achieved with FEV₁ and symptom at 80–90% sensitivity. These sensitivities exceeded the reported sensitivity of approximately 60% in previous reported studies^{25,26} in which screening was based on clinician review of daily spirometry. As might be expected, as detection sensitivity increases, so does the incidence of false alarms. The maximum sensitivity exceeded 90% in both test sets, suggesting that almost all events could be captured using the proposed method alone. It is at the user's discretion to balance sensitivity and tolerance of false alarms by setting the appropriate detection threshold.

Furthermore, automated detection provided early warning on average 7–10 days compared with routine care. Clearly, “events” that are identified by home monitoring require active investigation by care providers in order to differentiate between clinically significant and unimportant alarms.

LIMITATIONS

It is well known that spirometry alone does not allow recognition of the etiology of pulmonary dysfunction^{26,27} and that symptoms alone could not differentiate pulmonary rejection and infection.¹¹ Therefore, non-pulmonary events that affect pulmonary functions may not be distinguishable from pulmonary events on the basis of spirometry and symptom surveillance alone. Although a reported false alarm rate of three or four events per subject-year may be considered acceptable, it should be further noted that some of these false alarms were related to episodes that caused enough subject concern to seek medical attention (as was done by the subject case described in Fig. 3) and may thus impart some useful clinical information.

Rule testing for this study was performed using typical clinical data, which frequently contain missing values. In the cases in which missing data could have been related to the events, detection would have been compromised. One study that reported a non-adherence to home spirometry in connection to occurrence of events and graft survival²⁸ ap-

pears to support this speculation. Thus, the need for adherence to the monitoring protocol and data completeness cannot be overstated.

Conclusions

This study demonstrates a wavelet-based analysis of home-monitored spirometry/symptoms can indicate data anomalies associated with acute bronchopulmonary events and can provide a reliable means to detect these events at their earlier stage. More than 80% of events could be detected automatically using a low-cost noninvasive computerized analysis alone, which minimizes the need for human screening of large amounts of pulmonary function data. However, the use of home monitoring and detection does not preclude a visit to the clinic for formal examination and diagnoses. Once events are detected, discussion between the patient and the transplant center is needed to determine the proper course of further evaluation.

Acknowledgments

This study was supported in part by grants RO1NR02128 and RO1NR009212 from the National Institutes of Health.

Disclosure Statement

No competing financial interests exist.

REFERENCES

1. Studer SM, Levy RD, McNeil K, Orens JB. Lung transplant outcomes: A review of survival, graft function, physiology, health-related quality of life and cost-effectiveness. *Eur Respir J* 2004;24:674–685.
2. Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dobbeis F, Kirk R, Rahmel AO, Stehlik J, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: Twenty-eighth official adult lung and heart-lung transplantation report—2011. *J Heart Lung Transplant* 2011;30:1104–1122.
3. Lease ED, Zaas DW. Update on infectious complications following lung transplantation. *Curr Opin Pulm Med* 2011;17:206–209.
4. Finkelstein SM, Snyder M, Stibbe SE, Hertz M, Stibbe CE, Lindgren B, Sabati N, Killoren T. Staging of bronchiolitis obliterans syndrome using home spirometry. *Chest* 1999;116:120–126.
5. Otulana BA, Higenbottam T, Ferrari L, Scott J, Igboaka G, Wallwork J. The use of home spirometry in detecting acute lung rejection and infection following heart-lung transplantation. *Chest* 1990;97:353–357.
6. Bjortuft O, Johansen B, Boe J, Foerster A, Holter E, Geiran O. Daily home spirometry facilitate early detection of rejection in single lung transplant recipient with emphysema. *Eur Respir J* 1993;6:705–708.
7. Kugler C, Fuehner T, Dierich M, DeWall C, Haverich A, Simon A, Welte T, Gottlieb J. Effect of adherence to home spirometry on bronchiolitis obliterans and graft survival after lung transplantation. *Transplantation* 2009;15:129–134.
8. Adam TJ, Finkelstein SM, Parente ST, Hertz MI. Cost analysis of home monitoring in lung transplant recipients. *Int J Technol Assess Health Care* 2007;23:216–222.
9. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
10. Lindgren BR, Finkelstein SM, Prasad B, Dutta P, Killoran T, Scherber J, Stibbe CLE, Snyder M, Hertz MI. Determination of reliability and validity in home

- monitoring data of pulmonary function tests following lung transplantation. *Res Nurs Health* **1997**;20:539–550.
11. De Vito Dabbs A, Hoffman LA, Iacono AT, Zullo TG, McCurry KR, Dauber JH. Are symptom reports useful for differentiating between acute rejection and pulmonary infection after lung transplantation? *Heart Lung* **2004**; 33:372–380.
 12. Finkelstein SM, Snyder M, Edin-Stibbe C, Chlan L, Prasad B, Dutta P, Lindgren B, Wielinski C, Hertz MI. Monitoring progress after lung transplantation from home-patient adherence. *J Med Eng Technol* **1996**;20:203–210.
 13. Troiani JS, Carlin BP. Comparison of Bayesian, classical, and heuristic approaches in identifying acute disease events in lung transplant recipients. *Stat Med* **2003**;23:803–824.
 14. Troiani JS, Finkelstein SM, Hertz MI. Incomplete event documentation in the medical records of lung transplant recipients. *Prog Transplant* **2005**;15: 173–177.
 15. Lande JD, Patil J, Li N, Berryman TR, King RA, Hertz MI. Novel insights into lung transplant rejection by microarray analysis. *Proc Am Thorac Soc* **2007**;4:44–51.
 16. American Thoracic Society. Standardization of spirometry: 1994 update. *Am J Respir Crit Care Med* **1995**;152:1107–1136.
 17. Daubechies I. The wavelet transform, time-frequency localization and signal analysis. *IEEE Trans Inf Theory* **1990**;36:961–1005.
 18. Daubechies I. *Ten lectures on wavelets*. SIAM-CBMS-NSF Regional Conference Series in Applied Mathematics. Philadelphia, PA: SIAM, **1992**.
 19. Mallat S. A theory for multiresolution signal decomposition: The wavelet representation. *IEEE Trans Pattern Analysis Machine Intelligence* **1989**;11:674–693.
 20. Meyer Y. *Wavelets and operators*. Cambridge, UK: Cambridge University Press, **1992**.
 21. Vaidyanathan PP. *Multirate systems and filter banks*. Englewood Cliffs, NJ: Prentice Hall, **1992**.
 22. Page ES. Continuous inspection schemes. *Biometrika* **1954**;41:100–115.
 23. Finkelstein SM, Scudiero A, Lindgren B, Snyder M, Hertz MI. Decision support for the triage of lung transplant recipients on the basis of home-monitoring spirometry and symptom reporting. *Heart Lung* **2005**;34:201–208.
 24. *Wavelet toolbox*. MATLAB 7. Natick, MA: The Mathworks Inc., **2005**.
 25. Morlion B, Knoop C, Paiva M, Estenne M. Internet-based home monitoring of pulmonary function after lung transplantation. *Am J Respir Crit Care Med* **2002**;165:694–697.
 26. Wagner FM, Weber A, Park JW, Schiemanck S, Tugtekin SM, Guliemos V, Schuler S. New telemetric system for daily pulmonary function surveillance of lung transplant recipients. *Ann Thorac Surg* **1999**;68:2033–2038.
 27. Arcasoy SM, Kotloff RM. Lung transplantation. *N Engl J Med* **1999**;340: 1081–1091.
 28. Gottlieb J, Kugler C, Fuehner T, Simon AR, Welte T. Effect of non-adherence to home spirometry on graft survival and bronchiolitis obliterans syndrome (BOS) after lung transplantation. *J Heart Lung Transplant* **2008**;27–2:S69.

Address correspondence to:

Wayne Wang, PhD

c/o S.M. Finkelstein, PhD

Department of Laboratory Medicine and Pathology, MMC 609

University of Minnesota

Minneapolis, MN 55455

E-mail: wang0118@umn.edu

Received: November 21, 2012

Revised: January 8, 2013

Accepted: January 17, 2013