Improving survival outcomes in lung transplant recipients through early detection of bronchiolitis obliterans: Daily home spirometry versus standard pulmonary function testing

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BACKGROUND: Long-term lung transplant success is limited by bronchiolitis obliterans syndrome (BOS), a form of chronic allograft rejection that manifests in the majority of patients by five years post-transplant. Frequent monitoring of pulmonary function measurements through the use of daily home spirometry may have the capability to detect the onset of BOS sooner than standard pulmonary function testing. Early detection of BOS would confer a treatment advantage that may improve survival outcomes for lung transplant recipients.

METHODS: A systematic review of current evidence was used to determine the effectiveness of daily home spirometry as a BOS detection tool, in addition to its impact and survival outcomes. Articles were included in the present systematic review if they were randomized control studies and if their purpose(s) included investigation of spirometry as a BOS detection tool in lung transplant patients.

RESULTS: A primary search of databases yielded 115 unique citations, with an additional four citations identified through a secondary review of the reference lists of retrieved articles. After application of all inclusion and exclusion criteria through abstract and full-text review, eight randomized controlled trials were included in the review.

DISCUSSION: Forced expiratory volume in 1 s (FEV_1) has been identified as the most reliable diagnostic tool for detecting the onset of BOS. Two studies compared the use of traditionally scheduled pulmonary function testing with daily home spirometry and found BOS stage 1 to appear 341 days earlier with home spirometry (P<0.001). Other studies that investigated the impact early detection had on survival showed a positive trend toward freedom from BOS and reduced rates of retransplantation, although these results did not reach statistical significance (P<0.07).

CONCLUSION: Daily home spirometry has been shown to lead to earlier detection and staging of BOS when compared with standard pulmonary function testing. Although FEV_1 has been shown to be the most sensitive and reliable marker of BOS onset, the impact of earlier staging via home spirometry on survival has not been reliably determined.

Key Words: *Bronchiolitis obliterans; Forced expiratory volume; Home monitoring; Lung transplantation; Rejection; Spirometry*

Améliorer la survie chez des greffés pulmonaires grâce au dépistage précoce de la bronchiolite oblitérante : la spirométrie quotidienne à domicile ou l'exploration fonctionnelle respiratoire standard

HISTORIQUE : La réussite à long terme des transplantations pulmonaires est limitée par le syndrome de bronchiolite oblitérante (SBO), une forme de rejet chronique de l'allogreffe qui se manifeste chez la majorité des patients dans les cinq ans suivant la transplantation. La surveillance fréquente des mesures de fonction pulmonaire par la spirométrie quotidienne à domicile pourrait déceler l'apparition du SBO plus rapidement que l'exploration fonctionnelle respiratoire standard. Le dépistage précoce du SBO confère un avantage thérapeutique qui peut améliorer la survie des greffés pulmonaires.

MÉTHODOLOGIE : Les chercheurs ont procédé à l'analyse systématique des données probantes à jour pour déterminer l'efficacité de la spirométrie quotidienne à domicile comme outil de détection du SBO, ainsi que son effet sur la survie. Les articles étaient retenus s'il s'agissait d'études aléatoires et contrôlées dont l'un des objectifs consistait à évaluer la spirométrie comme outil de dépistage du SBO chez les greffés pulmonaires.

RÉSULTATS : Les chercheurs ont obtenu 115 citations uniques au moyen d'une recherche primaire des bases de données, et quatre autres après un examen secondaire des listes de références des articles extraits. Après l'application de tous les critères d'inclusion et d'exclusion par l'analyse des résumés et des textes intégraux, ils ont retenu huit essais aléatoires et contrôlés.

EXPOSÉ : Il a été établi que le volume expiratoire maximal par seconde (VEMS) est l'outil diagnostique fiable pour dépister l'apparition du SBO. Deux études comparant l'utilisation de l'exploration fonctionnelle respiratoire habituelle à la spirométrie quotidienne à domicile ont décelé que le SBO de stade 1 était décelé 341 jours plus tôt grâce à la spirométrie quotidienne (P<0,001). D'autres études sur l'effet du dépistage précoce sur la survie ont révélé une tendance positive vers la guérison du SBO et une diminution du taux de retransplantation, même si ces résultats n'étaient pas statistiquement significatifs (P<0,07).

CONCLUSION : L'analyse a révélé que la spirométrie quotidienne à domicile assure un dépistage et l'établissement du stade du SBO plus rapidement que l'exploration fonctionnelle respiratoire. Même si le VEMS est le marqueur le plus sensible et le plus fiable d'apparition du SBO, l'effet sur la survie de l'établissement du stade de la maladie par la spirométrie à domicile n'a pas été établi avec fiabilité.

Patients diagnosed with advanced lung disease remain significantly symptomatic despite medical therapy and experience statistically high short-term mortality (1). Many of these patients desperately seek symptomatic relief and would consider undergoing lung transplantation to improve their quality of life. Since the first successful heart-lung transplant was performed in 1981 by Dr Bruce Reitz (2), an accepted intervention has emerged for patients with end-stage cardiopulmonary disease. An estimate by the Global Observatory on Donation & Transplantation in 2011 reported an average of 3200 lung transplants performed each year from 2006 to 2010 worldwide (3), increasing to 3972 in 2012 (4). Although many patients live longer with an improved quality of life after lung transplantation, a significant proportion experience adverse effects and comorbidities, often leading to death sooner after transplant than predicted without (1).

The need for investigation is a result of notably poor survival outcomes for lung transplant recipients specifically. According to a 2008 publication from the Registry of the International Society for Heart & Lung Transplantation (ISHLT) (5), lung transplant recipients had an overall median survival of 5.3 years. The registry described long-term survival rates after lung transplantation of 79% at one year, 63% at

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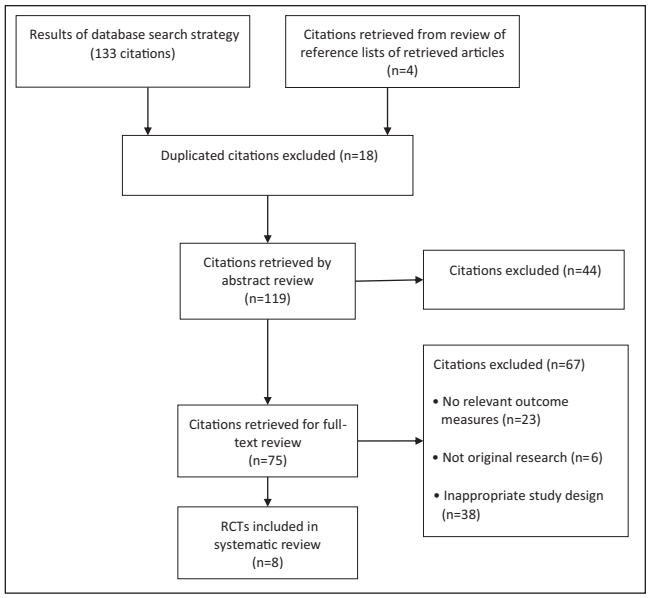

Figure 1) *Flow diagram of included trials. RCT Randomized controlled trials*

three years, 52% at five years and 29% at 10 years (5). Survival outcomes for lung recipients remain inferior by nearly one-half of those achieved with other solid-organ transplant procedures. Heart transplant recipients have survival rates of 88%, 75% and 56% at one, five and 10 years, respectively (5,6). Similar differences are apparent with recipients of deceased donor livers, having respective survival rates of 88%, 74% and 60% (5,6). Lung transplantation clearly has a significant early postoperative mortality rate and, often, the recipient may experience significant morbidity associated with transplant and immunosuppression (1).

The major cause of death post-lung transplantation has remained constant over the past three decades. Graft failure and infection have been the cause of most acute rejections (ie, first 30 days), whereas bronchiolitis obliterans syndrome (BOS) has been linked to the cause of almost all chronic rejections (ie, after the first year) (7-9). BOS presents as a fibrotic inflammatory process that affects the small airway bronchioles (9). The disease process can be devastating, involving rapidly progressive airways obstruction, eventually leading to respiratory failure (10-12). The development of BOS is believed to be due to chronic graft rejection and has been routinely treated with increased immunosuppression therapy. The concern is that most often, immunosuppression is not successful (9-11). Once BOS is identified, alterations in immunosuppression generally prove, at best, to be only of modest benefit (11). An irreversible decline in forced expiratory volume in 1 s (FEV_1) obtained through pulmonary function testing, has shown to be the most well-documented tool to diagnose BOS (11,13). Early intervention, which is essential to improving long-term survival, is dependent on the earliest possible detection. Several studies have suggested that the frequent monitoring of pulmonary function can provide such detection capability (13-19).

The relative lack of improvement in lung transplant rejection rates is a concern for an ageing population in which the burden of chronic lung disease is increasing. The present article systematically reviews current research regarding the use of spirometry as a tool for BOS detection in lung transplant recipients, particularly through FEV_1 values, and the role home spirometry can play in monitoring for FEV_1 changes sooner. A secondary outcome of interest in the present analysis was the impact of early detection using spirometry on survival.

METHODS

Search strategy

A primary search of computerized databases (PubMed, Scopus and MedlinePlus) was conducted in January 2014. Key terms for the search included "bronchiolitis obliterans", "lung transplantation", "rejection", "spirometry", "forced expiratory volume", "home monitoring" and "mortality". A secondary search using the reference lists of all retrieved articles was conducted to identify additional studies. Both searches were limited to human studies in English that were published between 1993 and 2014. No age, sex or race limitations were applied to the search.

Study selection

Articles were included in the present systematic review if they were randomized controlled studies and their purpose(s) included investigation of spirometry as a BOS detection tool in lung transplant patients. Articles were excluded from the systematic review if they exhibited any one of the following criteria: methodologies other than randomized clinical trials, including reviews, observational studies or commentaries; inadequate randomization methods; failure to report on a standardized outcome related to the purpose (ie, decrease in FEV_1, retransplantation or mortality); and the use of spirometry as a detection tool for pathologies other than BOS.

Systematic review process

The review team consisted of a clinical respiratory therapist (KSR) and a research respiratory therapist (AJW). Initial abstract review of all citations retrieved was performed by one investigator (KSR) and articles were chosen for further review based on the inclusion criteria (KSR). Full-text review of those articles was performed independently by both team members to determine potentially relevant studies for final inclusion. Any disagreement between the reviewers was resolved by consensus.

The Cochrane risk of bias framework for randomized controlled trials (20) was used to determine the risk of bias. Each study was independently critically appraised by the two researchers, and any disagreement between reviewers was resolved by consensus.

RESULTS

The primary search of the databases yielded 115 unique citations, with an additional four citations identified through a secondary review of the reference lists of retrieved articles. After application of all inclusion and exclusion criteria through abstract and full-text review, eight randomized controlled trials were included in the review. Each of the eight studies was determined to exhibit a low risk of bias. Figure 1 provides an overview of the trial flow.

The trials identified for inclusion in the present review are summarized in Table 1. All included trials used either a measured FEV_1 <20% of baseline predicted values or transbronchial biopsy (TBB), or a combination of the two, as criteria for diagnosing BOS. The primary outcomes of each trial were measured using spirometry to evaluate the utility of FEV_1 values as a staging tool for BOS (confirmed with TBB as the control), or to evaluate the detection capabilities of home spirometry versus routine clinical testing. In all studies, pulmonary function testing was performed following the standards established by the American Thoracic Society at each clinic visit.

DISCUSSION

The early identification of chronic rejection following lung transplantation is problematic due to the lack of reliable diagnostic testing. The once commonly used method of TBB to detect BOS is now rarely performed due to its low sensitivity (17). Therefore, the diagnosis of chronic airways rejection is generally based on changes in pulmonary function, specifically FEV_1. BOS has been commonly defined as a decline in FEV_1 of >20% from the post-transplant baseline in the absence of acute rejection or active infection (11,13-16). The terms 'BOS' and 'chronic rejection' have become synonymous with one

TABLE 1
Characteristics and primary outcomes of randomized controlled trials included in the present systematic review

Author (reference), year	Sample	Method of BOS identification	Comparison	Outcomes evaluated	Primary findings
Burton et al (13), 2007	346 SLT/DLT/HLT recipients	Average maximal FEV_1 obtained through spirometry >3 weeks apart	Maximal baseline FEV_1 obtained post-transplant	BOS grade 1 identified as a sustained FEV_1 <80% relative to baseline	Baseline FEV_1 values to be strongly associated with freedom from BOS stage 1, and long-duration BOS-free survival
Lama et al (14), 2005	197 SLT recipients alive >3 months post-transplant	FEV_1 <20% from baseline (determined from the average of 2 measurements made at least 3 weeks apart)	Maximal baseline FEV_1 and $FEF_{25\%-75\%}$ obtained post-transplant	Potential BOS (stage BOS 0-p) defined by an FEV_1 <10% to 19% baseline and/or >25% decrease in $FEF_{25\%-75\%}$	BOS 0-p was associated with higher sensitivity, specificity, and positive predictive values over $FEF_{25\%-75\%}$ criterion. Of patients who met BOS 0-p criterion, 81% developed BOS stage 1 or died within 3 years
Bjotuft et al (15), 1993	Eight SLT recipients with emphysema	TBB performed routinely at follow-up and when respiratory symptoms arose*	Persistent (>2 days) decrease in FVC or FEV_1 >10% over a 7-day average	Acute cellular rejection and/or chronic rejection confirmed through TBB	In 16 of 23 confirmed rejections, FEV_1 and FVC decreased significantly (P<0.001), with a >10% decrease in the 7-day average before TBB
Becker et al (16), 1994	31 LT recipients	TBB performed routinely or post-clinical suspicion of an acute process†	Best baseline FVC, FEV_1, and $FEF_{25\%-75\%}$ obtained postoperatively	The magnitude in the drop of FVC, FEV_1 and $FEF_{25\%-75\%}$ at the time of an abnormal biopsy when compared with baseline	A mean drop in FVC from 71% to 62% predicted (P<0.00001), and FEV_1 from 66% to 58% predicted (P<0.0001) compared with baseline. A statistically significant change was not apparent in $FEF_{25\%-75\%}$ (P=0.13)
Finkelstein et al (18), 1999	45 LT recipients	Clinical staging of BOS using the ISHLT algorithm based on FEV_1 changes relative to baseline obtained clinically	The average of 3 FVC manoeuvres performed once daily	Number of days from date of transplant to the first detection of any stage BOS (calculate from both clinical and home FEV_1 measurements)	Staging based on home measurements detected a decline to stage 1 an average of 341 days earlier than clinic measures (P<0.001), and further declines to stage 2 and stage 3 were detected an average of 144 days (P<0.05) and 159 days earlier than clinic-based staging
Lama et al (23), 2007	111 LT recipients	FEV_1 <20% predicted baseline post-transplant	FEV_1 % predicted at 0, 6, 12 and 18 months after BOS onset	Decline of FEV_1 after BOS stage 1 onset	The rate of decline of FEV_1 % predicted changed significantly during the first 2 years after BOS onset (P<0.0001). The steepest decline in FEV_1 % predicted was apparent in the first 6 months and was highly statistically significant (12% decline; P<0.0001)
Finkelstein et al (24), 1997	19 LT recipients	FEV_1 <20% predicted baseline values	The average of 3 FVC manoeuvres performed once daily	FEV_1 declines measured from daily spirometry at home	Using home spirometry, the onset of decline began an average of 284 days before diagnosis of chronic rejection, which was significantly earlier (P<0.05) than the decline observed with clinic pulmonary function testing
Sengpiel et al (27), 2010	56 LT recipients	Home spirometry-based FEV_1 <20% baseline predicted value	Home spirometry with data transfer equipped bluetooth	Time from onset of symptoms to physician consultation during the first 6 months after lung transplantation	Median time to first consultation (P=0.60) and frequency of consultation (P=0.06) did not differ significantly in the 2 groups

**All subjects underwent surveillance bronchoscopy with bronchoalveolar lavage and transbronchial biopsies one and two months after transplantation, and every two months during the remainder of the first post-transplant year. After one year, bronchoscopic examinations were continued every three months until the subject had 12 consecutive rejection-free months. In addition, the subjects underwent bronchoscopy with lavage and transbronchial biopsies whenever signs or symptoms suggestive of respiratory infection occurred, or when clinic forced expiratory volume in 1 s (FEV_1) decreased >15% compared with previous clinic visits; †All patients were screened for rejection with bronchoscopy and transbronchial biopsy (TBB) performed at three and six weeks, and at three, six, nine and 12 months, and every six months after the first year. BOS Bronciolitis obliterans syndrome; DLT Double-lung transplant; $FEF_{25\%-75\%}$ Forced expiratory flow between 25% and 75% of forced vital capacity (FVC); FEV_1 Forced expiratory volume in 1 s; HLT Heart-lung transplant; ISHLT The International Society for Heart & Lung Transplantation; LT Lung transplant; SLT Single-lung transplant*

another when considering lung transplant, and the use of monitoring declines in FEV_1 has been shown to be a reliable diagnostic tool. However, whether the use of spirometry to monitor FEV_1 changes is the best test for early detection of BOS is yet to be established. It is, therefore, necessary to consider other detection strategies to determine what will show signs of BOS in its earliest and most treatable stages.

TABLE 2
International Society for Heart & Lung Transplantation staging system for bronchiolitis obliterans syndrome (BOS)

BOS stage	1993 grading system	2002 revised classification system
BOS 0	FEV_1 >80% of baseline	FEV_1 >90% and $FEF_{25\%-75\%}$ >75% of baseline
BOS 0-p	Not applicable	FEV_1 81% – 90% and/or $FEF_{25\%-75\%}$ ≤75% of baseline
BOS 1	FEV_1 66% – 80% of baseline	FEV_1 66% – 80% of baseline
BOS 2	FEV_1 51% – 65% of baseline	FEV_1 51% – 65% of baseline
BOS 3	FEV_1 ≤50% of baseline	FEV_1 <50% of baseline

Adapted from reference 21. FEV_1 Forced expiratory volume in 1 s; $FEF_{22\%-75\%}$ Forced expiratory flow between 25% and 75% of vital capacity

Comparison of BOS detection strategies

A study by Cook et al (21) examined 22 transplant recipients at two points in time, approximately one and two years after the procedure. The inclusion of post-transplant patients who did not have BOS at either occasion acted as effective study controls. For the purpose of the study, they defined BOS as a 20% drop in FEV_1 in the post-transplant period. At the first examination, five of the 22 patients had BOS and, at the second examination, 10 of 22. These outcomes allowed the authors to examine the sensitivity and specificity of various other diagnostic tests at each point in time. The tests they studied included maximum mid-expiratory flow (MMEF), indexes of maldistribution of ventilation and perfusion derived from radioisotope scans (V/Q scan), and high-resolution computed tomography scans to examine air trapping, perfusion patterns and bronchial dilation (21).

Several of the studies included in the review examined the capacity and efficacy of different tests to detect BOS. Comparing the findings of Cook et al (21) with those whose focus was on BOS diagnostic testing, similar conclusions emerged throughout. Collectively, it was found that patients with BOS (based on low FEV_1) also had significantly lower than predicted MMEF (55.8%) (16,17,22). However, Cook et al (21) found that a significant portion of their subjects without BOS also had low MMEF (39.5%). V/Q scans showed somewhat less abnormality compared with MMEF, but often more in those without BOS. Overall, V/Q scan abnormalities at first examination did not predict the presence of BOS at second examination with any reliability (P=0.016). Computed tomography scanning was shown to be useful in relation to the severity of subsequent BOS (ie, subjects with severe BOS at the second examination were likely to have had abnormal perfusion and air trapping at the first examination) (21,22). However, the focus is not on detecting the severity of BOS, but rather on the detection of onset. Hence, it is evident that other forms of BOS detection show no strong evidence in being more useful or reliable than monitoring the decline in FEV_1 values.

BOS staging using spirometric measures

TBB was once considered to be the 'gold standard' for the diagnosis of BOS; however, the sensitivity for diagnosis varied from 15% to 78% (17). Due to poor sensitivity, and the associated morbidity and mortality, the BOS staging system was established by the ISHLT in 1993 (18,19). This staging system is based on airflow limitation (a percentage change from a baseline post-transplant FEV_1 obtained on formal clinical spirometry) with or without the diagnostic histological finding of BOS. The ISHLT concluded that FEV_1 was the most reliable and consistent clinical pulmonary function test parameter that could provide an indication of graft function (18,19). A staging algorithm based on FEV_1 was developed to classify the levels of dysfunction in BOS. Stage 0 is reserved for FEV_1 >80% of maximum baseline value and implies no significant abnormality. Stages 1 to 3 indicate a worsening condition, with 66% to 80%, 51% to 65% and ≤50% of maximum baseline values, respectively. The 1993 and revised 2002 ISHLT BOS stages are outlined in Table 2 (19).

Implementation of the ISHLT algorithm has been adopted worldwide by transplant and pulmonary function clinics as a means of monitoring BOS. Clinically, FEV_1 results are gathered through spirometry and are generally measured at monthly, quarterly or yearly intervals depending on the length of time since transplant. Results are interpreted based on declines in FEV_1 from the maximum FEV_1 levels attained since transplant (23). These maximum FEV_1 levels define the FEV_1 baseline for the allograft recipient, and are determined based on the average of the two previous highest consecutive FEV_1 measurements obtained in clinic at least three to six weeks apart. Declines are determined as percent decreases in FEV_1 from previously established baseline values (23,24). While the staging of BOS is primarily based on a decline in FEV_1, several studies have indicated that a decrease in forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25\%-75\%}$) is also a sensitive marker for the onset of BOS (14,16,23).

In 2002, the ISHLT consensus panel proposed a new stage, designated 'potential BOS' or 'BOS 0-p', defined as an FEV_1 of 81% to 90% of baseline or a $FEF_{25\%-75\%}$ <75% of baseline (14). This new stage (described in Table 2) is meant to alert the clinician to the increased risk for subsequent BOS among patients with slight declines in lung function, and to indicate the need for close functional monitoring. Spirometric measurements at regular intervals are critically important to detect evidence of airflow obstruction before the development of clinical symptoms. Thus, pulmonary function testing is strongly relied on as one of the earliest tests for detection of a graft complications such as BOS.

During the first year post-transplant, it is common practice that lung transplant recipients undergo biweekly or monthly spirometric testing. Monthly testing is deemed the minimum frequency in accordance with American Thoracic Society criteria for acceptability and reproducibility (25). At later points in time, measurements every two or three months are often performed instead (25). BOS, as a form of chronic graft rejection, is not often encountered before the first year post-transplant. The problem arises from less frequent monitoring occurring when the disease process is most likely to develop. More frequent monitoring via home spirometry may be an optimal solution. Daily home spirometry may detect a decline in pulmonary functional parameters earlier than regularly scheduled outpatient clinic visits, and may be invaluable as a regular component of follow-up for lung transplant recipients (25,26).

The effectiveness of home spirometry

The concept of home spirometry is not a new one in the field of lung transplantation. That is, patients are typically advised to record home spirometry measurements once or twice per day. They are instructed to report persistent decrements in values to their lung transplant centres or pulmonologist (25-27). There are inherent problems with home spirometry, such as intermittent or noncompliance with daily or twice-daily testing, difficulty with interpretation of the data points, and patient denial and rationalization when decrements in function are obtained (26). Whether home spirometry is being implemented efficiently for the benefit of BOS staging remains unclear.

In a study by Finkelstein et al (18), the researchers analyzed home spirometric data sent weekly to a data centre via telephone from the patients' homes. Unlike clinical testing, in which FEV_1 measures are relatively infrequent, staging based on home measurements of FEV_1 was determined for each day that home data were recorded. This made it possible to consider the persistence of the stage value when deciding on the actual occurrence of a new BOS stage. Persistence was defined as the number of consecutive reports for which the FEV_1 decline resulted in the same BOS stage. A change in BOS stage indicated either an improving (decrease in stage value) or a deteriorating (increase in stage value) condition. The study highlighted the effect of persistence on concordance between clinic and home determinations of staging and the time to detect a stage change was evaluated.

TABLE 3
Average number of days post-transplant to detect bronchiolitis obliterans syndrome (BOS) based on impaired forced expiratory volume in 1 s* values

BOS stage	Patients who declined to stage, n (total n=45)	Number of days to detect BOS, mean		
		Clinic-based staging	Home spirometry: 1-day persistence†	Home spirometry: 3-day persistence†
1	17	591	250 (P<0.001)	315 (P<0.001)
2	11	712	568 (P<0.05)	636 (NS)
3	7	844	685 (NS)	713 (NS)

**Defined BOS as stage 1 <80% of baseline value, stage 2 <65% of baseline value, stage 3 <50% of baseline value using both clinic-based testing and home measurement; †Persistence refers to the number of consecutive daily reports for which the decline in forced expiratory volume in 1 s resulted in the same BOS stage. Adapted from Finkelstein et al (20). NS Not statistically significant*

Persistence values of one to seven days were considered. The difference in the time to each stage using clinic and home BOS staging was evaluated using the paired *t* test, and the results are summarized in Table 3 (24).

Finkelstein et al (19) performed a follow-up retrospective analysis involving 45 lung transplant recipients participating in a home spirometry monitoring program. The subjects in that study served as their own control because clinical and home spirometry measurements were collected concurrently. The determinants of BOS staging were based on home and clinical FEV_1 values. Seventeen of the 45 subjects developed lung decline of at least BOS stage 1, at which time detection was an average of 341 to 276 days earlier with home spirometry.

These studies found that home spirometry can detect a decline in pulmonary function significantly earlier than clinic spirometry reflected by BOS detection times that were statistically significant for both persistence requirement studies (P<0.001) (18,19). What can be concluded is that home spirometry may be a reliable and safe alternative to frequent clinic-based pulmonary function testing in lung transplant recipients. Unfortunately, the study did not address the impact of early detection on survival outcomes.

The use of home spirometry for detection of BOS does not immediately diagnose the condition and still requires the lung transplant recipient to undergo bronchoscopy to exclude alternative diagnoses. It does allow for the steps toward diagnosing BOS to be made earlier and more conveniently for patients living great distances from transplant centres. It would stand to reason that this may have an impact on graft and patient survival.

Impact on survival

A secondary outcome of interest investigated by the present review was whether the interventions to date have improved the survival outcomes for lung transplant recipients. No randomized controlled trials were identified that described this outcome, with the exception of one observational study that was eliminated from the formal review (28). The authors of a prospective cohort study, completed through the University of Minnesota (Minnesota, USA), collected a total of 132,822 daily spirometry readings from January 27, 2002 to January 23, 2009 (28). The study involved 246 patients whose records were included for analysis. The mean (± SD) age of the subjects was 49.3±11.8 years and there were 146 (59.4%) deaths on or before January 23, 2007. To determine the effect of home monitoring on pulmonary-related death, a competing risks analysis was performed. The results yielded a risk ratio of 0.416 (95% CI 0.123 to 1.407) among pulmonary-related mortality and a risk ratio of 1.347 (95% CI 0.508 to 3.572) for non-pulmonary-related mortality (28).

These findings suggest that risk was reduced in subjects with good spirometry adherence, but subsequently died from pulmonary-related causes. The adherence to home monitoring in the early years of the post-transplant period resulted in a trend toward improved survival. The competing risk regression analysis showed that the benefit came largely in the group that subsequently died from pulmonary-related causes (28). This was to be expected because monitoring pulmonary function would be most helpful in alerting a disease condition, similar to BOS, that has direct bearing on the lung.

The present study showed that home monitoring for post-lung transplantation patients has a positive impact on survival. Kaplan-Meier event-free analysis showed decreased freedom from BOS time in nonadherers (30%) compared with good (43%) or moderate (19%) adherers (P<0.014), and a tendency toward lower retransplantation rates (P<0.07), although this did not reach statistical significance (28). Further analysis of mortality causes showed a trend in greater reduction of pulmonary-related mortality but this also did not reach statistical significance.

CONCLUSIONS

Pulmonary function testing is the cornerstone of lung transplant recipient monitoring. It has the advantage of being noninvasive, reproducible, may be performed frequently and daily by patients at home and, in some cases, may be automatically transmitted by telephone or electronic means to a hospital. It is a useful procedure for early detection of preclinical allograft complications and consecutive early treatment. The FEV_1 is a sensitive measure of allograft function and has been considered to be the most useful spirometric indicator for diagnosing and staging the extent of BOS. The ISHLT proposed that a persistent decrease in FEV_1 >20% of its baseline value be diagnostic criteria for BOS. The ISHLT staging system for assessing the extent of BOS is now widely accepted. However, BOS primarily affects the distal airways and FEV_1 is considered to reflect an already advanced obliterative process. For this reason, other functional parameters that show small airways dysfunction better than FEV_1 – such as $FEF_{25\%-75\%}$ – were proposed to be an earlier marker of BOS. The ISHLT was revised in 2002 to include $FEF_{25\%-75\%}$ measurements as a potential BOS marker.

Supportive evidence from several studies has led to the conclusion that FEV_1 was the most reliable and consistent clinical pulmonary functional parameter that provided an indication of graft function. The problem with detecting BOS using FEV_1 is that therapy seldom improves lung function, which is interpreted to indicate that the pathological process is irreversibly established. After examining the use of home spirometry in the largest study to date, it was found that BOS staging was detected notably sooner compared with clinic spirometric testing. Nonadherers did show decreased freedom from BOS, but it did not impact survival. Overall, home monitoring was shown to have a positive impact on survival, but was not statistically significant.

Whether the use of home spirometry for the detection of BOS achieves widespread use in the lung transplantation community is yet to be determined. Future investigations should consider evaluating the usage patterns of and barriers to widespread implementation of home spirometry in this context (29,30). Effort should also be made to identify the most effective means of treating BOS once an early diagnosis has been established (30). Currently, it remains to be seen whether a several-month lead time in the diagnosis of BOS will translate to earlier stabilization of pulmonary function, a less limited patient and improved survival.

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