Eur Respir J, 1993, 6, 705–708
Printed in UK - all rights reserved

European Respiratory Journal
ISSN 0903 - 1936

Daily home spirometry facilitates early detection of rejection in single lung transplant recipients with emphysema

Ø. Bjørtuft*, B. Johansen*, J. Boe*, A. Foerster**, E. Holter+, O. Geiran++

Daily home spirometry facilitates early detection of rejection in single lung transplant recipients with emphysema. Ø. Bjørtuft, B. Johansen, J. Boe, A. Foerster, E. Holter, O. Geiran. ©ERS Journals Ltd 1993

ABSTRACT: Eight single lung transplant recipients with emphysema, aged 40–58 yrs, have been followed up for 90 patient months.

Starting 2–4 weeks postoperatively, they recorded their forced vital capacity (FVC), and forced expiratory volume in one second (FEV_1), at a fixed time every morning using a Micro Spirometer. They were instructed to contact the hospital if the FVC or FEV_1 displayed a persistent (two days or more) decrease of 10%, compared with the average values during the last seven days. Transbronchial biopsies (TBB) were performed regularly in the follow-up, and whenever the patients had respiratory symptoms, or the FVC or FEV_1 displayed a persistent decline of more than 10%.

We performed 59 TBBs, and 23 biopsy specimens showed rejection. The FVC and FEV_1 values on the TBB day were compared with the mean values of the 7 previous days. FVC and FEV_1, associated with negative TBBs (16 events), showed no significant changes. However, FVC and FEV_1 decreased significantly ($p<0.001$, paired t-test) during rejections (mean percentage change 14 and 21% respectively, range +8% to -53%). In 16 of the 23 rejections, the FEV_1 decreased by >10%.

We recommend the use of daily home spirometry when monitoring single lung recipients with emphysema, and suggest that a persistent 10% decrease in FEV_1 or FVC for at least two days is an indication for hospital admission and possible TBB.
Eur Respir J., 1993, 6, 705–708.

Depts of *Thoracic Medicine, **Pathology, +Microbiology and ++Thoracic Surgery, Rikshospitalet, University of Oslo, Norway

Correspondence: Ø. Bjørtuft
Lungeavdelingen,
Rikshospitalet
0027 Oslo
Norway

Keywords: Daily home spirometry
emphysema
rejection
single lung transplantation

Received: July 27 1992
Accepted after revision February 6 1993

In patients with end-stage pulmonary emphysema with respiratory failure, single lung transplantation (SLT) is accompanied by a considerable improvement in lung function and an acceptable survival rate. [1–4]. Following lung transplantation, rejections and infections constitute the main problems. The early diagnosis and treatment of acute rejections may be of value in preventing obliterative bronchiolitis (OB) [5]. Infection with cytomegalovirus (CMV) is a major challenge in lung transplantation, and is responsible for high morbidity and sometimes death [6, 7].

Monitoring rejection and infection in lung transplant recipients is based primarily upon the examination of transbronchial biopsies (TBB) and bronchoalveolar lavage fluid (BAL), both obtained during fibreoptic bronchoscopy, combined with lung function measurements [8–11]. The home monitoring of spirometry is reported to be of value in heart-lung recipients [12]. We are unaware of any reports on this method in single lung transplantation (SLT). Accordingly, the aim of our study was to evaluate daily home spirometry in the follow-up of SLT patients with emphysema.

Patients and methods

Eight patients with end-stage emphysema had a single lung transplant (6 right, 2 left) in our hospital, between March 1990 and January 1992. The age at transplantation is shown in table 1. One patient had idiopathic emphysema, while the rest had emphysema due to $alpha_1$-antitrypsin deficiency. All the patients were alive, with a total observation time of 90 patient months, in March 1992.

Two to four weeks after surgery, depending on the postoperative course, the patients were trained to use a Micro Spirometer (Micro Medical Ltd, Kent, UK), the same device as was used in previous reports [11, 13]). They were instructed to measure forced vital capacity (FVC), and forced expiratory volume in one second (FEV_1), three times at a fixed time every morning, and to record the highest value in a diary. This procedure was continued after discharge from the hospital. The patients were told to contact the hospital if their FEV_1 or FVC displayed a persistent (two days or more) decrease of approximately 10% or more, compared with an estimate of the average values during the last seven days. They were then admitted to hospital. On the day of admission, or the next day, we performed TBB and BAL. This bronchoscopy was categorized as "symptom" TBB. Whenever the patients had clinical symptoms, such as dyspnoea, cough, expectoration, tightness of the chest or fever, without any decline in spirometry values, they were also admitted to hospital and TBB was performed and categorized in the same group ("symptom" TBB).

Table 1. – The age, observation time after transplantation and number of events (n) for each patient

	Patient								
	1	2	3	4	5	6	7	8	Total
Patient age yrs	41	52	48	48	58	40	52	43	
TBB (n)	12	4	10	17	3	4	4	5	59
Rejection episodes (n)	5	0	4	9	1	2	1	1	23
CMV diseases (n)	2	1	2	3	0	1	0	1	10
Bacterial pulmonary infections (n)	1	0	2	1	0	0	0	0	4
Observation time (months)	24	22	17	16	4	3	2	2	90

CMV: cytomegalovirus; TBB: transbronchial biopsies.

TBBs were also carried out on a fixed schedule, 2 weeks, 4 weeks, 3 months, 6 months and 12 months following transplantation ("control" TBB), and 3–4 weeks after each histologically verified rejection ("follow-up" TBB). The TBBs which were performed at hospital before the patients started daily spirometry are categorized as "early" TBB.

Whenever possible, 3–4 biopsies from each lobe were taken using alligator forceps, aiming at a total number of 10. The biopsies were examined histologically, and rejection was graded according to the working formulation for the standardization of nomenclature in the diagnosis of lung rejection [14]. The lavage fluid was examined cytologically and cultured for bacteria, fungi and viruses. The lavage fluid, and in some cases leucocytes from peripheral blood, were cultured in human embryo (HE) fibroblast cells, which were observed for typical cytopathogenic effects diagnostic of CMV.

An examination using immunofluorescence for CMV early antigen was performed in HE cells in shell vials 1–3 days after inoculation with the lavage fluid [15]. CMV early antigen in cell cultures was looked for by staining with fluorescein isothiocyanate (FITC) conjugated mouse monoclonal antibody against CMV early antigen (Whittaker Products, Wakersville, MD, USA). The immunohistochemical demonstration of CMV immediate early antigen was performed in leucocytes from peripheral blood [16].

Serum samples were tested for anti-CMV-immunoglobulin G (IgG) using Abbott's microparticle enzyme immunoassay (MEIA) or Behring's Enzygnost enzyme linked immunosorbent assay (ELISA). CMV antibody titres were calculated by testing tenfold dilutions of the sera with Enzygnost CMV-IgG ELISA. A fivefold increase in CMV-IgG titre was regarded as significant. Anti-CMV-immunoglobulin M (IgM) was detected using Abbott's MEIA.

A combination of pulmonary symptoms and characteristic CMV inclusion bodies, positive culture, antigen detection as described above, seroconversion, rising anti-CMV-IgG titre or the detection of anti-CMV-IgM titre was regarded as CMV disease and treated with ganciclovir, 10 mg·kg^{-1} daily for 3 weeks [17].

A patient with the combination of chest symptoms, opacities on the chest X-ray and bacteria cultivated from BAL was considered to suffer from a bacterial pulmonary infection.

The home spirometry data was collected and checked on every hospital admission or out-patient visit by one of the physicians (ØB) together with the patient, in order to discover any record failure. The data connected with every TBB were analysed statistically. The mean FVC and FEV_1 during the last seven days before each TBB was calculated and called (FVC "Home" and FEV_1 "Home"). This was compared with the FVC and FEV_1 on the day of TBB or the day of admission to hospital (FVC "TBB" and FEV_1 "TBB"). FVC and FEV_1 "Home" were also compared with the mean of days 5–9 after the start of treatment (FVC "After" and FEV_1 "After"). Means were compared by the two-tailed paired t-test.

Results

The patients meticulously performed their spirometry recordings and data was obtained for most days. There was no failure to report any persistent 10% decline in either FVC or FEV_1.

All the patients experienced either rejections or infections, with great variability among the different recipients (table 1).

The outcome of the TBBs is shown in table 2. Rejection occurred in 23 biopsies, Group A in figure 1; 20 acute cellular rejections, two acute vascular rejections and one chronic rejection (obliterative bronchiolitis). Both FVC and FEV_1 decreased significantly during rejection compared with the values at home before the rejection (table 3). After treatment, FVC and FEV_1 increased to statistically significantly higher values than before the rejection (table 3). The changes in FVC and FEV_1 during rejection varied from an 8% increase to a 53% decline. In 16 of the 23 rejections, the decline in FEV_1 was greater than 10%. An example of the FEV_1 and FVC values before, during and after rejection is shown in figure 2.

In eight events, both rejection and infection occurred; two bacterial pulmonary infections, five CMV diseases and one CMV and *Pneumocystis carinii* infection occurring simultaneously. When these combined events are excluded, we obtain 15 "pure" rejections, constituting Group B in figure 2, still showing a significant decline in FVC ($p<0.02$) and FEV_1 ($p<0.01$).

Table 2. – Outcome and number of procedures in the different TBB categories

Outcome	Early	Control	Symptom	Follow-up
Negative	11	9	4	7
Infection alone	0	0	5	0
Rejection without infection	0	2	10	3
Rejection and infection	0	0	8	0

TBB: transbronchial biopsy.

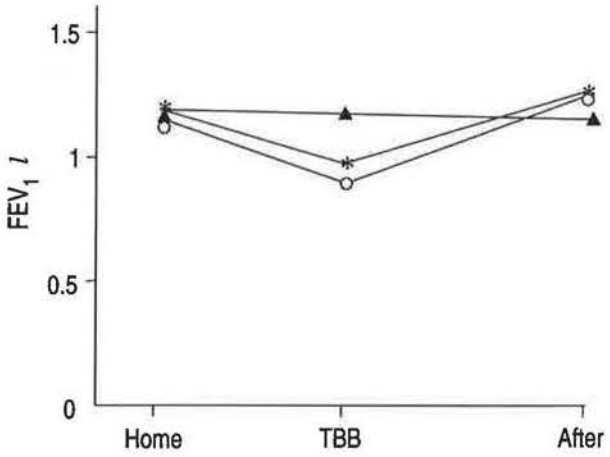

Fig. 1. – Mean values for FEV_1 for the different TBB result groups. —○— : Group A - all the rejections; —✱— : Group B - rejections without infection; —▲— : Group C - negative biopsies. TBB: transbronchial biopsies; FEV_1: forced expiratory volume in one second.

Table 3. – FVC and FEV_1 values during the last week prior to rejection ("Home") compared with 1) the day of TBB ("TBB" = rejection) and 2) the mean of days 5–9 after the start of rejection treatment ("After")

All 23 rejections	FVC *l*	FEV_1 *l*
"Home"	1.80±0.82	1.17±0.37
"TBB"	1.55±0.89	0.92±0.47
Change	-0.25±0.25 (14%) p<0.001	-0.25±0.20 (21%) p<0.001
"After" treatment	1.92±0.79	1.27±0.35
Change	0.12±0.21 (7%) p<0.02	0.09±0.15 (8%) p<0.01

Data are presented as mean±SD. FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; TBB: transbronchial biopsy.

The spirometry associated with the 16 bronchoscopies in the control and follow-up categories with negative biopsies showed no changes in FVC and FEV_1 (Group C, figure 1).

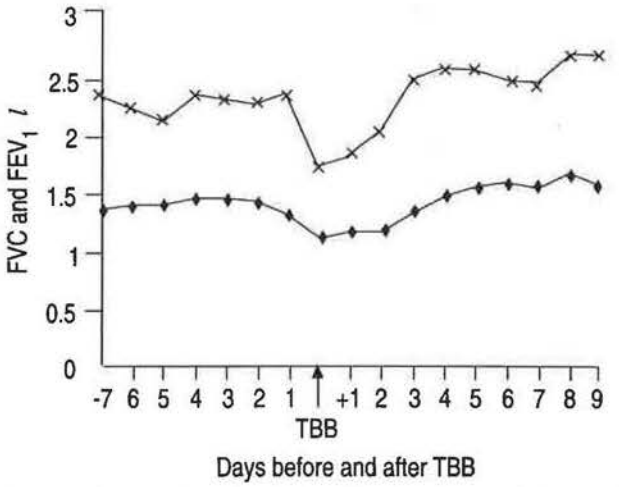

Fig. 2. – An example of FVC and FEV_1 values before, during and after a rejection, diagnosed with the aid of transbronchial biopsies (TBB) occurring 3 months after transplantation. —◆— : forced expiratory volume in one second (FEV_1); —×—: forced vital capacity (FVC).

We diagnosed five pulmonary infections without rejection, one bacterial pulmonary infection and four pulmonary CMV diseases. The spirometric values varied from a 30% decline to a 5% rise in FEV_1, the mean percentage change in FEV_1 was a 7.8% decline and in FVC a 2.2% decline, showing no significance ($p>0.1$).

Four patients had, on one occasion, lung symptoms combined with negative TBB. In three of these events, the patients had pleural fluid resolving very slowly after the transplantation. The last patient experienced continous symptoms, and a further TBB, two weeks after the negative one, showed rejection. The first three cases showed no spirometric changes in connection with the TBB. In the last case, the patient had a spirometric decline greater than 10%, probably due to rejection. None of these events are included in the analysis of the spirometric data.

Discussion

In a recent review article, MAURER [18] from the Toronto Lung Transplant Group, questioned the use of daily home spirometry in SLT recipients, particularly in emphysema patients. This is a view contradicted by our results, since we were able to demonstrate a significant decrease in FVC and FEV_1 during rejections in SLT emphysema patients.

The spirometer used and a "10% fall in FVC and FEV_1" as a limit, were chosen according to the suggestions of the Papworth group [12]. The mean value for the seven days prior to admission (FVC and FEV_1 "Home") was chosen as the basal value. This should be long enough to detect gradually falling values during an insidious onset of rejection. When the "Home" values were compared with the values "After" treatment, we found a significant increase after treatment. This suggests that the rejection had produced a gradual decrease in the spirometry during the last week before the diagnosis was confirmed.

An important benefit of daily spirometric measurements is the opportunity to monitor rejection treatment. Within a week of the start of therapy for rejection, spirometry values had normalized, and were slightly but significantly higher than the week before the event. Our patients are then usually still in hospital, but the self-monitoring of FVC and FEV_1 may enable us to treat rejections on an ambulatory basis.

In the normal course of postoperative recovery following SLT, the spirometric values gradually increase which may mask any decline. The symptoms of rejection may also be vague and unspecific, and difficult to recognize in the postoperative recovery period of these desperately ill patients. In these first weeks, we diagnosed rejections through routine TBBs, as has also been reported previously [8, 9]. It therefore appears to be of importance to perform TBB regularly in the initial 4–6 weeks.

A possible relationship between the development of chronic rejection and CMV infection has been reported previously [19]. In six of the rejection events we also diagnosed CMV disease either by the demonstration of the presence of the virus or by serological methods. It is possible that these findings were purely incidental and that the clinical symptoms related to rejection alone. It is also possible that the CMV infection triggered the rejection.

All 10% decreases in spirometry values were accompanied by respiratory symptoms, but the symptoms were often minor. A spirometric decrease was sometimes the only reason why developing symptoms were recognized by the patient. The combination of minor symptoms and decreases in FVC and FEV_1 enabled us to admit the patients to hospital at an early phase of rejection.

Our experience of daily home spirometric measurements in SLT recipients has been encouraging and has contributed to the diagnosis and treatment of rejections at an early stage. A 10% decrease as a limit value for FEV_1 appears to be a reasonable cut-off point. We thus recommend that single lung transplant emphysema patients are followed up by daily home spirometric measurements (FVC, FEV_1) using a pocket-sized spirometer.

References

1. Mal H, Andreassian B, Pamela F, *et al.* – Unilateral lung transplantation in end-stage pulmonary emphysema. *Am Rev Respir Dis* 1989; 140: 797–802.
2. Kaiser LR, Cooper JD, Trulock EP, *et al.* – The evolution of single lung transplantation for emphysema. *J Thorac Cardiovasc Surg* 1991; 102: 333–341.
3. Kriett JM, Kaye MP. – The registry of the international society for heart and lung transplantation: eighth official report - 1991. *J Heart Lung Transplant* 1991; 10: 491–498.
4. Geiran O, Lindberg H, Bjørtuft Ø, *et al.* – Single lung transplantation. Surgical experiences with the first seven patients. *Scand J Thorac Cardiovasc Surg* 1992; 26: 163–168.
5. Scott JP, Higenbottam TW, Clelland CA, *et al.* – The natural history of chronic rejection in heart-lung transplant recipients: a clinical, pathological and physiological review of 29 long-term survivors. *Transplant Proc* 1990; 22: 1474–1476.
6. Duncan AJ, Dummer JS, Paradis IL, *et al.* – Cytomegalovirus infection and survival in lung transplant recipients. *J Heart Lung Transplant* 1991; 10: 638–646.
7. Maurer JR, Tullis E, Scavuzzo M, Patterson GA. – Cytomegalovirus infection in isolated lung transplantations. *J Heart Lung Transplant* 1991; 10: 647–649.
8. Higenbottam T, Stewart S, Penketh A, Wallwork J. – Transbronchial lung biopsy for the diagnosis of rejection in heart-lung transplant patients. *Transplantation* 1988; 46: 532–539.
9. Starnes VA, Theodore J, Oyer PE, *et al.* – Evaluation of heart-lung transplant recipients with prospective, serial transbronchial biopsies and pulmonary function studies. *J Thorac Cardiovasc Surg* 1989; 98: 683–690.
10. Otulana BA, Higenbottam T, Scott J, *et al.* – Lung function associated with histologically diagnosed acute lung rejection and pulmonary infection in heart-lung transplant patients. *Am Rev Respir Dis* 1990; 142: 329–332.
11. Marshall SE, Lewiston NJ, Kramer MR, *et al.* – Prospective analysis of serial pulmonary function studies and transbronchial biopsies in single-lung transplant recipients. *Transplant Proc* 1991; 23: 1217–1219.
12. Otulana BA, Higenbottam T, Ferrari L, *et al.* – The use of home spirometry in detecting acute lung rejection and infection following heart-lung transplantation. *Chest* 1990; 97: 353–357.
13. Chowienczyk PJ, Lawson CP. – Pocket sized device for measuring forced expiratory volume in one second and forced vital capacity. *Br Med J* 1982; 285: 15–17.
14. Yousem SA, Berry GJ, Brunt EM, *et al.* – A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: lung rejection study group. *J Heart Transplant* 1990; 9: 593–601.
15. Gleaves CA, Smith TF, Shuster EA, Pearson GR. – Comparison of standard tube and shell vial cell culture techniques for the detection of cytomegalovirus in clinical specimens. *J Clin Microbiol* 1985; 21: 217–221.
16. van der Bij W, Torensma R, van der Son WJ, *et al.* – Rapid immunodiagnosis of active cytomegalovirus infection by monoclonal antibody staining of blood leukocytes. *J Med Virol* 1988; 25: 179–188.
17. Dunn DL, Mayoral JL, Gillingham KL, *et al.* – Treatment of invasive cytomegalovirus disease in solid organ transplant patients with ganciclovir. *Transplantation* 1991; 51: 98–106.
18. Maurer JR. – Therapeutic challenges following lung transplantation. *Clin Chest Med* 1990; 11: 279–290.
19. Keenan RJ, Lega ME, Dummer JS, *et al.* – Cytomegalovirus serologic status and postoperative infection correlated with risk of developing chronic rejection after pulmonary transplantation. *Transplantation* 1991; 51: 433–438.