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Smoking resumption after lung transplantation: a sobering truth

To the Editors:

About 40% of lung transplants (LTx) are performed for end-stage emphysema in former smokers [1]. Patients are principally only enrolled on the waiting list after having quit smoking for at least 6 months [1]. Some LTx recipients may resume smoking, which could complicate post-transplant outcome [2]. Surprisingly, most LTx centres do not monitor smoking habits. We assessed all 267 LTx recipients currently in follow-up at our centre for smoking, after informed consent and approval by the local Ethical Review Board.

Smoking behaviour was investigated by a standardised questionnaire, measurement of urinary cotinine (COT) and exhaled carbon monoxide (eCO) levels. The questionnaire addressed past and current smoking habits (regular or occasional active smoking and second-hand smoking, *i.e.* passive exposure *via* relatives or environmental exposure *via* social/work-related contacts) as well as the use of nicotine-replacement therapy (NRT). COT was assessed by gas chromatography and mass spectrometry (Thermo Scientific, Geel, Belgium) and eCO by using an electrochemical sensor (Bedfont Scientific, Kent, UK; detection limit 1 ppm), as previously described [3, 4]. Statistical analyses were performed with Graphpad Prism 4.0 (San Diego, CA, USA). An unpaired t-test, Mann–Whitney U-test or Fisher's exact test were used where appropriate and receiver–operating characteristic curve analysis was used for calculation of predictive values.

LTx recipients (bilateral/single/heart–lung transplantation n=190/59/18) were assessed at a median (interquartile range) of 3.4 (1.5–6.0) yrs after LTx. Prior to LTx, 166 (62%) out of 267 patients were former smokers and 101 (38%) out of 267 never-smokers. Former smokers reported smoking cessation at a median of 4.0 (1.5–10.0) yrs before LTx. The majority of former smokers were transplanted for COPD (n=109 out of 166, 41% of the studied cohort), the remaining for pulmonary fibrosis (10%), α_1-antitrypsin deficiency-related emphysema (5.2%) or various other indications (5.8%).

Based on the questionnaire, 30 (11%) out of 267 patients reported ever smoking after LTx, of which, the majority had been transplanted for emphysema due to COPD (n=25) or α_1-antitrypsin deficiency (n=2). Of these 30 patients, 27 were current active smokers at the time of evaluation (''smokers''). Three reported smoking only some cigarettes during a few weeks after LTx, but not at the time of evaluation, whereas the remaining 237 patients denied ever smoking after LTx (''nonsmokers''; n=240) (fig. 1). Second-hand smoking was reported in 105 (39%) out of 267 patients, of whom 86 had smoking relatives (of which 40 smoked indoors), 31 regularly attended smokey bars and/or three worked in smokey conditions. The abstinence period between pre-LTx smoking cessation and subsequent LTx was shorter in smokers compared with nonsmokers: 1.0 (0.5–2.0) *versus* 5.0 (2.0–11.0) yrs, respectively ($p<0.0001$). Smokers resumed smoking at a median of 1.0 (0.5–3.0) yr post-LTx and smoked 3 (2–5) cigarettes·day^{-1}. Smokers were more likely to be transplanted for emphysema (OR 17.5 (95% CI 4.1–75.6); $p<0.0001$), more

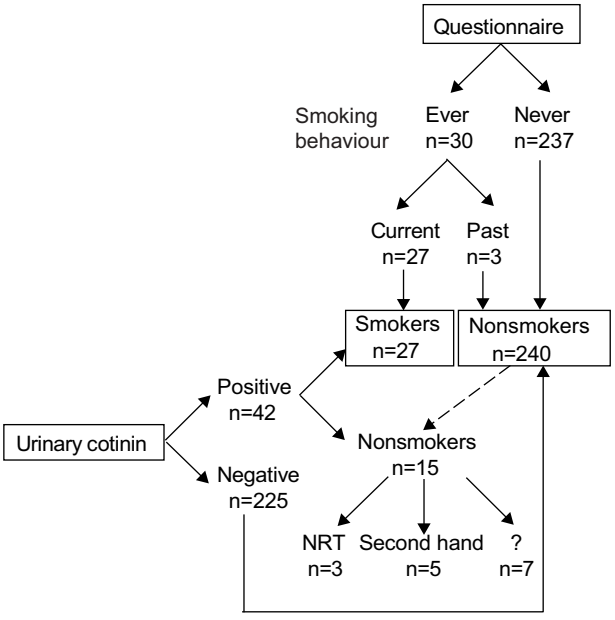

FIGURE 1. Flow-diagram of lung transplant recipients categorised according to reported smoking behaviour and urinary cotinin levels. NRT: nicotine-replacement therapy.

recently transplanted (p=0.036), more likely to be ever widowed (OR 4.7 (1.5–14.7); p=0.004) and had a lower socioeconomic status (OR 2.4 (1.0–6.0); p=0.048) compared with nonsmokers (table 1). Second-hand smoking was also higher in smokers compared with nonsmokers: 81% *versus* 35%, respectively (OR 7.5 (2.7–20.6); p<0.0001). Median eCO levels were higher in smokers compared to nonsmokers: 8 (6–17) *versus* 3 (2–4) ppm (p<0.0001). The optimal eCO cut-off for detecting current smoking was 4.5 ppm (area under the curve (AUC) 0.82 (0.73–0.92), likelihood ratio 4.15; p<0.0001) with a sensitivity and specificity of respectively 76.7 (70.9–81.9)% and 81.4 (61.9–93.7)%.

Using COT, 42 (16%) out of 267 patients were identified as nicotine-exposed, of which 27 had admitted and 15 denied current smoking. Of the 15 patients denying smoking, positive COT could be explained by NRT (n=3) or intensive second-hand smoking (n=5), whereas in the minority (n=7), no clear explanation was found. Of the 225 COT-negative patients, 222 patients had denied smoking and three reported temporarily smoking after LTx (as mentioned above). COT thus proved to be a sensitive marker for current smoking, with a sensitivity and specificity of 100.0 (95% CI 98.4–100.0)% and 64.3 (48.0–78.5)%, respectively. eCO levels were increased in patients with positive compared with negative COT: 6 (3–14) *versus* 3 (2–4) ppm (p<0.0001), respectively. eCO was higher in the COT-positive patients admitting (n=27) compared with those denying (n=15) current smoking: 8 (6–17) *versus* 3 (2–5) ppm (p=0.0009), respectively. In the 15 COT-positive patients denying smoking, eCO tended to be higher in the eight patients reporting NRT-use or second-hand smoking compared with the seven without a clear explanation for the positive COT: 4 (3–8) *versus* 2 (2–3) ppm (p=0.09). In general; the optimal eCO cut-off for a positive COT was again 4.5 ppm (AUC 0.72 (0.63–0.81), likelihood ratio 2.02; p<0.0001), with a sensitivity and specificity of 76.9 (70.9–82.3)% and 61.9 (45.6–76.4)%, respectively.

The most remarkable finding is undeniably the high prevalence of post-LTx smoking, as 11% of our LTx population and even 23% of the COPD patients admitted smoking resumption. Although this sobering truth may be shocking, these data are comparable to the 21% respectively 25% of heart and renal transplant recipients testing positive for post-transplant smoking [6, 7]. Risk factors for post-LTx smoking were a shorter pre-LTx smoking cessation period, emphysema, lower socioeconomic status, ever being widowed and passive smoking. Other established factors may furthermore indicate whether a smoker is more likely to resume smoking, such as an abstinence period of ⩽6 months, demographic (*e.g.* smoking at

TABLE 1 Characteristics of nonsmokers and smokers after lung transplantation

	Nonsmokers	Smokers	p-value
Subjects n	240	27	
Age at LTx yrs	50 (37–57)	54 (47–55)	0.22
Male/female n	127/113	12/15	0.44
Type of Tx: B/S/HLTx n	168/55/17	22/4/1	0.45
Pre-LTx diagnosis of emphysema (COPD or α_1-ATD)/other n	100/140	25/2	**<0.0001**
Year of LTx	2003 (2002–2005)	2005 (2002–2007)	**0.036**
Pre-LTx socioeconomic status# high/low	100/111	7/19	**0.048**
Pre-LTx marital status n			
Currently married/not-married	150/190	13/14	0.69
Ever/never divorced	29/211	6/21	0.14
Ever/never widowed	11/229	5/22	**0.004**
Pre-LTx alcohol consummation units·week^{-1}	1.0±3.0	0.7±2.1	0.78
Pre-LTx smoking behaviour			
Never/former smokers n	101/139	0/27	**<0.0001**
Cigarettes·day^{-1}	25 (15–25)	25 (14–25)	0.49
Pack-yrs	30 (16–37)	25 (14–40)	0.97
Time between pre-LTx smoking-cessation and LTx yrs	5.0 (2.0–11.0)	1.0 (0.5–2.0)	**<0.0001**
Post-LTx second-hand tobacco exposure			
Negative/positive n	157/83	5/22	**<0.0001**
From relatives/social/work-related contacts n	67/24/3	19/7/0	0.85
Time between LTx and assessment of smoking status yrs	4.0 (2.9–6.2)	3.4 (1.4–5.8)	1.00

Data are presented as n, median (interquartile range) or mean±SD, unless otherwise stated. Characteristics for nonsmokers (n=240) and smokers (n=27) were identified by means of a questionnaire. The p-value was calculated using Mann–Whitney U-test (absolute values) or Fishers' exact test (proportions). For the current study, we regrouped patients into two socioeconomic levels only: low (unemployed, manual employees, skilled and unskilled workers) and high (nonmanual employees, clerks, professionals, executives, administrators and entrepreneurs). Lung transplant (LTx) recipients who were studying (at middle school, high school or college) when joining the LTx waiting list were excluded for analysis (for nonsmokers 29 out of 240; smokers one out of 26). Tx: transplant; B/S/HLTx: bilateral/single/heart–lung transplantation; COPD: chronic obstructive pulmonary disease; α_1-ATD: α_1-antitrypsin deficiency. #: Socioeconomic status was assessed by categorising patients according to their previous or current occupation at the moment of listing for LTx, based on the Social Classes of the British Registrar General [5].

an older age, earlier age at initiation, previous quit attempts) or psychological factors (*e.g.* stress/anxiety, degree of nicotine dependence) [8, 9]. Therefore, besides evaluating a patient's likelihood of smoking resumption, active screening for smoking, both when listed for LTx and during post-LTx follow-up, should be performed. For the patients resuming smoking, a standardised smoking cessation plan should be implemented. Patients' relatives, who most often continue smoking after LTx, must be recommended to stop smoking. At present, however, most LTx centres neither monitor smoking nor perform post-LTx smoking cessation counselling.

The risk of smoking for worsening post-LTx outcome (*i.e.* by bronchiolitis obliterans syndrome, cancer or cardiovascular mortality) is currently unclear, yet long-term survival in heart transplantation is impaired by smoking due to chronic allograft rejection (graft coronary artery disease) [6]. Therefore, this ought to be investigated after LTx through a prospective study with repeated screening for smoking. The gold standard for screening, however, is currently unknown. Although a questionnaire is subjective; it has a good sensitivity/specificity to detect smoking and a good correlation with the COT test [10], a more objective assessment of the patient's nicotine-exposure [4, 11]. Despite being sensitive, COT conversely has a lower specificity as it may be falsely positive because of NRT or intensive second-hand smoking. False-negative values after pausing smoking are also possible as the half-life of COT is about 16 h [11]. False-negative tests could be prevented by repeated or unexpected COT tests. Although a lot less sensitive, eCO may be adequate to confirm the questionnaire or COT findings, but probably not to discriminate current from second-hand or nonsmokers as eCO may also be increased due to elevated airway neutrophilia after LTx [4].

In conclusion, the prevalence of post-LTx smoking is higher than generally assumed and active screening, both pre- and post-LTx, is crucial to detect smoking resumption. A standardised questionnaire and (preferably repeated) testing of COT is probably the best screening method. To confirm these findings we recommend eCO monitoring. Implementing a standardised smoking cessation plan after LTx must be considered. Finally, the importance of smoking resumption for the outcome after LTx should be investigated in a well-designed prospective study.

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New *DNAH11* mutations in primary ciliary dyskinesia with normal axonemal ultrastructure

To the Editors:

In primary ciliary dyskinesia (PCD; Mendelian Inheritance in Man database #242650), a rare genetic disorder, the dysfunctional motility of cilia and impaired mucociliary clearance result in a myriad of clinical manifestations including recurrent infections of the respiratory tract, eventually causing lung damage, such as bronchiectasis, laterality defects and male infertility