



## Longitudinal changes in gastro-oesophageal reflux from 3 months to 6 months after lung transplantation

A G N Robertson, C Ward, J P Pearson, et al.

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## LETTERS

## Thoracic ultrasound in malignant pleural effusion: a real world perspective

Qureshi and colleagues achieved impressive results using thoracic ultrasound (TUS) to predict malignant pleural effusion in their recent study.<sup>1</sup> TUS in their hands compared reasonably well with pleural CT.

However, we suggest that pleural CT still remains the gold standard and cannot be replaced by TUS except in situations where access to pleural CT is difficult. First, even in their expert hands, six out of the seven false-negative TUS examinations were resolved by pleural CT. The priority in the real world is to reduce the time to pleural CT which is the definitive investigation. In our experience, TUS is complementary to pleural CT but more helpful and informative after the CT to aid pleural intervention due to information from two different imaging modalities.

Secondly, this study was performed in a tertiary pleural centre by an extremely experienced internationally renowned thoracic radiologist and another thoracic radiologist with a special interest in pleural ultrasound in a cohort with a high proportion of mesothelioma. In addition, the proportion of pleural tuberculosis (TB) cases was low, but this remains an important differential in TB-prevalent populations. We suggest the results are not generalisable to TUS performed by non-radiologists with Royal College of Radiologists sublevel 3 training.<sup>2</sup> Although pleural thickening is commonly measured, the exact measurement of diaphragm thickness, resolution of all diaphragmatic layers and evaluation of diaphragmatic/pleural nodules and liver metastases are not performed routinely by sublevel 3 operators. These aspects of TUS are more complex than an "x marks the spot" to aid thoracocentesis that is commonly used by chest physicians.

Finally, pleural CT offers additional benefits. It can detect primary lung cancer, unsuspected primary non-lung cancer and metastatic disease (bone, liver) at the same time. In addition, it can detect TB pulmonary disease such as cavitation and extrapulmonary disease, as well as evaluating asbestos-related disease by examining the mediastinal pleura and looking for contralateral changes. Pleural CT is unlikely to be substituted when radical treatment of mesothelioma is contemplated. Although liver metastases are readily detected at TUS, most of the above changes are not reliably detected.

In conclusion, we suggest the real world priority is to perform pleural CT promptly. TUS is complementary but not a substitute, and more helpful after pleural CT. A simple "x marks the spot" will normally suffice for

most interventions, although knowledge about septation may assist with planning thoracoscopy.

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## Authors' reply

We would like to thank Drs Medford and Entwistle for their letter in response to our recent *Thorax* publication.<sup>1</sup> We entirely agree that pleural CT is the gold standard not only in terms of malignant pleural disease but also for intraparenchymal, mediastinal and distant disease. We would suggest that the priority in the "real world" is prompt diagnosis and subsequent management of the pleural effusion, with CT as currently the most useful technique. However, the widespread use of thoracic ultrasound may mean that it is readily available (eg, in the outpatient respiratory clinic) and, given the high diagnostic yield of thoracic ultrasound for malignant pleural disease, may allow patients with clear-cut evidence of malignancy (eg, gross pleural nodularity) to be triaged directly to thoracoscopy or image-guided biopsy. The high proportion of mesothelioma and malignant pleural disease seen in our study is indeed a result of the tertiary nature of our practice, and this will influence the sensitivity and specificity of the test. It is for this reason that we recommended that the diagnostic use of ultrasound for malignant pleural effusion should be assessed in a non-tertiary centre for the results to be more widely applied to practice. The prevalence of tuberculosis (TB) in our area of practice is also low, and ultrasound should be evaluated in this context in a higher prevalence area.

We agree with the authors of the letter that the skill of the operator is an important issue. The results of our study are not intended to apply to level 1 Royal College of Radiology (RCR)-trained chest physicians,<sup>2</sup> for whom ultrasound is a valuable

technique to diagnose the presence of effusion and aid intervention. However, physicians with increasing experience (eg, level 2) may be able to achieve a reasonable diagnostic sensitivity for malignant pleural effusion using ultrasound—this requires prospective testing and will be an interesting question for future studies. In addition, although we agree that measurements of pleural thickening, diaphragm assessment, etc. are not currently routinely conducted by sublevel 3 RCR operators, this may change with increasing subspecialisation and experience of respiratory physicians with an interest in pleural disease. In these circumstances, our study suggests criteria which may be used for the diagnosis of malignant pleural disease.<sup>1</sup>

Once again, we would like to thank the authors of the letter for their interest in our study.

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## Longitudinal changes in gastro-oesophageal reflux from 3 months to 6 months after lung transplantation

Gastro-oesophageal reflux (GOR) and micro-aspiration are implicated in the pathophysiology of asthma, chronic obstructive pulmonary disease, interstitial lung disease and chronic lung allograft dysfunction.<sup>1,2</sup> Aspiration, which is often asymptomatic, has been identified as a treatable allograft injury that may affect mortality.<sup>1,2</sup>

The potential for thoracic mechanical changes caused by advanced lung disease to predispose to reflux has been highlighted.<sup>2</sup> Although aspiration could cause lung damage, alternatively reflux might represent a secondary event. Longitudinal data are lacking,<sup>2</sup> so we have undertaken a prospective study of reflux in lung transplantation.

This allowed investigations in patients where thoracic mechanical changes associated with advanced lung disease had improved. We hypothesised that reflux was prevalent and could develop at different times following transplantation in patients with good allograft function.

## Methods

Between November 2007 and November 2008, 14 newly transplanted lung recipients were assessed with pH impedance monitoring (Ohmega, MMS, Utrecht, The Netherlands). Most patients tolerated the assessments but reported discomfort. A representative subset was verified by independent observers (AGNR, AJB). All patients were receiving treatment with proton pump inhibitors which remained unchanged during the study (see table 1 in online supplement).

## Results

Nine patients were assessed for GOR at 3 and 6 months after lung transplantation

using pH impedance; five patients refused a second test. The majority of assessments were abnormal,<sup>3</sup> with marked variability with time following transplantation (fig 1). Notably, in four of nine patients overall assessments for reflux that were normal at 3 months became positive at 6 months (fig 1, table 1 in online supplement). All patients received standard immunosuppression at similar levels (n=4) or decreased levels (n=5) during the period of assessment (table 1 in online supplement).

## Discussion

This is the first longitudinal study of reflux following transplantation which shows that, although repeated measurements are practicable, they were not tolerated by all patients with only 9/14 agreeing to a second test in this series. High levels of GOR were seen, with marked variability in the first 6 months after transplantation. Most patients studied had received two donor lungs. Our results therefore suggest that reflux can occur in allograft recipients with-

out frankly abnormal lung mechanics at a time of tapered-down immunosuppression.

GOR assessment is becoming adopted across lung transplant units due to its high prevalence and a suggested survival benefit of fundoplication.<sup>4</sup> Reproducibility has not been assessed in the lung transplant population but, in normal subjects, impedance monitoring has been shown to be at least as reproducible as pH monitoring.<sup>5</sup> Our results suggest that reflux may develop following negative initial assessments, but it is also possible that patients with reflux may improve with time. This emphasises that repeat assessments of GOR may be an advisable component of post-transplant follow-up. Our series demonstrates that multiple catheter-based assessments are unpopular with some patients, highlighting a need for identifying markers of GOR and aspiration which are specific and well tolerated.<sup>1</sup>

Although this represents the first longitudinal measurements of reflux following transplantation, our study was descriptive, not powered to detect changes with time and did not evaluate mechanisms. Further larger longitudinal studies are necessary. Such translational studies may be relevant to improving outcomes in lung transplantation and other lung and airway pathophysiology.

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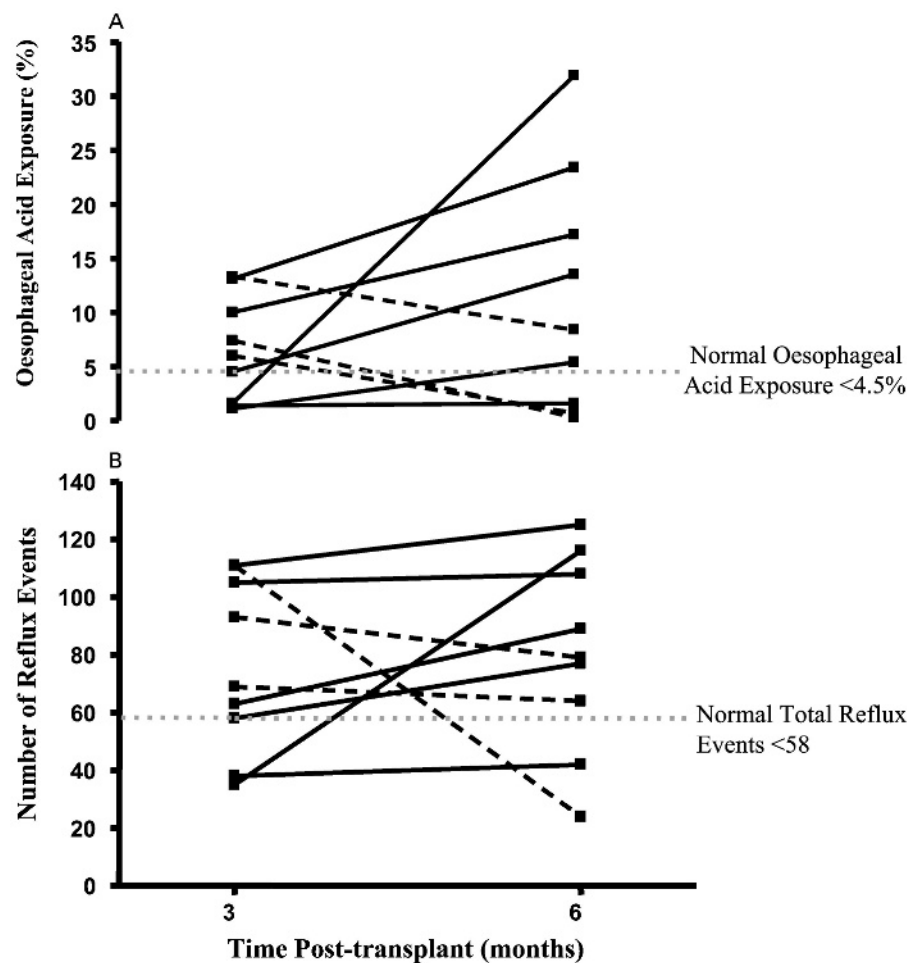
► Table 1 is published online only at <http://thorax.bmj.com/content/vol64/issue11>

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**Figure 1** (A) Oesophageal acid (pH <4.0) exposure, expressed as percentage of monitoring time. (B) Total number of reflux events measured by impedance at 3 and 6 months after transplantation. The dotted lines indicate accepted European normal cut-off values (<4.5% for acid exposure and <58 for total number of reflux events<sup>3</sup>), indicating the presence of clinically significant gastro-oesophageal reflux in most of the patients, with inter-subject and intra-subject variability over time.

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## Attitudes of patients towards a hospital-based rehabilitation service for obesity hypoventilation syndrome

Obesity hypoventilation syndrome (OHS) is characterised by a body mass index of  $>30$  kg/m<sup>2</sup>, with either diurnal or nocturnal hypoventilation in the absence of any other explanation for this.<sup>1</sup> If left untreated, OHS can be associated with significant morbidity and mortality. Currently, the mainstay of treatment for OHS is non-invasive ventilation. Pulmonary rehabilitation (PR) is an established form of treatment for patients with chronic obstructive pulmonary disease (COPD).<sup>2</sup> PR is increasingly offered to patients with various other chronic respiratory diseases, and a similar programme with particular emphasis on obesity can reasonably be expected to benefit patients with OHS.

At Papworth hospital, we have been interested in developing a multidisciplinary rehabilitation programme for patients with OHS and performed a questionnaire-based survey investigating the likelihood of patients participating in such a programme.

Patients were identified from the hospital database. A letter outlining the proposed rehabilitation programme (visiting the hospital twice a week for 8–12 weeks for a series of sessions involving supervised exercise, dietary advice and educational classes) and a short anonymous questionnaire were sent to 96 patients with OHS. The questionnaire required the patients to specify how likely they would be to attend the programme, if offered, and the reasons that might prevent them from attending. The patients were also asked if they would be more likely to attend the rehabilitation if travel was arranged and, if so, whether they would prefer the hospital to arrange transport or to be reimbursed for their own arrangements. The questionnaire included a section for any comments patients had.

Forty-six (48%) patients returned the questionnaire. Of these responses, 14 (30%) patients would either be “very likely” or “likely” to attend the rehabilitation programme, with 20 (43%) patients being “not at all” likely to attend. Travelling to the hospital was found to be the most significant concern amongst the group, with 27

(59%) patients saying the distance or travelling involved would prevent them from attending the programme. Out of these 27 patients, 11 (41%) would still not attend if their travel was arranged for them. Inconvenience (9%) and lack of spare time (13%) were also cited as reasons that prevented participation in the programme. Travelling was mentioned most frequently (37%) as well as patients reporting that the proposed rehabilitation programme would conflict with existing commitments such as work or child care (24%), that it would be more convenient if carried out in a local healthcare facility (13%) and that they needed more information in order to decide whether to attend (11%).

Given that the most common concern amongst patients was the travel required to attend the programme, one might predict that offering to help patients with their travel arrangements would increase the likelihood of attending rehabilitation. However, despite offering two options of travel assistance—arranged by the hospital or reimbursement for their own arrangements—41% of patients would still not attend.

This survey suggests that patients with OHS are poorly motivated to attend a rehabilitation programme. Providing more information about the benefits of exercise and diet-based interventions and a local service with adequate travel arrangements may increase the attendance at such programmes.

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## Merkel cell polyomavirus is prevalent in a subset of small cell lung cancer: a study of 31 patients

Merkel cell carcinoma (MCC) and small cell lung cancer (SCLC) share quite distinct similarities such as almost undistinguishable histological presentation (fig 1a,b) and highly aggressive biological behaviour with high rates of metastasis and poor survival rates.<sup>1,2</sup> While tobacco smoking and genetic susceptibility have been identified as risk factors for SCLC,<sup>3,4</sup> sun exposure and

immunosuppression are the main risk factors for MCC.<sup>1</sup> In January 2008, a new virus, called Merkel cell polyomavirus (MCPyV), was described by Feng *et al* as a likely causative agent of MCC, proving monoclonal MCPyV–genome integration in 8 of 10 MCCs.<sup>5</sup> Since then these findings have been reproduced by several groups.<sup>6,7</sup>

Because SCLC and MCC share obvious similarities in histological presentation, Wetzels *et al* recently published the first report looking for MCPyV prevalence in SCLC.<sup>8</sup> They investigated a small cohort of 10 patients with SCLC, finding no prevalence for MCPyV. We performed a molecular pathology study in a relatively large cohort of 31 patients (36 samples) analysing the presence of MCPyV DNA by PCR and chemiluminescence Southern blot hybridization of PCR products. These data are the first to test the findings of Wetzels and colleagues.

Based on the DNA sequences published by Feng *et al*, we designed two sets of primers in order to test the formalin-fixed and paraffin-embedded (FFPE) tissues for the presence of specific MCPyV DNA. After DNA extraction from FFPE tissues, PCR amplification using these primer combinations resulted in a 138 bp product (MCV138 forward: 5'-GGTTAGAGATGCTGGAAATGACC-3'; reverse: 5'-CAAATAAGCACCAGTACCAGGC-3') and a 191 bp product (MCV191 forward, 5'-CCACTTTATTATCTTAGCCCAT-3'; and reverse, 5'-TCCTTTTGGCTAGAACAGTGTGTC-3') targeting the large and small T-antigen region of MCPyV (isolate MCC-Mpt-LS2). Results were confirmed by chemiluminescence Southern blotting with specific probes for MCV138 and MCV191, omitting primer sequences and carrying a 5' digoxigenin label (DIG-MCV138 forward, 5'-GTAAGAAGTTTAAAGAAGCACCTAG-3'; and DIG-MCV191 forward, 5'-GATCTCG-CCTCAAACCTCACAAG-3'). DNA quality was confirmed by  $\beta$ -globin PCR using the GH20 (5'-GAAGAGCCAAGGACAGGTAC-3') and PCO4 (5'-CAACTTCATCCACGTTACC-3') primer set.

Of the 36 SCLC specimens, 35 revealed a  $\beta$ -globin PCR product. These 35 specimens were from 30 patients (13 women and 17 men, clinically not differentiated in limited and extensive disease; 2 patients with three samples each and 1 patient with two samples). Their mean (SD) age was 67.9 (8.6) years. MCPyV sequences were detected in 2 of 30 patients (7.5%), specifically in three of 35 samples (two of these three samples are from 1 patient, both positive for MCV138 (fig 1c,d) and the remaining sample was positive for MCV191). The PCR-negative controls, containing all other PCR components and water instead of DNA, were constantly negative in all experiments.

Based on the data presented here, it is unlikely that MCPyV plays a significant pathogenetic role in SCLC; nevertheless a supplemental role as cofactor in the pathogenesis of SCLC cannot be ruled out