from the multiple breath nitrogen washout technique are strongly associated with AHR in asthma, and opens up a wide range of clinical and basic research avenues to elucidate the topographical and mechanistic basis of relationships between ventilation heterogeneity, exhaled nitric oxide analysis and AHR.

Thorax 2007;**62**:653–654.
doi: 10.1136/thx.2006.073239

Correspondence to: Dr Jose Venegas, Department of Anesthesia and Critical Care, Massachusetts General Hospital, Boston, Massachusetts 02114, USA; jvenegas@partners.org

Funded by HL068011.

Competing interests: None.

REFERENCES

1 **Brown RH**. Marching to the beat of different drummers: individual airway response diversity. *Eur Respir J* 2004;**24**:193–4.
2 **Lutchen KR**, Jensen A, Atileh H, *et al*. Airway constriction pattern is a central component of asthma severity: the role of deep inspirations. *Am J Respir Crit Care Med* 2001;**164**:207–15.
3 **Obase Y**, Shimoda T, Mitsuta K, *et al*. Correlation between airway hyperresponsiveness and airway inflammation in a young adult population: eosinophil, ECP, and cytokine levels in induced sputum. *Ann Allergy Asthma Immunol* 2001;**86**:304–10.
4 **Reid DW**, Johns DP, Feltis B, *et al*. Exhaled nitric oxide continues to reflect airway hyperresponsiveness and disease activity in inhaled corticosteroid-treated adult asthmatic patients. *Respirology* 2003;**8**:479–86.
5 **Taylor DR**. Nitric oxide as a clinical guide for asthma management. *J Allergy Clin Immunol* 2006;**117**:259–62.
6 **Downie SR**, Salome CM, Verbanck S, *et al*. Ventilation heterogeneity is a major determinant of airway hyperresponsiveness in asthma, independent of airway inflammation. *Thorax* 2007;**62**:684–9.
7 **Engel LA**, Landau L, Taussig L, *et al*. Influence of bronchomotor tone on regional ventilation distribution at residual volume. *J Appl Physiol* 1976;**40**:411–6.
8 **Siegler D**, Fukuchi Y, Engel L. Influence of bronchomotor tone on ventilation distribution and airway closure in asymptomatic asthma. *Am Rev Respir Dis* 1976;**114**:123–30.
9 **Filuk RB**, Berezanski DJ, Anthonisen NR. Airway closure with methacholine-induced bronchoconstriction. *J Appl Physiol* 1987;**63**:2223–30.
10 **King GG**, Eberl S, Salome CM, *et al*. Airway closure measured by a Technegas bolus and SPECT. *Am J Respir Crit Care Med* 1997;**155**:682–8.
11 **King GG**, Eberl S, Salome CM, *et al*. Differences in airway closure between normal and asthmatic subjects measured with single-photon emission computed tomography and technegas. *Am J Respir Crit Care Med* 1998;**158**:1900–6.
12 **Pellegrino R**, Biggi A, Papaleo A, *et al*. Regional expiratory flow limitation studied with Technegas in asthma. *J Appl Physiol* 2001;**91**:2190–8.
13 **Brown RH**, Herold CJ, Hirshman CA, *et al*. Individual airway constrictor response heterogeneity to histamine assessed by high-resolution computed tomography. *J Appl Physiol* 1993;**74**:2615–20.
14 **Kotaru C**, Coreno A, Skowronski M, *et al*. Morphometric changes after thermal and methacholine bronchoprovocations. *J Appl Physiol* 2005;**98**:1028–36.
15 **Altes TA**, Powers PL, Knight-Scott J, *et al*. Hyperpolarized 3He MR lung ventilation imaging in asthmatics: preliminary findings. *J Magn Reson Imaging* 2001;**13**:378–84.
16 **Samee S**, Altes T, Powers P, *et al*. Imaging the lungs in asthmatic patients by using hyperpolarized helium-3 magnetic resonance: assessment of response to methacholine and exercise challenge. *J Allergy Clin Immunol* 2003;**111**:1205–11.
17 **Harris RS**, Winkler T, Tgavalekos N, *et al*. Regional pulmonary perfusion, inflation, and ventilation defects in bronchoconstricted patients with asthma. *Am J Respir Crit Care Med* 2006;**174**:245–53.
18 **Venegas JG**, Winkler T, Musch G, *et al*. Self-organized patchiness in asthma as a prelude to catastrophic shifts. *Nature* 2005;**434**:777–82.
19 **Tgavalekos NT**, Musch G, Harris RS, *et al*. Relationship between airway narrowing, patchy ventilation and lung mechanics in asthmatics. *Eur Respir J*, 2007 (epub ahead of print)..
20 **Fredberg JJ**, Inouye D, Miller B, *et al*. Airway smooth muscle, tidal stretches, and dynamically determined contractile states. *Am J Respir Crit Care Med* 1997;**156**:1752–9.
21 **Anafi RC**, Wilson TA. Airway stability and heterogeneity in the constricted lung. *J Appl Physiol* 2001;**91**:1185–92.
22 **Shin HW**, Condorelli P, George SC. A new and more accurate technique to characterize airway nitric oxide using different breath-hold times. *J Appl Physiol* 2005;**98**:1869–77.
23 **Shin HW**, Schwindt CD, Aledia AS, *et al*. Exercise-induced bronchoconstriction alters airway nitric oxide exchange in a pattern distinct from spirometry. *Am J Physiol Regul Integr Comp Physiol* 2006;**291**:R1741–8.

Staging of NSCLC

Evolution and science, progress and change

Frank C Detterbeck

Positron emission tomography in staging of intrathoracic lymph nodes in non-small cell lung cancer

Staging of non-small cell lung cancer (NSCLC) has undergone a significant evolution, from plain chest radiographs to anatomical imaging, invasive techniques and, most recently, metabolic imaging using positron emission tomography (PET) scans. Even the literature regarding PET imaging has undergone significant evolution. Initial reports were characterised by compelling yet anecdotal images. This was followed by approximately 10 years of studies showing that mediastinal staging by PET was superior to computed tomography (CT) which, of course, was not surprising because CT had already been shown to be notoriously misleading in many situations. Eventually authors began addressing the clinically more relevant question of whether PET can replace invasive mediastinal staging. The article by Tournoy and colleagues[1] in this issue of *Thorax* illustrates how far we have come (***see page 696***). Not only does this study use the most sophisticated technology—an integrated PET/CT scanner—but, more importantly, the authors have elevated the science a notch by thoughtfully evaluating nuances of scan interpretation in order to maximise what can be gained from this staging modality.

The overall scientific quality of the study by Tournoy and colleagues is good. An appropriate gold standard was used by requiring a surgical staging procedure after a negative needle staging test (transoesophageal ultrasound with needle aspiration, transbronchial needle aspiration, etc, which carry a 20–30% false negative rate).[2] The authors should also be commended for looking at enlarged and normal size nodes separately, since PET uptake in smaller nodules is more difficult to detect. In addition, the careful evaluation of different objective criteria to try to improve the reliability of the PET interpretation is a valuable addition. On the other hand, reporting results on a per node basis statistically biases the results in favour of PET. Furthermore, this makes the data less applicable clinically because we must decide how to manage patients, not individual nodes. Additionally, lumping together mediastinal and hilar nodes biases the study in favour of PET because it avoids a distinction that can be difficult to make on PET. This also makes the data less clinically applicable because involved N1 nodes are generally treated differently from involved N2 nodes. An additional criticism is that the final assessment of the nodes is vague (which would also tend to bias the results in favour of PET). It is unclear whether patients with a negative invasive staging went on to

resection, and whether further nodal sampling at the time of resection was done. Finally, it appears that node sampling was limited (average of 2.01 nodes per patient, including both mediastinal and hilar node stations).

In the end, the study by Tournoy *et al*[1] shows that evolution does not necessarily mean we are making progress. The study shows that PET is not adequate to avoid invasive staging in most instances despite the sophisticated technology of CT/PET, the evaluation of objective criteria and the inherent bias of a per node analysis. The key test parameters for a clinician in deciding whether a test is reliable enough to guide the management of an individual patient is the false positive or false negative rate. This study shows that a positive PET scan must be confirmed (false positive rate of 21% with enlarged nodes and 50% with normal size nodes).[1] Furthermore, the study shows that a negative PET result carries a significant false negative rate (9% with normal size nodes and 10% with enlarged nodes).[1] These results are generally consistent with that of other authors, which have shown a false negative rate of PET in the mediastinum of 20–30% in patients with discrete enlarged mediastinal nodes[3 4] and of 25% in patients with a normal mediastinum and enlarged N1 nodes.[4–6] However, the false negative rate of PET in the mediastinum is <5% for patients with a peripheral clinical stage I tumour.[5–10]

It is interesting to revisit the evolution of CT imaging. The early CT studies, involving limited numbers of patients and first generation scanners, reported sensitivity and specificity rates of >90%. Later studies, involving many hundreds of patients and fourth generation scanners, found sensitivity and specificity rates of approximately 60–70%.[11 12] It appears that broader application of CT (across many centres and more generally to patients) yielded worse results, despite major technological improvements (rapid, helical, higher resolution scanners). Similarly, the early studies of PET in NSCLC demonstrated sensitivity and specificity for mediastinal staging of over 90%,[13] while the more recent results show these rates to be around 70–80% despite advancing technology.[11 14] Is the study by Tournoy[1] showing that we have reached the limits of what PET imaging can give us with regard to mediastinal staging?

Invasive staging tests have also undergone an evolution. Needle aspiration has gone from a ''blind'' transcarinal aspiration to real-time image-guided aspirations via either transoesophageal ultrasound or endobronchial ultrasound. The data from these newer interventions appear to be much better than the older transbronchial needle technique.[15 16] Mediastinoscopy has evolved from a simple lighted tube to video-mediastinoscopy and video-mediastinoscopic lymphadenectomy, both of which have been reported to have better reliability than simple mediastinoscopy.[17–19] We will have to see whether the excellent results reported in the initial studies hold up as the technology disseminates.

So where does this leave us? Again, it is worth revisiting the evolution of CT imaging in lung cancer. There is no doubt that CT has become an integral and, for all practical purposes, an essential part of the assessment of a patient with lung cancer. This is because CT is invaluable in guiding the evaluation and choice of treatment in patients with NSCLC and not because it obviates the need for invasive mediastinal staging tests, as was originally anticipated. Chest CT scanning helps guide the need for extrathoracic imaging in that approximately 30% of patients with enlarged mediastinal nodes will have detectable distant metastases despite having no signs of symptoms of metastases,[7 20] whereas <5% will have distant metastases if they are asymptomatic and have a stage I tumour by CT scanning.[2 8 9 21 22] Patients who have a normal mediastinum by CT scanning but evidence of N1 node enlargement need invasive staging (because of a 20–25% incidence of mediastinal node involvement), whereas those with a peripheral stage I tumour have a very low incidence of N2,3 disease (<10%).[2 21] Furthermore, CT tells us how much lung would have to be removed if resection is to be done, and allows treatment planning for radiotherapy.

Perhaps we are not asking the right questions of PET imaging. The goal of the pretreatment evaluation of the patient is to predict the biological behaviour of the tumour and to allow us to choose a treatment strategy that has the best chance of being effective. Many studies have shown that PET intensity correlates with the propensity of tumours to reappear and spread.[23] Studies are beginning to address whether PET intensity can guide the need for invasive mediastinal staging.[24] The change in PET intensity a few days after a dose of chemotherapy is an excellent predictor of the response to that regimen.[23] Perhaps the study by Tournoy is telling us that the progress we can achieve through better PET technology and better science is limited if we are asking the same questions. Perhaps our conceptual framework of how we use tests to achieve better outcomes for patients needs to evolve and change.

Thorax 2007;**62**:654–656.
doi: 10.1136/thx.2007.077594

Correspondence to: Dr Frank C Detterbeck, Thoracic Surgery, Yale University School of Medicine, New Haven, Connecticut 06520-8062, USA; frank.detterbeck@yale.edu

Competing interests: None.

REFERENCES

1 **Tournoy KG**, Maddens S, Gosselin R, *et al.* Integrated FDG-PET/CT does not make invasive staging of the intrathoracic lymph nodes in non-small cell lung cancer redundant: a prospective study. *Thorax* 2007;**62**:696–701.
2 **Detterbeck F**, Jantz M, Wallace M, *et al. Invasive mediastinal staging of lung cancer: an ACCP evidence based clinical practice guideline,* 2nd edn 2007.
3 **Serra M**, Cirera L, Rami-Porta R, *et al.* Routine positron tomography (PET) and selective mediastinoscopy is as good as routine mediastinoscopy to rule out N2 disease in non-small cell lung cancer (NSCLC). *J Clin Oncol* 2006;**24**:371s, .
4 **Cerfolio RJ**, Bryant AS, Ojha B, *et al.* Improving the inaccuracies of clinical staging of patients with NSCLC: a prospective trial. *Ann Thorac Surg* 2005;**80**:1207–14.
5 **Pozo-Rodriguez F**, Martin de Nicolas JL, Sanchez-Nistal MA, *et al.* Accuracy of helical computed tomography and [18F] fluorodeoxyglucose positron emission tomography for identifying lymph node mediastinal metastases in potentially resectable non-small-cell lung cancer. *J Clin Oncol* 2005;**23**:8348–56.
6 **Verhagen AFT**, Bootsma GP, Tjan-Heijnen VC, *et al.* FDG-PET in staging lung cancer: how does it change the algorithm? *Lung Cancer* 2004;**44**:175–81.
7 **MacManus MP**, Hicks RJ, Matthews JP, *et al.* High rate of detection of unsuspected distant metastases by PET in apparent stage III non-small-cell lung cancer: implications for radical radiation therapy. *Int J Radiat Oncol Biol Phys* 2001;**50**:287–93.
8 **Viney RC**, Boyer MJ, King MT, *et al.* Randomized controlled trial of the role of positron emission tomography in the management of stage I and II non-small-cell lung cancer. *J Clin Oncol* 2004;**22**:2357–62.
9 **Reed C**, Harpole DH, Posther KE, *et al.* Results of the American College of Surgeons Oncology Group Z0050 Trial: The utility of positron emission tomography in staging potentially operable non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2003;**126**:1943–51.
10 **Meyers BF**, Haddad F, Siegel BA, *et al.* Cost-effectiveness of routine mediastinoscopy in computed tomography- and positron emission tomography-screened patients with stage I lung cancer. *J Thorac Cardiovasc Surg* 2006;**131**:822–9.
11 **Birim O**, Kappetein AP, Stijnen T, *et al.* Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer. *Ann Thorac Surg* 2005;**79**:375–82.
12 **Gould MK**, Kuschner WG, Rydzak CE, *et al.* Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. *Ann Intern Med* 2003;**139**:879–92.
13 **Patz Jr EF**, Lowe VJ, Goodman PC, *et al.* Thoracic nodal staging with PET imaging with ^{18}FDG in patients with bronchogenic carcinoma. *Chest* 1995;**108**:1617–21.
14 **Gonzalez-Stawinski GV**, Lemaire A, Merchant F, *et al.* A comparative analysis of positron emission tomography and mediastinoscopy in staging non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2003;**126**:1900–5.
15 **Herth FJ**, Eberhardt R, Vilmann P, *et al.* Real-time endobronchial ultrasound-guided transbronchial needle aspiration: a new method for sampling mediastinal lymph nodes. *Thorax* 2006;**61**:795–8.

16 **Yasufuku K**, Chiyo M, Koh E, *et al*. Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. *Lung Cancer* 2005;**50**:347–54.
17 **Leschber G**, Holinka G, Linder A. Video-assisted mediastinoscopic lymphadenectomy (VAMLA)—a method for systematic mediastinal lymphnode dissection. *Eur J Cardiothorac Surg* 2003;**24**:192–5.
18 **Venissac N**, Alifano M, Mouroux J. Video-assisted mediastinoscopy: experience from 240 consecutive cases. *Ann Thorac Surg* 2003;**76**:208–12.
19 **Kimura H**, Iwai N, Ando S, *et al*. A prospective study of indications for mediastinoscopy in lung cancer with CT findings, tumor size, and tumor markers. *Ann Thorac Surg* 2003;**75**:1734–9.
20 **Eschmann SM**, Friedel G, Paulsen F, *et al*. FDG PET for staging of advanced non-small cell lung cancer prior to neoadjuvant radio-chemotherapy. *Eur J Nucl Med Mol Imaging* 2002;**29**:804–8.
21 **Detterbeck F**, Falen S, Rivera MP, *et al*. Seeking a home for a PET, Part 2: Defining the appropriate place for positron emission tomography imaging in the staging of patients with suspected lung cancer. *Chest* 2004;**125**:2300–8.
22 **Farrell MA**, McAdams HP, Herndon JE, *et al*. Non-small cell lung cancer: FDG PET for nodal staging in patients with stage I disease. *Radiology* 2000;**215**:886–90.
23 **Detterbeck FC**, Vansteenkiste JF, Morris DE, *et al*. Seeking a home for a PET, Part 3: Emerging applications of positron emission tomography imaging in the management of patients with lung cancer. *Chest* 2004;**126**:1656–66.
24 **Bryant AS**, Cerfolio RJ, Klemm KM, *et al*. Maximum standard uptake value of mediastinal lymph nodes on integrated FDG-PET-CT predicts pathology in patients with non-small cell lung cancer. *Ann Thorac Surg* 2006;**82**:417–23.

Diagnosing primary ciliary dyskinesia

Christopher O'Callaghan, Mark Chilvers, Claire Hogg, Andrew Bush, Jane Lucas

A nationally funded diagnostic service should lead to improved outcome

The National Specialist Commissioning Advisory Group (NSCAG) has funded three centres to establish and provide a national diagnostic service for England for children and adults suspected of suffering from primary ciliary dyskinesia (PCD). This is welcomed, as state of the art diagnostic testing will be available nationally which will increase the numbers of patients diagnosed with a condition in which early diagnosis has a very significant effect on both short-term and long-term morbidity. Inheritance is autosomal recessive with an incidence of around 1:15 000 in the Caucasian population and, as expected, we have found a much higher incidence in ethnic groups where consanguineous marriages are common. Accurate diagnosis will allow appropriate genetic counselling of families.

PCD is caused by one of a number of different ciliary defects that result in ineffective mucociliary clearance. Although most patients with PCD have symptoms from birth or early infancy,[1] the diagnosis is frequently delayed[2] and it is likely that a significant number of patients are never diagnosed.[3] Failure to diagnose PCD leads to progressive and permanent lung destruction owing to obstruction of the airways with secretions and subsequent infection, leading to bronchiectasis. Early diagnosis of PCD is important as deterioration in lung function can largely be prevented by specialist respiratory care.[4] Failure to recognise the condition frequently leads to inappropriate ear, nose and throat (ENT) surgery. Grommet insertion may lead to persistent aural discharge with little improvement in hearing loss. A number of patients with unrecognised PCD present in infertility clinics. Infertility in males, although not inevitable, is due to sperm tails being affected as part of their PCD. There is an increased incidence of ectopic pregnancy due to defective movement of the cilia in the fallopian tube.[5]

As PCD testing is not a front line test for those with respiratory problems, who should be referred? Patients with situs inversus, which occurs in 40–50% of individuals with PCD, is an obvious indication. Of patients referred to our laboratory with situs inversus, 75% have been confirmed to have PCD. Of patients without situs inversus, those with bronchiectasis and life-long nasal symptoms in whom no other cause has been identified should be considered for referral. A significant number of patients with PCD will have a history of unexplained neonatal respiratory distress and persistent rhinitis from birth. The real aim, however, is to diagnose children before bronchiectasis develops and before they are subjected to repeated ENT surgery. The investigation of children with host defence problems—including PCD—who are at risk of developing bronchiectasis is frequently delayed. Reasons for the delay include the child's tendency to swallow rather than expectorate sputum, a distinct lack of auscultatory findings and temperature even during acute exacerbations, and the fact that the chest radiograph often appears normal.

So, how do we recognise a young child at risk of developing bronchiectasis? The important sign is that of a persistent "wet" sounding cough. If such a cough persists for more than 8 weeks or improvement is seen with antibiotic treatment but symptoms return when stopped, paediatric review should be arranged. In patients with PCD the cough never goes completely even with treatment and "has always been there". Testing for PCD should be considered if standard first line investigations to exclude cystic fibrosis (CF) and screening for immunological defects are negative and the child has a life-long history of a "wet" sounding cough and persistent nasal symptoms. A number of patients will have a history of unexplained neonatal respiratory distress. Hearing problems are only seen in half of cases. If the child is from a consanguineous marriage, suspicion should be higher. Nonetheless, symptoms may be mild; in one series, diagnosis was made in 10% as a result of family screening after the diagnosis in an index case.[6]

Diagnosis to date has largely been provided on an ad hoc basis, with lack of standardisation of, and inaccessibility to, diagnostic testing for the majority of patients in the UK. Screening tests for PCD exist, but there are problems associated with them. The saccharin test used to assess mucociliary function is difficult to perform and is unreliable in children. Measurement of nasal nitric oxide, which is very low in patients with PCD, is now accepted as the most sensitive and specific screening test for PCD.[7] Unfortunately this is not widely available and cannot be used in young children. The development of new methodologies over the last few years has allowed improved diagnostic testing for PCD. The traditional measurement of ciliary beat frequency alone has been shown to miss a proportion of patients with PCD whose ciliary beat frequency is normal but beat pattern abnormal.[8] Diagnostic assessment following biopsy will now include measurement of ciliary beat frequency, high speed analysis of ciliary beat pattern,[8] detailed electron microscopy of ciliary ultrastructure and, in cases where there are diagnostic uncertainties, cell culture[9] from biopsies. Although the genetics of