Spiral CT pulmonary angiography is an effective way of demonstrating pulmonary embolism in segmental and larger arteries.\textsuperscript{4} The basic sign of a filling defect within a well opacified pulmonary artery is straightforward enough. The case report by Oliver \textit{et al.}\textsuperscript{6} highlights the fact that there may be ancillary signs of pulmonary embolism on spiral CT scanning—in this case shift of the interventricular septum—which corroborates the diagnosis and, more controversially, provides prognostic information. Shift of the interventricular septum and other signs of right ventricular dysfunction are readily demonstrated on echocardiography, but in cases of suspected pulmonary embolism echocardiography does not provide the breadth of information of a spiral CT examination. For example, additional signs of pulmonary embolism, including a mosaic perfusion pattern of the lung parenchyma and radiographically cryptic pleural effusions or small pulmonary infarcts, can be readily picked up on spiral CT scanning. Conversely, because spiral CT scanning provides the “big picture”, an alternative diagnosis may be shown by spiral CT scanning in up to one third of patients investigated for suspected pulmonary embolism.\textsuperscript{3}

The application of image processing to volumetric spiral CT data can be broadly divided into graphic 3-D realisations—for example, virtual reality bronchoscopy\textsuperscript{6}—and the rendering of data so that it is suitable for quantitative analysis. However, progress towards routine volumetric (3-D) depictions of spiral CT data is likely to be slow.\textsuperscript{7} Even at this early stage of development it is possible to extract very precise volumetric measures of abnormal lung; the most obvious application is in the quantification of low attenuation lung (corresponding to emphysema) on inspiratory and expiratory spiral CT scans. Early results have shown remarkably good correlation between the extent of low attenuation lung derived from 3-D reconstructions of the lungs with functional indices of air flow obstruction and air trapping.\textsuperscript{8} With this new technique the entire lungs are evaluated, unlike the conventional “density mask” approach which can be applied only to individual CT sections, (which introduces problems with sampling). With the powerful combination of volumetric data from spiral CT scanning and advanced image processing, the excitement has only just begun.

Diagnosis of pulmonary sequestration by spiral CT angiography

José Franco, Roberto Aliaga, Maria L Domingo, Pedro Plaza

Abstract
The diagnosis of pulmonary sequestration traditionally requires arteriography to identify abnormal systemic vessels feeding the abnormal portion of the lung. Non-invasive imaging techniques have recently been used to replace arteriography. Conventional computed tomographic (CT) scanning is, however, at a disadvantage because of its inability to obtain multiplanar images. The combination of spiral CT scanning and computerised three-dimensional reconstruction (spiral CT angiography) can be used to visualise the anatomical detail of a wide range of vessels within the lung. Four cases of pulmonary sequestration are reported which were successfully diagnosed using spiral CT angiography. Spiral CT scanning allows simultaneous imaging of abnormal vessels and lung parenchyma in a single examination and is particularly useful in the diagnosis and assessment of pulmonary sequestration.

Keywords: pulmonary sequestration; spiral computed tomography

Pulmonary sequestration is a rare congenital pulmonary disorder defined as an area of dysplastic and non-functioning pulmonary tissue with an anomalous systemic blood supply. It has been classically described in two forms—intralobar sequestrations located within the visceral pleura and surrounded by normal lung, and extralobar sequestrations which have a separate pleural covering. Both types are supplied with blood from the aorta or its branches. The venous return of the intralobar sequestration is usually via the pulmonary veins while extralobar sequestrations generally have systemic venous drainage. Nevertheless, many variations and combinations of these classical patterns have been described.

Traditionally, the diagnosis of pulmonary sequestration requires arteriography to identify abnormal systemic vessels feeding the abnormal portion of the lung. More recently, other procedures have been advocated as a less invasive means of identifying the anomalous artery. Although conventional computed tomographic (CT) scanning can show both normal lung parenchyma and the systemic arterial supply, it lacks the multiplanar images which limit its usefulness in the diagnosis of sequestration. With the advent of helical technology, spiral CT angiography is able to delineate the aorta and its branches. The role of CT scanning in evaluating suspected pulmonary sequestration should therefore be re-evaluated.

In this report we describe the use of spiral CT angiography to image the aberrant systemic artery in four cases of pulmonary sequestration.

Methods
We performed four CT angiography studies with a PQ2000S helical scanner (Picker International Inc, Highlands Heights, Ohio, USA). Spiral volumetric CT scanning was performed with 4 mm slide thickness, 4 mm table speed, 3 mm reconstruction index, and smooth reconstruction algorithm. A non-ionic contrast medium (120 ml, iodine 300 mg/ml) was administered at a rate of 3 ml/s via the antecubital vein.

Figure 1  Spiral CT scan of case 1. (A) Contrast enhanced CT axial image showing the small aberrant artery (arrow) adjacent to the upper abdominal aorta (a). (B) Anterior view of helical CT angiogram. The anomalous artery (arrow) feeding the pulmonary lesion (L) arises from the coeliac axis.
A 25 second scan delay was used in order to optimise contrast in the systemic arterial phase of the study. Three-dimensional reconstruction (3D) was performed with a Voxel Q work station using a shaded surface display (SSD) program with segmentation option.

Case reports

CASE 1
A 32 year old man with a 34 pack-year history of cigarette smoking who still smoked two packs a day was admitted to the smoking cessation programme at our hospital. There was a history of pneumonia at the age of 14. A chest radiograph showed localised air trapping in the left lower lobe. A spiral CT scan (fig 1) revealed a multicystic lesion in the posterior basal segment of the left lower lobe supplied by an artery derived from the coeliac axis; venous drainage to the pulmonary veins was also demonstrated. The presence of the anomalous systemic artery and venous drainage were confirmed by aortography. The patient was asymptomatic and refused surgery.

CASE 2
A 28 year old man presented with a one month history of recurrent haemoptysis. He smoked one pack of cigarettes daily. Chest radiography showed a mass, 4 cm in diameter, in the right lower lobe. A spiral CT scan (fig 2) revealed a multicystic lesion in the posterior basal segment of the left lower lobe supplied by an artery derived from the coeliac axis; venous drainage to the pulmonary veins was also demonstrated. The presence of the anomalous systemic artery and venous drainage were confirmed by aortography. The patient was asymptomatic and refused surgery.

CASE 3
A 65 year old male cigarette smoker had a two week history of productive cough and fever. The patient improved with antibiotic therapy but a persistent cough developed. Radiography of the chest showed partial collapse of the left lower lobe and a mass like opacity with an air-fluid level. A CT scan demonstrated a non-homogeneous mass with multiple cystic appearing spaces and cavitating involving the posterior basal segment of the left lower lobe. Fibreoptic bronchoscopic examination disclosed no abnormality. A percutaneous fine needle aspiration biopsy specimen of the lesion revealed non-diagnostic findings. Spiral CT angiography (fig 3) showed a feeding systemic artery arising from the descending thoracic aorta and venous drainage to the pulmonary veins. At surgery an infected intralobar sequestration was found.

CASE 4
A 41 year old man was admitted to hospital with a 48 hour history of fever and pleuritic chest pain. There was no history of use of tobacco. Chest radiography revealed a homogenous density in the right lower lobe. The patient was diagnosed as having pneumonia and treated with clarithromycin. One month later he was

Figure 2  Spiral CT scan of case 2. (A) Contrast enhanced CT axial image showing the pulmonary mass (M) supplied by an anomalous systemic artery (arrow) arising from the upper abdominal aorta (a). (B) Right view of helical CT angiogram showing the course of the arterial vessel (arrow) to the pulmonary mass (M). Note the venous drainage (arrowhead) to the pulmonary veins (V).

Figure 3  Spiral CT scan of case 3. (A) Contrast enhanced CT axial image showing an anomalous systemic artery (arrow) feeding the pulmonary lesion (L) in the left lower lobe. (B) Left oblique view of helical CT angiogram demonstrating the anomalous artery (arrow) originating from the left wall of the thoracic aorta (a).
Diagnosis of pulmonary sequestration by spiral CT angiography

Both intralobar and extralobar sequestration characteristically involves the lower lobes of the lungs. Intralobar pulmonary sequestration accounts for 73% of all sequestrations and has a predilection for the posterior basal segment of the lower lobes. It occurs slightly more often in the left lung than in the right.2 The blind end of the systemic artery supply is usually dominated by the associated anomalies and the venous drainage. Surgery was not considered at the time this case was presented.

Discussion

Both intralobar and extralobar sequestration characteristically involves the lower lobes of the lungs. Intralobar pulmonary sequestration accounts for 73% of all sequestrations and has a predilection for the posterior basal segment of the lower lobes. It occurs slightly more often in the left lung than in the right.2 The blind ending bronchi, which may become distended trapping mucus, are prone to infection. In about two thirds of the cases reported the first symptoms occur after the age of 10 years and are usually secondary to a superimposed infection. Productive cough, fever, haemoptysis, recurrent pneumonia, and chest pain are typical presenting complaints. Extralobar sequestrations are frequently discovered during the neonatal period in infants with other congenital anomalies. The clinical picture is usually dominated by the associated anomalies although infection can occur, especially if there is a communication with the oesophagus or the stomach. Extralobar sequestrations that are not diagnosed in newborn infants are often asymptomatic and detected on routine radiography. In case 1 pulmonary sequestration was detected by routine radiography, while in case 2 haemoptysis was the presenting symptom of an intralobar sequestration. Case 3 had an intralobar sequestration typically manifested by symptoms of infection and case 4 had a postnatal examination of a transbronchial biopsy specimen and positive culture of bronchial aspirate. A spiral CT angiogram (fig 4) revealed a focal area of increased density in the right lower lobe supplied by an artery originating from the coeliac axis. An abdominal aortogram showed the anomalous artery and the venous return via the pulmonary veins. Because accessory arteries, pleural investment, and venous drainage are adequately determined intraoperatively, at some institutions only the presence and location of an aberrant systemic artery are considered essential for preoperative assessment.

Imaging strategies for suspected pulmonary sequestration are based on case reports or small series since it is a rare congenital disorder and no study exists that objectively compares imaging techniques for detection, definition, or cost effectiveness.4 Since the definitive step in the diagnosis of sequestration is the demonstration of the systemic arterial supply, for a long time diagnosis was made by conventional angiography. More recently all imaging techniques capable of showing the artery have been implicated in evaluating sequestration. Magnetic resonance (MR) imaging and MR angiography can be used together to diagnose pulmonary sequestration in a single non-invasive examination.6 Nevertheless, MR cannot accurately evaluate lung parenchyma and the airways and must be considered in terms of cost and availability. Sonography requires a favourable acoustic window and is ideally suited for evaluating the chest prenatally and postnatally.7 Other non-invasive techniques for evaluation of sequestration such as scintigraphy are only rarely necessary.

In all four cases described in this report spiral CT angiography successfully delineated the origin and course of the anomalous systemic artery. Axial images were enough to make the diagnosis but three-dimensional reconstruction aided both radiologists and referring clinicians by demonstrating anatomical relationships, particularly for vessels orientated in the z axis.8 On the other hand, venous drainage was also identified in the three cases in which lower pulmonary veins were included in contrast enhanced helical CT scans. We have performed...
three-dimensional reconstruction (3D-SSD) segmentation for a better understanding of the anatomy of the abnormal systemic arteries. However, as shown in case 2, three-dimensional imaging dedicated to the venous drainage can also be made.8

Spiral CT angiography is a minimally invasive technique for vascular imaging that is made possible by combining slip ring CT scanning and computerised three-dimensional reconstruction.9 Spiral CT angiography has several advantages over other non-invasive vascular imaging techniques.7–10 CT scanning, with its superior spatial resolution, yields the most information about the bronchial anatomy and the pulmonary parenchymal lesion. Sonography and MRI cannot evaluate lung abnormalities accurately although MRI can reveal the cystic nature of many intralobar sequestrations as well as the variable solid, fluid, haemorrhagic, and mucus-containing components. MR angiography is hampered by artefacts caused by respiratory motion whereas this problem is generally avoided in helical CT scanning. CT angiography is less expensive than MR angiography and can be used on patients with a metallic device or who do not tolerate the MR examination. Furthermore, helical CT scanning is faster resulting in less sedation and reduced amount of contrast medium. The disadvantages of helical CT scanning are minor and arise from exposure of the patient to ionising radiation and the administration of intravenous contrast material.

In summary, we report four cases of pulmonary sequestration successfully diagnosed using spiral CT angiography. By allowing simultaneous imaging of anomalous vessels and parenchymal lesions in a single examination, spiral CT angiography is a particularly efficacious technique and has the potential to become the procedure of choice in the diagnosis and assessment of pulmonary sequestration.


Interventricular septal shift due to massive pulmonary embolism shown by CT pulmonary angiography: an old sign revisited

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J T Murchison

Abstract

The computed tomographic (CT) pulmonary angiogram appearances of acute right ventricular dysfunction due to massive pulmonary embolus in a patient are described. Abnormal findings comprised right ventricular dilatation, interventricular septal shift, and compression of the left ventricle. These changes resulted following thrombolysis. Use of CT pulmonary angiography to diagnose pulmonary emboli is increasing. Secondary cardiac effects are established diagnostic features shown by echocardiography. These have not been previously described but are important to recognise as they may carry important prognostic and therapeutic implications.

(Thorax 1998;53:1092–1094)

Keywords: pulmonary embolism; right ventricular dysfunction; spiral computed tomography; pulmonary angiography

A 43 year old man collapsed while out walking. On admission to hospital he was dyspnoeic and cyanosed. On direct questioning he admitted to right leg pain. Examination showed that his heart rate was 105 beats/min, respiratory rate was 28 breaths/min, and blood pressure was 100/60 mm Hg. His jugular venous pressure was raised but examination was otherwise normal. Electrocardiography demonstrated sinus tachycardia; the chest radiograph was normal. Measurement of arterial blood gas tensions confirmed hypoxaemia with hypocapnia (PO2 8 kPa on 6 l/min oxygen, Pco2 4 kPa). An echocardiogram demonstrated dilatation of the right ventricle. The clinical features of syncope, cyanosis and dyspnoea with engorged neck veins in a patient with a normal chest radiograph and clinical suspicion of deep venous thrombosis led to a presumptive diagnosis of pulmonary embolus. A computed tomographic (CT) pulmonary angiogram was performed. A 3 mm spiral scan, reconstructed at 1.5 mm intervals, was undertaken on a Hi Speed Advantage scanner (General Electric Medical Systems, Milwaukee, Wisconsin, USA) using 150 ml of contrast (200 mg I/ml) at 4 ml/s. This showed multiple pulmonary emboli within the main and segmental pulmonary arteries. In addition there was dilatation of the right ventricle and atrium with normal wall thicknesses, the interven-
Interventricular septal shift due to pulmonary embolism on CT angiogram

1. The initial abrupt rise in pulmonary artery pressure causes increased right ventricular afterload which results in right ventricular dilatation and dyskinesia. Secondary effects of this are tricuspid regurgitation, right atrial enlargement, and loss of respiratory variation in calibre of the great veins. Increased right ventricular wall tension may reduce local coronary blood flow, resulting in ischaemia which impairs right ventricular function further. As the right ventricle dilates, the interventricular septum is displaced towards the left ventricle, the right ventricle assuming a circular axial configuration and the left ventricle a crescentic appearance more typical of the normal right ventricle. This septal shift, combined with the constraining influence of the pericardium, results in reduced left ventricular filling which is already compromised by reduced preload. The cardiac output falls.

2. Signs documenting this sequence such as right ventricular dilatation and hypokinesis (which may spare the apex), abnormal interventricular septal motion, pulmonary artery dilatation, tricuspid regurgitation, and loss in respiratory variation in inferior vena caval diameter can be detected at echocardiography. Echocardiographic assessment of the right ventricle has been recommended as an integral part of the investigative algorithm for suspected acute pulmonary embolus published recently by the British Thoracic Society working party.

3. “Right ventricular dysfunction” is an umbrella term which also includes more subjective echocardiographic findings such as abnormalities of the motion of the right ventricular wall. These findings are often encountered in lesser degrees of pulmonary embolus and have led to debate over the significance of the more objective signs. Acute right ventricular dilatation and interventricular septal shift have been associated specifically with massive pulmonary embolism and reversible septal displacement has been described in a series of patients requiring aggressive treatment for circulatory failure due to massive pulmonary embolism. Thrombolysis is an accepted treatment in massive life threatening pulmonary embolus and its administration in the case described here was associated with a rapid return of pulmonary and systemic arterial pressures towards normal. Recognition of the signs presented by CT scanning or echocardiography allows more aggressive therapy to be targeted to individuals at greatest risk.

4. CT pulmonary angiography is increasingly used to diagnose pulmonary embolus. It is non-invasive and quick to perform. In the case described the patient was imaged directly after initial assessment in the emergency room and spent less than 15 minutes in the imaging suite. Comparative studies have shown excellent correlation between CT and conventional pulmonary angiography in the detection of emboli in segmental or larger vessels and in many centres the technique has largely replaced conventional pulmonary angiography. Secondary signs of pulmonary embolus have not, to our knowledge, been described at CT pulmonary angiography. The interventricular septum is usually displaced to the left, and there was compression of the left ventricle (fig 1A). These features persisted throughout the cardiac cycle. A central venous catheter was placed and tissue plasminogen activator was infused into the central pulmonary arteries. Immediately before treatment the central venous pressure was 22 mm Hg, right atrial pressure was 30 mm Hg, right ventricular pressure was 33/13 mm Hg, and pulmonary artery pressure was 33/20 mm Hg. Five hours after treatment the pulmonary artery pressure had reduced to 20/10 mm Hg and systemic blood pressure had increased to 160/70 mm Hg. A continuing anticoagulation regime was commenced. A venogram showed thrombus within the right popliteal vein. A repeat CT angiogram five days after treatment showed considerable reduction in the load of embolic material within the pulmonary arteries together with a return of the interventricular septum to its normal position and resumption of normal right and left ventricular morphologies (fig 1B).

Discussion

Massive pulmonary embolism sets in sequence a chain of physiological events that ultimately lead to reduced systemic cardiac output. The...
LETTERS TO THE EDITOR

Cardiac risks with β agonists

Martin et al suggest that caution should be exercised when prescribing long acting oral β agonists to patients at risk of cardiac failure, based on results from a prescription event monitoring (PEM) study.

Firstly, all β agonists (short and long acting, oral and inhaled) should be used with caution in patients with severe cardiovascular disease, as is pointed out in the package insert for all drugs of this class.

Secondly, the study does not provide any evidence on this issue. PEM studies are not designed to study causal relations but to generate new hypotheses. Although the authors have made an attempt to consider several potential biases in the analyses, the study design is inappropriate compared with, for example, a prospective randomised controlled trial, and the results must be interpreted with great caution.

Thirdly, no support for an association between bumbuterol and an increased risk for cardiac failure has been found in our review of preclinical studies, clinical studies (including >3000 patients/healthy volunteers), or post-marketing surveillance (based on >130 million treatment days).

Fourthly, according to the authors there have been no spontaneous reports of cardiac failure with bumbuterol to the Committee on Safety of Medicines. This is in agreement with the WHO database Intdis, with no reports of cardiac failure for bumbuterol.

Finally, the paper suggests a doubled asthma mortality in patients receiving salmeterol. In our opinion the reported higher relative risk for non-fatal cardiac failure for bumbuterol and the doubled asthma mortality for salmeterol both appear equally explicable by factors other than direct causality, such as confounding by concomitant diseases and disease severity. Thus, PEM data may be of help in identifying signals with new drugs, but there is little if any merit in comparing drugs used in different populations and introduced to the market at different times.

Table 1 Rates of cardiac failure during the first month of exposure to bumbuterol or a cardiovascular drug studied by prescription event monitoring (PEM)

<table>
<thead>
<tr>
<th>Drug* (ranked by rate)</th>
<th>No. of patients with reported cardiac failure during month 1</th>
<th>No. of patient-months at exposure during month 1</th>
<th>Rate (events per 1000 patient-months of exposure)</th>
<th>Mean (SD) age</th>
<th>Males (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xamoterol 1</td>
<td>97</td>
<td>4463</td>
<td>21.7</td>
<td>70.8 (13.9)</td>
<td>53.0</td>
</tr>
<tr>
<td>Nicorandil 2</td>
<td>73</td>
<td>11 578</td>
<td>6.3</td>
<td>66.9 (11.2)</td>
<td>61.1</td>
</tr>
<tr>
<td>Bumbuterol 2</td>
<td>29</td>
<td>5 891</td>
<td>4.9</td>
<td>58.5 (18.6)</td>
<td>44.8</td>
</tr>
<tr>
<td>Losartan 2</td>
<td>53</td>
<td>12 980</td>
<td>4.1</td>
<td>63.5 (12.1)</td>
<td>40.2</td>
</tr>
<tr>
<td>Diltiazem 2</td>
<td>24</td>
<td>8 808</td>
<td>2.7</td>
<td>62.3 (13.9)</td>
<td>59.3</td>
</tr>
<tr>
<td>Enalapril 2</td>
<td>33</td>
<td>13 544</td>
<td>2.2</td>
<td>61.2 (14.9)</td>
<td>46.1</td>
</tr>
<tr>
<td>Perindopril 2</td>
<td>17</td>
<td>8 368</td>
<td>2.2</td>
<td>61.8 (12.7)</td>
<td>45.0</td>
</tr>
<tr>
<td>Nicardipine 2</td>
<td>17</td>
<td>9 517</td>
<td>1.8</td>
<td>62.9 (13.9)</td>
<td>48.4</td>
</tr>
<tr>
<td>Lisinopril 2</td>
<td>18</td>
<td>11 574</td>
<td>1.6</td>
<td>60.9 (14.3)</td>
<td>44.0</td>
</tr>
<tr>
<td>Ramipril 2</td>
<td>2</td>
<td>1 277</td>
<td>1.6</td>
<td>60.5 (12.4)</td>
<td>45.1</td>
</tr>
<tr>
<td>Amlodipine 2</td>
<td>12</td>
<td>12 085</td>
<td>1.0</td>
<td>61.8 (14.7)</td>
<td>46.9</td>
</tr>
</tbody>
</table>

*Betaxolol, doxazosin, iradipine not shown as number of patients with event was <2, or rate was <1.0 per 1000 patient-months of exposure.

Bertil Lindmark of Astra Draco makes five points about our study on the risk of non-fatal cardiac failure and ischemic heart disease with long acting β agonists. Firstly, he points out that all β agonists should be used with caution in patients with severe cardiovascular disease. The cardiac effects of β agonists are well described, but there is limited evidence available on whether or not the risks of adverse cardiac effects differ depending on the dose and method of administration of the drug.

Clearly, these are important questions for prescribing doctors faced with treating asthmatic patients with concomitant cardiac disease. An observational cohort study formed from health insurance databases from the Province of Saskatchewan, Canada found an increased relative risk of death from cardiovascular disease in users of β agonists taken orally or by nebuliser, but not in users of β agonists administered by metered dose inhaler. The deaths occurred in patients with significant cardiac disease, suggesting that β agonists taken orally or by nebuliser should be avoided in patients at high risk of cardiovascular events. We found that the oral β agonist bumbuterol, but not the inhaled β agonist salmeterol, was associated with an increased risk of non-fatal cardiac failure.

The results from both these studies are plausible as oral β agonists provide a greater systemic dose than that achieved with metered dose inhalers and tachycardia and prolonged Q-T interval have been reported principally with inhaled or oral β agonists. The advised total daily dose of oral bumbuterol


AUTHORS' REPLY Bertil Lindmark of Astra Draco

Martín et al suggest that caution should be exercised when prescribing long acting oral β agonists to patients at risk of cardiac failure, based on results from a prescription event monitoring (PEM) study.

Firstly, all β agonists (short and long acting, oral and inhaled) should be used with caution in patients with severe cardiovascular disease, as is pointed out in the package insert for all drugs of this class.

Secondly, the study does not provide any evidence on this issue. PEM studies are not designed to study causal relations but to generate new hypotheses. Although the authors have made an attempt to consider several potential biases in the analyses, the study design is inappropriate compared with, for example, a prospective randomised controlled trial, and the results must be interpreted with great caution.

Thirdly, no support for an association between bambuterol and an increased risk for cardiac failure has been found in our review of preclinical studies, clinical studies (including >3000 patients/healthy volunteers), or post-marketing surveillance (based on >130 million treatment days).

Fourthly, according to the authors there have been no spontaneous reports of cardiac failure with bambuterol to the Committee on Safety of Medicines. This is in agreement with the WHO database Intdis, with no reports of cardiac failure for bambuterol.

Finally, the paper suggests a doubled asthma mortality in patients receiving salmeterol. In our opinion the reported higher relative risk for non-fatal cardiac failure for bambuterol and the doubled asthma mortality for salmeterol both appear equally explicable by factors other than direct causality, such as confounding by concomitant diseases and disease severity.

Thus, PEM data may be of help in identifying signals with new drugs, but there is little if any merit in comparing drugs used in different populations and introduced to the market at different times.
(20 mg) is 200 times that of inhaled salmeterol (100 µg). 2

Secondly, Dr Lindmark reiterates our point that the results must be interpreted with caution because the study was observational, and more definitive evidence would come from a prospective randomised trial. Nevertheless, hypotheses about drug safety concerns are often generated from observational studies. 3 Such studies drive further research because they provide an “a priori” hypothesis and the formulation of a clinically relevant end point. Until results from prospective trials become available, observational research using cohort or case-control techniques remains an important source of evidence about the safety of drugs.

Thirdly, he states that a review by Astra Draco has found no evidence from pre-marketing or post-marketing studies of an association between bamberbol and cardiac vascular drugs. In general, pre-marketing studies have their own limitations, 3 as evidenced by the recent withdrawal on safety grounds of two newly launched drugs. 4 Similarly, different types of post-marketing surveillance studies, including PEM, have different advantages and disadvantages and, in general, one system cannot be relied upon to provide all the evidence needed. 5 This point also applies to the fourth comment. In particular, it should be noted that there is gross under-reporting of suspected adverse drug reactions to the Committee on Safety of Medicines 6 and other regulatory authorities, and there are many difficulties associated with interpreting data from spontaneous reporting schemes. 7

Finally, as is stated clearly in our paper, it is possible that the association may be explained by factors such as confounding by concomitant disease and disease severity. Interestingly, the rate of cardiac failure associated with bamberbol in the first month of treatment was higher than for 11 cardiovascular drugs previously studied by PEM (table 1). Only two cardiovascular drugs, including the inotropic sympathomimetic xamoterol (licensed for use in mild heart failure) had similar rates of cardiac failure. Since it is highly unlikely that the rate of cardiovascular disease in the bamberbol cohort was higher than in cohorts of patients taking cardiac drugs, and the bamberbol cohort was the youngest, these data provide further evidence that an association cannot be discounted. Our findings require confirmation, but we remain concerned about the size and biologically plausible of the association.

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Genetics and tuberculosis

Dr Richard Bellamy alludes to the important fact, frequently ignored by immunologists, geneticists and epidemiologists, that tuberculosis has several different clinical forms. 8 Physicians have emphasised the difference between primary tuberculosis, which is comparable to Lurie’s susceptible rabbits with disseminated disease, and post primary tuberculosis, best characterised by smear positive pulmonary tuberculosis and Lurie’s “resistant” rabbits. HLA associations with tuberculosis have indeed been inconsistent when all forms of tuberculosis are included. However, the HLA association with DR2, and particularly with its subtype DR15 in linkage disequilibrium with DQ5, was found only in patients with smear positive pulmonary tuberculosis. 9 HLA associations have been refined using DNA based HLA typing and have confirmed a link with the genes DRB1*1501 and DQBI*0502. 10 Antibody levels to epitopes of the 38kDa antigen of Mycobacterium tuberculosis restricted antigens were higher, suggesting an enhanced immune responsiveness in those with HLA-DR15. 11 The relative importance of the genes involved in susceptibility can be assessed by the gene frequency, but also by the attributable risk— that is, how much of the disease can be attributed to the presence or absence of a particular gene (34% with 95% confidence intervals of 16 to 43% were suggested for DR15 in one population). 12

The Lurie experiment suggests that a comparison between patients with different forms of tuberculosis, matched by ethnic origin, may be valuable in identifying candidate genes for susceptibility to tuberculosis. Since smear positive pulmonary tuberculosis is responsible for transmission of the disease, but also by the attributable risk— that is, how much of the disease can be attributed to the presence or absence of a particular gene (34% with 95% confidence intervals of 16 to 43% were suggested for DR15 in one population). 12

The relative importance of the genes involved in susceptibility can be assessed by the gene frequency, but also by the attributable risk— that is, how much of the disease can be attributed to the presence or absence of a particular gene (34% with 95% confidence intervals of 16 to 43% were suggested for DR15 in one population). 12

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Chlamydia pneumoniae and asthma

The paper by Cook et al 1 examines the possible association between Chlamydia pneumoniae infection and asthma. The authors conclude that their data do not support this association. However, we feel that the serological tests performed give important information on the prevalence of infection, but are not sufficiently complete to make definitive conclusions on the incidence of acute C pneumoniae infection in the populations under study. The major pitfall in the study, as pointed out by this authors, is the small proportion of patients from whom a convalescent serum sample was drawn. Moreover, the arbitrary exclusion of IgM positive patients for the diagnosis of acute C pneumoniae infection may have been misleading since the possibility of cross reactivity with rheumatoid factor could have been effectively ruled out by using IgG absorption prior to IgM micromotunfluorescence detection. 2

Analysis of table 1 indicates that the acute asthma and control populations appear to be significantly different in terms of age and sex distribution, the control population being significantly older and with a higher predominance. Both these factors are associated with increased C pneumoniae incidence and prevalence. The authors report using a logistic regression modelling method in which the age value is implemented as “>16 years”, which is roughly equivalent to the difference in mean age between the acute asthma and control populations.

This study is certainly noteworthy in that it underlines an association between C pneumoniae infection and severe chronic asthma, particularly “brittle” asthma, which will require further investigation in the future.

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Chlamydia pneumoniae and asthma

I read with interest the recent report by Cook et al 1 in which they report that, compared with hospital controls, outpatient with chronic asthma were statistically significantly more C pneumoniae antibody titres (IgG 64–256 and/or IgA ≥8) indicating previous infection, whereas unselected patients admitted to hospital for acute asthma attacks had titres similar to controls. They also found that serological evidence of acute (re)infection (presence of IgM, a fourfold change in titre, and/or IgG titre ≥1:512) was equal among groups.

These data are in accord with previous evidence suggesting an important role for chronic C pneumoniae infection as a promoter of asthma symptoms but a lesser role for acute infection as a cause for asthma exacerbations. 3 An additional recent report of positive therapeutic responses to antibiotics

in severe steroid dependent asthmatic patients (aged 13–65) further supports the possibility that antibody titres indicative of “previous infection” may also indicate persistant chronic infection.  

Acute primary (presence of IgM) or secondary (fourfold change in titre without IgM) C pneumoniae infection has been reported to initiate asthma in previously non-asthmatic individuals. Since the incidence of asthma in adults is very small (around one per 1000 per year) it is likely that most of the acute exacerbations occurred in patients who had previous wheezing episodes. It would be interesting to know whether Cook et al can retrospectively identify any patients who had their very first wheezing episode; this might be easier in general practice than in a hospital based study. 

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4 Hahn D. Incident wheezing and prevalent asthma have different serologic patterns of “acute” Chlamydia pneumoniae antibodies in adults. Proceedings of the Third Meeting of the European Society for Chlamydia Research, Vienna, Austria (Bologna: Societa Editrice Esculapi, 1996: 236).

Non-Hodgkin’s lymphoma with CFA

We read with interest the case report by Orchard et al on non-Hodgkin’s lymphoma arising in cryptogenic fibrosing alveolitis (CFA). Although the authors state that this has not been described previously, we recently reported six cases of pulmonary B cell non-Hodgkin’s lymphomas arising in patients with autoimmune disorders, three of whom had CFA. As in the case described by Orchard et al, prognosis in these three patients was much poorer than that in the patients with high grade pulmonary non-Hodgkin’s lymphomas unassociated with CFA, presumably due to the combined effects of the two diseases.

ANDREW NICHOLSON  
BRYAN CORRIN  
Department of Histopathology,  
Royal Brompton Hospital,  
Sydney Street,  
London SW3 6NR, UK


AUTHOR’S REPLY We are grateful to Dr Nicholson and Professor Corrin for pointing out their very interesting report, which was published after the original writing of our case report.

In the patient we reported the association was with cryptogenic fibrosing alveolitis (CFA) alone whereas, interestingly, the three patients they report had CFA associated with other systemic autoimmune disorders. The fact that CFA alone may be associated with B cell lymphomas, and the poorer prognosis seen by Nicholson and Corrin in their patients, as well as ours, supports the hypothesis that chronic local stimulation of the lymphoid system may play an important part in the aetiology and prognosis of these tumours.

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Letters, Book reviews, Notices, Correction

BOOK REVIEWS


A large amount of information has been packed into the 184 pages of this new guidebook in the Principles and Practice Series. This is a comprehensive review of the principles of ventilation and gas exchange with special emphasis on the implication of pulmonary function measurement during anaesthesia. The book details physiological principles and gives practical measurement guidance, with common sources of error, in the normal circumstances and during anaesthesia. The content is concise, the style direct and occasionally hard going. The text is clear and the diagrams are worth a special mention for their clarity and simplicity. This is not a textbook for beginners and requires a moderate familiarity with the principles of respiratory physiology, and the rules which govern respiratory mechanics and gas measurement. This guide represents excellent value for money and would be equally at home in the pulmonary function laboratory as well as the anaesthetics department. —SR


This is the third edition of an established book. Aiming to bring together all the recent information on basic mechanisms of asthma and also on clinical aspects and therapy to an in depth, this is achieved successfully. The scope of the book provides accessible reviews of all facets of asthma, from epidemiology and physiology to allergen avoidance, including recent developments in these fields. Modifications to the popular second edition include separate chapters on mediator antagonists and immunomodulators with consideration of the potential therapeutic benefits of intervening in the complex inflammatory and pharmacological pathways systematically covered in previous chapters. A new chapter on the pharmacoeconomics of asthma treatments provides a pertinent reminder that, after the wonders of basic science and the development of beneficial interventions, a wider perspective is required to successfully deliver benefits to those who require them. The addition of colour plates provides a welcome contrast to the previous black and white prints of the old edition which look a little drab in retrospect.

Well written by authorities in their fields and uniformly edited with an attractive presentation, this is an excellent book which succeeds in linking the rapidly developing body of knowledge on asthma with current treatment, while keeping the future constantly in mind.—AF

CORRECTION

Clinical features of non-smokers with α-antitrypsin deficiency

The authors of the paper entitled “Clinical features and prognosis of life time non-smokers with severe α-antitrypsin deficiency” by N Seersholm and A Kok-Jensen, which appeared on pages 265–8 of the April issue of Thorax, regret that some errors occurred in the text and in table 3. On page 267 the first line of column 1 should have read: “<0.001” instead of “<0.005” as published. On page 268 column 3 should read: “<0.001” instead of “<0.005” as published. On page 269 the first line of column 1 should read: “<0.001” instead of “<0.005” as published.

Table 3 Mean (SD) FEV1 % predicted and FEV1/FVC of index and non-index cases stratified by age at entry

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<tr>
<th>Age at entry</th>
<th>Index cases</th>
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<tr>
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<td>n = 27</td>
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<tr>
<td>FEV1 (% predicted) Sd</td>
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<td>N (%) with FEV1 pred &lt;70% Sd</td>
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<td>100 (19)</td>
</tr>
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<td>FEV1/FVC Sd</td>
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<td>0.80 (0.12)</td>
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<tr>
<td>N (%) with FEV1 pred &lt;70% Sd</td>
<td>4 (50%)</td>
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</tr>
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