Pulmonary embolism

We must express serious concerns about the internal validity and conclusions of the recent paper by Egermayer et al. in which the authors suggest that normal results of D-dimer, arterial blood gas tensions, and respiratory rate measurements can be used to rule out pulmonary embolism. With respect to blood gases, two earlier well designed studies reported that the PaO2 and PCO2 alone, or in combination, did not exclude pulmonary embolism.1 If a low PCO2 is taken as a reasonable surrogate for tachypnoea, these studies directly contradict Egermayer's findings. We attribute this discrepancy to a serious flaw in study design.

In any valid evaluation of the accuracy of a diagnostic test, comparison must be made with an appropriate reference standard.2 Being able to conclude that any test can exclude pulmonary embolism, as the authors have done, mandates that the selected reference standard accurately and objectively rules out pulmonary embolism in all patients who truly do not have it and confirms the diagnosis of pulmonary embolism in all those who truly do. What was the reference standard? The authors apply strict criteria for establishing an objective diagnosis of pulmonary embolism but make no attempt to rule it out with any degree of objectivity. It is clear that their composite reference standard does not divide patients into those with and without pulmonary embolism, but into those who meet the authors' criteria for "objective pulmonary embolism" and everyone else. In only 28 of the 507 patients with suspected pulmonary embolism (154 with normal lung scans, 36 with high probability scans, and 24 with pulmonary angiograms) was a diagnosis made; in the remaining 58% of cases pulmonary embolism was neither proven nor excluded. Furthermore, among the 27 patients who died within 10 days of evaluation, only five had a necropsy examination. The causes of death and, specifically, the possibility of fatal pulmonary embolism in the remaining 22 is unknown.

Among the 317 patients with non-diagnostic scans there were 135 indeterminate scan results and 182 low probability scans. In the PIOPED study3 pulmonary embolism was present in 29% and 12% of such patients, respectively. If we assume that the percentages here are similar, 61 of these patients would be expected to have pulmonary embolism. Yet from the results and conclusions published it is apparent that this entire group was designated as having had pulmonary embolism excluded4

The results as presented are highly misleading and cannot justify the conclusions. It is impossible to determine whether a test excludes pulmonary embolism when the reference standard to which it is being compared does not itself exclude pulmonary embolism. Unfortunately, by neglecting this fundamental aspect of study design the authors have invalidated their findings. All that has been shown is that patients with normal D-dimer levels, blood gas tensions, or respiratory rates are unlikely to have the combination of a high probability lung scan together with a high clinical suspicion of pulmonary embolism. Patients with "negative" test results still have a significant probability of pulmonary embolism and it is a dangerous mistake to think otherwise.

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AUTHORS' REPLY

Thank you for the opportunity to respond to the concerns raised by Stanbrook and Geerts regarding our recent study.2 Two retrospective studies cited to justify the conclusion that a PaO2 of >80 mm Hg (10.6 kPa) does not exclude pulmonary embolism. Neither was "well designed" in the sense of answering the questions we were addressing, since neither gave any information concerning the proportion of patients referred for pulmonary angiography who actually had their blood gas tensions measured. In our institution this figure would be approximately 50% (excluding those who were enrolled in our prospective trial). We did not conclude that normocapnia excludes pulmonary embolism since in our study four of 34 patients (12%) with objectively diagnosed pulmonary embolism had a PaO2 of >80 mm Hg. Allowing for the different methodology, this is similar to the findings of Blunt and colleagues.1 It would indeed be surprising if subsegmental pulmonary embolisms caused significant hypoxaemia. What we do conclude from our study and from previous studies is that the finding of normocapnia significantly reduces the likelihood of clinically important pulmonary embolism.

Contrary to what is stated, hypocarbia is not a reasonable surrogate for tachypnoea since in our study of 34 patients with a respiratory rate of ≥20 breaths/min had an arterial PCO2 of >35 mm Hg (authors' unpublished data). Stanbrook and Geerts may be confusing tachypnoea with hyperventilation, which in itself is a high minute volume. We have not drawn any conclusions about the usefulness of normocapnia or of the arterial–alveolar gradient for excluding pulmonary embolism. As far as we are aware, our study is the first to investigate prospectively the hypothesis that a normal respiratory rate excludes pulmonary embolism. We have found that this simple but useful observation is also often overlooked by doctors who wrongly assume that normal pulmonary angiography or a lung scan will provide a definitive diagnosis in all cases.4 It is suggested that a reference standard with 100% sensitivity and specificity is required to evaluate diagnostic tests properly. Such a standard does not exist in the area of venous thromboembolism. A reference standard in pulmonary angiography for pulmonary embolism falls far short of this standard due to technical limitations and interobserver disagreement in nearly 40% of cases involving smaller emboli.5

When we were interested in assessing the usefulness of various observations for predicting the absence of "objectively diagnosed" pulmonary embolism (according to our predetermining criteria),4 the most appropriate calculation for this purpose is the proportion of correct exclusions—that is, the predictive value—which is defined as true positives/true positives + false positives. This calculation does not require the accurate identification of true negatives. We were already aware from previous studies that the D-dimer test was likely to have a very poor specificity for diagnosing pulmonary embolism and did not consider it worthwhile to demonstrate this further.

Drs Stanbrook and Geerts are concerned about the possibility of unrecongnised pulmonary embolism among the 22 patients who died and did not have a necropsy examination. However, it would be unrealistic to assume that more aggressive investigations would detect most cases of major pulmonary embolism since these are often asymptomatic. Nevertheless, subsequent analysis of outcomes over two year's untreated patients with pulmonary embolism showed an excellent prognosis even without treatment.7 They overlook the more obvious problem of false positive diagnoses of pulmonary embolism in two of the five patients who did have a necropsy. Anticoagulant treatment was the direct cause of death in one of these. A previous study conducted at a different New Zealand hospital reported a similar false positive rate in their diagnosis of pulmonary embolism of nearly 50% among patients who underwent a necropsy examination following a perfusion lung scan.8 In addition, the finding of objectively diagnosed pulmonary embolism in our study, there were a further 68 patients who received a diagnosis of pulmonary embolism without adequate supporting evidence for example, in many cases, despite evidence to the contrary such as a normal lung scan or normal pulmonary angiogram. Of this group of 68 patients 19 (28%) had a negative D-dimer test, the result of which was not known to the physicians responsible for the care of the patient. It is possible that greater utilisation of tests which help to exclude pulmonary embolism could reduce the dangers of misdiagnosis and inappropriate treatment. Evaluating venous thromboembolism is a concept that many clinicians find difficult. The impulse is to continue searching until some evidence of thrombosis is found to justify the use of anticoagulant therapy. It is, of course, impossible to prove that a patient does not have venous thromboembolism. The best that can be aimed for is to reach a point where it is considered no longer profitable to continue the search. There is really only one possible methodology to achieve this pur-
pose: one must first carefully define what one is looking for and then prospectively search a large series of cases to see whether the entity exists. We identified 93 consecutive patients with a negative SimpliRED test and PaO2 of >80 mm Hg and did not find any with objectively diagnosed pulmonary embolism. We concluded that this combination of findings excluded objectively diagnosed pulmonary embolism with a very high level of confidence.

Whether or not it is “dangerous” to withhold anticoagulant therapy in patients with negative test results remains to be determined. Further prospective studies with a large series of cases are needed to see whether the entity exists. We identified 93 consecutive patients with non-productive cough with negative test results remains to be determined. Further prospective studies with a large series of cases are needed to see whether the entity exists. We identified 93 consecutive patients

Chronic cough

McGarvey et al have described the causes of cough and the predictive values of appropriate diagnostic tests in a group of patients presenting to a specialist clinic. They have used a histamine challenge test to support the diagnosis of asthma and to justify a trial of inhaled corticosteroid therapy. We agree with the authors’ conclusion that a negative histamine challenge effectively rules out asthma as the cause of chronic cough, but disagree that this obviates the need for a trial of inhaled corticosteroids. Eosinophilic bronchitis presents with a chronic cough and sputum eosinophilia, but without the variable airflow obstruction or airway hyperresponsiveness seen in asthma. In common with asthma and chronic nonproductive cough, we suggest that our group of patients had a methacholine provocation concentration causing a 20% fall in FEV1 (PC20) of >8 mg/ml, and a sputum eosinophilia (>3% non-squamous cells) in 12 (13.2%). All improved after treatment with inhaled budesonide 400 µg twice daily and in eight who had a follow up sputum analysis the eosinophil count decreased significantly from 16.8% to 1.6%.

The important practical implication of our findings is that a significant proportion of patients with corticosteroid responsive cough have normal airway responsiveness and no other features of asthma. We suggest that a trial of inhaled corticosteroid therapy, preferably after an assessment of airway inflammation, should be part of the diagnostic algorithm of chronic cough, whether there is hyperresponsiveness or not.

AUTHORS’ REPLY We welcome the comments of Drs Brightling and Pavord. The assessment of airway inflammation using induced sputum is not currently a routine part of our diagnostic algorithm. The data presented by Pavord et al suggest that our group of patients should have included approximately six patients with eosinophilic bronchitis. Since all our patients with a negative histamine challenge responded to treatment either for postnasal drip syndrome (PNDs) or gastrooesophageal reflux (GOR), or failed to respond to any treatment including inhaled steroids, (idiopathic coughers), we feel it unlikely that patients with steroid responsive cough were missed.

We do, however, recognise the concept of airway inflammation in non-asthmatic coughers and currently have an article in press in which we report that eosinophil numbers are significantly increased in bronchoalveolar lavage fluid from patients with GOR compared with controls. This was not the case for patients with PNDS or idiopathic cough. All the patients with GOR had resolution of cough with acid suppression therapy. Although bronchoalveolar lavage fluid findings may not be directly comparable to induced sputum findings, we suggest that not all patients with a chronic cough and a predominant eosinophil component to their airway inflammation require a trial of inhaled steroids.

We agree that assessment of airway inflammation should be considered when evaluating patients with chronic cough and induced sputum may prove to be the best technique. However, it does require certain expertise which may not be readily available in all units encountering patients with chronic cough.

Furthermore, airway inflammation is a dynamic process and sampling at one time point only may not reflect relevant airway events. In addition, there may be difficulties in interpreting the cellular profile in induced sputum as evidenced by analysis of samples obtained from mild asthmatics during exacerbations.


We read with great interest the article by McGarvey et al concerning the evaluation of patients with non-productive cough. Nowadays “chronic cough” is a well established, uniformly defined entity both in the English and German literature. Its relation to gastrooesophageal reflux disease (GERD) is generally acknowledged. The reader may be interested in a very early description of this entity by Thomas Mann in his novel “Buddenbrook” published in 1901 (Nobel Prize 1929), Volume 1, Part 6, chapter X, translated by H T Love-Porther in 1996 (Minerva paperback edition, Mandarin Paperbacks, London): “Never”, she (Tony Buddenbrook) said. And she gave a long audible outward breath and cleared her throat, also at length and deliberately. It was like a rattle, and I had of late become almost a habit with her, and had probably to do with her digestive trouble (in German “Magenleiden” i.e. gastric suffering).

By his persistent interest in medical issues, particularly tuberculosis, and his famous expertise in observing individuals, the novelist may have become the first to describe “chronic cough” due to GERD.
the past three years and one of us (AHT) has used it successfully in 28 consecutive patients.

A decision was taken at the BPRS to instigate a national study to compare the effectiveness of intrapleural urokinase with thoracic empyema.


Duchenne muscular dystrophy

In their recently published paper Simonds et al importantly emphasised the desirability of using non-invasive intermittent positive pressure ventilation (IPPV) rather than tracheostomy for optimising quality of life in patients with hypercapnic Duchenne muscular dystrophy, and suggested that the use of nocturnal nasal IPPV can help to prolong survival. They also noted that five of the 23 patients treated in this manner died from respiratory failure two years after beginning nocturnal nasal IPPV, and that most subsequent "admissions were for treatment of chest infections". In reality, nocturnal nasal IPPV is only likely to prolong the lives of those patients who would otherwise develop hypercapnic coma as they get weaker and weaker. This is uncommon in Duchenne muscular dystrophy. In fact, 90% of episodes of respiratory failure and death in these patients occur during treatment of intercurrent chest colds and result from the inability to cough out secretions. During these episodes non-invasive IPPV often needs to be provided 24 hours a day for ventilation and for air stacking maximal breaths to assist coughing. Also, with the use of non-invasive expiratory aids such as the combination of manually assisted coughing and mechanical insufflation-exsufflation, episodes of respiratory failure and death due to respiratory failure can be virtually eliminated in patients with Duchenne muscular dystrophy. This paper, like others before it, misses the point that just providing nocturnal nasal IPPV is insufficient compared with supporting both the inspiratory and expiratory muscles (non-invasively) during intercurrent chest colds.

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AUTHORS‘ REPLY There is no question that support of the inspiratory and expiratory muscles is helpful in patients with Duchenne muscular dystrophy and this is stressed in the discussion in our paper. Contrary to Ishikawa and Bach’s series, over 50% of our patients presented with symptoms diarrhoal hypercapnic respiratory failure without evidence of an acute chest infection. The suggestion that nocturnal nasal intermittent positive pressure ventilation (NIPPV) “misses the point” or is “insignificant in this group is ludicrous, and a more balanced approach is required. All our patients with Duchenne muscular dystrophy are taught to carry out regular physiotherapy with assisted coughing while receiving NIPPV, as described in the methods section of the paper. NIPPV combined with physiotherapy is therefore used to support the inspiratory and expiratory muscles. There is no firm evidence as yet that any one method of assisting cough is superior. Of the five patients who died, two had elected to receive palliative care only and so were not avoidable deaths, as is implied.

Notwithstanding the above arguments, the Emerson cough insufflator-exsufflator is not currently available for purchase by hospitals in the UK/Europe as it does not have the CE mark (personal communication, J H Emerson Co). Alternatives therefore need to be explored. Although the methods described by Ishikawa and Bach clearly may be effective, it is notable that they do not give their one year survival data either in the publications cited or elsewhere.

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Medical students’ knowledge of tobacco

The review on educating medical students about tobacco by Robyn Richmond published in the January issue of Thorax was very timely and informative. However, the information that no medical school in Italy has a syllabus which specifically teaches about tobacco related issues is out of date. At the University of Siena medical school we currently offer a specific course on “Tobacco smoke: health effects and the role of health operators”. The course, now in its second edition, takes the form of a three day, 12 hour series of interactive sessions with participation by experts in epidemiology, pathogenesis, toxicology, psychology, and ethical aspects of tobacco smoke and smoking cessation. Students are also involved in the design, completion, and analysis of small smoking related projects such as a survey on tobacco smoking inside the hospital. The course is open to students from all of the six years of the medical school and it provides 15 educational credits (over a total of 1000 credits required for graduation).

The awareness of tobacco related health issues by the medical profession is increasing, and reviews such as those published recently in Thorax are very helpful in advancing this process.

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UK Lung Volume Reduction Trial

The BUPA Charitable Foundation has agreed to fund a national multicentre randomised controlled trial of lung volume reduction surgery in the UK. One hundred and twenty suitable patients with severe emphysema will be recruited over a period of 1–2 years and assigned to either surgery and pulmonary rehabilitation or to pulmonary rehabilitation alone. Further details may be obtained from Professor D Lomas or Mr F Wells at Papworth Hospital, Ms Deirdre Watson at Norfolk & Norwich Hospital, Mr W Fountain at Harefield Hospital, Mr J Dussek at Guy’s Hospital, Dr M Morgan or Mr D Waller at Glenfield Hospital, Mr W Walker at the Edinburgh Royal Infirmary, or Mr P Rajesh at the Birmingham Heartlands Hospital.

Medical students’ knowledge of tobacco

Pulmonary and critical care medicine

In the editorial entitled “Pulmonary and critical care medicine: a peculiarly American hybrid?” by Martin J Tobin which appeared on pp 286–7 of the April issue of Thorax the name Edward Hines Jr which was part of the address mistakenly appeared as an author. The publishers apologise for this error.