Stable pulmonary capillary haemangiomatosis without symptomatic pulmonary hypertension

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The authors thank Professor Rubin M Tuder (Department of Pathology-Surgical Pathology Laboratory, University of Colorado Health Sciences Center) and Professor Takesaburo Ogata (Center for Medical Sciences, Ibaraki Prefectural University of Health Sciences) for their pathological review of the case. This work was supported by funding from the Ministry of Education of Japan.


LETTERS TO THE EDITOR

Vibration during high frequency ventilation in neonates

Since there is no report quantifying vibration imposed upon neonates, we prospectively studied the vibration produced during high frequency ventilation (HFV) and compared it with that during conventional mechanical ventilation (CMV) of studied patients and weight matched controls (±250 g) receiving CMV or breathing spontaneously. A non-invasive accelerometer sensor (Analog Devices ADXL05, Norwood, MA, USA) was placed at the mid sternum or postauricular cranium to measure the linear vibration transmitted to the body and head, respectively (amplitude in time and frequency domains expressed in units of “g”).

From April to October 1998 we enrolled seven neonates treated with HFV (mean (SD) weight 2210 (1680) g, gestation 32 (7) weeks) and 14 weight matched controls (CMV group: n=7, 2100 (1730) g, 31 (8) weeks; spontaneous breathing group: n=7, 2230 (1520) g, 32 (7) weeks). The groups were not different with regard to body weight, length, and head circumference. Neonates received HFV at a frequency of 12 Hz, mean airway pressure of 14 (2) cm H2O, amplitude of 39 (10) cm H2O, and back up CMV at 6 breaths/min. Higher amplitudes of vibration were detected during HFV than during CMV (0.098 (0.026) vs 0.017 (0.006) g) at the chest and 0.011 (0.003) vs 0.007 (0.001) g at the cranium, p<0.005 in six HFV treated neonates. One HFV treated neonate did not tolerate the switch to CMV. The vibrations at the chest and postauricular cranium in seven HFV treated neonates were higher than those of weight matched controls (fig 1, p<0.001), whereas no significant difference was found between the control groups. A higher amplitude of vibration at the chest was found in neonates with an adverse outcome than in normal survivors (0.136 (0.014) vs 0.087 (0.024) g, respectively), while demographic data and the duration and amplitude of HFV were not different. Interestingly, the vibration at the chest exceeded the limit of whole body vibration in adults (0.05g at 12.5 Hz third octave band for 24 hours per ISO 2631).

The significance of our observations is not known. While cardiovascular instability is commonly observed in neonates during HFV and has been related to a high lung volume ventilation strategy, cardiovascular effects of vibration have been reported in animal1 and clinical studies.2 We speculate that the vibration during HFV may also contribute to the haemodynamic instability in neonates.

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Figure 1 Vibration in neonates during high frequency ventilation (HFV, n=7), conventional mechanical ventilation (CMV, n=7), and spontaneous breathing (SB, n=7). (A) Representative vibration signals at the mid sternum of a neonate during HFV (left) and CMV (right). The upper panel shows the recorded time signal while the bottom panel displays the same information transformed to the frequency domain to display the dominant frequencies present in the signal. (B) Vibration detected at the mid sternum (left panel) and postauricular cranium (right panel). *p = 0.001 v HFV (ANOVA).
Furthermore, the effect of vibration on the developing brain is uncertain. We do not know whether the vibration will compromise the cerebral haemodynamic stability resulting in adverse neurological outcomes, especially in premature neonates who transmit vibration more efficaciously because of less body mass and fat compared with term neonates. Moreover, the combined effects of vibratory stress and environmental noise may contribute to hearing loss.

Although no definitive vibration disease has been recognised in neonates, we have demonstrated the inadvertent exposure of neonates to excessive vibration. Research is required to examine the significance of HFV induced vibration and to reduce the vibration without compromising its effectiveness in critically ill neonates.

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National survey of detention and TB

In England and Wales the power to detain individuals with tuberculosis who pose a threat to public health lies principally in sections 37 and 38 of the Public Health Act 1984. Section 37 authorises a local authority officer to remove an individual to a suitable hospital and section 38 authorises the “detention for a prolonged period” to remove an individual to a suitable hospital and to detain him for the aforesaid purpose.

The reasons for the increase in numbers of detention orders being issued are unclear. Increases in the incidence of tuberculosis outbreaks in healthcare settings and the scourge of drug resistant and multidrug resistant strains have, over the past decade, perhaps concentrated the minds of clinicians and public health physicians on ensuring that patients comply with treatment, and this may be playing a part.

The increase in the number of detention orders issued has been significant. From 1994 to 1999, there was a significant increase in the issuance of detention orders (p<0.005). The reasons for the increase in numbers of detention orders being issued are unclear. Increases in the incidence of tuberculosis outbreaks in healthcare settings and the scourge of drug resistant and multidrug resistant strains have, over the past decade, perhaps concentrated the minds of clinicians and public health physicians on ensuring that patients comply with treatment, and this may be playing a part.

The number of detention orders being issued for individuals with tuberculosis since 1994 has increased significantly (p<0.005). By 1999 0.2% of individuals notified with tuberculosis were issued with detention orders. Analysis, taking into account of health authority response rates and notification rates for pulmonary tuberculosis, shows a significant increase in the issuance of detention orders since 1994 (b=1.8283, p=0.9; fig 1).

For the increase in numbers of detention orders being issued are unclear. Increases in the incidence of tuberculosis outbreaks in healthcare settings and the scourge of drug resistant and multidrug resistant strains have, over the past decade, perhaps concentrated the minds of clinicians and public health physicians on ensuring that patients comply with treatment, and this may be playing a part. Elsewhere, notably in New York but also in Europe, consideration of the legal and ethical aspects of contemporary control measures has resulted in legislative amendments to public health laws which have enabled public health authorities to detain, for prolonged periods, patients with tuberculosis who will not or cannot comply with treatment. In tuberculosis control allied to insufficient resources to facilitate patients’ adherence to treatment, particularly in London, may also be contributing to the use of more restrictive measures by the authorities. An alternative explanation may be that, because of drug resistance and associated HIV infection, the treatment of tuberculosis is becoming increasingly complex, demanding greater commitment from patients and clinicians. This survey suggests that this is a need to monitor formally, in an ongoing fashion, trends in the issuance of detention orders for individuals with tuberculosis.

I thank the consultants in communicable disease control in England and Wales for assisting with this research and the Communicable Disease Surveillance Centre for providing the data on pulmonary tuberculosis notifications.

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Churg-Strauss syndrome

We read the review of Churg-Strauss syndrome (CSS) by Conron and Beynon with interest. The studies they quote are all reported from tertiary or national referral centres with inevitable referral bias. We have published our experience of 23 patients with CSS—the only study from a district general hospital which may be more representative of the natural history of this systemic vasculitis in
the general population. The mean age of onset was 57 years, significantly older than the 40 years reported in patients from tertiary centres and quoted by Conron and Beynon. We found there was a slight male preponderance (65%), also shown in many previous studies. The commonest sites of extrarespiratory involvement were, in descending frequency, the nervous system, joints and muscles, kidneys, skin, heart, and gastrointestinal tract. Involvement of the gastrointestinal tract occurred in only 30% and abdominal pain was uncommon. Cardiac involvement occurred in 44% and was the cause of death in two. Renal involvement, although occurring in nearly half the patients, was usually mild and none had severe renal failure.

The mean age of onset of asthma was 50 years and, although not reported, the asthma was not unusually troublesome or severe when the systemic vasculitis developed. Indeed, very few patients were on oral steroids for their asthma at that time. Very rarely, patients present with CSS who do not have asthma. In our series there was one such patient who satisfied the original histological features of Churg and Strauss.

We found that the criteria developed by Lanham et al were the most useful, particularly an eosinophil count of >1.5 × 10⁹/L. While this is arbitrary, only one of our patients had a level below this and that was 1.4 × 10⁹/L.

Acute rib fracture pain in CF

Recent papers in Thorax have described the high prevalence of low bone mineral density (BMD) in individuals with cystic fibrosis [2]; these patients are at increased risk of fractures. 1 Rib fracture pain can often be difficult to treat, despite standard analgesia such as non-steroidal anti-inflammatory drugs and opiates. Rib pain can impair sputum clearance and lead to an exacerbation of CF pulmonary disease. There are reports that calcitonin can relieve bone pain for patients with osteolytic metastases3 and osteoporotic vertebral fractures. Recently, we have successfully used subcutaneous calcitonin for the treatment of rib fracture pain in two patients with CF.

A 25 year old woman fractured two ribs when she was crushed in the crowd at a rock concert and a 28 year old man fractured ribs following a bout of coughing. Both patients had CF related low BMD with DEXA Z scores at the lumbar spine of –2.5 and –3.6, respectively. They had been taking long term oral prednisolone at a dose of 10 mg per day. Both patients had continuous uncontrolled pain from their fracture sites despite regular oral analgesics. The female patient was taking paracetamol 1 g qds and morphine sulphate modified release 30 mg bd; the male patient was taking paracetamol 1 g qds and ibuprofen 600 mg tds. Both patients were given courses of antibiotics as the pain was leading to an exacerbation of their CF lung disease. Subcutaneous calcitonin (SCT) was given in a dose of 50 units once daily. The pain completely resolved within 48 hours in both cases, and the patients were able to mobilise, perform sputum clearance, the other analgesics were withdrawn, and the chest exacerbations resolved. The calcitonin injections were continued for a total of 7 days, then stopped without recurrence of any pain. Neither patient experienced any side effects from the calcitonin.

Although calcitonin is involved in the regulation of bone turnover, the mechanism of its analgesic action is unknown. It reduces bone resorption and bone pain and serum pain may also have central analgesic effects. Conversely, intravenous bisphosphonates, given to improve bone density, were associated with severe bone pain in individuals with CF. Pain control is essential in patients with CF and rib fractures if adequate sputum clearance is to be achieved and an acute deterioration in lung disease avoided. Calcitonin should be considered as an analgesic in this situation. SCT may help in maintaining bone resorption and bone blood flow, but may also reduce morbidity and mortality associated with rib fractures in this group of patients.

Endothelin in acute exacerbations of COPD

We read with interest the article by Roland et al on endothelin-1 (ET-1) levels in exacerbations of chronic obstructive pulmonary disease (COPD). The authors found increased sputum levels of ET-1 in patients with COPD during an exacerbation, which was reflected by a smaller rise in venous ET-1 levels.

We have recently performed a study to evaluate pulmonary and renal ET levels in nine consecutive COPD patients during an acute exacerbation. ET was detected by radioimmunoassay in venous and arterial blood as well as in a timed urine specimen. For each subject the ratio of systemic arterial/venous mixed venous ET-1 levels (ir-ETart/ir-ETven) was evaluated as an index of pulmonary clearance/production of the peptide. The ir-ETart/ir-ETven ratio was evaluated in patients with COPD examined both during an exacerbation and at recovery (0.75 (0.12) and 0.77 (0.13), respectively). Otherwise, the calculated ir-ETart/ir-ETven ratio in patients with COPD was significantly lower than that calculated in patients with acute pulmonary embolism, a condition in which pulmonary endothelial dysfunction is likely to occur. A significant difference was found with respect to a constant 24 hour ir-ET urinary excretion between COPD patients during an exacerbation and at recovery (142.1 (12.8) ng/24 hours and 89.0 (15.1) ng/24 hours, respectively). Furthermore, renal clearance of ET was higher in COPD patients during an exacerbation (29.2 (5.2) ml/min) than at recovery (17.5 (3.9) ml/min), suggesting an increase in renal ET production in patients with COPD during an exacerbation. These significant changes in ET-1 circulating levels.

We therefore think that increased ET-1 levels found in patients with COPD during an acute exacerbation could represent a true increase in local ET production, but with a firm relationship between venous and sputum ET-1 levels could not be established.

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CF and antistaphylococcal prophylaxis

Dr Robinson’s review of cystic fibrosis (CF) touches on the use of continuous antistaphylococcal antibiotic prophylaxis. Dr Robinson reiterates the oft repeated assertion that there is an association between the use of prophylactic antibiotics and the early acquisition of pulmonary infection with Pseudomonas aeruginosa in patients with CF. This association has entered CF folklore but is not supported by any published evidence. The paper cited by Robinson describes a pilot study of cephalexin which lasted 2 months. A subsequent multicentre randomised placebo-controlled trial of cephalexin, commenced in children under 2 years, has been undertaken and its methodology described. However, no results have so far appeared in the published literature.

We have recently published an updated systematic review of randomised controlled trials of prophylactic antibiotics in CF. This describes data from three studies involving 189 children. We found that fewer children...
who received prophylaxis from birth had one or more isolates of Staphylococcus aureus over a 3 year period. There was also evidence at 2 years that less time was spent in hospital in the prophylaxis group. The number of children receiving prophylaxis who had one or more isolates of P aeruginosa over a 3 year period was half that of the control group who had intermittent antibiotic treatment only. This was not, however, statistically significant (Peto odds ratio 0.54, 95% confidence interval 0.23 to 1.26).

The steering group of the North American cephalexin trial have indicated that its results will be published soon (Eliezer Nussbaum, personal communication). However, until there is published evidence from at least one properly designed randomised controlled trial, the proposal that prophylaxis encourages pulmonary infection with P aeruginosa remains entirely speculative.

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AUTHOR’S REPLY I thank Drs Smyth and Walters for their comments concerning the issue of whether antistaphylococcal prophylaxis leads to a higher risk of colonisation with Pseudomonas aeruginosa in patients with cystic fibrosis. I share their concern as to the lack of definitive data supporting this notion and, indeed, tried to illustrate this in my article by stating “There is some evidence that it may be associated . . .” I would suggest, however, that the authors’ evidence of a lack of association is equally thin—to quote a multicentre trial whose methodology was presented as an abstract some 9 years ago but whose results do not appear to have ever been published in a peer reviewed journal is certainly not basing one’s evidence on hard evidence based facts. I did not mention the review by Smyth and Walters’ in my own paper as I submitted my review some 18 months before theirs had been published; however, the authors did not include in their own letter discussion of the recent paper by Patijn et al using data from the German CF database which included 639 patients, all under 18 years of age and P aeruginosa negative prior to entry in the study. 48.2% of the patients received continuous antistaphylococcal treatment, 40.4% received intermittent antibiotic treatment, and 11.4% received no antibiotic treatment. While the rate at which patients acquired positive respiratory cultures for Pseudomonas aeruginosa was significantly lower in the group receiving continuous antistaphylococcal antibiotic treatment than in those receiving no such treatment, patients receiving continuous antistaphylococcal antibiotic treatment had a significantly higher rate of P aeruginosa acquisition than patients receiving only intermittent or no antibiotic treatment. This difference was especially apparent for children under the age of 6 years. The authors concluded that “continuous therapy with antistaphylococcal antibiotics directed against Staph aureus increases the risk of colonisation with P aeruginosa”.

This interesting study I believe again supports my original statement that “there is some evidence that it (continuous antistaphylococcal antibiotic therapy) may be associated with earlier acquisition of P aeruginosa”.

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NOTICES

The Dr H M (Bill) Foreman Memorial Fund

The Trustees of the above fund invite applications for grants relating to study in respiratory disease and allied fields. Limited funds are available for registered medical practitioners to assist in travelling to countries other than their own to study respiratory disease, and also for support for clinical research abroad.

The HMF Fund has been able to fund two medical student projects in the last 18 months, one on TB in Malaysia and one on TB in Ghana, and has awarded three travel grants to study the following aspects of respiratory disease: Dr Veronica White (London) to study TB in Bangladesh; Dr R T Jagoe (Newcastle upon Tyne) to study the ATP-ubiquitin-proteasome proteolytic system in Boston, USA; Dr J S Parmar (Cambridge) to study cell motility in Toronto; and a grant to Dr Anne Chang (Brisbane) to study the relationship between cough and asthma.

Intending applicants should write for further details to Dr Brian H Davies, Llandough Hospital, Penarth, Vale of Glamorgan CF64 2AA, UK.

Pharmacology of Asthma

A course on the “Pharmacology of Asthma” organised by Professor Peter Barnes will be held at the Imperial College School of Medicine at the National Heart & Lung Institute in collaboration with the Royal Brompton Hospital, Dovehouse Street, London SW3 6LY, UK on 26–29 November 2001. The course is suitable for physicians or scientists with an interest in the pharmacology and therapeutics of asthma. For further information please contact the Postgraduate Education Centre, Imperial College School of Medicine at the National Heart & Lung Institute, Dovehouse Street, London SW3 6LY. Telephone: 020 7351 8172. Fax: 020 7351 8246. Email: shortcourses.nlh@ic.ac.uk

Respiratory Medicine

A conference on Respiratory Medicine will be held at the Royal College of Physicians of Edinburgh on 26 October 2001. For further information contact Ms Eileen Strawn, Symposium Coordinator. Telephone 0131 225 7324. Fax 0131 220 4393. Email: e.strawn@rcpe.ac.uk. Website: www.rcpe.ac.uk.
Acute rib fracture pain in CF

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