5. **Ward C**, Walters EH, Zheng L, *et al*. Increased soluble CD14 in bronchoalveolar lavage fluid of stable lung transplant recipients. *Eur Respir J* 2002;**19**:472–8.

Repeated thrombolytic therapy after initial unsuccessful thrombolysis in massive pulmonary embolism

In patients with massive pulmonary embolism threatened by haemodynamic instability, thrombolytic treatment is recommended.¹ But when it fails, therapeutic options remain limited and are mainly guided by local expertise. In the current case, we report a potential treatment modality for this situation.

A 60-year-old male patient collapsed several times at home. He had a history of a curative left upper lobe lung resection 2 months previously because of a squamous cell lung carcinoma. On admission he suffered from severe dyspnoea. Physical examination showed an elevated central venous pressure and a systolic fixed splitting of the valve sounds. His systolic blood pressure was just below 80 mm Hg, with a pulse of 122 bpm. Thoracic CT angiography (angio-CT) confirmed suspected massive pulmonary embolism (fig 1A) with an increased right ventricular diameter/left ventricular diameter ratio (RV/LV ratio) of 1.76. Because of haemodynamic instability, he received thrombolysis with alteplase (10 mg bolus, 90 mg/2 h), which stabilised his systolic blood pressure at around 100 mm Hg, and then was commenced on nadroparin and coumarins.

Despite thrombolytic treatment, he still had severe orthostatic hypotension, and 5 days after the initial event he collapsed again. Repeat angio-CT showed the same configuration of pulmonary embolism (fig 1B), with an RV/LV ratio of 1.57. We thereafter started treatment with urokinase using an initial bolus infusion of 2000 IU/kg and continuous infusion at 2000 IU/kg/h for 48 h; in the meantime, nadroparin was continued. Within the first 24 h, the patient's clinical condition did not improve but at 48 h he had neither symptoms of orthostatic hypotension nor resting tachycardia. Angio-CT after 48 h of urokinase treatment showed no signs of residual central embolism (fig 1C) and a decrease in RV/LV ratio to 1.12, indirectly indicating a decrease in right ventricular overload. Four days later the patient was discharged.

To date, apart from a very small ($n = 8$) randomised trial, there is no solid scientific evidence for using thrombolytic agents in the treatment of patients with haemodynamic instability due to massive pulmonary embolism.² This worsens when treatment fails in this situation, which has been reported to occur in up to 8% of patients.³ When initial thrombolytic treatment fails,

surgical rescue embolectomy, interventional radiology or using a second thrombolytic drug remain treatment options.¹ Recently, a single centre registry showed that rescue embolectomy resulted in lower in-hospital mortality compared with treatment with a second thrombolytic drug.³ In this study, the second attempt to achieve thrombolysis was performed with either streptokinase or alteplase, depending on which drug had been given previously, but only for a 2 h period. Based on this evidence, the alternative treatment option in our case would have been surgical pulmonary embolectomy which, in skilled hands, has a 1 year survival

rate of 86%.^{3,4} However, because of the patient's recent thoracic surgery as well as the availability of an alternative treatment option, we decided not to perform surgery.

In our case, we choose to give urokinase for a prolonged period, considering the short half life of thrombolytic agents (alteplase 4–6 min, urokinase 4–20 min, streptokinase 18–23 min) as well as the fact that alteplase in a 2 h regimen might be too short to achieve lysis of an extensive clot. Although the effectiveness of prolonged alteplase (24–72 h) for venous thromboembolic disease has been reported, we choose a different agent because of its reported initial ineffectiveness in our patient.⁵ In addition, our preference for urokinase over alteplase was related to our previous experiences with this regimen and its known capacity to induce thrombolysis in longstanding clots.⁶

Prolonged thrombolytic treatment in patients with massive pulmonary embolism, who fail to respond to initial alteplase therapy, might be considered a good treatment alternative.

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Competing interests: None.

Thorax 2008;**63**:89. doi:10.1136/thx.2007.084616

REFERENCES

1. **Kucher N**, Goldhaber SZ. Management of massive pulmonary embolism. *Circulation* 2005;**112**:e28–32.
2. **Jerjes-Sanchez C**, Ramirez-Rivera A, de Lourdes Garcia M, *et al*. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. *J Thromb Thrombolysis* 1995;**2**:227–9.
3. **Meneveau N**, Seronde MF, Blonde MC, *et al*. Management of unsuccessful thrombolysis in acute massive pulmonary embolism. *Chest* 2006;**129**:1043–50.
4. **Leacche M**, Unic D, Goldhaber SZ, *et al*. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. *J Thorac Cardiovasc Surg* 2005;**129**:1018–23.
5. **Protack CD**, Bakken AM, Patel N, *et al*. Long-term outcomes of catheter directed thrombolysis for lower extremity deep venous thrombosis without prophylactic inferior vena cava filter placement. *J Vasc Surg* 2007;**45**:992–7.
6. **Pilloud J**, Rimensberger PC, Humbert J, *et al*. Successful local low-dose urokinase treatment of acquired thrombosis early after cardiothoracic surgery. *Pediatr Crit Care Med* 2002;**3**:355–7.

Figure 1 (A–C) Selected pictures from CT angiography (angio-CT) at the main pulmonary artery (PA) level. (A) On admission. (B) Five days after alteplase treatment. (C) Forty-eight hours after initiation of urokinase treatment. Note: the patient had a lobectomy of the left upper lobe (see text). AA, ascending aorta; DA, descending aorta; VC, superior caval vein. The white arrows indicate the actual pulmonary embolism at this section of the angio-CT.

Bronchial hyperresponsiveness (BHR) and physical activity

We read with interest the recent paper by Shaaban *et al*¹ who report a negative

relationship between bronchial hyperresponsiveness (BHR) and physical activity. Several hypotheses are invoked to explain this association, including a suggestion that physical activity reduces bronchial inflammation by altering airway physiology.

Their major hypothesis is that obesity reduces physical activity and that it is this reduction in physical activity which causes, in some mysterious way, the increase in BHR observed. Their proposed mechanism—that this lack of exercise is associated with a decrease in deep inspiration—is truly breathtaking.

We suggest a much more obvious explanation, which is supported by the published evidence. In our recent survey reported in *Thorax*² we demonstrated a highly significant association of body mass index with chronic cough. Other associations observed in this study infer that the cough of obesity is reflux in nature. If obesity leads to reflux-related respiratory symptoms, can this form of upper airway reflux cause BHR?

Unfortunately, Shaaban *et al*¹ do not provide us with any information concerning the incidence of classic reflux symptoms in their population. In a study of patients with dyspepsia and endoscopically proven gastroesophageal reflux by Bagnato *et al*,³ over one-third had significant BHR. These subjects had no personal/family history or symptoms suggestive of asthma.

However, about two-fifths of patients in the study by Shaaban *et al* had asthma-like symptoms, defined as wheeze and sedentary breathlessness. We suggest that these patients could still have reflux-related symptoms as one-third of patients with chronic reflux cough, as demonstrated by pH monitoring, complain of exertional wheeze and dyspnoea.⁴

With the rising levels of obesity in the population, the accurate recognition of the aetiology of the associated BHR is vital to avoid the spurious diagnosis of “late onset” asthma. Perhaps reflux asthma would be a better—but, as yet, unproven—term.

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Competing interests: None.

Thorax 2008;**63**:89–90. doi:10.1136/thx.2007.084350

REFERENCES

1. Shaaban R, Leynaert B, Soussan D, *et al*. Physical activity and bronchial hyperresponsiveness: ECRHS II. *Thorax* 2007;**62**:403–10.
2. Ford AC, Forman D, Moayyedi P, *et al*. Cough in the community: a cross sectional survey and the relationship to gastrointestinal symptoms. *Thorax* 2006;**61**:975–9.
3. Bagnato GF, Gulli S, Giacobbe O, *et al*. Bronchial hyperresponsiveness in subjects with gastroesophageal reflux. *Respiration* 2000;**67**:507–9.
4. Everett CF, Morice AH. Clinical history in gastroesophageal cough. *Respir Med* 2007;**101**:345–8.

Bronchial responsiveness and airway inflammation in trained subjects

We read with interest the paper by Shaaban and coworkers¹ on the protective effect of physical activity against bronchial hyper-reactivity (BHR) in the general population. The authors suggest that a beneficial effect of deep inspirations during exercise could account for the lower prevalence of BHR in physically active subjects compared with sedentary subjects, while the accompanying editorial² favours an “anti-inflammatory” effect of exercise as the most plausible explanation.

We have studied lung function and airway cell biology in non-asthmatic amateur athletes^{3,4} and found that both modulation of airway responsiveness and downregulation of airway inflammation occur with training. At rest, the response to single-dose methacholine inhalation in the absence of deep breaths was significantly lower in amateur runners than in age-matched sedentary controls.³ Shortly after a marathon race the response to methacholine was further blunted, suggesting a causal relationship between endurance exercise and low bronchial responsiveness,³ possibly mediated by ventilation at increased lung volumes.

We have previously reported large numbers of neutrophils in induced sputum of runners.⁴ However, this finding was not associated with evidence of neutrophil activation after intense exercise, since expression of adhesion molecules by airway neutrophils decreased and the elastase concentration in sputum supernatants was unchanged after a marathon race compared with baseline.⁴ Similarly, inflammatory cell infiltration in the airways was not associated with activation of the NFκB pathway in endurance-trained mice,⁵ while airway inflammation was found to decrease strikingly in ovalbumin-sensitised trained mice compared with sedentary mice.⁶ Exercise therefore appears as a model of tightly regulated airway inflammation, possibly secondary to exercise-induced mild bronchial epithelial damage.⁵ Along the same line, physically active smokers appear to be protected against lung function decline and the risk of developing chronic obstructive pulmonary disease compared with sedentary smokers,⁷ supporting a role for regular exercise in blunting airway inflammation.

We acknowledge that athletes, even at the amateur level, do not represent the general population. On the other hand, a publication bias may have favoured preferential reporting of exercise-associated BHR in athletes, especially those training under extreme environmental conditions (such as “ski asthma”) or exposed to irritants (such as swimmers). It is time to reconsider the beneficial effects of regular exercise as a strategy to preserve respiratory health.

Studies like that by Shaaban and coworkers will certainly help us to move in this direction.

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Competing interests: None.

Thorax 2008;**63**:90. doi:10.1136/thx.2007.084855

REFERENCES

1. Shaaban R, Leynaert B, Soussan D, *et al*. Physical activity and bronchial hyperresponsiveness: ECRHS II. *Thorax* 2007;**62**:403–10.
2. Mahler DA. Is physical activity anti-inflammatory on the airways? *Thorax* 2007;**62**:376.
3. Scichilone N, Morici G, Marchese R, *et al*. Reduced airway responsiveness in non-elite runners. *Med Sci Sports Exerc* 2005;**37**:2019–25.
4. Bonsignore MR, Morici G, Riccobono L, *et al*. Airway inflammation in nonasthmatic amateur runners. *Am J Physiol* 2001;**281**:L668–76.
5. Chimenti L, Morici G, Paternò A, *et al*. Endurance training under standard laboratory conditions damages small airway epithelium in mice. *Am J Respir Crit Care Med* 2007;**175**:442–9.
6. Pastva A, Estell K, Schoeb TR, *et al*. Aerobic exercise attenuates airway inflammatory responses in a mouse model of atopic asthma. *J Immunol* 2004;**172**:4520–6.
7. Garcia-Aymerich J, Lange P, Benet M, *et al*. Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: a population-based cohort study. *Am J Respir Crit Care Med* 2007;**175**:458–63.

Propionibacterium acnes in granulomas of a patient with necrotising sarcoid granulomatosis

Necrotising sarcoid granulomatosis (NSG) was first described by Liebow¹ in 1973. It is defined by three pathological features: the presence of a conglomerate mass of sarcoid-like granulomas; varying degrees of necrosis within the confluent granulomas; and vasculitis with granulomas and giant cells involving the walls of muscular arteries and veins. The relationship between NSG and classic sarcoidosis is controversial. In NSG hilar lymphadenopathy is not seen as frequently as in sarcoidosis, extrapulmonary involvement is rare and serum levels of angiotensin-converting enzyme (ACE) are not necessarily raised.²

The cause of sarcoidosis is unknown, but it has been hypothesised that it results from exposure of a genetically susceptible individual to specific environmental agents. Abe *et al*³ isolated *Propionibacterium acnes* (*P acnes*) in culture from sarcoidosis biopsy specimens, and recently the *P acnes* genome has been detected in sarcoid lymph nodes by