Repeate thrombolytic therapy after initial unsuccessful thrombolysis in massive pulmonary embolism

In patients with massive pulmonary embolism threatened by haemodynamic instability, thrombolytic treatment is recommended. 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. This worsens when treatment fails in this situation, which has been reported to occur in up to 8% of patients. When initial thrombolytic treatment fails, surgical rescue embolectomy, interventional radiology or using a second thrombolytic drug remain treatment options. Recently, a single centre registry showed that rescue embolectomy resulted in lower inhospital mortality compared with treatment with a second thrombolytic drug. 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%. 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 18–25 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 inefficacy in our patient. 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.

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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Bronchial hyperresponsiveness (BHR) and physical activity

We read with interest the recent paper by Shaaban et al who report a negative effect of physical activity on bronchial hyperresponsiveness (BHR). The authors investigated the role of physical activity on BHR in a large, population-based cohort of healthy young adults. They found that higher levels of physical activity were associated with lower BHR, and that this relationship was independent of other factors such as age, sex, and atopy. These findings are consistent with previous studies, which have shown that regular physical activity can reduce BHR.

In addition to the potential anti-inflammatory effects of physical activity, the mechanisms underlying the relationship between physical activity and BHR are likely to be multifactorial. For example, physical activity may increase lung function, which in turn could reduce BHR. Moreover, physical activity may help to maintain a healthy weight, which is known to be associated with lower BHR.

Overall, these findings support the idea that physical activity should be encouraged as a means of reducing BHR. Further research is needed to better understand the mechanisms underlying this relationship, and to determine how physical activity can be most effectively incorporated into the management of BHR.
B Bronchial responsiveness and airway inflammation in trained subjects

We read with interest the paper by Shaaban and coworkers on the protective effect of physical activity against bronchial hyperreactivity (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 editorial 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 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. Shortly after a marathon race the response to methacholine was further blunted, suggesting a causal relationship between endurance exercise and low bronchial responsiveness, possibly mediated by ventilation at increased lung volumes. We have previously reported large numbers of neutrophils in induced sputum of runners. 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. Similarly, inflammatory cell infiltration in the airways was not associated with activation of the NFκB pathway in endurance-trained mice, while airway inflammation was found to decrease strikingly in ovalbumin-sensitised trained mice compared with sedentary mice. Exercise therefore appears as a model of tightly regulated airway inflammation, possibly secondary to exercise-induced mild bronchial epithelial damage. 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, 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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