LETTERS

Serum LDH and exercise capacity in COPD

Lactate dehydrogenase (LDH) is the enzyme that catalyses the final step in the glycolytic metabolism, regenerating NAD^+ from reduced NADH, by conversion of pyruvate to lactate.¹ Recently, increased muscle LDH activity has been found in elderly male patients with chronic obstructive pulmonary disease (COPD) who were susceptible to contractile fatigue of the quadriceps femoris muscle following constant work rate cycle exercise performed at 80% of the predetermined peak work rate.² Moreover, increased resting serum LDH activity has been found in patients with COPD compared with healthy smoking and non-smoking peers.³ To date, it remains unknown whether and to what extent increased resting serum LDH activity may be linked to a reduced functional exercise capacity and to self-reported daily symptoms of dyspnoea in patients with COPD.

Therefore, pulmonary function, functional exercise capacity (6 min walking distance, $2\times$), overnight fasting fat free mass (bioelectrical impedance assessment), the original Medical Research Council (MRC) dyspnoea grade and serum LDH activity were assessed in 178 elderly male patients with COPD who were referred for pulmonary rehabilitation to the Centre for Integrated Rehabilitation for Organ failure (CIRO) in Horn, The Netherlands (additional details on the methodology used can be found in the online repository facility).

On average, patients had moderate to severe COPD, impaired carbon monoxide transfer factor, normal body mass index and normal fat free mass index (table 1). In addition, most patients reported that they had to stop because of breathlessness after walking 100 m or after a few minutes of walking on the level.

Thirty patients (16.9%) had increased serum LDH activity (defined as >480 U/l). No significant differences were found in age, pulmonary function or body composition after stratification of the patients by normal or increased serum LDH activity. In contrast, patients with normal serum LDH activity had a significantly lower MRC dyspnoea grade and a higher functional exercise capacity than patients with increased serum LDH activity. This was also true after correction for height, age and body weight (table 1).

Approximately one-sixth of male patients with COPD who were referred for pulmonary rehabilitation had increased serum LDH activity. Although only a weak inverse relationship was found between functional exercise capacity and serum LDH activity ($r = -0.29$, $p = 0.0001$), we believe that the present findings can still be of clinical interest. Firstly, the statistically significant differences in the 6 min walking distance between patients with normal and increased serum LDH activity clearly exceeded the minimal clinically important difference of 54 m. Secondly, patients with increased serum LDH activity experienced a significantly higher sensation of dyspnoea during daily life, while no significant differences were found in age, lung function impairment or body composition. This may imply that increased serum LDH activity may be a reflection of qualitative and/or quantitative changes in the skeletal muscles of patients with COPD. Indeed, increased serum LDH activity may, at least in part, be a direct consequence of changes in the mitochondrial respiratory function and/or skeletal muscle fibre-type shifts in COPD.^{4,5}

In conclusion, the present findings are hypothesis generating rather than definitive. In fact, future studies should take into account the fact that LDH is expressed as five isoenzymes, which were not assessed in the present study. Nevertheless, physical inactivity has been shown to shift fibre

LDH isoenzymes from an oxidative to an anaerobic profile.⁶

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Adalimumab-induced bronchospasm: not a class effect

A 48-year-old man with rheumatoid arthritis (RA) was admitted with shortness of breath due to bronchospasm and hypoxaemia (PaO_2 5.9 kPa (44 mm Hg)). He had no history of pulmonary disease or allergy/atopy. About 3 years before this admission he was treated with infliximab. He was switched from infliximab to etanercept because of its more convenient subcutaneous form of administration. He was switched from etanercept to adalimumab because his RA persistently flared on the former treatment. Three days before admission he had received adalimumab for the second time. Blood count showed a new eosinophilia of $0.8 \times 10^9/\text{l}$ (normal range 0–0.4). He was treated with inhalation medication (salbutamol and ipratropium bromide) and prednisolone 50 mg/day. Pulmonary function tests were performed 3 days after admission and showed an obstructive pattern: forced expiratory

Table 1 Patient results

	Total group	Normal LDH	Increased LDH	p Value
No of male patients	178	148	30	–
Age (y)	66.0 (9.2)	65.7 (9.0)	67.7 (10.4)	0.2832
FEV ₁ (% predicted)	39.9 (14.2)	39.7 (13.6)	40.7 (17.5)	0.7350
Tlco (% predicted)	48.2 (18.3)	48.0 (18.6)	49.8 (17.2)	0.6719
MRC dyspnoea grade	3.8 (1.1)	3.7 (1.2)	4.4 (0.9)	0.0050
BMI (kg/m^2)	25.1 (4.6)	24.8 (4.6)	26.4 (4.8)	0.0867
FFMI (kg/m^2)	17.3 (2.2)	17.2 (2.1)	17.8 (2.3)	0.1589
6MWD (m)	404.3 (130.1)	417.8 (128.4)	333.8 (117.2)	0.0016
6MWD (% predicted)	60.3 (18.9)	61.9 (18.6)	52.1 (19.0)	0.0114
Borg score D (points)	4.5 (2.2)	4.4 (2.2)	5.1 (2.1)	0.1124
Borg score F (points)	3.8 (2.3)	3.9 (2.3)	3.6 (2.4)	0.6004
LDH (U/l)	404.1 (96.0)	372.8 (57.5)	559.4 (98.8)	0.0001

Values are mean (SD).

6MWD, 6 min walking distance; BMI, body mass index; D, dyspnoea; F, fatigue; FEV₁, forced expiratory volume in 1 s; FFMI, fat free mass index; LDH, lactate dehydrogenase; MRC, Medical Research Council; Tlco, carbon monoxide transfer factor; U/l, micromoles per minute/litre.

Figure 1 The patient was instructed to monitor his peak expiratory flow (PEF) twice a day. The first 2 days after the third adalimumab administration he had a stable PEF of approximately 450 l/min. On the third day he developed dyspnoea, wheezing and a reduction in his PEF to 290 l/min. His PEF went back to baseline after 2 weeks.

volume in 1 s (FEV₁) reduced to 1.7 litres (46.8% of predicted) and FEV₁/forced vital capacity (FVC) ratio 55.9%. Since his RA responded favourably on adalimumab and there was not enough evidence to ascribe his respiratory complaints to this drug, it was decided to rechallenge him with adalimumab. During the third administration of adalimumab he still used prednisolone 20 mg/day and inhaled budesonide/formoterol twice daily. On the third day following adalimumab administration he developed dyspnoea, wheezing and a reduction in his peak expiratory flow (PEF) from 450 to 290 l/min (fig 1). These symptoms were less severe than at admission, probably because of concomitant treatment with corticosteroids. The prednisolone was increased to 50 mg/day and his PEF went back to baseline after 2 weeks. He resumed treatment with infliximab. His RA remained controlled and he did not suffer from bronchospasm again.

Bennett *et al* reported a patient with presumed adalimumab-induced asthma.¹ They hypothesised that once the tumour necrosis factor (TNF) α blocking adalimumab was introduced the T helper cell (Th)1 response characteristic for RA was suppressed, allowing the Th2-activated pathway to express itself as asthma.¹ However, patients with asthma have upregulation of the TNF α axis so one would expect suppression of asthmatic inflammation.^{2,3} Since Bennett and colleagues assumed that the pathophysiological mechanism causing adalimumab was a direct effect of the TNF α blockade, they suggested a class effect and decided not to treat their patient with other TNF α blocking agents.¹ Our patient used etanercept, adalimumab and infliximab within a short time frame and only reacted to adalimumab. This case therefore refutes the hypothesis that the asthmatic response is caused by blockage of TNF α , as well as the existence of a class effect. Symptoms

started 3 days after drug administration which is not compatible with anaphylaxis. A delayed-type T-cell mediated hypersensitivity reaction would be more likely.

At present it is unclear how often adalimumab has induced asthma-like symptoms. Because the use of adalimumab is increasing, this adverse event may become more prevalent in the future. We are the first to report adalimumab-induced bronchospasm with a positive rechallenge on the agent itself and negative challenges on etanercept and infliximab. We believe it is justified to make a switch to a different TNF α blocker under strict medical observation.

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Renal impairment in cystic fibrosis

We read with interest the paper by Bertenshaw *et al*¹ on the incidence of acute renal failure (ARF) in patients with cystic fibrosis (CF) and would like to supplement these results with our findings. With increasing survival and therefore consideration for lung transplantation, monitoring adult patients with CF for renal impairment is assuming increasing importance (creatinine clearance <50 mg/ml/min is a contraindication to lung transplantation).²

We examined the prevalence of renal impairment in our stable adult CF population³ in Birmingham using the Cockcroft-Gault formula⁴ for estimating glomerular filtration rate (GFR). Between 1 January 2004 and 9 February 2005, 207 of our 273 adult patients with CF had at least one serum creatinine measurement; eight were excluded from analysis owing to established renal failure, one had subnormal creatinine precluding analysis and in six cases the data were incomplete, leaving 192 patients for analysis. Using the Cockcroft-Gault formula and the United Kingdom National Kidney

Foundation definition of renal impairment (GFR <90 ml/min), 50 of the 192 patients analysed had renal impairment; 26 of these had a current infective exacerbation of which 12 were receiving intravenous antibiotics. Thus, excluding those in a current exacerbation and those with established renal failure, 24/192 (12.5%) of our patients with stable CF had renal impairment. This is probably a conservative estimate as we know from a study in Liverpool in a *Pseudomonas*-colonised CF population that 24-hour urine collection diagnoses more renal impairment than the Cockcroft-Gault formula.⁵ Only one of the 50 patients identified as having renal impairment by the Cockcroft-Gault formula had a raised serum creatinine level, which is often the only test that first draws our attention to the problem.

Our findings support the need for regular renal assessment in adult patients with CF using measures superior to raised serum creatinine levels alone (eg, at least using the Cockcroft-Gault GFR formula for all routine annual reviews) to enable early diagnosis while we await “firmer inferences to be drawn regarding the causation of ARF in CF and allow avoidable precipitating factors to be identified”.

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Is bronchodilation required routinely before diagnostic sputum induction? Evidence from studies with tuberculosis

Sputum induction (SI) by inhalation of nebulised hypertonic saline is an efficient