Endurance exercise and the production of growth hormone and haematopoietic factors in patients with anaemia

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Background: Physical activity has been shown to stimulate haematopoiesis in patients with anaemia due to chronic renal failure or haematological malignancies.

Objective: To evaluate the effect of moderate exercise on the production of haematopoietically active factors.

Methods: Ten patients (four men and six women, mean (SD) age 51 (10) years) with a haemoglobin concentration under 130 g/l (men) or 120 g/l (women) carried out five three minute exercise bouts at an intensity of 80% of the maximal heart rate, corresponding to a lactate concentration of 3 (0.5) mmol/l. Patients rested for three minutes between bouts. The concentrations of interleukin 6, stem cell factor, granulocyte-monocyte colony stimulating factor, granulocyte colony stimulating factor, erythropoietin, and growth hormone (GH) were evaluated before and in the eight hours after exercise.

Results: GH had risen significantly 15 minutes after exercise (1.1 (1.3) v 2.7 (2.8) ng/ml; p<0.05). No change in the concentration of the other cytokines and growth factors was observed in the eight hours after exercise.

Conclusions: In patients with anaemia, submaximal exercise does not affect the concentration of haematopoietically active cytokines. However, it leads to an increased concentration of GH. This may be responsible for the improved haematopoiesis observed after an exercise programme in patients with chronic diseases.
RESULTS
The mean (SD) walking speed during the intensive workloads was 4.5 (0.5) km/h (range 3.5–5.5) and the mean walking distance 1.32 (0.4) km (range 780–2000 m). The mean heart rate was 135 (9) beats/min, corresponding to 77 (5)% of the maximum cardiac frequency; the mean lactate concentration was 2.4 (0.5) mmol/l. The intensity of effort on the Borg scale corresponded to a score of 13 (1).

As expected, baseline concentrations of erythropoietin showed a substantial correlation with the severity of anaemia (calculated as the difference between expected and actual haemoglobin concentration, \( r = 0.50 \)). Concentrations of erythropoietin (basal concentration 100 (49) pg/ml, GM-CSF (65 (63) pg/ml), G-CSF (65 (58) pg/ml), and stem cell factor (902 (55) pg/ml) showed no significant changes in the eight hours after physical exertion (p>0.05 for all values; table 2). However, the concentration of GH had increased 1.5-fold 15 minutes after exercise (1.1 (1.3) v 2.7 (2.8) ng/ml; p<0.05) and returned to the initial values after 60 minutes (table 2, fig 1). Seven patients had interleukin 6 concentrations below the detection limit (2 pg/ml) in all evaluations. Mean packed cell volume and haemoglobin and creatinine concentrations remained unchanged in the eight hours after the training session, suggesting no relevant change in plasma volume after exercise.

DISCUSSION
Haematopoiesis is a complex process, which is affected by the interaction of several hormones, cytokines, and growth factors. In this study we detected a significant increase in the concentration of GH after exercise in anaemic patients. Several in vivo and in vitro studies have shown that GH directly or indirectly (through the secondary mediator insulin-like growth factor) stimulates the myeloid and erythroid progenitor colonies and has a regulatory effect on haematopoiesis.10 11 Exhausting or prolonged exercise is known to increase the release of GH. However, recent studies suggest that there is a linear correlation between the intensity of exertion and the production of GH.12 Our results support this hypothesis and show that, in patients with chronic disease, even moderate intensity exertion may substantially increase the production of GH.

Studies evaluating the changes in the concentration of erythropoietin after physical activity have yielded contradictory results.3 11 4 Our findings do not support a substantial role for erythropoietin in the exercise related activation of haematopoiesis observed in patients with chronic disease. Furthermore, studies on the effects of exercise in patients with chronic renal failure suggest that other factors are involved, as the damage to kidney parenchyma results in impairment of erythropoietin production.

Some cytokines with haemopoietic activity are produced by lymphocytes after stimulation by primed macrophages. In our study, four patients had leucopenia (absolute white blood cell count of less than 1500/ml) caused by treatment or disease. Thus we did not evaluate the effect of exercise on interleukin 3, a cytokine with pleiotropic functions on haematopoiesis which is produced by T lymphocytes. Not much is known about the production of other haematological growth factors (G-CSF, GM-CSF, and macrophage colony stimulating factor) during leucopenia. These cytokines are produced by T cells but also by fibroblasts and endothelial cells. We cannot rule out the possibility that cytokines produced by T lymphocytes and monocytes play a role in the exercise related stimulation of haematopoiesis. However, we have previously reported that endurance exercise reduces the duration of aplasia in patients after high dose chemotherapy.7 As all patients who participated in that study had severe leucopenia (white blood cell count less than 1000/ml), an effect of the lymphocyte produced cytokines on the observed outcomes is unlikely.
The mechanism of exercise on haematopoiesis may also not be related to increased production or release of stimulating cytokines. In patients with chronic disease, anaemia can be a result of the long lasting inflammatory reaction. During inflammation, increased concentrations of tumour necrosis factor, interleukin 1, and other pro-inflammatory cytokines cause a defect in iron transport and metabolism thereby impairing the synthesis of haemoglobin. It has been shown that exercise may reduce the concentration of proinflammatory cytokines in patients with chronic heart failure. It remains to be seen whether this mechanism also reduces anaemia in patients with other chronic diseases.

We conclude the following. (a) The effects of an exercise programme on haematopoiesis in patients with chronic disease are probably not related to increased production of haematopoietically active cytokines and growth factors. (b) In patients with anaemia, submaximal short duration exercise results in a significant increase in GH, which may partially explain the effects of physical activity on haematopoiesis in patients with chronic disease.

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Accepted 29 March 2004

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