

histology resulted in total villous atrophy. Positivity for antiendomysium antibodies (EMA) and response to gluten-free diet enabled us to make a diagnosis of coeliac disease. We re-examined the report of a previous upper endoscopy (carried out for reflux-like symptoms) where the duodenal folds were described as normal. Unfortunately, we have not previous biopsy specimens of duodenum, because in this site biopsies were never been previously carried out. However, an arcival serum sample obtained before IFN and ribavirin treatment showed EMA positivity.

On March 1998, a 42-year-old man with a 6 years history of chronic active hepatitis, histologically confirmed, started on treatment with IFN- α (6 MU three times weekly) for 6 months. The patient had no previous history of gastrointestinal illnesses or iron-deficiency anaemia. After 5 months of treatment, diarrhoea, weight loss, fatigue, and iron-deficiency anaemia developed. The patient stopped the IFN treatment and underwent upper endoscopy that showed loss of duodenal folds. Distal duodenal histology revealed total villous atrophy. Positivity of EMA and healing of intestinal architecture after 8 months gluten withdrawal confirmed the diagnosis of coeliac disease. In this case, both previous biopsy samples of duodenal mucosa and serum sample were not available.

Autoimmune side-effects, such as hyperthyroidism, hypothyroidism, diabetes mellitus, interstitial pneumonitis, autoimmune thrombocytopenic purpura, rheumatoid arthritis, haemolytic anaemia, and systemic lupus erythematosus have been reported to develop during α -IFN therapy. In clinical practice IFN- α may at times provoke autoimmune diseases either by direct effects on tissues or by interaction with the immune system, altering the link between lymphocyte populations and the pattern of cytokines produced. IFN- α is important in inducing the differentiation of Th2 cells to Th1 cells and in enhancement of T-cell and natural killer cell cytotoxicity. Thus, increased level of Th1 cytokine pattern (eg, IL-2 and IFN- γ) and imbalance of cytotoxic/suppressor T-cell may induce immune activity in tissues. However, although the actual mechanisms responsible for the tissue damage in coeliac disease are as yet only partly characterised, evidence suggests that CD4 T cells are central in controlling an immune response to gluten that causes immunological diseases.⁴ Furthermore, gluten-induced activation of lamina propria Th1-like cells followed by secretion of IFN- γ is an important and genetically determined pathogenic mechanism in coeliac disease. This cytokine alone or together with other mediators may directly cause damage of enterocytes or indirectly stimulate their proliferation (crypt hyperplasia) and alter their maturation.

We propose that patients are screened for EMA testing before IFN treatment. In cases of EMA positivity, the need for therapy has to be balanced carefully against the risk to develop an overt coeliac disease or, alternatively, IFN treatment might be associated with a strict gluten-free diet.

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Yoga and chemoreflex response to hypoxia and hypercapnia

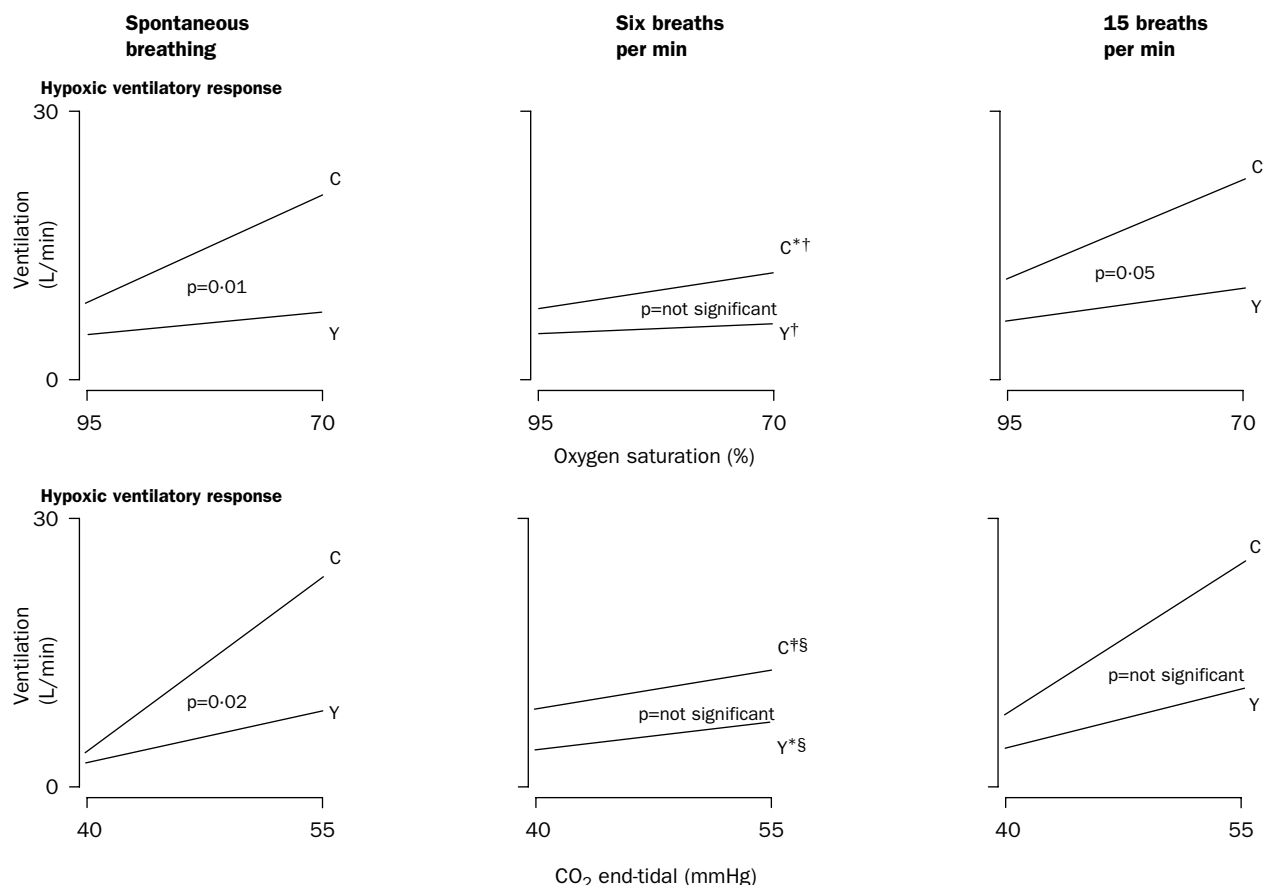
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We tested whether chemoreflex sensitivity could be affected by the practice of yoga, and whether this is specifically because of a slow breathing rate obtained during yoga or as a general consequence of yoga. We found that slow breathing rate per se substantially reduced chemoreflex sensitivity, but long-term yoga practice was responsible for a generalised reduction in chemoreflex.

Yoga trainees learn to breathe slowly (about six breaths per min) and deeply, mobilising in sequence the diaphragm and the lower and upper chest ("complete yoga breathing").¹ Training patients with chronic heart failure to slow their breathing frequency, through the practice of complete yoga breathing, reduces dyspnoea and improves exercise performance.² Because an increased hypoxic and hypercapnic chemosensitivity accounts for the sensation of dyspnoea in these patients and for the reduced tolerance to exercise³ we hypothesised that yogic respiration might also improve clinical symptoms by reducing the chemoreflex response. We tested whether the hypoxic and hypercapnic chemoreflex sensitivity could be affected by yoga, and sought to establish whether this was specifically because of the slow breathing rate or as a general consequence of yoga.

Re-breathing manoeuvres to isocapnic hypoxia and normoxic hypercapnia⁴ were done by ten healthy yoga trainees (mean age 33 years [SD 3]; six women, four men; mean weight 59.4 kg [2.5]; mean body surface area 1.71 m² [0.05]; mean years of practice 7.9 [1.7]) and in 12 healthy controls who had never practised yoga (mean age 31 years [3]; six women, four men; mean weight 64.7 kg [3]; mean body surface area 1.77 m² [0.05]). All individuals gave informed consent to the study which was approved by the local ethics committee. All individuals randomly performed three hypoxic-normocapnic and three hypercapnic-normoxic re-breathing tests, while spontaneous normoxic breathing or during a fixed breathing frequency at six and 15 breaths per min. At the end of each intervention the maximal ventilatory capacity and the respiratory frequency was assessed. The chemoreflex sensitivity to hypoxia or hypercapnia was obtained from the slope of the linear regression of ventilation per minute versus either oxygen saturation or end-tidal CO₂. Non-invasive blood pressure and heart rate were continuously assessed.

During spontaneous breathing the ventilatory responses to both hypoxia and hypercapnia were substantially lower in yoga trainees compared with controls (table, figure). Before re-breathing, yoga trainees had lower breathing frequency, lower ventilation per minute, and higher end-tidal CO₂ compared with the controls. Unlike controls, only minor or no changes in breathing frequency and minute ventilation were induced by re-breathing. In yoga trainees, six breaths per min re-breathing tests induced a further small depression of chemoreflex response, compared with spontaneous breathing. In the controls, the chemoreflex response at six breaths per min decreased substantially and became similar to that of yoga trainees. In yoga trainees the chemoreflex sensitivity at 15 breaths per min slightly increased, but remained lower than the controls, who showed a chemoreflex sensitivity similar to sensitivities noted when spontaneously breathing. The ventilation capacity reached at the end of each test remained well below the maximal voluntary ventilation at



Mean ventilatory responses to hypoxia and hypercapnia obtained during spontaneous and controlled breathing rates

* $p < 0.05$; † $p < 0.05$; ‡ $p < 0.001$, six breaths per min vs spontaneous breathing. § $p < 0.01$ vs 15 breaths per min controlled breathing.

Y=yoga trainees. C=controls.

each breathing frequency, indicating that the responses obtained were not the result of a mechanical impairment to an increase in ventilation. Similar results were found after correction for weight or body surface area. Blood pressure and heart rate were similar at baseline but increased during all manoeuvres, without significant differences between groups and tests.

This study shows that yoga breathing decreased chemoreflex hypoxic and hypercapnic responses. This was caused to a large extent by the slower breathing frequency that these individuals exhibited spontaneously, because a similar reduction in ventilatory responses was also noted in controls when they breathed at six breaths per min.

However, if the slower breathing frequency were the only factor reducing the chemoreflex, then chemoreflex sensitivity should have been increased to values similar to controls when tested at a higher frequency (15 breaths per min). Because only a minor increase was found, we conclude that long-term effects of yoga may also independently reduce chemoreflex sensitivity. A preliminary report of reduced ventilation and chemosensitivity after sustained exposition to hypoxia supports this hypothesis.⁵ Possible explanations include the adaptation of peripheral/central chemoreceptors to chronic retention of CO₂ and/or a chronic adaptation of the pulmonary stretch receptors to the long-lasting habit of a slow deep respiration, followed by an attenuation of the vagal afferent discharge to the bulbopontine centres. A hypometabolic state—as a result of relaxation training—could allow yoga trainees to tolerate stress conditions such as hypoxia or hypercapnia with less increase in metabolic demand. Conversely, our findings in control individuals

would be better explained by the acute effect of slowing the breathing rate.

The practice of yogic respiration may perhaps have clinical relevance because overactivation of the chemoreflex is common in conditions such as chronic heart failure.

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