REVIEW ARTICLE

Postrace upper respiratory tract 'infections' in ultra-marathoners — infection, allergy or inflammation?

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Abstract

Despite more than 20 years of research into mechanisms which could result in the increased predisposition of athletes to 'infection' incidence following excessive and prolonged exercise, definitive explanations are not yet available. A strong temporal relationship between the incidence of upper respiratory tract infection symptoms and immune system changes following excessive exercise load (EEL) have not been shown. T-helper cells are functionally polarised according to the cytokines which they produce. While exercise-induced upregulation of T-helper-2 (T_H2) cells and type 2 cytokines is indicative of enhanced activation of allergic responses, downregulation of T-helper-1 (T_H1) cells and type 1 cytokines confirms suppression of cellular immune functions. The current knowledge regarding the exercise-induced kinetics of interleukin (IL)-4, a cytokine that is crucial in the activation of the T_H2 cells, does, however, not appear to provide sufficient support for an upregulation of a type 2 response. Lowered or unchanged circulating concentrations of type1 cytokines (IL12, IL-2 and interferon γ) and short-term suppression of lymphocyte, natural killer cell and neutrophil function following EEL, reflect a transient, post-exercise suppression of cellular immunity. Despite a partial dampening thereof by the anti-inflammatory actions of IL-10, IL-1ra and IL-6, the evidence supporting a pro-inflammatory response to prolonged exercise and overtraining is unequivocal. At present, the data appear to support the theory that symptoms of 'infection' experienced by athletes are the manifestation of a significant pro-inflammatory response, combined with a modest, transient suppression of cellular immune functions which may be clinically insignificant.

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Introduction

The most common reason for absence from training in elite sportsmen is the presence of upper respiratory tract infections, followed by acute and chronic injuries. (Berglund and Hemmingson[2])

In 1983 Professor Eric Bateman and I described an increased prevalence of self-reported symptoms of upper respiratory tract 'infections' following participation in a 56 km ultramarathon in runners when compared with the prevalence in matched non-running, sedentary controls during the same time period.[58] Both runners and controls had reported the incidence of runny noses, sneezing, sore throats and coughs with or without accompanying fever, immediately before and during the 2 weeks following the 1982 Two Oceans Ultramarathon. The incidence of these self-reported symptoms was found to be significantly higher in runners than in controls and the post-race symptoms highest amongst the runners who ran the fastest.[58]

This finding has been repeated numerous times, both in South Africa and abroad.[33,44,46,59] Research focus in the rapidly developing field of exercise immunology has subsequently been placed on identifying: (*i*) the mechanisms which possibly result in this high prevalence of 'infection' during the post-race period; and (*ii*) nutritional and pharmacological intervention strategies in an attempt to reduce the higher 'infection' risk experienced by ultradistance athletes during the 3 - 72 hour post-event 'open-window' period (Fig. 1) and during periods of excessive training. During the last 25 years, no less than 1 500 studies have been published in this rela-

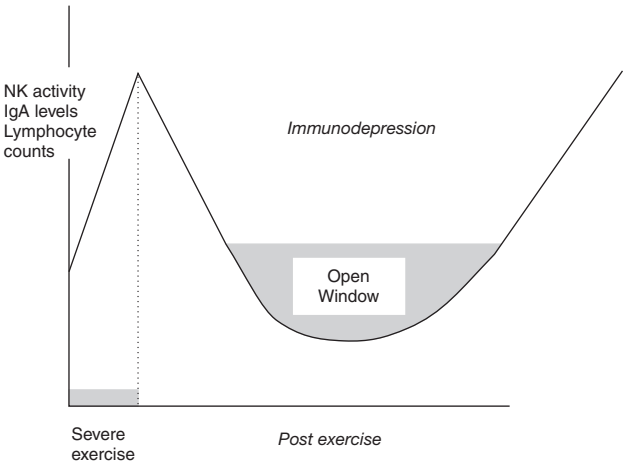

Fig. 1. The exercise-induced open-window period (adapted from Pedersen and Ullum.[52])

tively new field of exercise immunology. As Noakes, however, so appropriately concludes in his most recent version of *The Lore of Running*,[47] 'it is my impression that a considerable amount of research has been done in this field without any practical advances being made'.

In 1994 Nieman[45] postulated that the relationship between exercise-load and 'infection risk' could be modelled in the form of a J-shaped curve, suggesting that although the risk of upper respiratory tract infection (URTI) may decrease below that of a sedentary individual undergoing moderate exercise training, risk may rise above average during periods of excessive amounts of high-intensity exercise.[45] In 1999 he introduced a further dimension to this graphic model; while 'infection risk' increased, 'immunsurveillance' decreased and vice versa (Fig. 2).[39]

Temporary modulations of innate and adapted immune function have been alleged to be the basis for the relationship between the level of physical activity and susceptibility to infection. While limited evidence of enhancement of immune function has been found following moderate exercise exposure,[4,25,30,38] it has been shown that excessive prolonged exercise transiently suppresses markers of both cellular and humoral adaptive immunity[15,26,28,35,42,70] and to a lesser degree, some aspects of non-specific immunity including neutrophil respiratory burst[8,61-63,66,78] and natural killer (NK) cell activity.[21,26,27]

Yet a consistent correlation between this temporary 'suppression' of markers of immune function and incidence of URTI infection symptoms following excessive exercise load (EEL) has not been found. The closest link that has been shown has been in the work of exercise immunologists of the Australian Institute of Sport and University of Queensland who were able to show that a decrease in salivary immunoglobulin (IgA) concentration is associated with a corresponding enhanced infection incidence in elite, overtrained swimmers and kayakers.[12,16-19,65] However, the recent debate regarding the validity of the practise of expressing salivary IgA as a function of salivary total protein or albumin concentrations when these have different origins,[3] makes explanation of the results elusive and leaves exercise immunologists

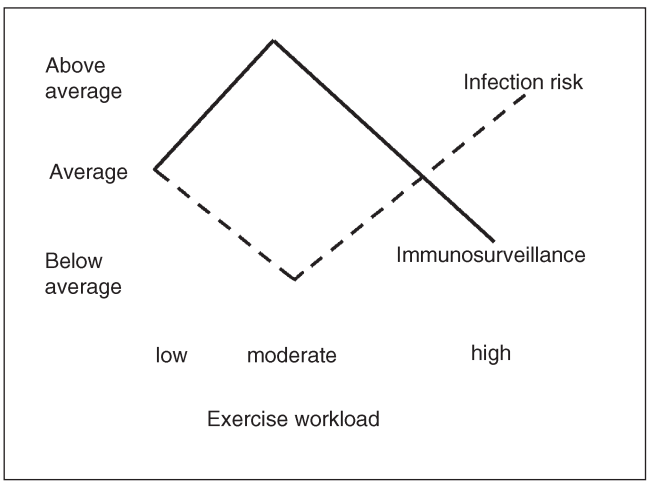

Fig. 2. The paradoxical relationship between workload, infection risk and immunosurveillance in athletes (adapted from Nieman et al.[38])

with little alternative but to acknowledge that the transient suppression of markers of immune function which have been reported in the last two decades may not be of clinical significance.

In re-examining possible factors which could account for the higher incidence of what have primarily been self-reported symptoms of URTI, a number of interesting new perspectives and hypotheses have arisen. Broadly, these can be divided into three general categories: those supporting allergy, inflammation or infection. Let us examine each of these in turn.

A case in favour of allergic origins?

An enlightening dimension of recent immunological studies on exercising individuals has involved the analysis of the post-event cytokine milieu (Table I).

It is well accepted that the CD4 lymphocyte subsets, T-helper-1 (TH1) and T-helper-2 (T_H2), impact differentially on cellular and humoral lymphocyte function.[14,67,77] As direct measurement of the CD 26 (T_H1) and 30 (T_H2) cell surface molecules is not possible due to their instability, a comprehensive picture of the cytokine milieu created by cells of the immune system is the best evidence which we presently have of T_H1:T_H2 balance following EEL. Whereas the type 1 cytokines, interleukin (IL)-2, interferon gamma (IFN γ), tumour necrosis factor (TNF)α and IL-12 activate the development and activation of T_H1 cells which upon recognition of antigens, stimulate cell-mediated immunity increasing CD8 and NK cell cytotoxic activity as well as activating macrophages and neutrophils to kill the bacteria they harbour, T_H2 upregulation has been shown to augment B-cell antibody production via the release of the type 2 cytokines, IL-4, IL-5, IL-6, IL-10 and IL-13. Suzuki *et al*.[77] and Smith[72] have recently proposed an hypothesis which suggests an exercise-induced shift in cytokine balance from type -1 to type-2 cytokines with an upregulation of T_H2 cells (as confirmed by substantially elevated post-exercise concentrations of IL-6 and IL-10) and a relative downregulation of T_H1 helper cells, as expressed in elevated circulating cortisol and prostaglandin E2 concentrations[73] and unchanged/slightly decreased type 1 cytokine concentrations following EEL (Table I). This exercise-induced 'tipping' of the T_H1: T_H2 balance (Fig. 3) differs significantly from the cytokine milieu present in auto-immune disorders which present with elevated IL-2, IFNγ and IL-12 concentrations. The high prevalence of exercise-induced asthma, anaphaxis and systemic histamine release recently reported by Helenius *et al*.,[13] Mucci *et al*.,[23] Shadick *et al*.,[69] and Sue-Chu *et al*.,[76] has encouraged exercise immunologists to look more deeply into this shift in T_H1:T_H2 balance following exercise which appears to support upregulation of humoral immunity and allergic responses with simultaneous downregulation of cell-mediated immunity.

While IL-10 plays an important role in upregulating T_H2 cells and inhibiting T_H1 lymphocyte development,[72] it is well accepted that IL-4 is the dominant cytokine in the upregulation of T_H2 lymphocytes promoting their differentiation and inducing further type 2 cytokine production.[67] This cytokine is therefore the 'key player' in supporting humoral immunity and possible allergen-derived activation of eosinophils/mast cells and IgE production. There is, however, presently little

evidence of exercise-induced elevation of circulating IL-4 concentrations and preferential post-exercise synthesis of IgE following exercise.[32,75] Although IL-6 (which rises dramatically during prolonged exercise[24,29,31]), is thought to stimulate the production of IL-4, Steensberg *et al*.[75] were not able to show evidence of its production in CD4+ cells. Additional work on the kinetics of IL-4 is therefore required before the TH1 -TH2 hypothesis can be substantiated. The significant post-exercise elevations of IL-10, a potent suppressor of cell-mediated immunity and anti-inflammatory cytokine, as well as the multifunctional IL-6 and chemotactic IL-8 (Table I), further complicate the argument in favour of a cytokine balance which is exclusively associated with allergic-type reactions.

The case for and against infectious origins

Despite the above-described evidence of the presence of a type 2 post-exercise cytokine milieu which points to modest, transient downregulation of the cellular components of specific and innate immunity, it would appear that, at this stage, there is little support for a truly infectious origin of the URTI symptoms experienced by athletes following an EEL. As findings of transient suppression of lymphocyte count and proliferation,[34,41] NK-cell counts and cytolytic activity,[21,26] salivary IgA concentrations[11,12,20] and phagocytic oxidative burst activity[8,37] have not been shown to be paralleled by increased incidence of 'infection', the clinical significance of these findings is in question.

TABLE I. The cytokine milieu in the blood following prolonged exercise in excess of 2 hours

Cytokine	Primary cell source	Primary functions	Exercise-induced changes in peripheral blood
Tumour necrosis factor (TNF)∝	Activated macrophages, NK, T-cells, B-cells	Primary mediator of SIRS; stimulation of release of acute phase proteins, lymphocyte proliferation & killing	Changes inconsistent, but concentrations remain within clinically normal range[32,48,56,57]
Interferon (IFN) ∝ & ß	Epithelia, fibroblasts, macrophages	Antiviral; activation of NK cells	No change
Interferon (IFN)γ	Activated T_H1 cells, NK cells	Antiviral; activation of macrophages, neutrophils, NK cells, inhibition of T_H2 cells	50% ↓ (Steensberg *et al*.[75]*) No change Undectectable (Nieman *et al*.,[32] Gannon *et al*.[9])
Interleukin-1 ß (IL-1 ß)	Macrophages, monocytes	Mediator of SIRS; activation of phagocytosis, B-cell proliferation; Ig production	1.5 - 2-fold↑ (Nieman *et al*.,[40] Ostrowski *et al*.[48,50])
Interleukin-2 (IL-2)	Activated T_H1 cells, NK cells	Modulator of T_H2 cell proliferation & function; IgG expression	32% ↓ Suzuki et al.[77]) 50 % ((Steensberg *et al.* [75]*)
Interleukin-4 (IL-4)	T_H2 cells, mast cells, basophils, eosinophils	Downregulation of TNFα and IL- 1ß; induction of IL-6, IL-10, IL- 1ra synthesis; B-cell proliferation and class switching to IgE expression.	No change (Nieman *et al*.[32] Malm[22], Steensberg *et al*.[75]*) Delayed onset secretion after 2 hrs (Susuki *et al*.[79])
Interleukin-5 (IL-5)	T_H2 cells, mast cells, eosinophils	Eosinophil & B-cell growth and differentiation.	No consistent change (Malm[22])
Interleukin-6 (IL-6)	Activated T_H2 cells, APCs, active skeletal muscle fibres	Multi-functional; B-cell proliferation and Ig & acute phase protein synthesis; inhibition of synthesis of TNFα and IL-1ß; induction of cortisol, IL-10 & IL-1ra synthesis	30-fold ↑ (Steensberg *et al*,[75]*) 30-fold ↑ (Peters *et al*.[57]) 100-fold ↑ (Starkie *et al*.[74])
Interleukin-8 (IL-8)	Macrophages	Chemotaxis, superoxide release, granule release	6-fold↑ (Peters *et al*.[55]) 6.7-fold ↑(Ostrowski *et al*.[49])
Interleukin-10 (IL-10)	Activated T_H2, CD8 and B lymphocytes, macrophages	Inhibition of synthesis of TNFß, IL- 1ß, IFNγ, IL-6, IL-8 by T_H1 cells, NK cells & APCs; promotion of B-cell proliferation & antibody responses, mast cell growth	60-fold ↑ (Peters *et al*.[56]) 40-fold↑ (Nieman *et al*.[32])
Interleukin 12 (IL-12)	Monocytes	Activation of T_H1 cells NK stimulating factor IFN γ production	Undetectable (Nieman *et al*,[32] Suzuki *et al*.[79], Gannon *et al*.[9]) Increased† (Akimoto *et al*.[1])
Interleukin 13 (IL-13)	T_H2 cells	B-cell growth & differentiation, inhibition of pro-inflammatory cytokine production	No exercise-related data available
Interleukin 15 (IL-15)	Skeletal muscle cells, endothelium, monocytes.	T and B-cell proliferation, increase of myosin heavy chain expression in skeletal muscle.	No change (Ostrowski *et al*.[48]).
Interleukin-1ra (IL-1ra)	Macrophages, T_H2 cells	Inhibition of pro-inflammatory action of IL-1 by blocking IL-1 α & ß receptors; no agonist activity	20 fold↑ (Peters *et al*.[56]) 40 fold↑ (Toft *et al*.[80]) 214 fold↑(Suzuki *et al*.[79])

* Intracellular concentrations (CD4 + cells).
†Short-term maximal exercise.
APC = antigen presenting cell; T_H1 = T-helper-1; T_H2 = T-helper-2; Ig = immunoglobulin; SIRS = systemic inflammatory response syndrome.
(Ganong,[10] Janeway and Travers,[14] Roitt *et al*.,[67] Smith[72])

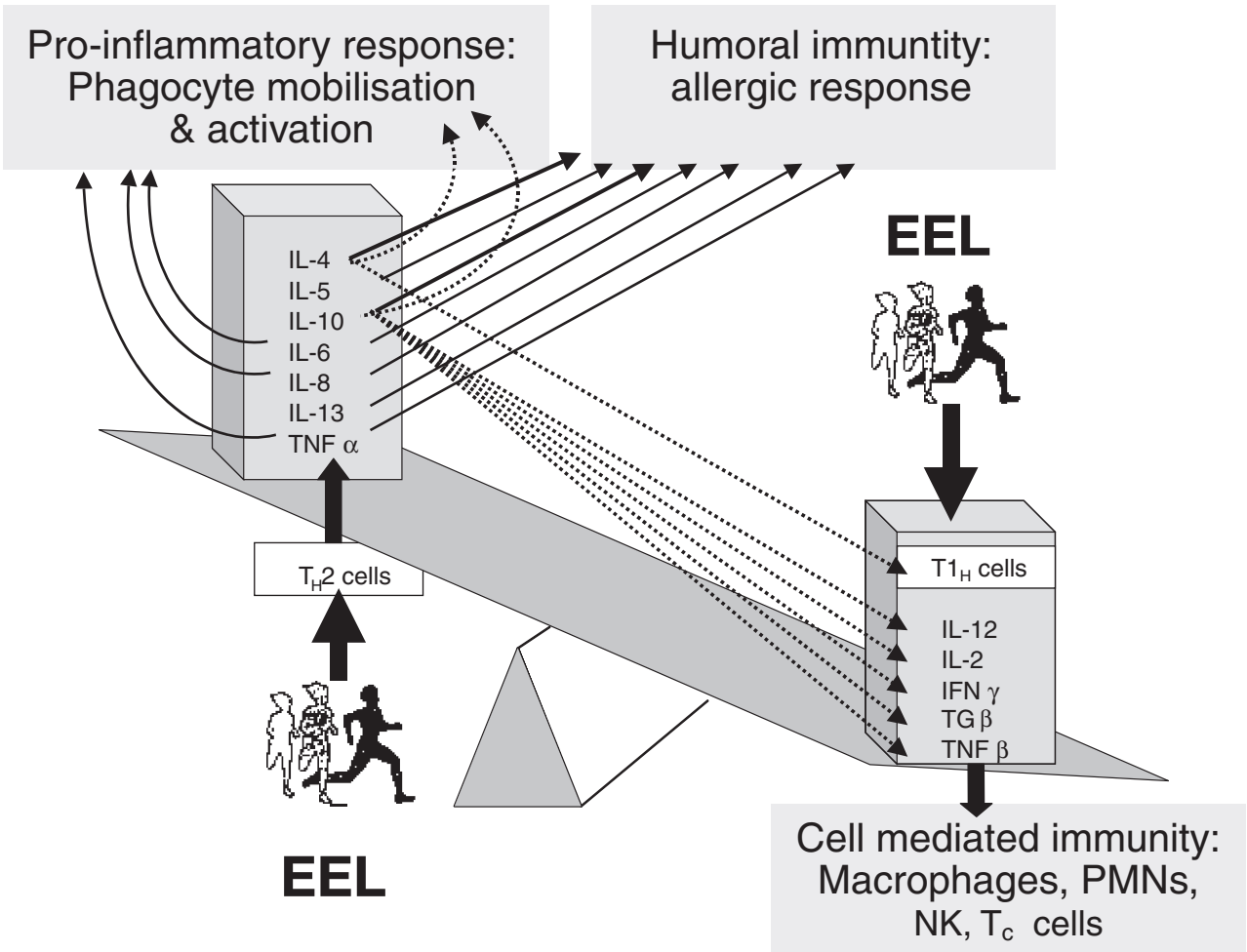

Fig. 3. The exercise-induced disturbance of cytokine equilibrium: a downregulation of type 1 and upregulation of type 2 cytokines. ⟶ promotion; ⋯⟶ inhibition; EEL : excessive exercise load; T_H1: T-helper-1; T_H2: T-helper-2; PMN : polymorphonuclear neutrophils; T_c : cytotoxic T-cells; NK cells: natural killer cells.

Although the open-window hypothesis of Pedersen and Ullum[52] and Pedersen *et al*.[54] describes a period of increased susceptibility to infection which may last from 3 to 72 hours post-exercise, most exercise-induced haematological perturbations have returned to baseline values within 16 hours post-exercise.[60] As Shepard and Shek[71] point out, 'it is difficult to reconcile a 2-to 3-hour reduction of NK cell activity with the reported 2-to 6- fold increase in the incidence of URTIs in the weeks following participation in a marathon or ultramarathon run'.

Furthermore, antibody responses following vaccination have not been shown to be influenced by exercise training,[5] while negative bacterial throat swabs obtained by Schwellnus *et al*. following the Two-Oceans 56 km Ultramarathon also appear to rule out the possibility of enhanced incidence of post-race infection symptoms being of infectious origin (M Schwellnus — personal communication). As false-negative bacterial throat swabs are, however, a common occurrence in clinical practice, we cannot, at this stage, consider these data as conclusive. The evidence in support of a decrease in delayed type hypersensitivity (DTH) reactions, the T-cell-dependent activation of macrophages and inflammation in response to a previously encountered antigen, is also presently conflictling; while Bruunsgaard *et al*.[5] found decreased DTH after a one-half Ironman race, Jansen *et al*. (personal communication), failed to show any change following 8 weeks of training in excess of 110 km/week.

The case in favour of inflammatory origins

The evidence in favour of an inflammatory response both to epithelial tissue damage in the upper respiratory tract and muscle fibre damage in the contracting skeletal muscle fibres, as manifested in systemic markers of an inflammatory response, is, however, strong.

During prolonged endurance exercise increased ventilatory rates and volumes, with actual damage to sensitive mucous membranes in the respiratory tract, and an inflammatory response at the sites of muscle cell damage have been linked to the development of an acute phase reaction.[80]

Evidence of systemic manifestation of pro and anti-inflammatory response to exercise-induced microtrauma (whether this be in the contracting muscle itself or in the respiratory tract membranes exposed to excessive mouth

breathing) has been confirmed by numerous studies focusing on exercise-induced cytokine changes.

In addition to the early studies which consistently confirm the presence of increased prostaglandin E_2 concentrations,[53,73] the endocrine,[43,44,64,72] cytokine,[36,48-51] acute phase protein,[6,7,81] and enzymatic[66] milieu in the circulation favours an inflammatory response (Fig. 4).

In three consecutive studies following the 90 km ultramarathon, we have confirmed systemic evidence of a pro-inflammatory response.[55-57] Not only are markers of an acute phase reaction, CRP and amyloid A consistently elevated, peaking 24 hours after a race and reaching concentrations in excess of those reported following myocardial infarctions,[55,57] but also a cascade of pro-inflammatory and chemotactic cytokines[40,56] and systemic markers of phagocyte activation including myeloperoxidase, elastase and neutrophil/ monocyte adhesion factors.[55,61,66] Our most recent research findings confirm elevated concentrations of neutrophils and monocytes expressing CD11 a and b integrins which control the movement of leukocytes towards areas of inflammation following 2.5 hours of treadmill running at 70% VO_{2max}. (Peters *et al*., unpublished data).

The substantial elevation of circulating anti-inflammatory mediators, IL-10, IL-1ra and IL-6 (Fig. 5) do, however, point towards a partial dampening of this pro-inflammatory response. Despite this endogenous attempt to counter the exercise-induced inflammation, systemic markers of an acute phase reaction peak at 24 hours post-event.

In 1997 Schwellnus *et al*.[68] reported that administration of the local antimicrobial and anti-inflammatory agent, Fusafungine, significantly reduced post-race URTIs in 48 participants during the 9 days following the 1996 Two Oceans 56 km Ultramarathon. However as this nasobuccopharangeal spray has both anti-inflammatory and anti-infective properties, this intervention study on its own does not provide conclusive evidence that the increased incidence of infection following EEL is solely attributable to an inflammatory response.

Perhaps we should also not ignore the early finding of Pedersen *et al*.[53] that administration of the non-steroidal anti-inflammatory agent, indometacin, which inhibits prostaglandin E_2 release and the inflammatory response, reduces post-exercise suppression of NK cell activity and restores post-exercise neurophil chemiluminescence in peripheral blood. As the authors concluded, these findings strongly indicate that prostaglandins released from monocytes and neutrophils, are involved in the downregulation of NK cells, again pointing towards systemic manifestation of an inflammatory response.

An answer?

At this stage, there is not enough evidence in favour of an exclusive contribution of allergic, inflammatory or infective origins to the incidence of post-event URTI symptoms.

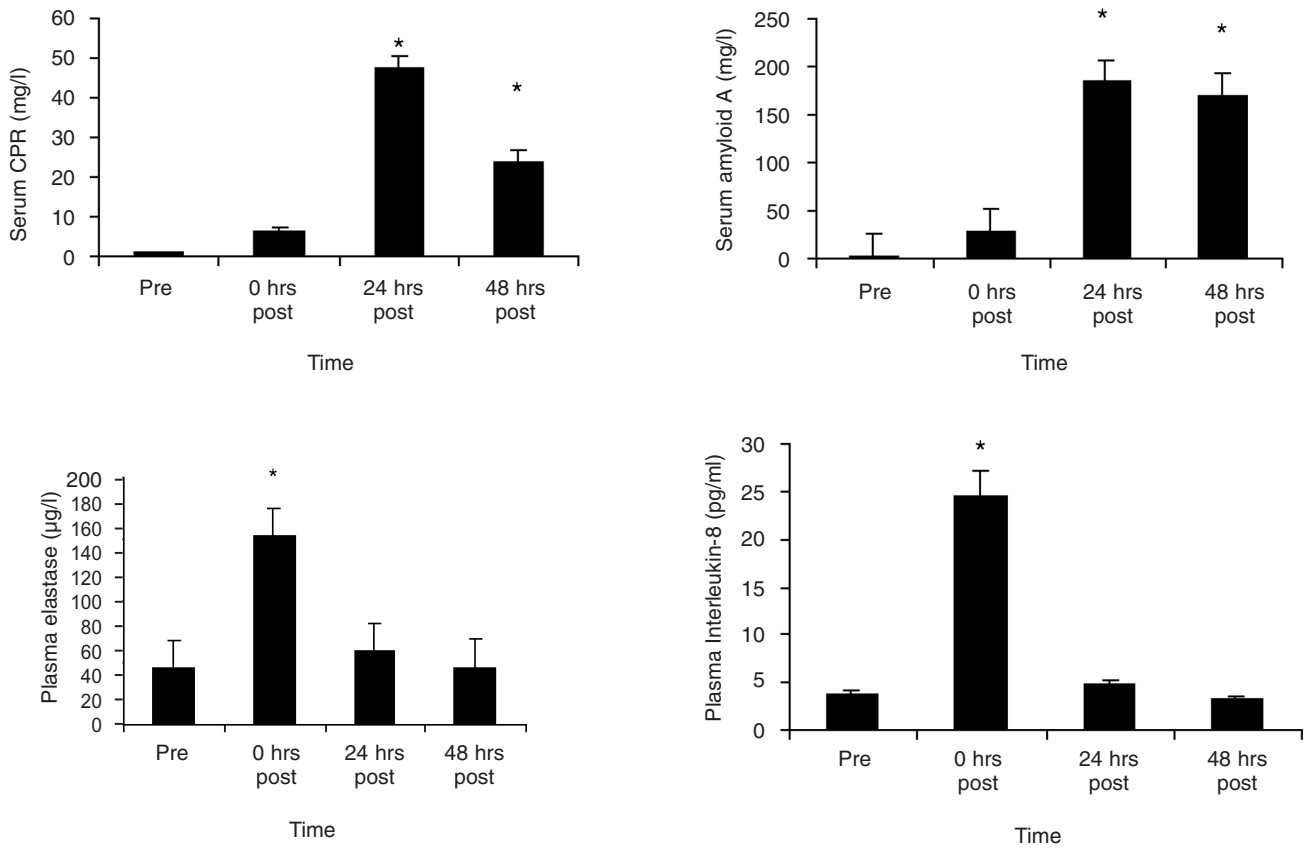

Fig. 4. Mean (± SEM) circulating acute phase protein (CRP and amyloid A), elastase and interleukin-8 concentrations before and after a 90 km ultramarathon, which support an upregulation of inflammatory responses (data from Peters* et al. *[55]) *P > 0.05 (N = 29).

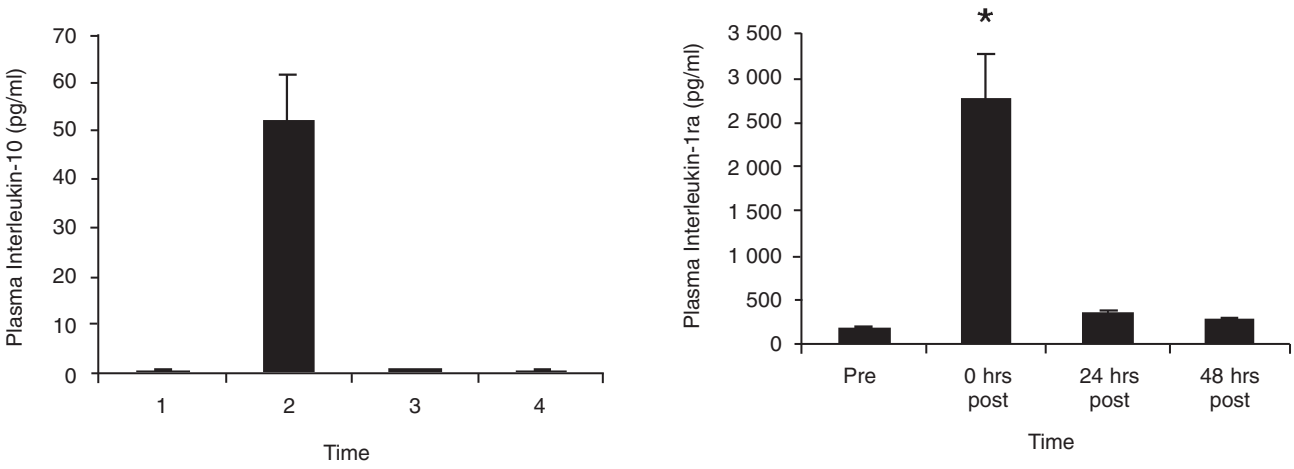

Fig. 5. Mean (± SEM) circulating IL-10 and IL-1ra concentrations before and after a 90 km ultramarathon, which support an upregulation of anti-inflammatory mechanisms (data from Peters* et al. *[56]). *P > 0.05 (N = 29).

In terms of the T_H1: T_H2 balance hypothesis which favours an allergic response, the evidence in favour of exercise-induced production of IL-4 requires further elucidation. The exercise-induced 'switching' of B-cells to a preferential production of IgE and significant upregulation of IgG_1 production in response to mast cell activation also requires further confirmation.

In terms of the inflammation and infection-based hypotheses, supportive data are undoubtedly strong. While transiently and modestly suppressed cellular components of immunity including cytotoxic T lymphocytes, NK cells and in the case of EEL, neutrophil function are supported by a relative downregulation of type 1 cytokines, the post-exercise cytokine, acute phase protein and adhesion molecule milieu strongly supports an upregulation of inflammatory responses.

Shephard and Shek[71] have eloquently referred to the 'active enmeshment' of the immune system in the muscle tissue repair and inflammation process. It is indeed possible that a significant upregulation of inflammatory response is accompanied by a simultaneous modest, but clinically insignificant, transient downregulation of the cellular cytotoxic activity of the T and NK cells; that the observed immunological changes during and after physical exercise which have been previously interpreted as 'depressed immune function,' reflect a proactive inflammatory response which is a necessity for optimal adaptation following the increased physical demand of EEL and should therefore not be viewed in a negative light. A paradox, indeed!

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