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A mathematical model of Interleukin-6 dynamics during exercise

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Abstract— **Physical exercise is known to reduce the inflammatory status that leads to Type 2 Diabetes. Its beneficial effects seem to be exerted trough a primary production of Interleukin-6 (IL-6) which triggers a cascade of anti-inflammatory cytokines. Consequently, IL-6 has a central role in the description of the metabolic effects of exercise. The aim of this study was to develop a model of IL-6 dynamics during exercise. A model constituted by two non-linear differential equations is proposed. Input to the model is represented by heart rate, which is known to correlate well with exercise intensity. Model implementation in a Matlab-based parametric identification procedure allowed optimization of adjustable characteristic coefficients of IL-6 dynamics during exercise. From the reported results, it can be concluded that this model is a suitable tool to reproduce IL-6 time course during the execution of a physical exercise. This model was the first step of a project aimed at describing the complete immune system response to exercise and at giving a comprehensive sight of the effects that exercise has on the metabolic system.**

Keywords— **Inflammation, physical activity, cytokines, metabolic syndrome.**

I. Introduction

Type 2 Diabetes (T2D) is one of the most common diseases all over the world and is characterized by a deficit in insulin action and secretion. This deficit seems to entail a state of low-grade inflammation giving T2D the aspect of a chronic inflammatory disease [1]. The inflammatory milieu originates in the adipose tissue, considering that, in this pathological situation, adipocytes are inflamed and release pro-inflammatory cytokines [2]. Exercise has the ability to contrast and delay the evolution of the disease. In fact, contraction of skeletal muscles during exercise is able to induce a series of modifications of the inflammatory pathway [3], which eventually induces a reduction of insulin resistance [4]. Interleukin-6 (IL-6) was identified as the first cytokine increasing in the circulation during exercise and stimulating the secretion of a cascade of anti-inflammatory cytokines [5, 6]. Plasma IL-6 was shown to augment up to 100-fold depending on exercise intensity and duration. The exercise-induced increase of plasma IL-6 is not linear over time; repeated measurements during exercise showed an accelerating increase of the IL-6 in plasma in an almost exponential manner [7]. Furthermore, the peak IL-6 level is reached at the end of the exercise or shortly thereafter, followed by a rapid decrease towards pre-exercise levels [7]. Although exercise is one of the major factors acting on T2D mechanisms, there are only few mathematical models describing its effects on the metabolic system [8–10], and none of these describing them at immunological level. Thus, the aim of the present study was to fill this gap and formulate and validate a mathematical model of IL-6 dynamics during exercise.

II. Methods

A. Model equations

Since IL-6 dynamics depends on the intensity of the exercise performed and considering that heart rate (HR) correlates well with exercise intensity, the HR signal was used as input to the model. The model is constituted by the following two non-linear differential equations:

$$\frac{dIL6(t)}{dt} = k_1 e^{\frac{Y(t)}{\tau}} - k_2 IL6(t) + \frac{Ra_{IL6}}{V} \quad (1)$$

$$\frac{dY(t)}{dt} = -\frac{1}{T_{HR}}[(HR(t) - HR_b) - Y(t)] \quad (2)$$

In eq. (1), *IL6(t)* represents IL-6 concentration in the plasma compartment. In eq. (2), taken from Dalla Man et al. [10], *Y* is a delayed version of the suprabasal *HR(t)* signal. The first nonlinear term on the right hand side of eq. (1) accounts for IL-6 increase from its basal value in response to muscle contraction during exercise and it is conceived as non-linearly dependent on a delayed version of the suprabasal HR signal. The second term of the same equation represents IL-6 removal from the circulation after exercise. Finally, the third term accounts for IL-6 production during non-perturbed conditions, and is mainly representing adipose tissue contribution [11]. *V* is the volume of distribution. The initial conditions are: $IL6(0) = IL6_b$ and $Y(0) = 0$. From measurements of the basal levels of plasma IL-6, and

the k_1, k_2 and V parameters, the value of Ra_{IL6} was calculated imposing steady-state conditions.

B. Clinical data and model parameter estimation

The model output was tested against the values of mean IL-6 plasma concentration taken from an experimental study that investigated the dynamics of several cytokines in ten male athletes before, during and after 2.5 hours of treadmill running at 75% of maximal oxygen consumption (VO_2max) [12]. Plasma IL-6 and HR were measured at each time point.

The model consists of five independent parameters (Table 1). *V and* T_{HR} were assigned numerical values as obtained from reported observations [10, 13], value for τ was manually adjusted while k_1, and k_2 were assumed as "free" and their optimal value was estimated by setting up a weighed least squares (WLS) fitting procedure implemented in Matlab.

Errors in IL-6 measurements were assumed to be normally distributed random variables with zero mean and a constant percent coefficient of variation (CV%) equal to 6.9% [7]. Precision of parameter estimates was expressed as $CV(p_i)\% = SDp_i/p_i \bullet 100$, where p_i is the i-th component of the model parameters vector and SDp_i is the related standard deviation computed as the square root of diagonal terms of the inverse of the Fisher information matrix.

Table 1 Values of model parameters

Parameter	Value (CV%)	Units
k_1(*)	0.0056 (4)	$pg \cdot ml^{-1} \cdot min^{-1}$
τ	20	beats per min
k_2(*)	0.0045 (4)	min^{-1}
V	8250	ml
T_{HR}	1	min
Ra_{IL6}	7.385	$pg \cdot min^{-1}$

(*) Parameters were estimated by fitting to clinical data as described in the Methods. Fixed values of T_{HR} *was taken from Dalla Man et al.* [10] *whereas V was taken from* [13] *Value for* τ *was manually adjusted.*

III. RESULTS

Estimates (with CV% in round brackets) of the free model parameters are given in Table 1 (asterisk marked parameters). In Fig. 1, the model predicted profile (solid line) of IL-6 plasma concentration in response to exercise was compared to experimental data from Ostrowsky et al. [7].

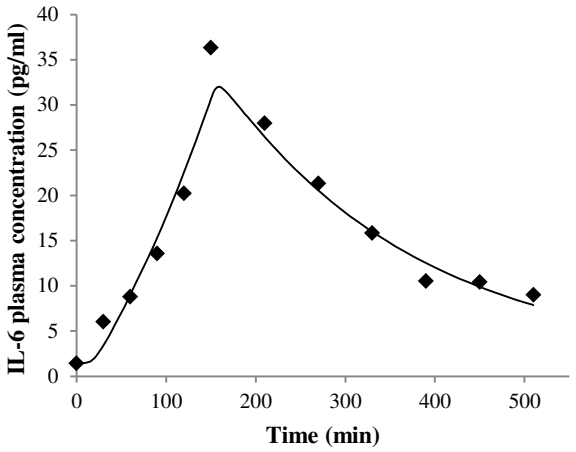

Fig. 1. The profile of mean values of plasma IL-6 measured in 10 healthy human males during 2.5 hour running (black diamonds) are compared with the corresponding IL-6 profile estimated by the proposed model (solid line).

IV. DISCUSSION

Beneficial effects of exercise on insulin resistance leading to T2D seem to be initiated by IL-6 secretion due to skeletal muscle contraction. Subsequently, IL-6 is able to stimulate the secretion of anti-inflammatory cytokines.

This study proposed and validated a mathematical model of IL-6 during exercise. IL-6 increase in the circulation during exercise is hypothesised to be non-linearly dependent from exercise intensity. In particular, an exponential dependence from HR, taken as a marker of exercise intensity, was hypothesized. Even if IL-6 dynamics is mainly regulated by skeletal muscle contraction, in non-perturbed conditions, IL-6 is released by adipose tissue. Experimental data showed that IL-6 is released from the adipocytes and is thereby able to act as a endocrine mediator [11]. The proposed model accounts for both contributions.

V. CONCLUSIONS

The good approximation of experimental data shows that the proposed model is a suitable tool to reproduce IL-6 time course during exercise. This model constitutes the first step in describing the complete immune system response during exercise and paves the way to the mathematical description of the physiological effects of exercise on the metabolic system [14].

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Conflict of Interest

The authors declare that they have no conflict of interest.

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