

# Relationship Between Exercise Intensity and IL-6 Increase During a Long-distance Running Race

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## Original Research Article

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# Abstract

## *Objectives*

IL-6 plasma concentration (IL-6PC) reflects the systemic inflammation related to the exercise intensity level. This study aims to describe IL-6PC kinetic during a long-distance running.

## *Methods*

IL-6PC was measured in 20 male runners before (0 km), at each refreshment points (at 21 and 53 km *i.e.*,  $k_{21}$  &  $k_{53}$ ) and at the end of an 80-km long-distance running ( $k_{80}$ ). IL-6PC variations (absolute and relative values in each of the 3 sections (S)) were calculated over S1 [0- $k_{21}$ ], S2 [ $k_{21}$ - $k_{53}$ ] and S3 [ $k_{53}$ - $k_{80}$ ] and compared with the exercise intensity (duration\*speed race), within each section.

## *Results*

The average race speed decreases progressively:  $9.9 \pm 0.8$  in S1,  $7.0 \pm 0.8$  in S2 and  $6.1 \pm 0.8$  km.h<sup>-1</sup> in S3. Mean IL-6PC increased during the running:  $2.1 \pm 0.6$  ng.l<sup>-1</sup> at 0 km,  $21.0 \pm 11.3$  ng.l<sup>-1</sup> at  $k_{21}$ ,  $38.9 \pm 13.0$  ng.l<sup>-1</sup> at  $k_{53}$  and  $49.8 \pm 11.9$  ng.l<sup>-1</sup> at  $k_{80}$ . Exercise intensity increase between S1 ( $24.2 \pm 0.5$ ) - S2 ( $51.9 \pm 3.2$ ) ( $p=0.04$ ) but not between S2 and S3 ( $67.4 \pm 4.5$ ) ( $p=0.69$ ). A association was retrieved between exercise intensity and IL-6PC at the end of each section: S1 ( $p=0.03$ ), S2 ( $p=0.04$ ) and S3 ( $p<10^{-3}$ ). IL-6PC variation was associated with exercise intensity within S1 ( $p=0.03$ ) and S2 ( $p=2.10^{-3}$ ) and showed a least a trend within S3 ( $p=0.06$ ).

## *Conclusion*

IL-6PC increase occurs during the early stage of a long-distance running, is associated with the running intensity and remains stable after intensity reduction related to speed running decrease.

# Introduction

The impact of moderate and regular physical activity on the primary prevention of at least 35 chronic conditions (1) and on cardiovascular diseases is established (2). Its beneficial effects are partly due to the exercise anti-inflammatory effect involving biological mediators among which are interleukins (IL) (3, 4).

Long-distance exercises, particularly running races, are gaining more popularity and are becoming widespread all over the world (5, 6). Initially defined as a distance over 42 kilometres, to date a long-distance running race is defined by a duration of at least 6 hours (7, 8).

Interleukin-6 (IL-6), one the most studied cytokine, is an inflammatory cytokine playing a central role as a mediator propagating the systemic inflammatory response. IL-6 plasma concentration is associated and predicts the risk of future cardiovascular events (9), especially atherosclerosis (10) and cardiovascular

events (myocardial infarction and heart failure) (11) and death (9). Nevertheless, no causal association between IL-6 plasma concentration and illness occurrence is, to date, clearly established.

IL-6 is released from the skeletal muscle cells into the blood related to metabolism and energy deprivation (12). The IL-6 plasma concentration increases early, within 30 minutes, after acute intense exercise (13). Thereafter, there is an increase in the IL-6 plasma concentration in an almost exponential manner (4) reaching a peak at the end of the exercise before returning to pre-exercise plasma concentration within the first 24 hours (14). During acute exercise, IL-6 has been particularly studied (15) in order to reflect the systemic inflammation response. However, previous studies design assessed pre- and post-race IL-6 plasma concentration (16–19) not its kinetic during the race. Factors determining IL-6 plasma concentration are mainly represented by exercise duration (15, 20–22) and exercise intensity (21, 23). Exercise intensity may be indirectly represented by the muscle mass involved for running and/or by the speed of the race (24–26). During a long-distance running race, because the running speed progressively decrease due to tiredness, the exercise intensity varies, consequently the relationship between exercise intensity and IL-6 plasma concentration is not linear. To date, to the best of our knowledge, no study reports IL-6 kinetic during a long-distance running race.

This study aims to describe the IL-6 kinetic among runners during an 80 kilometres long-distance running race and its relationship with the exercise intensity.

## Methods

Twenty male participants of the 80-km Ecotrail of the Paris Ile-de-France© 2014 race (total climb of 1500 m) were prospectively included in the study. Three refreshment points were predefined by the race organisation, respectively, at 21 kilometres, at 53 kilometres and at 80 kilometres. The race started at noon. Throughout the race, participants had free access to food and water.

These 20 volunteers were electronically recruited before the start of the race using an announcement on the race's website ([www.traildeparis.com](http://www.traildeparis.com)).

Adult (age > 18 years), male gender, and completion of an ultra-endurance race (distance > 50 km) during the previous 12 months were included.

Younger than 18 years old and/or female gender - in order to avoid the effects of unknown pregnancy - and/or illness or injury within 1 month before the race and/or any medication and drug use within 3 months before the race were not included in the study.

All participants gave their written informed consent for participation before the start of the race.

Blood samples (1 ml) were collected before the race start (0 km), during the race at the end of each section (21 km and 53 km) and immediately on the finish line (80 km). Blood drawing required only a 1-minute stop. Blood samples were drawn by a nurse, collected and immediately stored on ice and sent to a

hospital in Paris to be analysed later. IL-6 plasma concentration was measured by the immunochemiluminescence method (Roche Diagnostics©).

The 3 refreshment points (21, 53 and 80 km) allowed to define 3 sections: section 1 (S1): 0 to 21 kilometres [0-k<sub>21</sub>], section 2 (S2): 21 to 53kilometres [k<sub>21</sub>-k<sub>53</sub>] and section 3 (S3): 53 to 80 kilometres [k<sub>53</sub>-k<sub>80</sub>].

In order to assess exercise intensity, absolute and relative IL-6 plasma concentration variations were calculated within each of the 3 sections and compared with the exercise intensity. The race intensity was assessed by duration\*speed race, within the same section respectively.

Continuous variables with a normal distribution are expressed by mean ± standard deviation (SD) whereas continuous variables with a non-Gaussian distribution are expressed by median and interquartile range [1st quartile – 3rd quartile]. Categorical data are expressed as absolute value and percentage.

Comparisons were performed using a Wilcoxon test. Statistical significance was defined by a p value of < 0.05. All analyses were performed using R 3.4.2© (<http://www.R-project.org>; the R Foundation for Statistical Computing, Vienna, Austria).

The race's organization committee, the French committee on public safety Paris Ile-de-France IV approved the protocol (Reference: 2014/07) and from the National Heart Agency (Number EudraCT: 2014-A00205-42) on 2014 March 14th .

## Results

On 2014 March 14th, the day of the race, the weather was clear (no rain), and the temperature was 14 degrees Celsius.

All subjects were trained with a training mean time of 5 ± 3 hours per week for the last 12 months, corresponding to 46 ± 18 km per week.

The demographic characteristics of the volunteers are summarized in Table 1.

Table 1  
 Characteristics of the runners. Data are expressed as mean  $\pm$  standard deviation (SD).

Parameter	
Age (years)	43 $\pm$ 7
Body weight (kg)	74 $\pm$ 8
Height (cm)	176 $\pm$ 7
Body mass index (kg.m <sup>-2</sup> )	23.7 $\pm$ 2.3
Weekly covered distance (km)	46 $\pm$ 18
Weekly training duration (hours)	5 $\pm$ 3
Trial experience (years)	6 $\pm$ 4
Number of trails per year	5 $\pm$ 3

None of the subjects reported having run or played any sport in the 2 days prior to the race.

No subject declared any medication or drug use in the previous 3 months, and none reported illness within 1 month before the race.

All subjects were examined and benefited from blood sample drawing at the end of each section. All subjects reached the finish line.

The mean race duration was 668  $\pm$  60 (minimum = 549; maximum = 762) minutes.

The average race speed was 7.3  $\pm$  0.7 (minimum = 6.3; maximum = 8.8) km.h<sup>-1</sup> but progressively decreased along the 3 sections from S1 to S3: 9.9  $\pm$  0.8 in S1, 7.0  $\pm$  0.8 in S2 and 6.1  $\pm$  0.8 km.h<sup>-1</sup> in S3 (Table 2 and Fig. 1).

Table 2

Values of IL-6 PC, speed race within section, IL-6 plasma concentration variation between sections. Data are expressed as mean  $\pm$  SD.

Parameter	S1	S2	S3
IL6-PC (ng.l <sup>-1</sup> ) [N < 7.5]	21.0 $\pm$ 11.3	38.9 $\pm$ 13.0*	49.8 $\pm$ 11.9*
Speed race (km.h <sup>-1</sup> )	9.9 $\pm$ 0.8	7.0 $\pm$ 0.8*	6.1 $\pm$ 0.8*
Exercise intensity	24.2 $\pm$ 0.5	51.9 $\pm$ 3.2*	67.4 $\pm$ 4.5*
IL-6 PC variation between sections (ng.l <sup>-1</sup> )	21.0 $\pm$ 11.3	17.9 $\pm$ 15.2*	10.9 $\pm$ 13.9
<i>Legend:</i> IL6-PC = interleukin 6 plasma concentration. S1: section 1 from 0 to 21 kilometres, S2: section 2 from 21 to 53 kilometres and S3: section 3 from 53 to 80 kilometres.			
Values into brackets refer to normal range.			
* means significant difference vs S1 (p < 0.05)			

Mean IL-6 plasma concentration significantly increased, reaching its maximal value in the last race section: 2.1  $\pm$  0.6 ng.l<sup>-1</sup> before the race, 21.0  $\pm$  11.3 ng.l<sup>-1</sup> at k<sub>21</sub>, 38.9  $\pm$  13.0 ng.l<sup>-1</sup> at k<sub>53</sub> and 49.8  $\pm$  11.9 ng.l<sup>-1</sup> at k<sub>80</sub> (Fig. 1).

Exercise intensity (speed\*duration) significantly increase between S1 (24.2  $\pm$  0.5) and S2 (51.9  $\pm$  3.2) (p = 0.04) but not between S2 and S3 (67.4  $\pm$  4.5) (p = 0.69) (Table 2).

IL-6 plasma concentration variation significantly differs between S1 (21.0  $\pm$  11.3 ng.l<sup>-1</sup>) & S2 (17.9  $\pm$  15.2 ng.l<sup>-1</sup>) (p = 0.01) but not between S2 & S3 (10.9  $\pm$  13.9 ng.l<sup>-1</sup>) (p = 0.21) and S1 & S3 (p = 0.19) sections.

A significant association was retrieved between exercise intensity and IL-6 plasma concentration at the end of each section: S1 (p = 0.03), S2 (p = 0.04) and S3 (p < 10<sup>-3</sup>).

IL-6 plasma concentration variation was significantly associated with exercise intensity within S1 (p = 0.03) and S2 (p = 2.10<sup>-3</sup>) but not within S3 (p = 0.06).

## Discussion

During a long-distance running race, we observed a significant IL-6 plasma concentration increase significantly associated with the running race intensity. IL-6 increase during a long running race occurs during the early stage of the race and remains stable after intensity reduction related to speed race running decrease.

To the best our knowledge, this study is the first to assess the evolution of IL-6 plasma concentration indexed by exercise intensity.

Interleukin-6 (IL-6) is one of the most studied cytokine (15), is an inflammatory cytokine propagating the systemic inflammatory response after released from the skeletal muscle cells into the blood in order to related to meet energy deprivation (12). Previous studies reported that after an early concentration increase (4, 13), IL-6 plasma concentration reaches a peak at the end of the exercise (4) before returning to pre-exercise plasma concentration within the first 24 hours (14). Nevertheless, the relationship between IL-6 plasma concentration and intensity during the exercise intensity was never explored because of methodological approaches - previous studies design assessed pre- and post-race IL-6 plasma concentration (16–19).

Exercise duration (15, 20–22) and intensity (21, 23) are the main factors determining IL-6 plasma concentration. Because during a long-distance running race, the running speed progressively decrease due to tiredness, the exercise intensity also decreases suggesting that the relationship between exercise intensity and IL-6 plasma concentration is not linear. We could suppose that the reduction of the speed race running mainly explain the negative relationship between IL-6 and intensity. Moreover, this assumption is supported by the constant muscle mass involved for running explaining that IL-6 plasma concentration also more influenced by the speed of the race than by the race duration (24–26). Because individual innate and acquired characteristics influence IL-6 plasma concentration at rest as well as in response to exercise (15, 27–30), we choose to assess the variation between section, each volunteer being considered as its own control. Moreover, because the length of the race, IL-6 plasma concentration was indexed on the corresponding speed for each section.

Our results are consistent with previous studies reporting the IL-6 plasma concentration increase with exercise duration (15, 31, 32) and return to baseline after the end of the exercise (13, 14, 33). For running, the ability to maintain speed depends on the muscle mass of the limbs involved (34, 35). The relatively lower values of plasma IL-6 concentration observed in our study compared to previous studies could be explained by the fact that for long distance running, a smaller muscle mass seems to be more efficient, in contrast to short distance running requiring higher explosiveness (24–26).

There are strengths and limitations with the current study. This is a small sample size study. Food and drink intakes were not standardised between all volunteers and may partly contribute to the IL-6 plasma concentration. Only male volunteers were involved in the study; thus, we cannot extrapolate the results to the female gender. We cannot exclude that the participants involved in the current study do not have an “extra-normal” level of the underlying inflammatory state and/or a moderate response (28), related to their frequent practice of long-distance exercises suggesting a potential adaptation of the organism to the intensity of long-term running practice. We cannot exclude that participants had unknown illnesses, or injury influencing baseline of IL-6 plasma concentration and/or modulating the host response. Due to the study design, we are not able to determine whether the participants reached their maximal performances. The methodological design does not allow any causal conclusion between long-distance race exercise and IL-6 increase. This study reports an IL-6 plasma concentration increase without being able to determine its origin(s): blood and/or muscle and/or neuronal and/or adipocyte cells. In addition we defined intensity by speed \* race duration; nevertheless, intensity definition is not consensual (20, 21, 36).

Despite these limitations, this study is the first to assess the IL-6 plasma concentration and its variation indexed on intensity during a long-distance race observing a peak on IL-6 increase not reported after intensity indexation. The early IL-6 plasma concentration peak may be related to speed and we can suppose that the intensity decrease reflected by speed race decrease may be related to a decrease in the sympathetic reserve, associated with a progressive heart rate decrease, and a speed decrease, which, in long-distance race, tending towards a limit value, depending on the maximum catabolic rate of the organism (37).

## Conclusion

A significant IL-6 plasma concentration increase occurs during the early stage of a long-distance running race. This escalation remains stable after intensity reduction related to speed race running decrease. Further studies are needed to confirm these preliminary results and their significance on health.

## Declarations

**\* Ethics approval and consent to participate:** French committee on public safety Paris Ile-de-France IV approved the protocol (Reference: 2014/07) and from the National Heart Agency (Number EudraCT: 2014-A00205-42) on 2014 March 14<sup>th</sup>

**\* Consent for publication:** All participants gave their written informed consent for participation before the start of the race.

**\* Availability of data and materials:** Data are available on reasonable request.

**\* Competing interests:** The authors declare that they have no competing interests

**\* Funding:** none

**\* Authors' contributions:** *Study concept and design:* RJ, *acquisition of data:* RJ, *analysis and interpretation of data:* RJ, JFT, *drafting of the manuscript:* RJ, JA, *critical revision of the manuscript for important intellectual content:* RJ, JA, JFT, DA, NM.

All authors read and approved the final manuscript.

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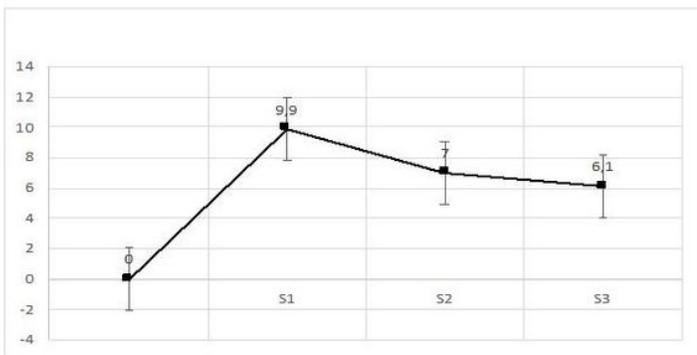
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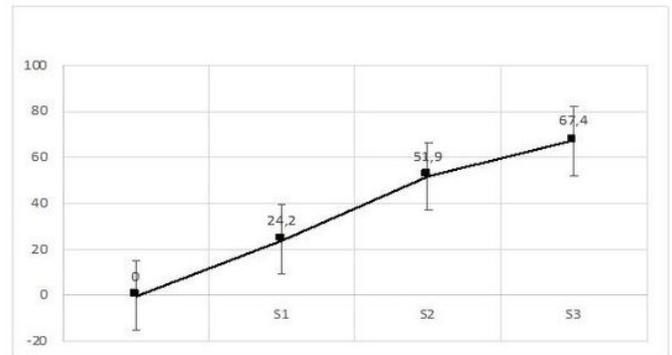
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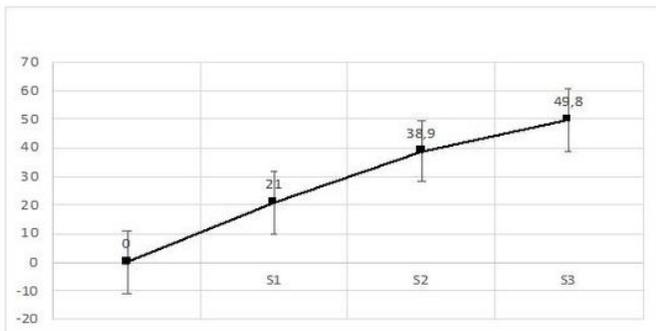
## Figures



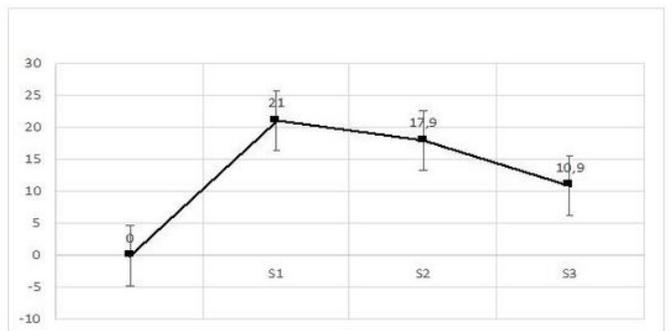
Legend: Speed race within each section.



Legend: Exercise intensity within each section.



Legend: IL-6 plasma concentration at the end of each section.



Legend: IL6-plasma concentration variation between sections.

## Figure 1

Evolution of speed race, intensity, IL-6 absolute and relative variations among the different sections.