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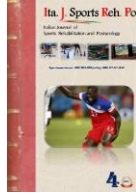


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Acute Inflammation Response to Stretching : a Randomised Trial

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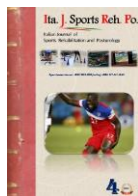
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Abstract

Background: The aim of the study was to examine the effects of an intense stretch on selected serum-based muscle inflammation biomarkers. Methods: A randomised within-subject crossover trial was conducted with 12 healthy recreationally active males (age: 29±4.33yrs, mass: 79.3±8.78kg, height: 1.76±0.06m) participating in both an intense stretching and control intervention. During the stretch intervention the hamstrings, gluteals and quadriceps were exposed to an intense stretch by the same therapist, in order to standardise the stretch intensity for all participants. The stretch was maintained at a level rated as discomfort and/or mild pain with use of a numerical rating scale (NRS). Each muscle group was stretched for 3 x 60 seconds for both sides of the body equating to a total of 18 minutes. During the control intervention, participants rested for an equivalent amount of time. A 5ml blood sample was collected pre-, immediately post, and at 24h post for both conditions to assess the levels of interleukin (IL)-6, interleukin (IL)-1β, tumour necrosis factor (TNF)-α, and high sensitivity C-reactive protein (hsCRP). Participants provided information about their level of muscle soreness 24, 48, and 72h post treatment, using a numeric rating scale. Results: hsCRP increased significantly at 24h compared to control and immediate post stretch intervention, for time (p=0.005), and time x condition (p=0.006). No significance was observed for IL-6, IL-1β or TNF-α (p>0.05). Conclusion: It is observed that intense stretching may lead to an acute inflammatory response supported by the significant increase in hsCRP.



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Introduction

Stretching refers to movement applied by an external and/or internal force principally aimed at increasing joint range of motion (ROM) ¹. Individuals engage in stretching programmes for reducing muscle soreness and risk of injury, increased mobility and gait, as well as for improvement in athletic performance²⁻⁵.

Stretching is a complex time-dependent condition relying on intensity, duration and frequency ⁶. Of these three factors, intensity, defined as the magnitude of force applied to a joint during stretching ⁷, may directly influence ROM levels ⁶. Intensity may play a primary role in determining stretching outcomes; if it is too low it may induce an elastic response with little or no ROM gains, whereas if the applied force is too high it may trigger an inflammatory response ⁸. Acute inflammation refers to a generalized response of the body to tissue injury (i.e., chemical, thermal or mechanical), with the sole purpose of healing ⁹

A previous study comparing different stretching types, concluded that static stretching produced higher levels of delayed onset muscle soreness (DOMS) than ballistic stretching ¹⁰. It revealed that stretching was associated with the release of creatine kinase (CK), a marker of muscle damage ¹⁰. In turn, muscle damage has been associated with the release of pro-inflammatory cytokines, namely IL-6, IL-1, and TNF- α , which have overlapping functions in the immune response¹¹⁻¹⁵. Of the proinflammatory cytokines released, IL-6 features prominently in the release of C-reactive protein (CRP), a principal downstream mediator of the acute phase response ^{16,17}, stimulated in response to physical trauma¹⁸. However, it is not entirely clear whether intense stretching is responsible for an inflammatory response.

In this study, measurement of high sensitivity C-reactive protein (hsCRP) was utilised as a method for quantifying CRP in serum. Studies conducted with apparently healthy individuals require hsCRP methods¹⁹, allowing for the detection of CRP levels an order of magnitude lower than traditional assays, enabling measurement of low-level elevations in CRP where there was local, low grade inflammatory component²⁰.

Therefore, given the dearth of relevant data, the aim of this study was to examine the effect of a mechanical force in the form of an intense stretch on inflammatory biomarkers (IL-6, IL-1 β and TNF- α), the acute phase protein CRP, and participants' perceptions of muscle soreness.

Methods

Participants

Twelve recreationally active athletes ("Mean \pm SD") (age: 29 \pm 4.33 yrs, mass: 79.3 \pm 8.78 kg, height: 1.76 \pm 0.06 m) were recruited for the study. Each participant read and signed an informed consent form and answered a health and safety questionnaire, with the rights of each participant being protected. The University of Wolverhampton Ethics Committee granted ethical approval. Participants were advised to refrain from any new forms of physical activity that may cause DOMS.



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Exclusion criteria included any form of physical limitations with regard to their hips, knees and ankles.

Power Calculations

C-reactive protein was selected as the primary end-point for its importance as an inflammatory biomarker as it has been previously assessed pre- and post-exercise in stretching²¹. Assuming a detectable difference of 2 mg/L with 2 mg/L standard deviation, a 80% power with an alpha level of 5%, a sample of 11 participants was required; to allow for potential drop-outs we recruited 12 participants (nQuery Advisor v 6.0, Statistical Solutions, MA, USA)

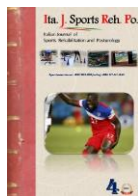
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Procedures

Each participant was randomised into an intense stretch or control group using a computer-randomising program (www.sealedenvelope.com). They were all tested in a controlled setting at the University of Wolverhampton's, physiology laboratory. Participants acted as their own controls by taking part in both the intense stretching and control conditions, with testing set a week apart. With the clearance of CRP from the plasma having a biological half-life of 19 hours, falling by up to 50% per day afterwards, this week between conditions ensured a full clear out of any potential effects. During the first session, participants were familiarised with their respective activity (stretch intervention and/or control) and measurements for height and body mass were taken.

Intense Stretch Intervention

Participants were asked to rest in the supine position on a floor mat for 10 minutes with support provided under the knees. After the rest period, a trained therapist started stretching the muscles of the lower extremity (hamstrings, gluteals and quadriceps) for each participant. The therapist was instructed to maintain a constant pressure on the muscle groups throughout the duration of each stretch (60 seconds). With the perception of discomfort or pain varying amongst the participants, a numerical rating scale (NRS) adopted from McCaffery et al ²², was utilised in order to standardise the intensity of the stretch. This scale was anchored at zero (0) 'no pain' to ten (10) 'worst pain possible'. Since participants were required to experience pain and discomfort during each stretch during the stretch intervention, they were verbally encouraged to maintain a level equivalent to an eight out of 10 on this scale. All participants were stretched for three sets. Each set consisted of stretching the right hamstring and gluteal muscles in the supine position followed by both the right and left quadriceps muscles in the prone, proceeding with the left gluteal and hamstring muscles. The stretches were completed with no rest between sets. The total time for the completion of the three sets was approximately 18 minutes. Blood samples were collected immediately post and at 24h post stretch intervention.



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Control Intervention

Similar to the stretch intervention, participants rested on a floor mat in the supine position with support provided under the knees for 10 minutes. This position was maintained for a further 18 minutes, mimicking the time allotted for the stretch intervention. Blood samples were collected post rest ending the control session, as well as 24 hours post control session.

Biomarkers

Approximately 5 ml of the participant's blood was drawn from the cephalic vein of the arm of choice by a certified phlebotomist pre, post and 24 hours following both the intense stretching and control sessions. Serum hsCRP (eBioscience – BMS8288FF), IL-6 (eBioscience – BMS8213FF), IL-1 β (eBioscience – BMS8224FF) and TNF- α (eBioscience – BMS8223FF) were measured by means of a FlowCytomix Simplex Kit (San Diego, CA, USA).

Questionnaire

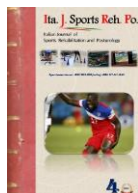
All participants were asked to provide information about their pain and or soreness levels for all muscle groups stretched during the stretch intervention, immediately post as well as at 24, 48 and 72h post intervention with use of the same 10-point numerical rating scale used during the stretch intervention. The high validity and reliability of these scales to rate a subjective sensation such as soreness have been previously established²²⁻²⁷.

Statistical Analysis

Pre analysis screening using the Kolmogorov-Smirnov test was employed to establish distribution of all the variables. Accordingly, logarithm transformation was used to overcome skewness and kurtosis in the dependent variables of interest (hsCRP, IL-6, IL-1 β , and TNF- α) in relation to the independent variables (stretch intervention and control). A repeated measures ANOVA evaluated the changes in the dependent variables over time and time X conditions (stretch interventions and control), with the LSD post hoc test evaluating any differences based on the observed main effect. With the level of significance set at $p < 0.05$ all statistical analyses were performed via SPSS (version 20.0, SPSS Inc., USA).

RESULTS

A repeated measures ANOVA revealed statistical significance for hsCRP for time ($p = 0.005$) and time x condition ($p = 0.006$), with no significance observed for IL-6 (time, $p = 0.274$; time x condition, $p = 0.537$), IL-1 β (time, $p = 0.277$; time x condition, $p = 0.815$), and TNF α (time, $p = 0.462$; time x condition, $p = 0.435$) (Table 1). With respect to soreness, no significant difference was observed

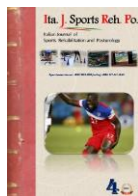


between participants in any of the muscle groups studied up to 72h post intense stretching (Table 2, Fig 2)

The LSD post hoc test revealed a significant difference between pre and 24h post measurements for hsCRP ($p=0.012$). The mean and standard deviation log transformed values for pre control and intense stretching (0.604 ± 0.155 mg/L and 0.727 ± 0.378 mg/L) compared with 24h post (0.604 ± 0.155 mg/L and 1.343 ± 0.599 mg/L) support this increase (Table 1, Fig 1). There were no withdrawals from the study.

Intervention Time Period	hs-CRP (mg/L)		IL-6 (mg/L)		IL-1 β (mg/L)		TNF- α (mg/L)	
	Control	Intense Stretching	Control	Intense Stretching	Control	Intense Stretching	Control	Intense Stretching
Pre	0.604 \pm	0.727 \pm	0.005 \pm	0.189 \pm	0.121 \pm	0.309 \pm	0.035 \pm	0.415 \pm
	0.155	0.378	0.012	0.613	0.351	0.739	0.097	1.285
Immediately Post	0.567 \pm	0.913 \pm	0.007 \pm	0.191 \pm	0.174 \pm	0.333 \pm	0.0402	0.363 \pm
	0.219	0.448	0.017	0.613	0.374	0.676	\pm 0.111	1.091
24h post	0.604 \pm	1.343 \pm	0.005 \pm	0.191 \pm	0.121 \pm	0.296 \pm	0.035 \pm	0.354 \pm
	0.155	0.599	0.012	0.613	0.351	0.693	0.097	1.052

Table 1. Summary of blood biomarkers (log transformed)



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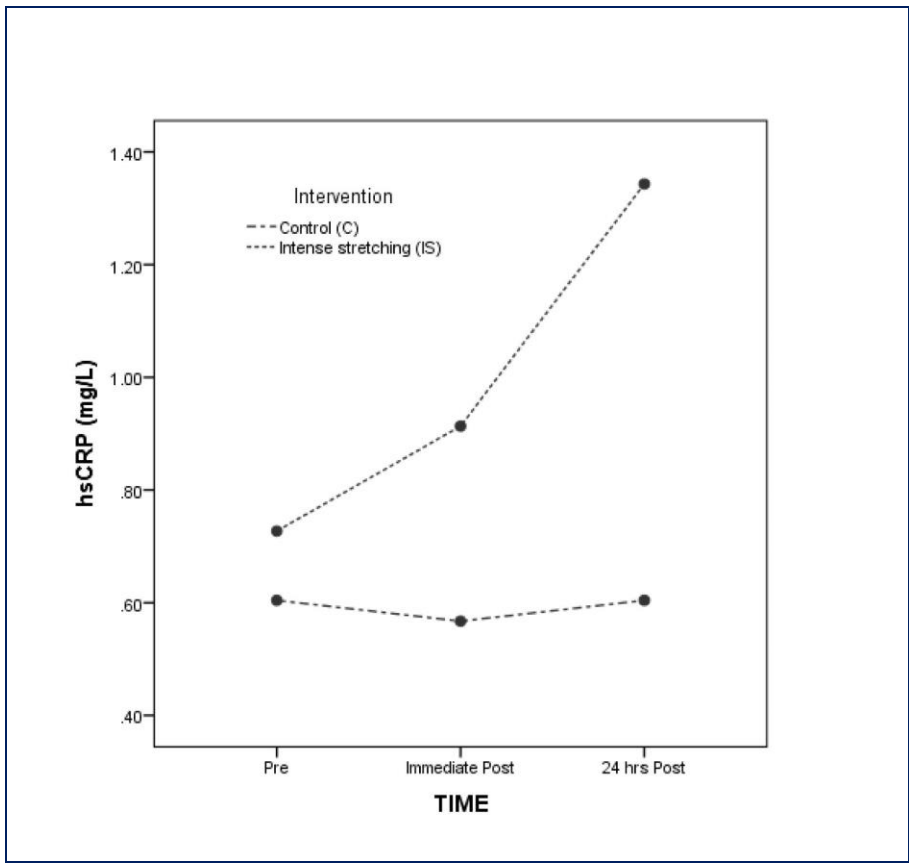


Figure 1. Change of hsCRP over time (log transformed).

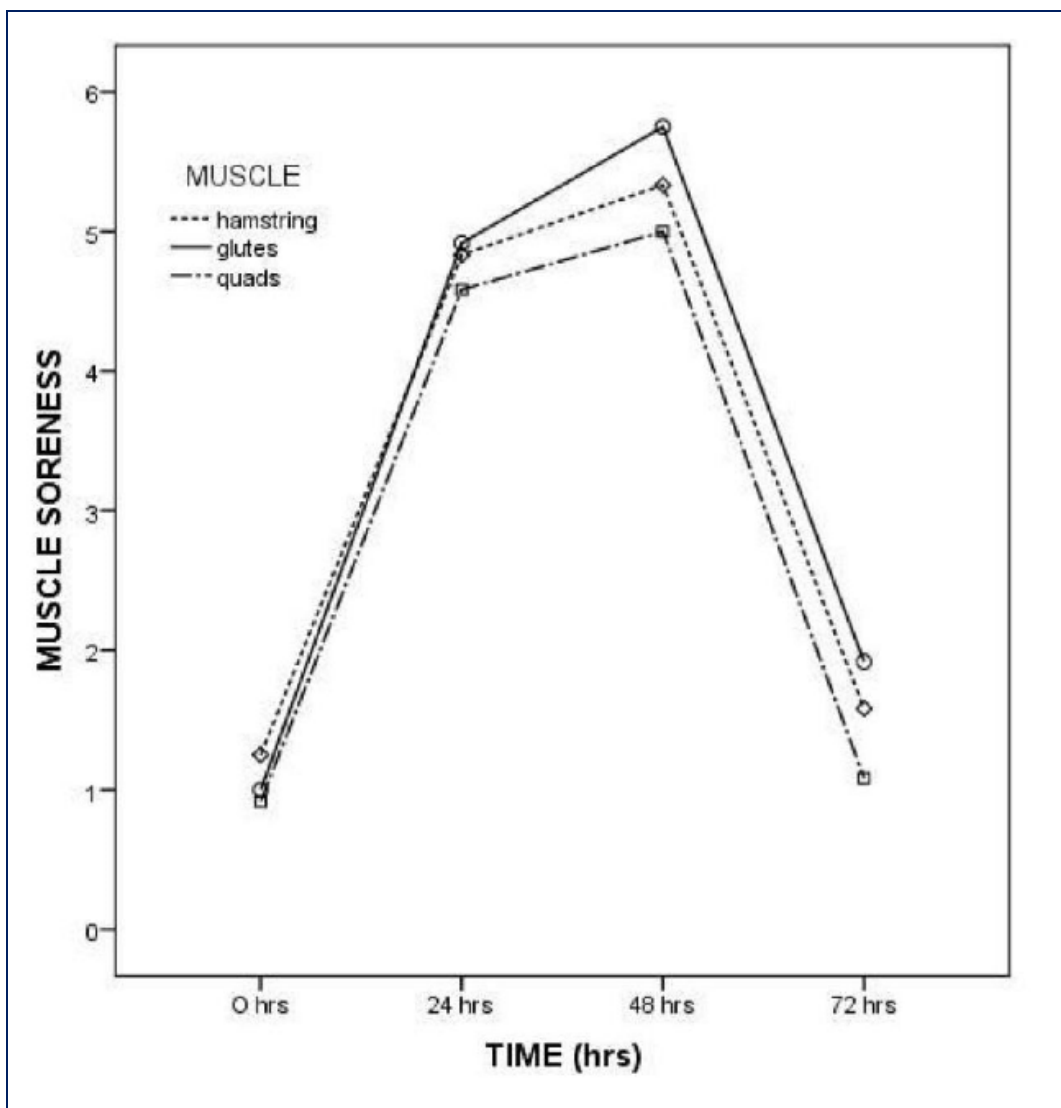
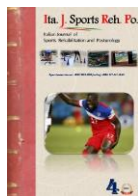
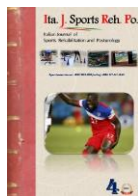


Figure 2. Perceived soreness levels over time for stretch intervention



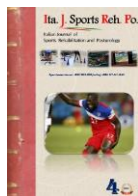
Time	Muscle		
	Hamstrings	Glutes	
0 hours	1.25±0.622	1.00±0.603	0.92±0.515
24 hours	4.83±2.791	4.92±2.75	2.58±2.78
48 hours	5.33±2.06	5.75±2.93	5.00±2.52
72 hours	1.58±1.56	1.92±2.39	1.08±0.793

Table 2. Descriptive Statistics Soreness Levels of muscles post intense stretching

Discussion

The aim of the study was to assess whether intense stretching results in acute inflammation by specifically referring to selected inflammatory biomarkers (hsCRP and pro-inflammatory cytokines). We found a significant increase in hsCRP at 24 hours post intervention compared to control and immediate post intervention. However, no such significant differences were observed in the pro-inflammatory cytokines (IL-6, IL-1 and TNF α). The reaction of muscle to the intense stretching may have triggered inflammation, since it has already been established that too much force in the form of stretching may result in inflammation⁸. In addition, though an increase in soreness levels was observed for all the muscle groups, this was not statistically significant. According to Gullick et al²⁸, the degree of discomfort causing soreness depends largely upon the intensity and duration of effort as well as the type of activity. We postulate that since participants were stretched passively while lying down, and were not involved in active stretching, this may account for the observed results.

To our knowledge, this is the first study to show the relationship of an intense stretch and acute inflammation with reference to inflammatory biomarker (hsCRP). These aforementioned biomarkers are capable of cross regulating one another. For instance, IL-1 and TNF- α can induce the production of IL-6, with IL-6 inversely regulating TNF- α expression²⁹. This synergistic



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relationship is in an attempt to regulate the immune response and the inflammatory reaction²⁹. The increase in IL-6 has been related to an acute phase inflammatory response^{11,12,14,30}, subsequently associated with a delayed increase in CRP as well as to the growth and repair process following intense exercise^{11,12}.

In line with the aforementioned studies, a delayed sharp increase in hsCRP has been observed in the present study the day after the intense stretching session. Unlike these studies, we did not observe an increase in IL-6 as expected. According to Pedersen³¹ IL-6 is produced in larger amounts than any other cytokine during exercise with a peak in concentration levels (half-life) ranging between one to two hours post prolonged activity.(i.e. marathon running). In contrast, with an eccentric exercise model IL-6 levels did not peak until 1 - 1.5 hours post activity^{32,33}. Therefore, we postulate that an increase in IL-6 may have occurred explaining the sharp increase in hsCRP seen in this study approximately 24 hours later, since the half-life for hsCRP is approximately 19 hours³⁴. Support for this view has been demonstrated in studies that have observed a relationship between IL-6 and CRP^{16,17}.

This increase in hsCRP may indirectly reflect muscle damage, because of its relationship to IL-6, as mentioned above. A study by Bruunsgaard et al³³ showed a significant correlation between IL-6 and CK ($r=0.722$, $p=0.028$) two hours post strenuous activity, suggesting that this increase in serum IL-6 may reflect a pronounced inflammation in muscle. However, our data suggest that this may not be accompanied by muscle soreness. With respect to TNF- α and IL-1 β , both increase post strenuous exercise with TNF- α exhibiting a small increase in concentration³⁵. Interleukin-1 β concentrations also increased post exercise however since they are produced locally (site of trauma) they are rapidly cleared from the circulation³⁵. Again since blood in this study was extracted 24 hours post intervention, it may account for our inability to observe any rise in these inflammatory biomarkers.

In the current study participants were not subjected to aggressive forms of activities such as rugby^{11,12}, plyometric exercise¹⁴, or a long duration run^{30,36}, but to an intense passive stretching exercise of a relatively short duration (18 minutes). Nevertheless, similar to these studies we observed a significant increase in the concentration levels of hsCRP post treatment, with the rise increasing 14 fold. It is interesting to note that the study by Kim et al showed a 23 fold increase in hsCRP in the latter half of a 200 km ultra-marathon race³⁰. Though we are not claiming that intense stretching is similar to intense physical activities of high duration or eccentric exercise, this rise in the concentration of hsCRP following intense stretching is very interesting. Increases in the concentration of this acute phase protein has been shown to increase a 1000-fold with acute inflammatory events such as trauma³⁷. This increase may be in response to local inflammation occurring at the muscles during intense stretching possibly triggering the release of IL-6, which in turn may stimulate the delayed systemic release of hsCRP as measured. In addition, according to Febbraio et al³⁸ the appearance of IL-6 into circulation may also depend on the mass of muscle recruited. This was observed in both a 160 km triathlon race³⁹ and a 6-day ultramarathon⁴⁰, where the sharp increase in IL-6 resulted in a massive increase in CRP, 50.8 and 37.5 mg/L, respectively. In relation to this study, though the value for hsCRP for 24h post was not as high (1.34 mg/L), the



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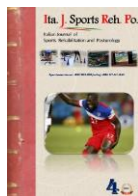
increase in hsCRP relative to the pre and immediately post values (Table 1) may also be a reflection of the intense stretching being applied to more than one muscle group (hamstrings, gluteal and quadriceps) resulting in acute inflammation. Therefore, in order to show the importance of the relationship between IL-6 and hsCRP further studies are needed with blood samples taken at least two hours post intense stretch, as well as comparing stretches that may involve just one muscle group.

In turn, the measurement of CK will help to determine if muscle damage does occur since this relationship has already been established by Bruunsgaard et al³³ with regards to IL-6.

Conclusion

In conclusion, and within the study's limitations, the present data demonstrated that intense stretching produced a several fold increase in systemic hsCRP. This rise in hsCRP levels may be attributed to inflammation occurring at muscle groups subjected to an intense stretch. Further research into the probable causes of inflammation with regard to intense stretching will elucidate if this form of activity is detrimental to the health of the muscle tissue and its proper function.

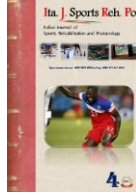
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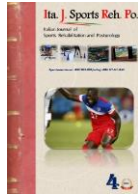
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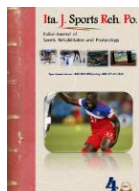
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