Stretch Intensity vs. Inflammation: A Dose-dependent Association?

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Abstract
The intensity of stretching is rarely reported in scientific literature. In this study, we examined the effects of stretching intensities at 30%, 60%, and 90% of maximum range of movement (mROM) on the inflammatory response of the right hamstring muscle. Methods: A randomised within-subject trial was conducted with 11 healthy recreationally active males over a three week period. Participants were strapped into an isokinetic dynamometer in the supine position, with the right knee fastened in a knee immobilizer. After randomising the ROM percentages, the hamstring muscle was moved to one of the three chosen ROM percentages for that week and held there for 5 x 60 seconds followed by a 10 second rest between repetitions. A 5ml blood sample was collected pre-, immediately post, and at 24 hours post intervention for high sensitivity C-reactive protein (hsCRP) assessments. Results: Significant increases in hsCRP levels were observed between 30% mROM and 90% mROM (p=0.004) and 60% mROM and 90% mROM (p=0.034), but not between 30% and 60% (p>0.05). Conclusions: Muscle stretching at submaximal levels does not elicit a significant systemic inflammatory responses.

Keywords: Stretch intensity, inflammation, hsCRP

1. Introduction
The training parameters of intensity, duration and frequency, feature prominently in stretching and training programmes (Marschall, 1999; Mujika et al., 1995), with appropriate combinations of these parameters believed to produce an adaptive response (Mujika, et al., 1995; Wyon, Felton, & Galloway, 2009).

Stretching has been defined as movement applied by an external and/or internal force in order to increase joint range of motion (Weerapong, Hume, & Kolt, 2004). Fundamental to stretching are the connective and muscular tissues and their ability to adapt to a mechanical load. Stretching is used to modify muscle length and to avoid disabilitating events such as muscle damage, which may lead to a decline in muscle performance (Wyon, Smith, & Koutedakis, 2013). If stretching is viewed as a mechanical force/load applied to the tissue, this force/load may be defined as a physical stress. Over a given area of tissue, application of this force results in stress to the tissue (σ=force/area), where the force...
may be applied in any direction [tension, shear, compression]) (Mueller & Maluf, 2002). The magnitude of force or torque being applied to the joint during a stretching exercise is the intensity of the stretch (Jacobs & Sciascia, 2011). This intensity is very important for too little force may result in an elastic response with little or no gain in ROM, however application of too much force may injure the tissue resulting in inflammation (Jacobs & Sciascia, 2011).

In response to a protocol of passive stretching in animals, it was observed that passive stretching induced an elevation of neutrophils within the skeletal muscle (Pizza, Koh, McGregor, & Brooks, 2002). Activated neutrophils have been shown to secrete different cytokines such as interleukin (IL)-1, IL-6, and tumour necrosis factor (TNF)-α (Gresnigt et al., 2012). IL-6, a proinflammatory cytokine features prominently in the release of the acute phase protein, C-reactive protein (CRP), a principal downstream mediator of the acute phase response primarily derived via IL-6 dependent hepatic biosynthesis (Pradhan, Manson, Rifai, Buring, & Ridker, 2001; Gabay, 2006; Kilicarslan, Uysal, & Roach, 2013). This response occurs in response physical trauma (Kilicarslan, et al., 2013). Both IL-6 and CRP are markers of systemic inflammation (Pradhan, et al., 2001). The release of IL-6 initiates a systemic response, with the acute phase changes reflecting the presence and intensity of inflammation, with the increase in CRP levels being proportional to the inflammatory stimulus. In this study measurement of hsCRP was conducted as a method of quantifying CRP in serum. Studies conducted with apparently healthy individuals require high-sensitivity CRP (hs-CRP) methods (Roberts et al., 2001), allowing for the detection of CRP levels an order of magnitude lower than traditional assays (Pearle et al., 2007). This enabled the measurement of low-level elevations in CRP where there was a local, low grade inflammatory component (Pearle, et al., 2007).

Given the importance of stretching on performance as well as the dearth of relevant studies on stretch intensities, the aim of the present study was to examine whether stretching at different percentages of an individual’s mROM (% mROM) may cause systemic inflammation.

2. Methods

2.1 Subjects

Eleven recreational athletes (n=11) were recruited for this study (age: 26±6.2 yrs, mass: 85.4±8.6 kg, height: 1.79±0.6 m) and there were no withdrawals. Each participant read and signed an informed consent form and answered a PARq, prior to participation in the study. The study was approved by the ethics committee of the University of Wolverhampton. Participants were advised to maintain usual levels of physical activity, refraining from the introduction of new forms of exercise that may cause delayed onset muscle soreness (DOMS) for the period of the study.

2.2 Procedure

As part of the familiarisation process, during their first visit in the laboratory, maximum range of movement (mROM) for the right hamstring muscle for each participant, using an isokinetic dynamometer (Kin Com, East Ridge, Tennessee, USA), was measured. All measurements and the relevant stretching interventions were conducted in the biomechanics laboratory of the University of Wolverhampton. Lying in the supine position, the right knee was fitted with a knee immobilizer brace which straightened and locked the knee in a straight position while preventing knee flexion. With the pelvis, left leg and the upper body immobilised, the fulcrum of the lever arm of the Kin Com was aligned with the greater trochanter of the right leg. With use of the Kin Com dynamometer, the straight leg was raised, increasing hip flexion until mROM was achieved, indicated by the sensation of maximal physical pain/effort by the participant. This procedure was repeated three times with the best value, often the last value, recorded as their mROM. Following the identification of the mROM (independent variable), the three stretch angle interventions were calculated as 30%, 60%, and 90% of the individual’s mROM. All participants completed the three stretch interventions within a three week period, being randomised into each percentage of mROM using a computer randomisation programme (www.graphpad.com).

During their second visit to the laboratory, participants were informed about the percentage of ROM that they would be tested on that day (i.e., 30%, 60% or 90% of their mROM), with the other percentages of mROM also being randomised by graphpad, and performed during the following consecutive two weeks. Prior to each intervention, a 5ml blood sample was withdrawn from the cephalic vein of the arm by a certified phlebotomist. With the right knee placed in the immobiliser, participants were strapped in the Kin Com in the supine position. The straight right leg was then moved to the selected angle by the dynamometer and held in that position for 60 seconds. After a minute, the leg was lowered to the starting position to rest for 10 seconds. The sequence was repeated another four times (total 5 x 60sec with 4 x 10sec rest in between). Post intervention blood was immediately taken, with a third sample taken at 24 hours post intervention. All stretch interventions were performed with the right leg, over three consecutive weeks. Each stretch intervention conducted on one day during the week was followed by a one week rest period. This rest period ensured a full clear out of any potential residual effects. This was decided since the clearance of CRP from the plasma has a biological half-life of approximately 20 hours (Marino & Giotta, 2008; Vigushin, Pepys, & Hawkins, 1993), falling by up to 50% per day when the acute stimulus is resolved.

2.3 High Sensitivity C-reactive protein

Blood was collected in a vacutainer (BD Vacutainer, K2E EDTA). After the whole blood was left to rest in the vacutainer for 10 minutes, it was spun at 3000 rpms in a centrifuge (SciQuip Sigma 2-6E) for another 10 minutes. Serum hsCRP (eBioscience – BMS8288FF), was measured by means of a FlowCytomix Simplex Kit (San Diego, CA,
USA). Analysis of serum CRP was conducted with use of hsCRP methods since this enabled measurement of low-level elevations in CRP where there was a local, low grade inflammatory component (Pearle, et al., 2007)

2.4 Statistical Analyses

Pre analysis screening using Shapiro-Wilk test was performed to investigate the distribution of all variables. Accordingly, logarithm transformation was used to overcome skewness and kurtosis in the dependent variable of interest (hsCRP). A repeated measures ANOVA evaluated the changes in hsCRP over time and time X % mROM, with the LSD post hoc test evaluating any differences based on the observed main effect. Homogeneity of variance was computed. In turn, a linear regression was conducted in order to determine a correlation between % mROM (independent variable) and hsCRP. With level of significance set at p<0.05 all statistical analyses were performed via SPSS (version 20.0, SPSS Inc., USA).

3. Results

The repeated measures ANOVA revealed that Mauchly’s test of sphericity was violated, for both time (p=0.001), and for time X % mROM (p=0.001). With the degrees of freedom corrected using the Greenhouse-Geisser estimates of sphericity for time (ε = 0.566) and time X %mROM (ε = 0.547), significance was revealed for time (p=0.011) but not for time X intensity (p=0.506). Tests between-subjects effects was significant (p=0.001). With time as the observed main effect, an LSD post hoc analysis reported significant differences between 30% and 90% (p=0.004) and 60% and 90% (p=0.034), but not between 30% and 60% (p=0.089). A comparison of the means of the log transformed values for hsCRP for 30% mROM *POST* (0.475±0.242 mg/L) and for 60% mROM *POST* (0.567±0.237 mg/L) as well as for 30% mROM *24h POST* (0.461±0.232 mg/L) and for 60% mROM *24h POST* (0.578±0.198 mg/L) were quite similar. However, the hsCRP concentration for 90% mROM *POST* (0.977±0.612 mg/L), and 90% mROM *24h POST* (1.016±0.656 mg/L) increased substantially (Figure 1).

![Figure 1. % mROM, hsCRP*POST*, and hsCRP*24h POST*](image)

The standardised beta (B) calculated from the linear regression between % mROM and hsCRP *POST* was 0.464 with a statistical significance of p=0.007, with the unstandardised beta coefficient (B) = 0.251, CI₉₅ = 0.075 (lower bound) – CI₉₅ = 0.427 (upper bound). The results suggest that with every increase in % mROM (from 30 to 60 to 90) there was a moderate positive increase of 0.251 mg/L of hsCRP *POST*. The standardised beta (B) for % mROM and hsCRP *24h POST* was 0.487 with a statistical significance of p=0.004. With the unstandardised beta coefficient (B) = 0.277, CI₉₅ = 0.095 (lower bound) – CI₉₅ = 0.459 (upper bound). Similar to hsCRP *POST*, a moderate-positive increase was observed, indicating that for every increase in % mROM (from 30 to 60 to 90), there was an increase of 0.277 mg/L of hsCRP *24h POST*.

4. Discussion

To our knowledge, the current study was the first to report the effects of different ranges of motion (% of mROM) on an inflammatory biomarker (hsCRP). The results suggest that stretching between 30% and 60% mROM did not elicit an
increase in blood hsCRP concentrations, with the mean values being quite similar for both post and at 24h post intervention. However, when comparing 30% mROM to 90% mROM, and 60% mROM to 90% mROM there was a marked increase in the concentration of hsCRP levels for both post and 24 hour post stretch interventions.

C-reactive protein is an acute phase protein induced during an acute phase response, in response to inflammation (Kushner & Rzewnicki, 1994). With the results observed in the study, the increased concentration of hsCRP with the 90% mROM stretch, may be suggestive that the homeostasis of the hamstring muscle tissue was upset due to the intense stretch. This observation was further supported by the linear regression which suggested a moderate positive relationship for both hsCRP post and 24h post.

The extent of muscle tissue disruption is reliant on the conjunction between the intensity and the severity of the exercise (Tiidus & Ianuzzo, 1983). With regard to stretch injuries it has been proposed that the initial mechanical injury of the stretch is followed by a secondary or collateral injury that is coincident with neutrophil invasion (Toumi, F'guyer, & Best, 2006). Neutrophils play a critical role in acute inflammation through removal of necrotic tissue or cellular debris and release of cytokines to modulate chemotaxis (Tidball, 1995). Neutrophils cause the secondary injury with the damaged myofibres responsible for the production of IL-6, a ubiquitous intercellular cytokine associated with the control and co-ordination of immune responses (Toumi, et al., 2006). Since IL-6 feature prominently in the release of CRP (Gabay, 2006; Kilicarslan, et al., 2013), the marked increase in concentration of hsCRP associated with 90% mROM, versus 30% mROM and 60% mROM may suggest a possible association of intense stretching and inflammation in lieu of strain to muscle tissue.

Studies referring to stretching intensity (Marschall, 1999; Wyon, et al., 2009; Wyon, et al., 2013) demonstrate a disagreement, with some reporting a benefit for increased ROM occurring following low intense stretch (Wyon, et al., 2009; Wyon, et al., 2013), whereas at least one study observed that maximum stretches lead to significantly ROM increases (Marschall, 1999). Regardless of what is reported with regard to stretching intensity, what is consistent is that intensity is difficult to measure quantitatively explaining the plethora of stretching articles referring to duration and frequency, which are easily quantifiable.

Assessing the degree of the intensity of a stimulus is highly variable (Melzack & Katz, 1999), with the transformation of the intensity of a physical stimulus into a perception following the power law proposed by Stevens (Baliki, Geha, & Apkarian, 2009). Perception is regarded as an internal, outwardly directed, ‘adaptive’ or ‘matching’ response to stimulation, generated within the organising system (McKay, 1963). According to Stevens’s law, sensation magnitudes grow as power functions of stimulus intensities that produce them, describing the relationships between human sensations as well as other subjective impressions and the physical stimuli evoking them (Zwislocki, 2009).

In this study, a moderate positive correlation was observed between the independent variables (30% mROM, 60% mROM, and 90% mROM) and the dependent variable (hsCRP) The increase in the concentration of hsCRP associated with the different percentages of mROM may potentially suggest a method for quantifying stretch intensity using a blood biomarker. More research is needed to verify such a hypothesis.

5. Conclusions

The current data revealed that increases in the % mROM is associated with an increase in hsCRP. Since hsCRP is associated with inflammation, the optimal intensity for not causing inflammation was between 30% mROM - 60% mROM, suggesting that at these intensities one is less likely to cause injury to muscle. Therefore, athletes and therapists need to be aware of stretch intensity, and it’s potential for causing inflammation. To avoid such inflammation, submaximal stretching should be a preferred exercise mode as opposed to maximal intensities. Future studies need to determine what would be the optimal stretch intensity within the 30% – 60% of an individual’s mROM.

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