Heart and musculoskeletal hemodynamic responses to repetitive bouts of quadriceps static stretching

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Abstract (250 w)

The role of sympathetic and parasympathetic activity in relation to the repetitive exposure to static stretching (SS) on heart and musculoskeletal hemodynamics in stretched and resting muscles is still a matter of debate. The aim of the study was to determine cardiac and musculoskeletal hemodynamics to repetitive-bouts of unilateral SS. Sympathetic and parasympathetic activity contribution to the central hemodynamics and local difference in circulation of stretched and resting muscles were also investigated. In eight participants, heart rate (HR), cardiac output (CO), mean arterial pressure (MAP), HR variability (HRV), blood pressure variability (BPV), blood flow in passively stretched limb (SL) and control (CL, resting limb) were measured during 5 bouts of unilateral SS (45s of knee flexion and 15s of knee extension). SS increased sympathetic (≈20%) and decreased parasympathetic activity (≈30%) with a prevalence of parasympathetic withdrawal. During SS, HR, CO, and MAP increased by ≈18 BPM, ≈0.29 $l \cdot min^{-1}$, ≈12 mmHg, respectively. Peak blood flow in response to the 1^{st} stretching maneuver increased significantly (+377±95 $ml \cdot min^{-1}$) in the SL, and reduced significantly (-57±48 $ml \cdot min^{-1}$) in the CL. This between-limb difference in local circulation response to SS disappeared after the 2^{nd} SS bout. These results indicate that heart hemodynamic responses to SS are primarily influenced by the parasympathetic withdrawal rather than by the increase in sympathetic activity. The balance between neural and local factors contributing to blood flow regulation was affected by the level of SS exposure, likely associated with differences in the bioavailability of local vasoactive factors throughout the stretching bouts.

New & Noteworthy

Repetitive-exposure to static stretching (SS) on heart and musculoskeletal hemodynamics in stretched and remote muscles may be influenced by neural and local factors. We documented that SS-induced heart hemodynamic responses are primarily influenced by parasympathetic withdrawal. The balance between neural and local factors contributing to the regulation of musculoskeletal hemodynamics is dependent on SS exposure possibly because of different local vasoactive factors bioavailability during the subsequent stretching bouts.

Keywords

Hemodynamics, stretching, sympathetic activity, parasympathetic activity

Glossary

SS, passive static stretching; FL, flexion phase; EX, extension phase; FBF, femoral blood flow; SL, stretched leg; CL control resting leg; HR heart rate; CO, cardiac output; SV, stroke volume; MAP, mean arterial pressure; VC, vascular conductance; HRV, heart rate variability; RMSSD, root mean square of the squared differences of successive RR intervals; LF, low frequency; HF, high frequency; BPV, blood pressure variability; SBP, systolic blood pressure; DBP diastolic blood pressure; Δpeak, relative changes; AUC, area under the curve.

Introduction

The control of musculoskeletal blood flow is a complex integrative mechanism that equalizes the vasoconstrictive and vasodilatory triggers to distribute blood flow within and between skeletal muscles (6, 36). The homeostasis of systemic (neural) and local factors is crucial for the control of skeletal muscle blood flow, with an important factor being the balance between sympathetically-mediated vasoconstriction and the vasodilation induced by local factors, such as nitric oxide (NO) (15). At rest, the equilibrium between vasoconstriction and vasodilation results in a smooth muscle tone near 60% of the total resistance vessel vasodilatory capacity (39). However, when this balance is altered by the increases in muscle sympathetic nerve activity, the vasculature of resting skeletal muscles can achieve elevated levels of vasoconstriction (39).

During physical exercise, general agreement exists on the key role of the autonomic nervous system in the response to voluntary skeletal muscle activation (30). Indeed, sympathetic and parasympathetic activity are modulated, at least in part, by the parallel activation of the central motor pathways and the feedback that arises from mechano- and metabo-receptor activation in the skeletal muscle(1, 10, 16, 42). Differently to physical exercise, static stretching (SS) is characterized by the absence of exercise-induced increase in muscle metabolism and the lack of central command, both of which would generate a sympathetic-mediated increase in heart rate. Hence, the increase in HR observed during SS has been attributed to a decrease in vagal activity and the concomitant small rise in sympathetic discharge (9). However, whether or not cardiac output (CO), stroke volume (SV), and mean arterial pressure (MAP) response to passive SS is primarily influenced by the sympathetic-mediated activation or by the parasympathetic withdrawal is still poorly understood (30).

The acute physiological effects of passive SS on the above-mentioned heart and musculoskeletal hemodynamics have been recently debated (18, 19, 42), documenting either

no detectable change in net blood flow, MAP, and popliteal artery vascular conductance (VC) (18, 19) or an increase in heart rate (HR) and CO, coupled with a hyperemia to the stretched skeletal muscles (42). The latter observation has been likely explained by the mechano-reflex activation (42) and local nitric oxide (NO) release (29, 37). Other seminal studies on this subjects issue, though, reported that the HR and blood pressure responses to calf muscle stretch are independent of the metabo-reflex activation (10) and can decrease spontaneous baroreflex sensitivity and other indexes of vagal tone (7). However, the mechanisms underpinning the contribution of local (vasodilatory) and systemic (vasoconstrictive) factors to these physiological changes and their transitory nature (~35 s) are not completely understood. Further insights on this phenomenon may come from a new approach involving repetitive exposures to SS. Given the generally low bioavailability of NO as a local vasodilator factor (22), several bouts of SS should deplete temporarily the NO reserve and blunt the SS-induced hyperemia. Moreover, whether or not the mechano-reflex induced increases in sympathetic activity may differently affects the circulation of stretched and remote muscles not directly involved in SS is not clear.

Therefore, the aim of the present study was to compare the heart and musculoskeletal hemodynamic responses to repetitive bouts of unilateral *quadriceps* muscle SS. The contribution of sympathetic and parasympathetic activity to the heart hemodynamics was also investigated. Specifically, by studying HRV, heart hemodynamics, blood pressure variability (BPV), blood flow in passively stretch limb (SL), and control (CL, resting limb) during 5 bouts of unilateral SS (45 s of knee flexion and 15 s of knee extension), we tested the following hypotheses: (i) the heart hemodynamic responses to SS might be primarily influenced by the parasympathetic withdrawal rather than by the increase in sympathetic activity; (ii) the blood flow response to SS in the passively stretched limb would be initially greater in comparison to the contralateral limb; and (iii) this regional difference in peripheral

circulation response to SS would be dependent on the repetitive exposures to SS (number of bouts) that are administered to the investigated muscle.

Methods

Participants: Eight young healthy men (age: 25 ± 2 yrs; body mass: 71 ± 8 kg; stature: 1.80 ± 0.06 m; mean ± standard deviation) participated in this study. None of the participants were smokers and all were moderate physically active. All procedures conformed to the standards set by the Declaration of Helsinki and were approved by the ethical committee of the University of Milan. The participants gave written informed consent prior to their participation after full explanation of the purpose of the study and of the experimental procedures. The participants reported to the laboratory in the morning (9 - 10 AM) in a fasted state. They were asked to abstain from consuming caffeine 24 hours prior the test, and to report to the laboratory without any form of physical exercise of heavy intensity in the previous 48 hours.

Experimental design: After a first visit for familiarization purpose, the participants reported to the laboratory a second time, during which single leg SS was performed. All the experimental procedures, from which experimental data were collected, were accomplished during the second visit.

Static stretching (SS): The participants rested in a supine position for 20 minutes before starting the data collection and remained in this position throughout the entire duration of the data collection (Figure 1). As previously reported, SS protocol consisted of 5 minutes of resting baseline followed by passive static knee flexion for 45 s and passive knee extension for 15 s, repeated five times (5, 20, 21). During the entire SS protocol, knee extensors were

stretched by the same operator up to a point of discomfort lower than 2. This cut-off of discomfort level was chosen in the current investigation in order to minimize the activation of peripheral pain pathways that might interact with group III and IV afference feedback and potentially accentuate the central hemodynamic response (1). The level of discomfort was assessed by a 0-10 visual analogue scale, being 0 = no discomfort at all and 10 = maximum discomfort (25). The knee joint angle was continuously recorded using a dual-axial goniometer (mod. TSD 130A, Biopac System, CA, USA). Force output between the passively stretched leg and the operator arms was recorded during the protocol by a load cell (model SM-2000 N, Interface, Crowthorne, UK). Specifically, the load cell was positioned 5 cm above the ankle of the passively stretched leg and a member of the research team pushed perpendicularly the load cell in order to stretch the leg extensor for 45 seconds (Figure 1). The mean force output during the 45 seconds of the consecutive FL of the SS protocol was than recorded.

***Central hemodynamics*:** HR, SV, CO, and MAP were determined on a beat-by-beat basis using a finger photoplethysmography device (FinometerPro Finapres Medical Systems, Amsterdam, The Netherlands). The photoplethysmographic cuff was placed on the third finger of the left hand. The height adjustment sensor and reference were positioned following the manufacturer's instructions. The blood pressure signal was calibrated in accordance to the procedure indicated by the manufacturer. SV was estimated using the Modelflow algorithm (Beatscope version 1.1a; Finapres Medical Systems) (4). CO was then calculated as the product of HR and SV. The same method has been documented to accurately track CO during exercise (2, 35), and, as reported in previous investigations, the absolute changes from rest values have been demonstrated to be accurate (38, 40, 41).

Femoral blood flow (FBF): The measurements of arterial blood velocity and vessel diameter were performed in the passively stretched leg (SL) and control resting leg (CL), distal to the inguinal ligament and proximal to the deep, superficial femoral bifurcation with two Logiq S7pro ultrasound systems (General Electric Medical Systems, Milwaukee, WI, USA). The systems were equipped with 12-14 MHz linear array transducers. The common femoral artery diameters were determined along the central axis of the scanned areas. The blood velocity (v) was measured using the same probe at a frequency of 5 MHz. The measurements of v were obtained second-by-second with the probe positioned to maintain an insonation angle of 60° or less and the sample volume were centered and maximized according to vessels size. After arterial diameter and mean v (v_{mean}) assessment, FBF was automatically calculated using the Logiq S7pro software as:

$$FBF = v_{mean} \cdot \pi \cdot (\frac{vessel\ diameter}{2})^2 \cdot 60$$

where FBF is in milliliters per minute. All scanning and blinded analyses were performed by experienced and skilled sonographers. To account for potential differences in MAP, VC was calculated as: FBF/MAP.

Heart rate variability (HRV): The computer analysis of spontaneous HR and inter-beat intervals oscillation in consecutive cardiac cycles has been recognized to be a credible quantitative marker to assess the activity of the sympathetic and parasympathetic branches of the autonomic nervous system (8). Several indexes have been developed, in both the time and frequency domain, in order to characterize the contribution of the vagal and the sympathetic efferent activity to the cardiovascular control. In the time domain, the root mean square of the squared differences of successive RR (RMSSD) estimates short term variation of HR (8), thus detecting high frequency oscillations caused by parasympathetic activity. In the frequency

202 domain analysis, the variance of the signal, namely the distribution of power as a function of
203 frequency (power spectral density, PSD), is calculated by means of short fast Fourier
204 transform and, according to the frequency bands classification proposed by the HRV Task
205 Force (8), it is divided in three components: very low frequency, low frequency (LF) and high
206 frequency (HF). The very low frequency component (≤ 0.04 Hz) is not usually considered in
207 short recordings (5 minutes). Power component of LF band (0.04-0.15 Hz) includes
208 sympathetic as well as parasympathetic influences, while HF (0.15-0.4 Hz) band is mainly
209 influenced by the efferent activity of the vagal tone (8). Both markers could be measured in
210 absolute units of power (ms^2) and in normalized units (n.u.). While the former provides
211 information about the total power of the band, the latter allows to assess the fractional
212 contribution to HR oscillation given by the two bands (LF and HF), excluding the very low
213 frequency component (43). Therefore, the ratio between normalized LF and HF (LF/HF) is
214 computed as an index of the sympatho-vagal balance (3).
215 During this study HR was derived from the electrocardiographic signal (ECG) collected by
216 the photoplethysmography device at 500 Hz. R-peaks of each QRS complex from the
217 continuous ECG signals were detected by a derivative-threshold algorithm. The inter-beat
218 interval series (R-R interval tachogram) was obtained as the difference between the
219 occurrence times of consecutive R-peaks. An expert operator checked the signal and, in case
220 of ectopic beats, the RR series were corrected through a cubic spline interpolation (28). The
221 time domain and frequency domain analysis of the R-R series were conducted considering 5
222 minutes of signal for each condition (Rest Vs Stretching) (8). In view of the frequency
223 domain analysis, the unevenly time-sampled tachogram was interpolated at 4 Hz by a cubic
224 spline function and successively down sampled at 1 Hz. The PSD, was calculated by means of
225 short fast Fourier transform and the normalized LF and HF bands were subsequently obtained
226 to compute LF/HF values. The very-low-frequency component requiring longer data series
227 was not addressed in the present study.

228 The cardiac sympatho-vagal balance was obtained by the LF/HF index while variation in
229 parasympathetic activity was estimated, from the time domain analysis, by the RMSSD.
230
231 ***Blood pressure variability (BPV):*** Blood pressure measurement, if collected concurrently
232 with HR, is known to allow the simultaneous assessment of markers of efferent sympathetic
233 vascular modulation (31). In light of this, the beat-by-beat systolic blood pressure (SBP) and
234 diastolic blood pressure (DBP) series were obtained from the continuous blood pressure
235 signal to characterize blood pressure oscillations (blood pressure variability, BPV). By the
236 previously described photoplethysmography approach, SBP and DBP were measured for 5
237 minutes during baseline condition, and 5 minutes during the SS procedure. SBP series was
238 composed by the maximum of BP in each RR interval, while the DBP series was made by the
239 minimum of BP following each SBP detection. Being DBP changes negatively related to
240 muscle sympathetic nerve activity burst incidence (23, 34), changes in the mean values of
241 DBP series were computed and considered as an index of the (vessels) sympathetic activity.
242 Moreover, as like HRV analysis, also SBP series can be evaluated in the frequency domain
243 therefore being ~~as~~ oscillation in the LF component of the SBP power spectral density (LF_{SBP})
244 associated with an increase in the sympathetic drive (32), it was used as an additional BPV
245 marker of sympathetic activity (11).
246
247 ***Data collection and analysis:*** SV, CO, MAP, ECG, and knee joint angle and force output
248 underwent A/D conversion system (mod. UM150, Biopac System, Santa Barbara, CA, USA)
249 and were simultaneously acquired (1000 Hz) by commercially available data acquisition
250 software (AcqKnowledge 4.2, Biopac Systems, Goleta, CA, USA). The software allowed
251 beat-by-beat analysis of HR, SV, CO and MAP throughout the experimental protocols. v_{mean}
252 was analyzed with 1Hz resolution on the Doppler ultrasound systems (GE Logiq S7pro) for
253 30 s at rest and during the 5 minute of repetitive single leg SS. From the velocity and femoral

artery diameter, net FBF was calculated on a second-by-second basis. Prior to analysis, all hemodynamic data were smoothed using a 3 s rolling average. As the response to passive stretching is transient and vary between individuals, a peak response was determined for all variables on an individual basis. Maximal absolute (Peak), relative changes (Δpeak) and the area under the curve (AUC) were determined for each subject in all measured variables.

Statistical analysis: Raw data were analysed using a statistical software package (IBM SPSS Statistics v. 22, Armonk, NY, USA). In light of a previous article of our group (42), where a difference of about 15% in femoral blood flow (main outcome) was observed under SS, a sample size of eight participants was selected to ensure a statistical power higher than 0.80 with a type 1 error <0.05. To check the normal distribution of the parameters, a Shapiro-Wilk test was applied. Student's t-test was utilized to determine potential differences between baseline and passive SS measurements in the HRV and BPV normally distributed data. A two-way ANOVA for repeated measures [time (6 levels: baseline + 5 stretching bout) x limb (2 levels: stretched (SL) and control limb (CL))] was used to establish differences among conditions for peripheral hemodynamic data. A two-way ANOVA for repeated measures [time (6 levels: baseline + 5 stretching bout) x knee joint position (2 levels: flexion (FL) and extension (EX))] was used to establish differences among conditions for central hemodynamic data. A one-way ANOVA [time (5 stretching bouts)] was used to establish differences for ROM and FO. A Tukey's post hoc test was applied to define the location of the difference, when necessary. If Shapiro-Wilk test did not disclose a normal distribution, for central hemodynamic, knee-joint angle of stretched limb, and the force output during the repetitive bouts of SS, a repeated measure ANOVA on ranks test was applied. A Wilcoxon-Signed Rank test was conversely applied whereby HRV and BPV variables failed the normality test. The level of significance was set at $\alpha < 0.05$. Unless otherwise stated, data are presented as mean ± standard error of the mean.

Results

All the participants took part in this experimental protocol without reporting discomfort during the stretching procedures. On a scale from 0 to 10, the average discomfort across all 5 stretch cycles on the passively stretched leg was 1.4 ± 1.1 and did not differ among the repetitive bouts of SS 1.3±0.9, 1.6±0.9, 1.6±1.3, 1.7±1.1and 1.5±1.2 during 1st, 2nd, 3rd, 4th and 5th FL respectively.

Heart rate variability (HRV) response to passive static stretching: the effect of 5 consecutive bouts of one leg SS on HRV indexes is summarized in Figure 2 (panel A and B). After the passive SS, RMSSD significantly dropped by ~20% (p=0.041, Figure 2, panel A), whereas the LF/HF index significantly increased by ~63% p = 0.039; (Figure 2, panel B).

Blood pressure and BPV response to passive static stretching: After 5 consecutive bouts of one leg SS, the Wilcoxon Signed Rank Test found a significant increase in mean DBP values (~13%, p=0.008; Figure 2, panel C) whereas no changes occurred in LF_{SBP} (Figure 2, panel D).

Central hemodynamics during flexion (FL) and extension (EX) phases of consecutive bouts of one leg static stretching: All central hemodynamic values during 5 consecutive bouts of one leg SS are summarized in Table 1 and Figure 3. ANOVA disclosed significant main effects in MAP for Time (F = 42.7; $P < 0.001$) and knee-joint position (F = 1702; $P < 0.001$), as well as a time x knee joint position interaction (F = 135; $P < 0.001$). Similarly, main effects for Time (F = 59.1; $P < 0.001$) and knee-joint position (F = 62.7; $P < 0.001$) and time x knee joint position interaction (F = 3.1; p = 0.012) were retrieved in SV. In HR no main effect for time was found (F = 0.39; p = 0.85), while there was a main effect for factor knee-joint

306 position (F = 1266; p< 0.001), and an interaction between time and knee joint position (F =
307 44.4; $p < 0.001$). Similarly, in CO no main effect CO for time was retrieved (F = 0.98; p =
308 0.43), while a main effect for knee-joint position (F = 29.6; p < 0.001) and a time x knee joint
309 position (F = 2.4; p = 0.046) were found. During the 1st FL procedure MAP was initially
310 increased by 5% (p < 0.05; Figure 3, panel A). This transitory MAP increase was followed by
311 a significant drop 8% (p < 0.05) and a subsequent rise 11% (p < 0.05) of the MAP. This MAP
312 sinusoidal response to SS was not present during the 2nd, 3rd, 4th and 5th FLs, while there was a
313 robust and sustained increase in MAP- Δpeak and AUC (Table 1 and Figure 3). During all the
314 passive knee extension phases (EXs) of SS, MAP rapidly dropped to values similar to
315 baseline (Table 1; Figure 3, panel A). During the 1st FL, SV increased by ~22 ml (p < 0.05;
316 Figure 3, panel B), and remained significantly elevated from baseline for ~30 s. This SV-
317 Δpeak was blunted (~13 ml) during the 2nd, 3rd, 4th and 5th FLs, while the response was longer
318 42 s (Table 1 and Figure 3). During all the passive extension phases (EXs) of SS, SV
319 increased by ~13 ml (Table 1; Figure 3, panel B). During all the FLs phases of SS, both HR
320 and CO rapidly increased by ~18 BPM and 0-31 $l \cdot min^{-1}$ respectively (p < 0.05; Figure 3,
321 panels C and D). HR and CO values remained significantly elevated from baseline for ~42 s.
322 During all the EXs phases of SS, HR and CO rapidly dropped to values similar to baseline
323 (Table 1; Figure 3, panels C and D).
324
325 ***Knee joint range of motion (ROM) and force output (FO) during consecutive bouts of SS***
326 The ROMs and FO attained during the consecutive bouts of SS are reported in Table 2. Both,
327 ROM and FO did not increase from the 1st to the 5th SS bout, and no differences were found
328 in any comparison (p=0.203 and p=0.993, respectively).
329
330 ***Peripheral hemodynamics during flexion (FL) and extension (EX) phases of consecutive***
331 ***bouts of unilateral static stretching:*** All peripheral hemodynamic outcomes recorded during

5 consecutive bouts of SL and resting-CL are summarized in Table 2 and Figure 4. ANOVA disclosed significant main effects in FBFpeak for Time ($F = 207$; $P < 0.001$) and limb ($F = 2741$; $P < 0.001$), and a significant time x limb interaction ($F = 270$; $P < 0.001$). Similarly, main effects in VC-peaks for factor Time was ($F = 190$; $P < 0.001$) and limb ($F = 2453$; $P < 0.001$) and a significant time x limb interaction ($F = 243$; $P < 0.001$) were found. In the SL, during the 1st FL procedure both FBF and VC were transiently increased from the 3rd to the 24th second (Figure 4, panels A and B). This initial stretch-induced hyperemic response of SL, in terms of Δpeak, and AUC, was greater in comparison to the 2nd, 3rd, 4th and 5th FLs. Interestingly, a local reduction of FBF and VC was present in the SL from the 3rd, to the 5th FL. Notably, during all the FL phases of SS, FBF and VC of CL rapidly dropped below the baseline value (Table 2; Figure 4, panels A and B). During the 3rd, 4th and 5th FL procedures FBF and VC of SL and CL were similar. During all the EX phases of SS, FBF and VC of SL rapidly increased by ~455 ml/min and ~72 ml/min/mmHg, respectively (Table 2; Figure 4, panels A and B). While at contrary, FBF and VC of CL rapidly increased to values similar to baseline (Table 2; Figure 4, panels A and B).

Discussion

Although heart and musculoskeletal hemodynamic response to SS have been recently investigated, the role of sympathetic and parasympathetic activity in relation to heart hemodynamic and musculoskeletal circulation in stretched and contralateral muscles has received so far only little attention. In the present study, we investigated the heart hemodynamics and musculoskeletal blood flow responses to repetitive bouts of unilateral SS of the *quadriceps* muscle. The contribution of the sympathetic and parasympathetic activity to the heart hemodynamics and local difference in the circulation of stretched and contralateral muscles were also investigated. In accordance with our hypothesis, the main findings of the current study were: (i) the heart hemodynamic responses to SS seemed to be primarily

influenced by the parasympathetic withdrawal rather than the increase in sympathetic activity; (ii) the stretch-induced hyperemia in the passively stretched limb was initially greater in comparison to the contralateral limb; and (iii) this local difference in musculoskeletal hemodynamic response to SS was dependent on the repetitive exposures to SS (number of bouts), indicating that after a transiently local hyperemia, a peripheral vasoconstriction occurred presumably triggered by the stretch-induced mechano-reflex.

Interaction between skeletal muscle stretching, autonomic nervous system and central hemodynamics: The present findings advance the knowledge on the interactions between autonomic nervous system and central hemodynamics in the response to SS, during which the sympathetic and parasympathetic activity are partially modulated by the feedbacks that arise from mechano-receptors activation in the skeletal muscle (1, 10, 42). The data from the current investigation indicate that SS influences the sympatho-vagal balance. However, the rise of the LF/HF index, describing the sympatho-vagal balance of the heart, could occur as a result of an increase of the sympathetic activity, a withdrawal of the vagal tone or a combination of both. Given the decrease of RMSSD, a direct marker of the parasympathetic drive, and the lack of any changes in LF_{SBP}, a marker of the sympathetic activity, it is reasonable that the increase of LF/HF index during SS could be ascribed mainly to the parasympathetic withdrawal in combination with an increase in sympathetic activity (Figure 2). Similarly to the blood pressure effect induced by the exercise pressure reflex, the mean DBP rise found in the present study could be likely due to the increases in intramuscular pressure produced during flexion phases of SS (30). In accordance with a previous study (9), such stretch-induced changes in autonomic nervous system discharge were coupled with significant central hemodynamic responses (Table 1, Figure 2), supporting the first hypothesis that not only the cardioacceleration, but also the increase in CO, SV and MAP are primarily influenced by the parasympathetic withdrawal triggered by the mechano-reflex (9, 30).

Stretch induced hyper- and hypo-emia in the passively stretched and contralateral limb: From the current study, the high-resolution analysis of peripheral circulation of the passively SL revealed a marked hyperemia in response to the 1st stretching maneuver, which was likely explained by local release of vasoactive substances overcoming sympathetically-mediated vasoconstriction that was likely more relevant at peripheral level in comparison to central level (37, 42). Conversely, the concomitant FBF and VC were significantly reduced in the CL. This phenomenon could explain the rise in mean DBP and be likely ascribed to the stretch-induced increases in sympathetic activity, at vascular level, evoked by the mechano-reflex activation triggered by SS in the SL (Table 2 and Figure 4). Indeed, the current data on the stretch-induced hyperemia are in agreement with previous studies that adopted a similar technical approach (12-14, 26, 38, 42). However, this hyperemia in the SL is partially in disagreement with the data reported by a recent study (19), in which the investigators observed no detectable change in net blood flow and VC measured at popliteal artery during 5 minutes of SS on the plantar flexors. This discrepancy could be possibly explained by the volume of the stretched muscle, which, in turn, can generate different NO release and greater hyperemia in a larger muscle (42). However, it could be argued that it would be the same when normalized to muscle mass, thus the concentration of NO in the muscle would be comparable resulting in similar impact on vasodilation. Alternatively, this discrepancy may be explained by differences in the magnitude of muscle fiber lengthening. Specifically, a change in joint angle of 90 degrees at the knee and ankle may not yield the same change in muscle fiber length of the muscles that span those joints, due to differences in tendon length and fiber pennation angle. Moreover, in a recent murine study has been demonstrated that passive stretching does not increase NO synthase activity in skeletal muscle (17). Therefore, other physiological mechanisms are potentially involved in this phenomenon. To the best of the authors' knowledge, the current investigation is the first study that have documented a SS-

induced hypo-emia on a remote muscle not involved in the stretching procedure, therefore a comparison with previous studies is not possible.

Transitory nature of musculoskeletal stretch-induced hyperemia: From the current study, the analysis of peripheral circulation during consecutive bouts of passive *quadriceps* muscle SS revealed that the hyperemia in response to the 1st stretching maneuver rapidly disappeared during the 2nd SS procedure. Interestingly, during the 3rd, 4th and 5th repetitions of SS the blood flow to the stretched muscle was significantly reduced, overlapping that in the CL. This finding suggests that the hyperemia evidenced in the 1st SS maneuver was likely mediated by local factors, but due to the plausible reduced bioavailability of these factors, the systemic sympathetic-mediated vasoconstriction that was activated by the stretch-induced mechano-reflex prevailed thereafter. Due to the transitory and unstable nature of these local vasoactive factors, such as NO, their direct measurements are rather complicated. In the past NOS inhibitors activators was utilized to understand the role of NO during dynamic passive stretching (37). However, to our knowledge, no studies have investigated the role of NO during SS. In a prospective view, future potential studies could explore the individual contributions of peripheral vasodilators, such as NO, and mechanoreceptor activation on this immediate hyperemic response. For instance, the use of NOS inhibitors activators and afferent blockade in separate or combined stretching trials would be interesting to compare these influences.

Data from the current study indicate no detectable change in the hyperemia of SL during all the five 15-s (EXs) of the SS protocol. Specifically, this constant FBF response during the EX phases could be likely supported by a mechanical reduction in stretch-induced peripheral resistance and the contribution of some metabolic vasodilatory factors released in response to the reduction of venous return following the muscle stretch of the muscle. Indeed,

436 SS maneuver likely collapsed the venules and veins thereby reducing venous return. The build
437 of metabolic bioproducts, not due to increased production but rather to decreased clearance,
438 might result in vasodilation and transient hyperemic response observed during the extension
439 phases. These metabolic bioproducts would be quickly washed out and therefore the
440 hyperemic response would be short lived. In a previous investigation (27), it was revealed that
441 FBF was clearly influenced by knee joint angle. In detail, FBF was documented to increase as
442 the knee was extended from the lower (90°) to the middle and upper (0°, full extension) range
443 of knee joint angle. It was concluded that the factors likely involved in this response were
444 muscle length-dependent changes in capillary tortuosity and vessel diameter (24, 33). Overall,
445 our data indicate that, in the absence of the local metabolic perturbation, triggered by
446 voluntary exercise, the balance among neural and local factors contributing to the regulation
447 of skeletal muscle blood flow, was likely dependent on the repetitive exposures to SS
448 (number of bouts) and influenced by the reduced bioavailability of local vasoactive factors
449 (i.e., NO) that are released during the initial, passive stretch of the skeletal muscle.
450
451 **Conclusions**
452 This study documented that heart hemodynamic responses to SS are primarily
453 influenced by the parasympathetic withdrawal rather than the increase in sympathetic activity.
454 The musculoskeletal hemodynamic responses documented in the SL and CL during repetitive
455 exposures to SS, suggest an initial limb-difference in local circulation response to SS, that
456 disappeared during the 3rd repetition of SS. Overall, these results indicate that, the balance
457 among neural and local factors contributing to the regulation of musculoskeletal blood flow,
458 is dependent on the SS exposure suggesting that after a transiently local hyperemia, a
459 systemic sympathetic-mediated vasoconstriction prevailed via the stretch-induced mechano-
460 reflex.
461

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Table 1: Central hemodynamics during the flexion (FL) and extension (EX) phases of consecutive bouts of one leg static stretching (SS).

			1st	2nd	3rd	4th	5th
MAP	Δpeak (mmHg)	FL	-7.1±1.2	14.2±1.3 §	11.7±1.5 §	10.8±1.4 §	11.8±1.3 §
		EX	-15.0±1.3 *	-15.1±1.4 *	-18.7±1.7 *	-19.8±1.6 *	-19.0±1.8 *
	AUC (mmHg·s)	FL	0.01±0.01	7.5±0.03 §	6.6±0.09 §	6.9±0.07 §	7.6±0.05 §
		EX	-2.08±0.01 *	-2.58±0.02 *	-2.25±0.02 *	-2.56±0.02 *	-2.88±0.03 *
SV	Δpeak (ml)	FL	21.8±2.4	13.6±2.5 §	14.3±1.9 §	12.1±1.9 §	13.0±2.2 §
		EX	16.7±2.5	9.0±2.2 §	8.1±2.9 §	10.2±1.6 §	8.0±3.2 §
	AUC (ml·s)	FL	10.6±0.32	8.3±0.28	8.9±0.22	7.9±0.22	7.1±0.24
		EX	1.2±0.02 *	0.5±0.08 *§	0.4±0.02 *§	0.6±0.02 *§	0.7±0.04 *§
HR	Δpeak (BPM)	FL	18±1.9	16±1.9	18±2.0	20±1.8	20±2.8
		EX	-16±2.1 *	-16±2.3 *	-18±2.9 *	-18±2.9 *	-18±3.8 *
	AUC (beats)	FL	11.5±0.9	8.5±0.8	11.3±0.9	12.2±0.82	12.9±0.9
		EX	-2.46±0.11 *	-2.91±0.10 *	-3.35±0.10 *	-3.36±0.11 *	-3.25±0.09 *
CO	Δpeak ($l \cdot min^{-1}$)	FL	0.32±0.08	0.26±0.07	0.25±0.09	0.35±0.09	0.27±0.10
		EX	-0.16±0.07 *	-0.30±0.05 *	-0.28±0.07 *	-0.26±0.08 *	-0.31±0.09 *
	AUC (l)	FL	0.14±0.02	0.16±0.03	0.15±0.03	0.21±0.02	0.15±0.02
		EX	-0.03±0.01 *	-0.04±0.01 *	-0.04±0.01 *	-0.04±0.01 *	-0.05±0.02 *

Δpeak, absolute change; AUC, area under the curve. Cardiac output (CO), stroke volume (SV), heart rate (HR), mean arterial pressure (MAP),
* = $p < 0.05$ from FL; § = $p < 0.05$ from 1st. Data are presented as mean ± SEM.

Table 2: Knee-joint angle, force output and peripheral hemodynamics during the flexion (FL) and extension (EX) phases of consecutive bouts of one leg static stretching (SS).

			1st	2nd	3rd	4th	5th
KJA_{SL}	ROM (°)		112±9	116±11	117±11	118±11	118±1
FO	Mean (N)	FL	52.7±9.7	53.0±9.6	50.7±9.3	51.1±9.7	50.4±10.1
FAD_{SL}	Mean (mm)	FL	0.85±0.5	0.85±0.4	0.85±0.4	0.85±0.3	0.87±0.3
	Mean (mm)	EX	0.85±0.5	0.85±0.6	0.85±0.3	0.84±0.4	0.84±0.3
FAD_{CL}	Mean (mm)	FL	0.84±0.4	0.84±0.5	0.84±0.6	0.84±0.4	0.84±0.5
	Mean (mm)	EX	0.84±0.4	0.84±0.5	0.84±0.4	0.85±0.4	0.84±0.5
FBF_{SL}	Δpeak ($ml \cdot min^{-1}$)	FL	377±95	78±103 §	-179±99 §#	-221±89 §#‡	-220±91 §#‡
		EX	464±115	432±123 ¶	411±119 ¶	525±119 ¶	479±111 ¶
	AUC (ml)	FL	80.6±8.1	-81.5±9.2 §	-92.3±6.2 §#	-120.4±9.9 §#‡	-121.0±9.8 §#‡
		EX	73.6±4.1	72.6±5.3 ¶	71.6±6.2 ¶	84.2±5.9 ¶	72.1±5.8 ¶
FBF_{CL}	Δpeak ($ml \cdot min^{-1}$)	FL	-57±48 *	-132±98 *§	-160±92 §#	-153±99 §#	-190±97 §#‡†
		EX	114±44 ¶*	111±43 ¶*	121±42 ¶*	133±49 ¶*	114±47 ¶*
	AUC (ml)	FL	-30.2±4.2 *	-83.9±8.1 §	-96.7.4±9.2 §#	-94.3±8.9 §#	-111.7±8.8 §#‡†
		EX	23.2±3.3 ¶*	23.4±3.1 ¶*	25.7±4.1 ¶*	27.6±3.9 ¶*	22.9±3.8 ¶*
VC_{SL}	Δpeak ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	FL	3.77±0.05	1.20±0.07 §	-2.22±0.09 §#	-2.28±0.08 §#	-2.67±0.09 §#
		EX	4.82±0.04	4.85±0.05 ¶	5.06±0.06 ¶	6.16±0.07 ¶	5.53±0.08 ¶
	AUC ($ml \cdot mmHg^{-1}$)	FL	0.84±0.09	-0.54±0.08 §	-1.20±0.11 §#	-1.32±0.08 §#	-1.58±0.08 §#
		EX	0.82±0.08	0.84±0.07 ¶	0.85±0.07 ¶	0.98±0.09 ¶	0.84±0.08 ¶
VC_{CL}	Δpeak ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	FL	-0.72±0.04 *	-1.61±0.08 *§	-1.74±0.09 §	-1.65±0.08 §	-2.00±0.08 §#‡†
		EX	1.59±0.05 ¶*	1.52±0.09 ¶*	1.70±0.08 ¶*	1.89±0.07 ¶*	1.63±0.07 ¶*
	AUC ($ml \cdot mmHg^{-1}$)	FL	-0.30±0.06 *	-1.02±0.07 §	-1.07±0.10 §	-1.04±0.08 §	-1.21±0.07 §#‡†
		EX	0.28±0.05 ¶*	0.29±0.06 ¶*	0.33±0.09 ¶*	0.36±0.09 ¶*	0.31±0.09 ¶*

ROM, range of motion; FO, force output; Δpeak, absolute change; AUC, area under the curve. Knee-joint angle in stretch leg (KJA_{SL}), Femoral artery diameter in stretched leg (FAD_{SL}), Femoral artery diameter in control leg (FAD_{CL}), Femoral blood flow in stretch leg (FBF_{SL}), femoral blood flow in control leg (FBF_{CL}), vascular conductance in stretch leg (VC_{SL}), vascular conductance in control leg (VC_{CL}).
¶ = $p < 0.05$ from FL; * = $p < 0.05$ from stretch leg; § = $p < 0.05$ from 1st; # = $p < 0.05$ from 2nd; ‡ = $p < 0.05$ from 3rd; † = $p < 0.05$ from 4th. Data are presented as mean ± SEM.

Figure legends

Figure 1: Schematic figure showing the position of the subject during the SS procedure. Stretched leg (SL) and control resting leg (CL), range of motion (ROM).

Figure 2: Sympathetic and parasympathetic indexes during baseline and passive static stretching. Panel A, B, C and D, illustrate respectively the root mean square of the squared differences of successive NN intervals (RMSSD), the ratio between low and high frequency (LF/HF) of the heart rate variability (HRV), mean diastolic blood pressure (DBP), and the low frequency component of systolic (LF_{SBP}) blood pressure (BPV). Data are mean ± SEM; * significantly different from baseline.

Figure 3: Changes in central hemodynamic responses to repetitive bouts of one leg static stretching. Panels A, B, C, and D illustrate mean arterial pressure (MAP), stroke volume (SV), heart rate (HR), and cardiac output (CO), at baseline (BL), during knee static passive flexion (FL) and static passive extension (EX) respectively. Data are mean ± SEM; * significantly increased from baseline (BL); † significantly reduced from baseline.

Figure 4: Changes in femoral blood flow and vascular conductance in the stretched leg (SL) and control resting leg (CL) to 5 sequences of SS, at baseline (BL), during knee static passive flexion (FL) and static passive extension (EX) respectively. Data are mean ± SEM; * significantly increased from baseline (BL); † significantly reduced from baseline; and gray areas indicate significantly different values between SL and CL.

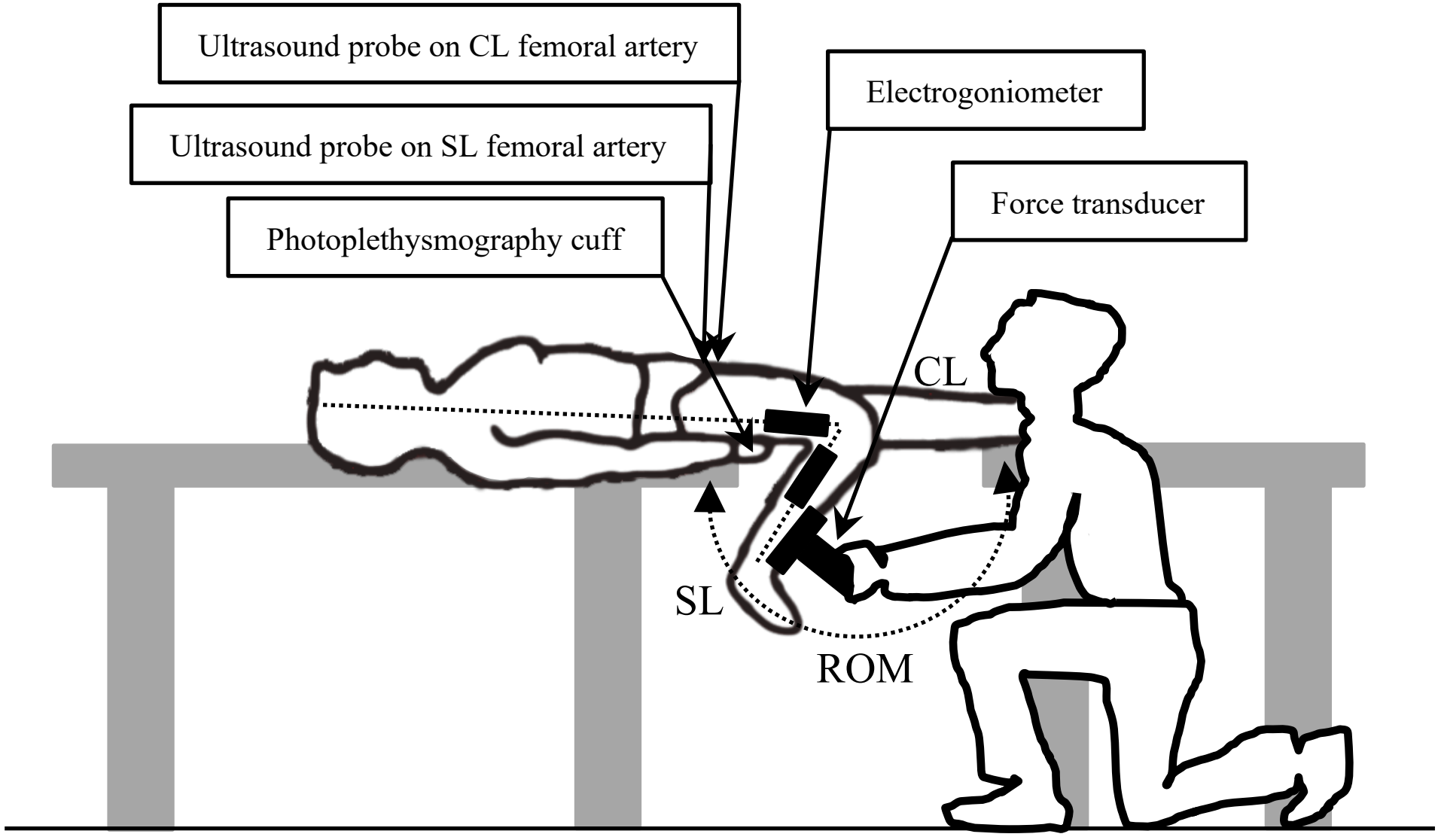
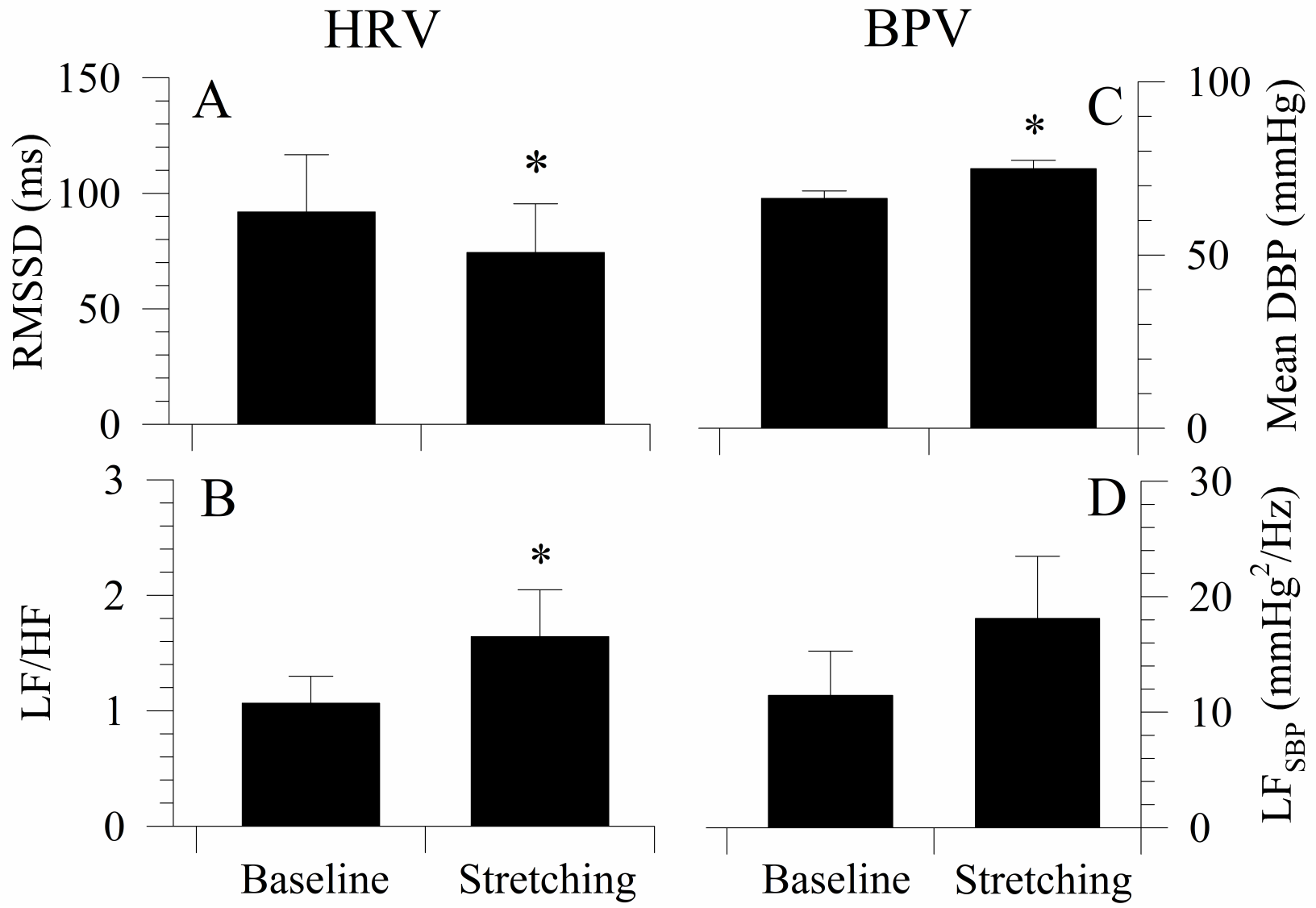


Fig 1



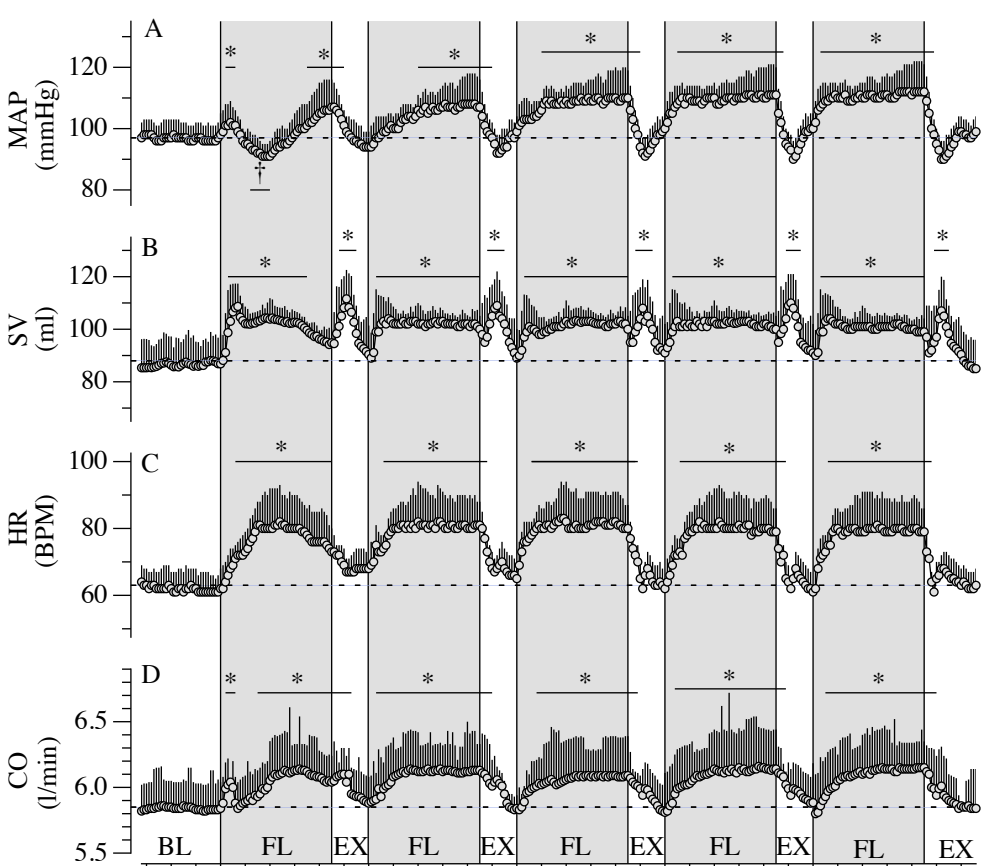


Figure 3

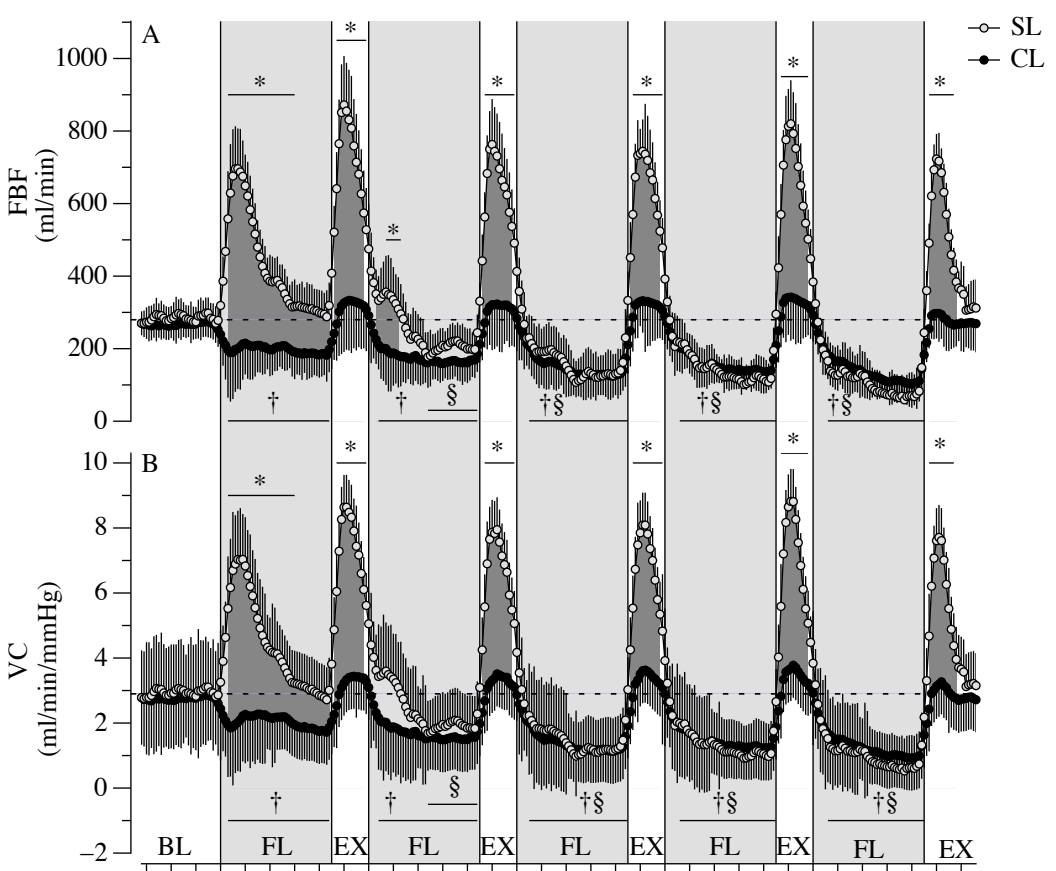


Figure 4