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RESEARCH ARTICLE

The effect of leg preference on mechanical efficiency during single-leg extension exercise

Massimo Venturelli,[1,2] Cantor Tarperi,[1,3] Chiara Milanese,[1] Luca Festa,[1] Luana Toniolo,[4] Carlo Reggiani,[4] and Federico Schena[1]

[1]*Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Verona, Italy;* [2]*Department of Internal Medicine, University of Utah, Salt Lake City, Utah;* [3]*Department of Clinical and Biological Sciences, University of Turin, Turin, Italy; and* [4]*Department of Biomedical Sciences, University of Padua, Padua, Italy*

Abstract

To investigate how leg preference affects net efficiency (η_{net}), we examined central and peripheral hemodynamics, muscle fiber type, activation and force of preferred (PL) and nonpreferred (NPL) leg. Our hypothesis was that PL greater efficiency could be explained by adaptations and interactions between central, peripheral factors, and force. Fifteen young participants performed single-leg extension exercise at absolute (35 W) and relative [50% peak power-output (W_{peak})] workloads with PL and NPL. Oxygen uptake, photoplethysmography, Doppler ultrasound, near-infrared-spectroscopy deoxyhemoglobin [HHb], integrated electromyography (iEMG), maximal isometric force (MVC), rate of force development ($RFD_{50–100}$), and muscle biopsies of both vastus lateralis were studied to assess central and peripheral determinants of η_{net}. During exercise executed at 35 W, η_{net} was 17.5 ± 5.1% and 11.9 ± 2.1% ($P < 0.01$) in PL and NPL respectively, whereas during exercise at the 50% of W_{peak} was in PL = 18.1 ± 5.1% and in NPL = 12.5 ± 1.9 ($P < 0.01$). The only parameter correlated with η_{net} was iEMG, which showed an inverse correlation for absolute ($r = -0.83$ and -0.69 for PL and NPL) and relative workloads ($r = -0.92$ and -0.79 for PL and NPL). MVC and $RFD_{50–100}$ were higher in PL than in NPL but not correlated to η_{net}. This study identified a critical role of leg preference in the efficiency during single-leg extension exercise. The whole spectrum of the central and peripheral, circulatory, and muscular determinants of η_{net} did not explain the difference between PL and NPL efficiency. Therefore, the lower muscle activation exhibited by the PL is likely the primary determinant of this physiological phenomenon.

NEW & NOTEWORTHY This study examined the impact of leg preference on efficiency during single-leg exercise. The results revealed lower efficiency of the nonpreferred leg during exercises performed at absolute and relative workloads. Central (cardiac output) and peripheral (fiber typing) determinants of efficiency did not explain the difference between the legs. However, the lower muscle activation of the preferred leg that was inversely correlated with efficiency is likely the primary determinant of this physiological feature.

dominance; fiber type; muscle activation; leg extension

INTRODUCTION

The bipedal nature of the human locomotion, coupled with the extensive unilateral recruitment of the preferred side, has influenced the skeletal muscle phenotype of the preferred upper limb (1). The specialization of preferred upper limb offers benefits in terms of maximal force and neuromuscular coordination (2). Contrarily, lower limbs are usually recruited bilaterally for locomotion, and the potential difference between the preferred (PL) and not preferred lower limb (NPL) is not fully explored (3).

For instance, previous studies compared PL and NPL during monolateral or bilateral movements (4–6). Recent investigations have shown that high levels of muscular strength are accompanied by increased skeletal muscle efficiency (7, 8), which in turn, can be associated with leg preference (9). Moreover, a recent study has shown a greater proportion of myosin heavy-chain (MHC) I and I/IIa fibers in the PL of resistance-trained men, suggesting structural adaptations associated with the leg preference (10).

Few studies have investigated the difference in oxygen uptake ($\dot{V}O_2$) and its determinants between PL and NPL during relatively complex (one-leg cycling) exercise tasks, reporting contrasting results (11, 12). For instance, Carpes et al. (11) reported no differences in $\dot{V}O_2$ and mechanical efficiency in professional and nonprofessional cyclists performing at the same relative single-leg workload with PL and NPL. On the contrary, Iannetta et al. (12) found that PL can achieve greater $\dot{V}O_{2peak}$ and peak power-output compared with NPL in double- and single-leg cycling. Interestingly, in the same study, the near-infrared-spectroscopy (NIRS) deoxyhemoglobin amplitudes ([HHb]) were found to be greater in

Correspondence: M. Venturelli (massimo.venturelli@univr.it).
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the PL during a ramp-incremental test, potentially suggesting the presence of greater peripheral adaptations. However, it is not clear if these peripheral differences in [HHb] responses were associated with adaptations of the skeletal muscle fiber phenotype. It is important to note that some determinants of $\dot{V}O_2$ (such as blood flow) and consequently also of efficiency, are comparable only at equivalent absolute workload, while others only at equivalent relative workload (for example the blood lactate concentration). This combined comparison is currently missing.

Among the wide spectrum of dynamic exercise tasks that are potentially influenced by leg preference, the dynamic single-leg extension exercise (DLE) is particularly interesting because this exercise model allows the precise and simultaneous measurement of the $\dot{V}O_2$, the cardiac output (CO), and the local blood flow to the exercising-muscle during a controlled unilateral task. This exercise model is characterized by a localized recruitment of a muscle group (knee extensors) of which vastus lateralis, where EMG is recorded, is a representative component. In this scenario, previous investigations have studied the muscle contraction-relaxation pattern and blood flow interactions during the DLE (13–15). However, it has not yet been clarified whether the muscle activation pattern of the PL and NPL can interfere with blood flow and [HHb].

Mechanical efficiency is the ratio of work accomplished to energy expenditure during steady-state exercise (16, 17). Previous studies suggested that asymmetries in muscle activation are related to mechanical efficiency (18). More recent investigations revealed similar muscle activation, $\dot{V}O_2$, and mechanical efficiency in the PL and NPL, when the exercise was executed at absolute or relative workloads to the maximal exercise capacity (11, 12, 19). However, there are no studies that have measured mechanical efficiency and muscle activation in PL and NPL exercising independently at the same absolute and relative workloads.

Therefore, the aim of the present study was to investigate how limb preference affects the physiological determinants of mechanical efficiency. We tested the following hypotheses: *1*) the PL would exhibit greater submaximal mechanical efficiency during exercise executed at absolute and relative submaximal workloads; *2*) this difference in mechanical efficiency at submaximal workload could be explained in relation to maximal muscle force, rate of force development (RFD), skeletal muscle fiber type, muscle activation (iEMG), and peripheral circulation [femoral blood flow (FBF), vascular conductance (VC)].

METHODS

Participants

Based on previous studies (11, 12), we adopted here differences in net efficiency (η_{net}) as main outcome. With an α level of 0.05 and a required power ($1-\beta$) of 0.80, the desired sample size, computed using statistical software (G-Power 3.1, Dusseldorf, Germany) resulted in 12 participants and 7% expected difference of η_{net}. Accordingly, the study sample was 15 participants. All the 15 healthy male participants were physically active, and none was, in the past, specifically trained in unilateral sports. All participants were right-handed and right-legged, evaluated by the Edinburgh Handedness Inventory Test (20). Lower leg preference was verified by a simple motor task such as kicking a ball and confirmed by the Waterloo inventory Test (21). The participants performed an incremental ramp test on a standard bilateral cycle ergometer (Lode Excalibur Sport) with both PL and NPL (initial workload 80 W increased by 20 W/min to task-failure). Participants were informed of all possible risks associated with the experimental protocol before providing written consent. The study was approved by the University of Verona Institutional Review Board.

Exercise Model

A single-leg extension ergometer was built partially replicating the device reported in previous papers (Fig. 1*A*) (22–24). Specifically, a cycle ergometer Monark Ergomedic 828E was adapted for the purpose of this investigation. Via a fixed gear, the original flywheel of the ergometer was joined to the pedal and connected with a light-pole to a boot fitted to the preferred and not preferred foot of the exercising participant. The resistance of the ergometer was controlled by measuring the tension of the friction-belt surrounding the flywheel by a load cell (UU-K20-20kg, D1110062. DAcell, Korea). The signals of the flywheel velocity and the tension of the friction-belt were integrated into a PowerLab-16/35 data acquisition system (ADInstruments, Bella Vista NSW, Australia). Participants performed 1 Hz contractions of the knee-extensor muscles with the PL, and with NPL. The lower leg range of motion was from 90° to 170° flexion, and the flywheel inertial-momentum assisted in the return of leg to the starting point, without hamstring contraction. To maintain the same external constant workload, fine calibration was done before each trial on the ergometer resistance system, and workload was adjusted throughout the entire test. Moreover, a single-leg extension isometric ergometer (Fig. 1*B*) as reported in a previous investigation (25) was utilized for the determination of the maximal isometric force in the PL and NPL.

Preliminary Test

To exclude a learning effect of this exercise, the participants trained 5 h for 3 days on the dynamic single-leg extension ergometer (DLE) (Fig. 1*C*). Practice consisted of single-leg DLE (as previously described) with the PL and NPL.

Maximal Incremental Test

On two separate days, participants performed two graded maximal DLE exercise tests. Specifically, the participants performed 5 min of very light exercise consistent of DLE without external resistance followed by progressive increases of the ergometer workload (initial workload of 5 W increased by 5 W/min) while the exercise cadence was maintained constant during the entire duration of the exercise (1 Hz, corresponding to 60 rpm of the flywheel). When cadence dropped to 50 rpm for more than 10 s, the exercise was terminated.

Experimental Design

After the practice sessions and maximal incremental tests, each subject performed a constant workload exercise test on

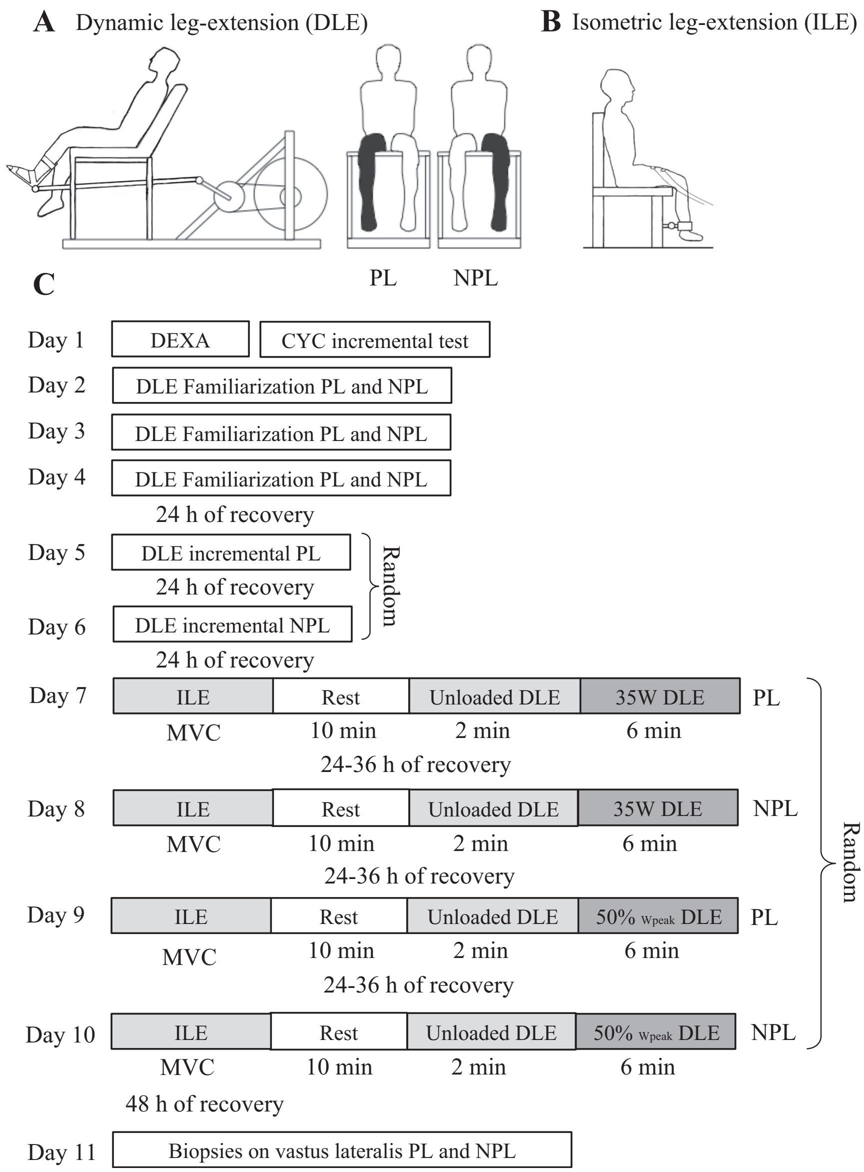

Figure 1. Flow chart of the study procedures. *A* and *B*: represent the dynamic leg-extension (DLE) and the isometric leg-extension (ILE) ergometers, respectively. *C*: reports the flow chart of the study procedures. On *day 1* were executed dual-energy X-ray absorptiometry (DEXA) and incremental maximal exercise on cycle ergometer (CYC). On *days 2*, *3*, and *4*, the participants familiarized with DLE with both preferred leg (PL) and non-preferred leg (NPL). On the *days 5* and *6*, the participants performed graded maximal DLE exercise tests with the PL, and NPL. On the *days 7*, *8*, *9*, and *10*, the participants executed four maximal isometric voluntary contractions (MVC) of the knee extensors on the ILE ergometer. After 10 min of rest, the participants performed 2 min of unloaded leg-extension exercise (DLE ergometer with no tension applied) and 6 min of constant workload exercise at absolute and relative workloads [35 W and executed at 50% of the peak power output (50% of W_{peak})] with PL and NPL. On *day 11*, samples of skeletal muscle were obtained from both the vastus lateralis of the PL and NPL.

four separate days, with 24–36 h between tests for recovery (Fig. 1*C*). The participants rested in a seated position in a room with controlled temperature (19–22°C) for 30 min, and before the beginning of the DLE exercise, the participants performed four maximal voluntary muscle isometric contractions of the leg extensors muscles of the PL and NPL. After 10 min of recovery, the participants performed 2 min of unloaded DLE (ergometer with no tension applied) and 6 min of submaximal constant workload exercise at absolute workload (35 W) and at relative workload [50% of the peak power-output (50%W_{peak})] with PL and NPL. On a separate day, biopsy samples of skeletal muscle were obtained from both the vastus lateralis of the PL and NPL.

Body Composition and Lower Limb Mass

Total body composition was measured by dual-energy X-ray absorptiometry (DXA) (QDR 4500 W, Hologic Inc., Bedford, MA). PL and NPL mass (thigh mass and lower leg mass) were measured from DXA subregions of interest (26–28).

Femoral Blood Flow

Measurements of arterial blood velocity and vessel diameter were taken in the PL and NPL, distal to the inguinal ligament and proximal to the deep, superficial femoral bifurcation with an Acuson P50 ultrasound system (Siemens AG, Munich, Germany). The ultrasound system was equipped with an 8–12 MHz linear transducer. Artery diameter was determined parallel to the central axis of the scanned area. Blood velocity was measured using the same probe with a frequency of 5 MHz. Measurements of blood velocity were obtained with the probe correctly positioned to maintain an insonation angle of 60° or less; the sample volume was aligned and maximized according to vessel size. Arterial diameter was measured, and 12 s of mean blood velocity (angle-corrected and area below the curve) were automatically calculated using Doppler software (Acuson P50). Using arterial diameter and V_{mean}, blood flow was calculated as:

$$\text{Blood flow} = V_{mean} \cdot \pi \left(\frac{1}{2}\text{vessel diameter}\right)^2 \cdot 60$$

where blood flow is in liters per minute.

Central Hemodynamic Variables

Heart rate (HR), cardiac output (CO), and mean arterial pressure (MAP) were determined using a Portapres model-2 (Finapres Medical Systems, Amsterdam, The Netherlands). Stroke volume (SV) was calculated using the Modelflow algorithm (Beatscope version 1.1a; Finapres Medical Systems). The same method has been shown to correctly track CO during exercise (29). CO was then calculated as the product of HR and SV. Vascular conductance in PL and NPL was calculated as leg blood flow/MAP.

Metabolic Measurements

Ventilation ($\dot{V}E$) and pulmonary gas exchanges ($\dot{V}O_2$, $\dot{V}CO_2$) were measured breath-by-breath at rest and during the DLE exercise trials using a metabolic cart (Quark B^2; COSMED, Rome, Italy).

Blood Lactate Concentration

Arterialized blood samples (4 μL) from the earlobe were taken and blood lactate concentration [La^-] was determined using a lactate analyzer (Labtrend LT14187; Bio Sensor Technoly GmbH, Berlin, Germany) at rest and every 60 s of the DLE executed with PL and NPL.

Near-Infrared Spectroscopy

Deoxyhemoglobin [HHb] was measured using a NIRS system (Oxiplex TS, ISS, Champaign, IL). The NIRS probe consisted of eight light-emitting diodes (690–830 nm wavelengths) and one detector fiber bundle (source-detector space = 2.0–3.5 cm). The probe was fixed to the distal section of the vastus lateralis muscle, secured with adhesive tape, with Velcro straps around the thigh. Before the exercise trials, the NIRS system was calibrated and the skin area carefully shaved. To verify any shifting during the DLE exercise, the probe margins were marked on the skin with ink. The exercising thigh and NIRS probe were covered with an elastic band to avoid light interfering with the NIRS signal. [HHb] was recorded at 25 Hz and digitally averaged into 1-s value using OxiTS software (OxiTS 3.1, ISS, Champaign, IL). Potential differences between PL and NPL in terms of subcutaneous fat interfering with the NIRS signal were determined with ultrasound approach. Specifically, sagittal ultrasound images of the vastus lateralis muscle, corresponding to the area marked on the skin with ink, were recorded with a Doppler ultrasound (Siemens AG, Munich, Germany) equipped with a 12–14 MHz linear transducer. The distance between the skin and the superficial aponeurosis of the muscle was measured.

Muscle Activation

Vastus lateralis electromyography (EMG) was continuously recorded with a wireless system (ZeroWire, Aurion, Italy). Two surface Ag/AgCl electrodes (Blue sensor, Ambu, Ballerup, Denmark) were attached to the skin with a 2-cm interelectrode distance in the PL and NPL. The electrodes were placed longitudinally, in line with the underlying muscle fibers arrangement and with an interelectrode distance (center-to-center) of 2 cm. Before electrode application, the skin was shaved and cleaned with alcohol to minimize impedance. The EMG transmitter connected to the electrodes was secured with adhesive tape to avoid movement-induced artifacts. The raw EMG signal was amplified and filtered with a band-pass filter (low-pass cut-off frequency 10 Hz, high-pass cut-off frequency 1 kHz) and digitized online at a 5 kHz sampling frequency. Acquisition of the EMG data was done using a computer-based data acquisition and analysis system (hardware: PowerLab 16/30; ML880, ADInstruments, Colorado Springs, CO and software: LabChart 6, ADInstruments, Colorado Springs, CO). Integrated electromyography (iEMG) for each muscle contraction was calculated and averaged over the last 30 s of each minute and normalized to the EMG signal obtained during the maximal isometric force (MVC) performed before the exercise.

Maximal Leg Isometric Force

During the *visits 7* and *10* (Fig. 1*C*), maximal voluntary isometric contractions of the PL and NPL muscles were measured utilizing a custom-made setup (Fig. 1*B*) (25). Participants were seated in an upright position with back support. The hip and the knee were flexed at 90°, and the ankle was attached, via a strap and rigid steel bar, to a force transducer (DBBSE-100kg, A2829, Applied Measurements Limited, Aldermaston, Berkshire, UK). In this position, the participants performed four maximal isometric voluntary contractions of the leg extensor muscles of the PL and NPL. Participants were instructed to extend their knee (in isometric condition) “as fast as possible” and “as hard as possible,” strong verbal encouragements were provided. Each contraction lasted 5 s and the recovery among the contractions was 60 s. A visual feedback of the torque output was offered to the subject via a monitor connected to a PowerLab-16/35 data acquisition system (ADInstruments, Bella Vista NSW, Australia). The force output was amplified (INT2-L, London Electronics Limited, Sandy Bedfordshire, UK), and recorded at a sampling rate of 5 kHz. EMG data were continually recorded during maximal isometric contractions of the PL and NPL. The EMG activity recorded during the maximal isometric contractions was utilized for the normalization of the EMG signal during the dynamic exercise with the PL and NPL.

Rate of Force Development

The rate of force development (RFD) was determined as the ratio between the force and time during isometric contractions. Specifically, the time and force level at 50, 100, and 200 ms from the onset of the force were identified. Then, the mean RFD was calculated at the time intervals of 50–100 ms ($RFD_{50–100}$) and 100–200 ms ($RFD_{100–200}$) from the linear slope of the force-time curve (30, 31). The onset of the force development was identified as the point at which the level of force reached three standard deviations over the resting baseline (32). This method has been chosen because it offers a reliable method to determine the onset of the muscle contraction (31).

Rating of Perceived Exertion

Rating of perceived exertion (RPE) was obtained at rest and every minute of exercise using the Borg's modified CR10 scale (33).

Workload of Dynamic Single-Leg Extension Ergometer

Ergometer resistance was adjusted by modifying the friction between belt and flywheel ergometer, thus the workload was calculated as: $W = F \times S$; where F is the force in newton applied to the ergometer-belt (recorded by a force transducer UU-K20-20kg, D1110062. DAcell, Korea), and S is 6 m/s for flywheel velocity at 60 rpm. It is important to note that the flywheel velocity was kept constant during the DLE exercise.

Data Acquisition

HR, SV, CO, and MAP underwent A/D conversion and were simultaneously acquired by commercially available data acquisition software PowerLab-16/35 data acquisition system (ADInstruments, Bella Vista NSW, Australia). The data acquisition software allowed high-resolution analysis of HR, SV, CO, and MAP throughout the exercise protocols. Mean HR, SV, CO, and MAP were calculated for 120 s at rest, and during the exercises. Mean blood velocity was analyzed with 1 Hz resolution on the Doppler ultrasound system (Siemens Acuson P50) for 120 s at rest, and during exercise.

Muscle Biopsy and Myosin Isoform Distribution

Muscle samples (∼6–8 mg) were obtained from the mid vastus lateralis muscle on both left and right legs of all individuals with a 14-gauge tru-cut needle (34). After the biopsy, muscle samples were frozen in isopentane, cooled down on liquid nitrogen, and stored at −80°C for subsequent analysis. No complications were registered after the biopsy and all the volunteers went back to normal life and training within 3 days.

Fragments of muscle biopsy samples were pulverized in a mortar cooled in liquid nitrogen, dissolved in Laemmli solution and analyzed to determine the composition in myosin heavy chain (MyHC) isoforms, which are considered as molecular markers of fiber types (35). MyHC isoform composition of each sample was determined on 8% polyacrylamide slab gels (18 cm wide, 16 cm high, 1 mm thick) after denaturation in SDS (SDS-PAGE) (36). Electrophoresis was run for 26 h, at 70 V for 1.5 h and at 230 V for the remaining time. The gels were then stained with Coomassie blue. Three bands were separated in the region of 200 kDa, corresponding (in order of migration from the fastest to the slowest) to MyHC-1, MyHC-2A, and MyHC-2X. The relative proportions of MyHC isoforms were determined by scanning the gels at high resolution and measuring the brightness area product (B.A.P.), i.e., the product of the area of the band by the average brightness subtracted from local background after black-white inversion). For each sample, all procedure was repeated three times.

Data Analysis

In the current investigation, the pulmonary $\dot{V}O_{2peak}$ was extrapolated from the intersection of the $\dot{V}O_2/W$ slope <75% W_{peak} and the peak workload achieved during the DLE. Although this indirect approach is subjected to an uncertain amount of error, this method reduces the potential overestimation of pulmonary $\dot{V}O_{2peak}$ caused by the recruitment of ancillary muscles during maximal exercise workloads (37).

Net efficiency (η_{net}) was calculated for each leg as the ratio of mechanical work (i.e., Watts converted to kcal/min) to exceeding energy expenditure above the resting metabolism as reported in the formula:

$$\eta_{net} = (\text{power output} \times \text{energy expended above resting metabolism}^{-1}) \times 100$$

Both power output and $\dot{V}O_2$ recorded during the last 120 s of DLE were expressed as kcal/min for all the above calculations (16, 17).

Two-way ANOVAs (α = 0.05) was performed to detect potential differences in CO, HR, MAP, FBF, VC, [HHb], skeletal muscle fiber type, and EMG between PL, NPL, and exercise workloads (35 W vs. 50% W_{peak}). Pearson's coefficients were calculated to evaluate the level of correlation between η_{net} and the other outcomes. Where appropriate, a Tukey post hoc analysis was performed. Student's t tests were used to compare mean values for PL and NPL muscular masses, as well as maximal workload and $\dot{V}O_{2peak}$ reached during the maximal tests. Statistical analysis was performed using StatPlus for Macintosh, version 2020 (AnalystSoft Inc., Alexandria, VA). All data are presented as means ± SD.

RESULTS

Characteristics of Participants

The average physical characteristics of the participants were the following: age 26.4 ± 5.1 yr (range: 22–36 yr), height 174.2 ± 4.1 cm (range: 168–182 cm), body mass 73.3 ± 5.0 kg (range: 65–82 kg), total body fat 14.6 ± 2.5% (range: 12%–18%), and their average $\dot{V}O_{2max}$ determined on the cycle ergometer was 3.4 ± 0.3 L/min. Muscular mass was similar between preferred and not preferred limb [PL thigh mass = 8.6 ± 1.9 kg; NPL thigh mass = 8. 4 ± 2.1 kg (P = 0.8)]; [PL lower leg mass = 4.1 ± 0.25 kg; NPL lower leg mass = 4.1 ± 0.19 (P = 0.9)]. The average diameter of the common femoral artery was similar in both legs, 1.08 ± 0.07 cm in PL and 1.04 ± 0.07 cm in NPL (P = 0.8).

Peak Values and Rate of Force Development of Preferred and Nonpreferred Leg

The maximal workload achieved with the PL during the incremental test was 72.0 ± 4.7 W and 60.2 ± 5.4 W for the NPL (P = 0.02; F = 2.56). $\dot{V}O_{2peak}$ of the PL was 1.55 ± 0.11 L/min and 1.38 ± 0.13 L/min for the NPL (P = 0.03; F = 2.69). The maximal isometric torque recorded before the constant workload dynamic exercise executed at 35 W was 260.3 ± 24.7 Nm for the PL and 238.2 ± 22.4 Nm for the NPL (P = 0.04; F = 2.88). Similarly, before the dynamic exercise executed at the 50% of W_{peak}, the maximal isometric torque was 262.3 ± 28.5 Nm for the PL and 239.4 ± 23.7 Nm for the NPL (P = 0.01; F = 3.60). The $RFD_{50–100}$ calculated during the maximal isometric contractions recorded before the exercise at 35 W was significantly greater in the PL 4,247 ± 914 N/s compared with the NPL 3,491 ± 693 N/s (P = 0.01; F = 3.5). On the contrary, the $RFD_{100–200}$ was not different between the two legs (PL = 1,783 ± 465 N/s; NPL = 1,703 ± 488 N/s; P = 0.61; F = 0.72). With a similar trend, also the $RFD_{50–100}$ calculated during the maximal isometric contractions recorded before the exercise at 50% of W_{peak} was significantly greater in the PL 4,194 ± 810 N/s compared with the NPL 3,451 ± 907 N/s (P = 0.02; F = 3.3), whereas the $RFD_{100–200}$ was 1,741 ± 429 N/s in the PL and 1,681 ± 378 N/s in the NPL (P = 0.70; F = 0.54).

Effects of Leg Preference on Pulmonary Gas Exchange, [La^-], and (η_{net})

Pulmonary gas exchange and [La^-] at rest and during the DLE exercise are presented in Fig. 2. Mean values at rest during the 120 s of unloaded DLE and during the last 120 s of the constant workload (35 W and 50% of W_{peak}) DLE are displayed in the Table 1. The ergometer workload corresponding to 50% of W_{peak} was 37 ± 5 W for the PL and 29 ± 5 W for the NPL. Resting and unloaded DLE values of $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, and [La^-] were similar between the PL and NPL, whereas, on the contrary, during the DLE executed at 35 W or 50% of W_{peak} the NPL exhibited significantly greater $\dot{V}O_2$, $\dot{V}CO_2$, $\dot{V}E$, and [La^-] compared with the PL. Mean values of (η_{net}) calculated during the last 120 s of the constant workload DLE are displayed in the Table 1. During exercise executed at 35 W, η_{net} was significantly greater in PL. Similarly, PL exhibited a significantly higher η_{net} during exercise executed at the 50% of W_{peak}.

Effects of Leg Preference on Central, Peripheral Hemodynamics, and [HHb]

CO, HR, MAP, FBF, VC, and [HHb] data are summarized in Table 1 and Fig. 3. No difference in the central and peripheral hemodynamics were detectable between PL and NPL at rest and during unloaded DLE. However, a significantly greater increase in the CO, HR, MAP, FBF, and VC was detected during the steady-state DLE executed with the NPL compared with the PL at 35 W. Similarly, during the exercise executed at 50% of W_{peak}, NPL exhibited higher values of CO, HR, MAP, and FBF compared with the PL.

Interestingly, these differences in central and peripheral hemodynamics were not coupled with significant differences of the [HHb], between the PL and NPL both at absolute and relative workloads.

Muscle Activation

The percent change in iEMG signal during DLE executed with the PL and NPL are reported in Table 1 and Fig. 4. A significantly greater iEMG activity was detected during the steady-state DLE executed with the NPL when compared with the PL, for both absolute and relative exercise intensities.

Rating of Perceived Exertion

The values of the rating of perceived exertion (RPE) are reported in Table 1. No difference in RPE was detectable between PL and NPL at rest and during unloaded DLE. Moreover, there was no difference in RPE detected during the steady-state exercise executed with the PL and NPL at 35 W versus 50% W_{peak} (F = 0.18; P = 0.9) respectively. Significantly greater RPE was reported by the participants during the steady-state DLE executed with the NPL compared with PL for both absolute (F = 5.7; P = 0.0002) and relative exercise intensities (F = 3.8; P = 0.009).

Skeletal Muscle Fiber Types in PL and NPL

Muscle fiber type distribution in vastus lateralis of PL and NPL was estimated by the % distribution MyHC isoforms, which are considered molecular markers of fiber type (35). As can be seen from Fig. 5, no significant difference was detectable between the two vastus lateralis muscles.

Correlations between η_{net}, Central, and Peripheral Factors

Interactions between central hemodynamics (CO, HR, MAP), peripheral circulation (FBF, VC), peripheral oxygen extraction [HHb], muscle activation (iEMG), maximal isometric force, and the rate of force development (MVC, $RFD_{50–100}$, $RFD_{100–200}$) with the η_{net} calculated during DLE with the PL and NPL are presented in the Table 2. Specifically, the values of the iEMG recorded during the DLE significantly correlated with the η_{net} (Fig. 6).

DISCUSSION

The present study was designed to determine the effect of leg preference on submaximal mechanical efficiency and its central and peripheral determinants during dynamic single-leg extension exercise (DLE). Consistent with our first hypothesis, we found that η_{net} was significantly greater in the PL for both the exercise modalities (absolute and relative workloads). Interestingly, this difference in submaximal mechanical efficiency between the PL and NPL was coupled with higher levels of [La^-], HR, CO, MAP, FBF, VC, RPE, and iEMG during steady-state exercise executed with the NPL. In contrast, no difference was detected for NIRS-derived oxygen extraction [HHb] and distribution of MyHC isoforms in vastus lateralis of PL and NPL. The different values of iEMG that point to different levels of muscle activation between PL and NPL at similar exercise intensity, the inverse linear correlation retrieved between η_{net} and iEMG (Fig. 6), and the higher initial RFD of PL compared with NPL suggest that the greater submaximal mechanical efficiency of PL compared with NPL is determined by the different muscle activation. This view is in agreement with previous studies that have proposed a major role of neuromuscular factors in modulating muscle work efficiency (7).

Evidence That Submaximal Mechanical Efficiency Is Lower in the Nonpreferred Knee Extensors Muscles

Our results demonstrate significant greater η_{net} in the PL than in the NPL during DLE performed at same absolute (35 W) or relative (50% of W_{peak}) power, in both cases submaximal workloads. The impact of leg preference on submaximal mechanical efficiency has been studied in few recent investigations. For instance, during one-leg cycling in professional and nonprofessional cyclists, Carpes et al. (11) reported similar levels of mechanical efficiency in PL and NPL. With a similar approach, Iannetta et al. (12) found that during one-leg cycling executed at maximal lactate steady state, the efficiency was similar between PL and NPL, 20% and 19.5%, respectively. Possible explanation for the difference between our results and those showing similar

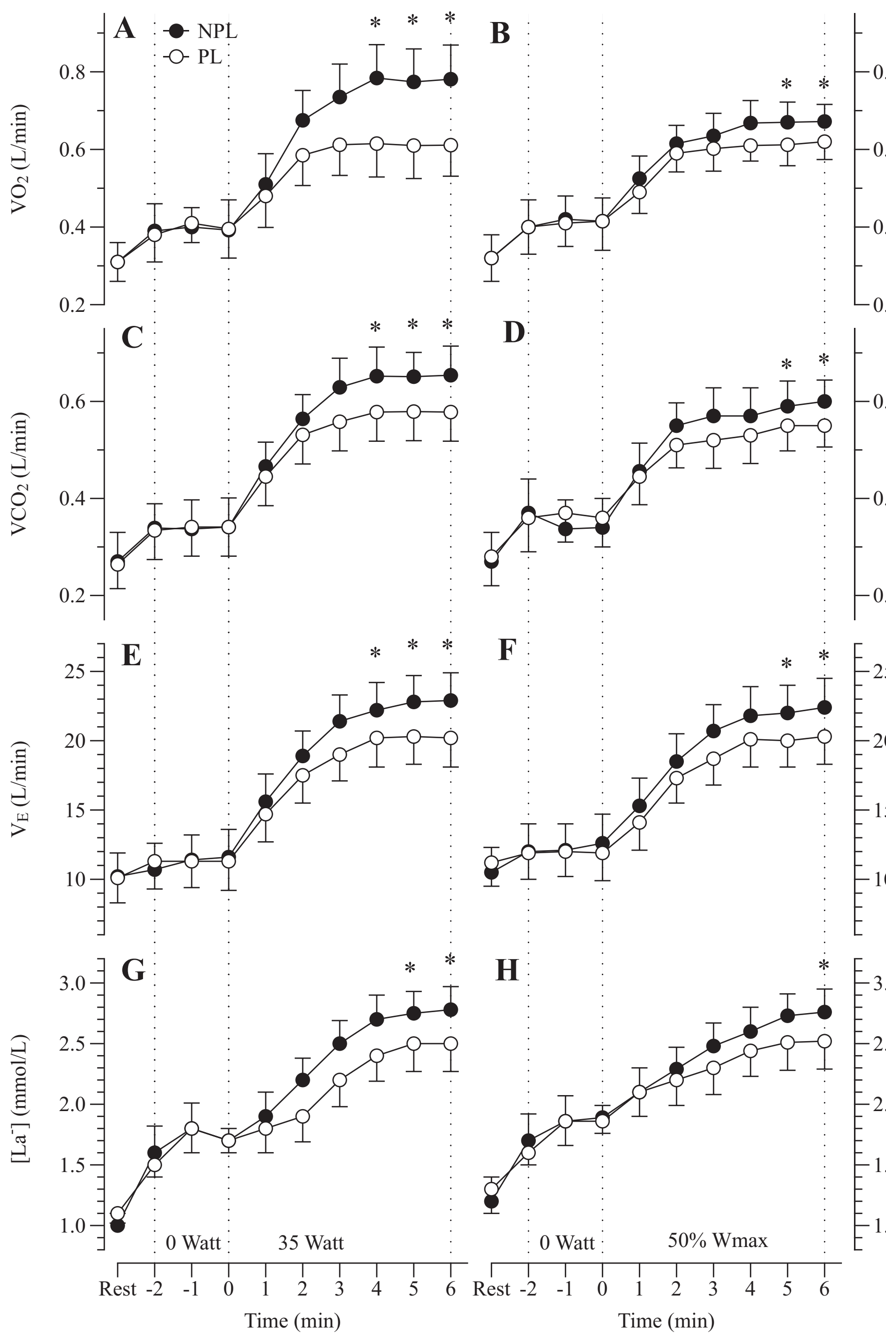

Figure 2. Pulmonary gas exchange at rest, during unloaded dynamic leg-extension (DLE) and constant-workload DLE exercise executed at absolute (35 W) and relative intensities [50% of the peak power output (50% of W_{peak})]. The open circles represent the values recorded with the preferred leg (PL), and the solid circles with the nonpreferred leg (NPL). $\dot{V}O_2$, oxygen uptake (*A* and *B*); $\dot{V}CO_2$, carbon dioxide production (*C* and *D*); $\dot{V}E$, minute ventilation (*E* and *F*); [La$^-$], blood lactate concentration (*G* and *H*); Wmax, maximal work-load. Values are means ± SE. *Significant differences between PL and NPL.

efficiency is likely related to the different ergometer used. In fact, the DLE exercise model utilized for the present investigation requires a precise and localized muscle contraction of the knee extensors muscles that cannot be achieved during the single leg cycling, which requires the recruitment of several leg- and thigh-muscles (38), and greater variability of the recruitment pattern, see review by Wakeling et al. (39, 40).

Moreover, when compared with a highly automatized motor skill as cycling, the DLE motor pattern is less usual, and we cannot rule out a different learning process for the PL and NPL leg motor control (see *Evidence That the Lower Submaximal Mechanical Efficiency in NPL Is Influenced by the Muscle Activation* section).

Evidence That the Lower Submaximal Mechanical Efficiency in NPL Is Not Influenced by Central and Peripheral Determinants of Oxygen Consumption

Since the mechanical efficiency is calculated as the ratio of mechanical work to energy expended calculated from oxygen consumption, both central and peripheral determinants of the $\dot{V}O_2$ are potentially implicated in this physiological scenario. It is important to note, that at submaximal DLE exercise intensities, the relatively small muscle mass

Table 1. *Mean values at rest, unloaded, 35 W, and 50% of maximal dynamic leg extension*

	35 W			50% W_{peak}			Interaction
	PL	NPL	*P* (*F*)	PL	NPL	*P* (*F*)	*P* (*F*)
η, %	17.5 ± 5.1	11.3 ± 2.1	0.00012 (6.1)	18.0 ± 4.8	12.5 ± 2.2	0.00034 (5.4)	0.74 (0.8)
iEMG, % MVC	16.3 ± 1.8	22.1 ± 2.3	0.00006 (11.8)	16.2 ± 1.9	18.7 ± 1.7	0.0003 (5.2)	0.002 (10.9)
$\dot{V}O_2$, L/min							
Rest	0.31 ± 0.05	0.31 ± 0.05	0.7(0.3)	0.32 ± 0.03	0.32 ± 0.04	0.8 (0.2)	0.9 (0.01)
UE	0.41 ± 0.05	0.40 ± 0.06	0.5 (0.6)	0.41 ± 0.07	0.42 ± 0.06	0.3 (1.1)	0.2 (1.5)
SS	0.61 ± 0.08	0.77 ± 0.06	0.00006 (8.7)	0.62 ± 0.06	0.67 ± 0.05	0.056 (2.7)	0.004 (8.9)
$\dot{V}CO_2$, L/min							
Rest	0.26 ± 0.04	0.27 ± 0.05	0.6(0.7)	0.28 ± 0.05	0.27 ± 0.04	0.7 (0.6)	0.3 (1.0)
UE	0.34 ± 0.05	0.33 ± 0.04	0.8(0.3)	0.37 ± 0.05	0.36 ± 0.04	0.5 (0.8)	0.7 (0.07)
SS	0.56 ± 0.07	0.69 ± 0.06	0.00006 (8.1)	0.55 ± 0.05	0.59 ± 0.05	0.02 (3.3)	0.02 (5.6)
$\dot{V}E$, L/min							
Rest	10.6 ± 1.7	11.1 ± 1.2	0.2 (1.6)	11.2 ± 1.25	10.5 ± 1.16	0.2 (1.3)	0.9 (0.007)
UE	11.7 ± 1.7	12.6 ± 1.2	0.09 (1.7)	11.9 ± 1.17	12.6 ± 1.18	0.15 (2.0)	0.8 (0.04)
SS	20.2 ± 1.9	23.1 ± 1.2	0.00007 (7.2)	20.3 ± 1.9	22.4 ± 1.19	0.04 (3.5)	0.0007 (12.3)
$[La^-]$, mmol/L							
Rest	1.22 ± 0.26	1.18 ± 0.20	0.5 (0.9)	1.32 ± 0.35	1.18 ± 0.31	0.2 (1.8)	0.7 (0.2)
UE	1.84 ± 0.42	1.87 ± 0.45	0.7 (0.5)	1.86 ± 0.47	1.76 ± 0.39	0.5 (0.9)	0.4 (0.5)
SS	2.60 ± 0.41	2.92 ± 0.30	0.00006 (9.2)	2.52 ± 0.28	2.76 ± 0.26	0.0009 (4.9)	0.03 (4.6)
HR, beats/min							
Rest	71.5 ± 6.3	74.1 ± 8.0	0.2 (1.7)	70.9 ± 5.9	73.8 ± 6.4	0.2 (1.2)	0.9 (0.003)
UE	86.2 ± 3.6	88.2 ± 2.0	0.1 (2.2)	88.3 ± 3.8	88.0 ± 3.7	0.7 (0.2)	0.2 (1.7)
SS	116.3 ± 6.8	127.7 ± 3.9	0.00006 (10.4)	115.9 ± 4.9	120.9 ± 4.6	0.002 (4.5)	0.005 (8.5)
CO, L/min							
Rest	6.25 ± 0.25	6.34 ± 0.34	0.08 (1.8)	6.08 ± 0.17	6.21 ± 0.21	0.19 (1.8)	0.6 (0.2)
UE	8.17 ± 0.50	8.16 ± 0.54	0.9 (0.1)	8.15 ± 0.37	8.08 ± 0.42	0.7 (0.6)	0.8 (0.05)
SS	9.78 ± 0.79	11.07 ± 0.57	0.00006 (10.2)	9.68 ± 0.55	10.11 ± 0.62	0.01 (3.4)	0.001 (11.6)
MAP, mmHg							
Rest	94.6 ± 2.5	95.8 ± 2.6	0.2 (1.3)	95.1 ± 2.7	96.0 ± 2.6	0.4 (0.9)	0.8 (0.1)
UE	108.5 ± 3.9	106.6 ± 3.7	0.1 (2.0)	109.7 ± 3.9	108.2 ± 3.1	0.2 (1.6)	0.8 (0.04)
SS	119.2 ± 4.4	124.9 ± 2.6	0.0001 (4.5)	118.4 ± 4.8	121.3 ± 3.9	0.02 (2.2)	0.1 (2.5)
FBF, mL/min							
Rest	437.8 ± 103.2	436.4 ± 122.3	0.9 (0.05)	435.4 ± 175.2	407.9 ± 98.2	0.4 (1.1)	0.6 (0.2)
UE	1,557.5 ± 181.9	1,484.5 ± 230.4	0.3 (1.4)	1,644.1 ± 255.5	1,541.4 ± 199.4	0.9 (0.1)	0.5 (0.5)
SS	3,066.2 ± 211.1	3,517.1 ± 219.3	0.00006 (10)	3,099.3 ± 281	3,270.6 ± 235.1	0.009 (3.8)	0.003 (9.6)
VC, mL/min/mmHg							
Rest	4.62 ± 1.15	4.48 ± 1.24	0.7 (0.5)	4.57 ± 0.83	4.24 ± 0.83	0.4 (1.2)	0.7 (1.3)
UE	13.56 ± 3.77	13.93 ± 2.09	0.7 (0.6)	14.21 ± 1.93	14.44 ± 2.92	0.8 (0.3)	0.9 (0.01)
SS	25.75 ± 1.46	28.16 ± 1.82	0.0001 (5.8)	26.19 ± 1.65	26.95 ± 1.39	0.2 (1.8)	0.04 (4.0)
[HHb], µM							
Rest	22.7 ± 3.4	24.7 ± 3.3	0.06 (2.7)	23.2 ± 2.4	24.3 ± 1.9	0.3 (1.5)	0.5 (0.3)
UE	33.1 ± 4.9	32.7 ± 3.1	0.8 (0.3)	31.8 ± 9.4	31.3 ± 2.4	0.8 (0.4)	0.9 (0.002)
SS	41.8 ± 6.9	44.3 ± 4.9	0.3 (1.5)	44.7 ± 7.2	44.0 ± 5.6	0.8 (0.4)	0.3 (0.9)
RPE (0–10)							
Rest	0	0		0	0		
UE	1.06 ± 0.62	1.23 ± 0.59	0.4 (0.9)	1.06 ± 0.37	1.2 ± 0.41	0.5 (1.0)	0.9 (0.01)
SS	3.86 ± 0.8	5.27 ± 1.22	0.0002 (5.7)	3.71 ± 0.88	4.80 ± 0.87	0.009 (3.8)	0.3 (0.9)

Values are means ± SD. η_{net}, Net efficiency; CO, cardiac output; FBF, femoral blood flow; [HHb], near-infrared spectroscopy deoxyhemoglobin; HR, heart rate; iEMG, integrated electromyography; $[La^-]$, blood lactate concentration; MAP, mean arterial pressure; NPL, nonpreferred leg; PL, preferred leg; RPE, rate of perceived exertion; SS, steady-state exercise; UE, unloaded exercise; $\dot{V}CO_2$, carbon dioxide production; VC, vascular conductance; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, oxygen uptake; 35 W, exercise executed at 35 W; 50% W_{peak}, exercise executed at 50% of the peak power output.

recruited (quadriceps muscles) does not seem to find a limiting factor in the central (lungs and heart) determinants of the $\dot{V}O_2$ (23, 41). Accordingly, the data from the present study demonstrate that the difference in submaximal mechanical efficiency between the PL and NPL was coupled with higher levels of HR, CO, and MAP during steady-state exercise executed with the NPL (Figs. 2 and 3). It is important to note that the differences between the PL and NPL were significant both at absolute (35 W) and relative (50% of W_{peak}) workloads.

As to the peripheral metabolic and circulatory factors, we observed a higher FBF and VC in the NPL compared with the PL exercising at the same absolute workload (Fig. 3). In accordance with previous studies showing that muscle activation patterns, metabolic demand, and limb blood flow are well matched during DLE (13, 15, 42), our data indicate that the augmented FBF and VC exhibited by the NPL were the result of the increased metabolic demand, likely related to the higher activation of the skeletal muscles (increased level of iEMG) recruited for the DLE performed with the NPL. The increase in FBF and VC were sufficient to provide the required oxygen delivery as confirmed by the lack of detectable changes in NIRS-derived oxygen extraction [HHb] (Fig. 3).

It is worth to recall that Iannetta et al. (12) observed greater [HHb] values during the incremental single-leg cycling

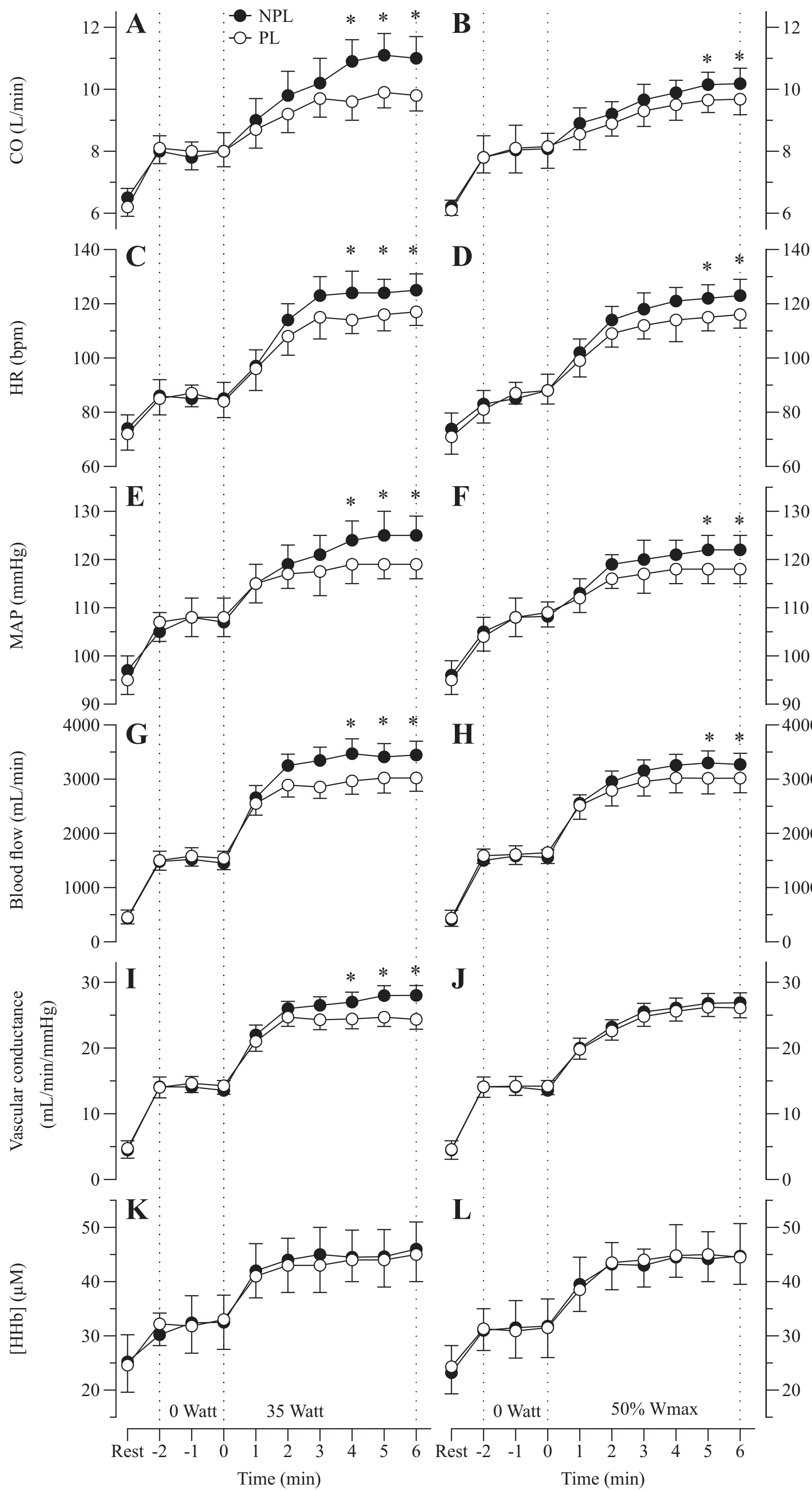

Figure 3. Central, peripheral hemodynamic, and near-infrared spectroscopy deoxyhemoglobin at rest, during unloaded dynamic leg-extension (DLE), and constant-workload DLE exercise executed at absolute (35 W) and relative intensities [50% of the peak power output (50% W_{peak})]. The open circles represent the values recorded with the preferred leg (PL), and the solid circles with the nonpreferred leg (NPL). CO, cardiac output (*A* and *B*); HR, heart rate (*C* and *D*); MAP, mean arterial pressure (*E* and *F*); femoral blood flow (*G* and *H*); femoral vascular conductance (*I* and *J*); [HHb], near-infrared spectroscopy deoxyhemoglobin (*K* and *L*); Wmax, maximal work-load. Values are means ± SE. *Significant differences between PL and NPL.

exercise test performed with the PL, suggesting a greater maximal capacity to extract oxygen in the PL skeletal muscle. This finding can provide a mechanistic explanation for the higher peak power and peak oxygen consumption of the PL and can suggest a different fiber type distribution between PL and NPL. Actually, Arevalo et al. (10) showed a greater proportion of type I and I/IIa fibers in the PL of resistance-trained men. However, while there is no doubt that the

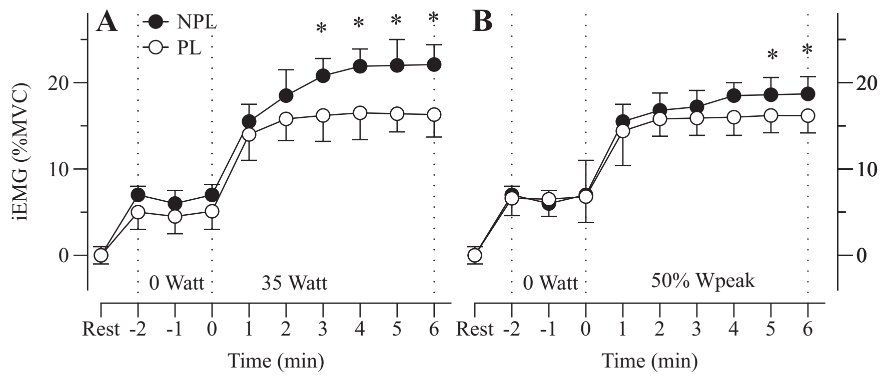

Figure 4. Percent change in integrated electromyography (iEMG) at rest, during unloaded dynamic leg-extension (DLE), and constant-workload DLE exercise executed at absolute (35 W; *A*) and relative intensities [50% of the peak power output (50% W_{peak}; *B*)]. Values are represented as the percent of integrated electromyography (%iEMG) activity normalized for the iEMG recorded during maximal voluntary isometric contractions (%MVC). The open circles represent the values recorded with the preferred leg (PL), and the solid circles with the nonpreferred leg (NPL). Values are means ± SE. *Significant differences between PL and NPL.

energy cost of isometric force generation is much lower in slow fibers than in fast fibers, only minor, if any, difference is present between slow and fast fibers in mechanical efficiency during active shortening (43). Moreover, the influence of skeletal muscle fiber-type distribution on whole body exercise efficiency is even more controversial. Indeed, a significant positive relationship has been reported between the percentages of type I fibers and mechanical efficiency in some (44–46), but not all, studies (47). Our results (Fig. 5) show a negligible difference in the % distribution of MyHC isoforms between vastus lateralis of PL and NPL and, thus, rule out that fiber-type composition is a determinant factor for the difference in submaximal mechanical efficiency observed between the PL and NPL.

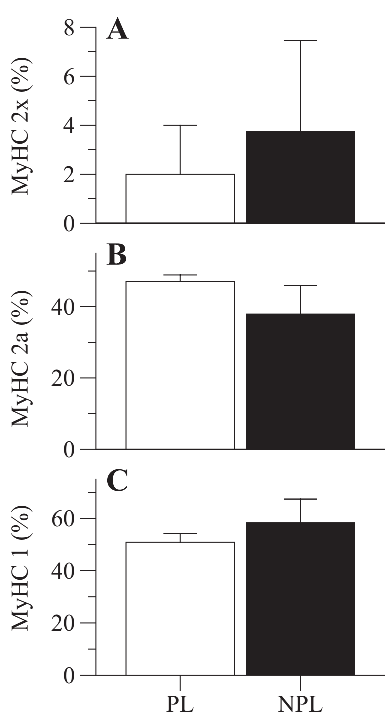

Figure 5. Distribution of myosin heavy chain (MyHC) isoforms in vastus lateralis of preferred (PL) and nonpreferred (NPL) legs. *A*–*C*: represent MyHC2x, MYHC2a, and MyHC1, respectively. Values are means ± SE. No significant difference was present.

Evidence That the Lower Submaximal Mechanical Efficiency in NPL is Influenced by the Muscle Activation

Wakeling et al. (39, 40) reported that the same mechanical workload during cycling can be achieved with different patterns of muscle activation as detectable with EMG recordings followed by appropriate analysis tools. Therefore, the power that can be produced by a group of muscles seems to be correlated to the synergies of those muscles, and different activation synergies might have an effect on muscular efficiency. Partially in accordance with this view, Carpes et al. (11) showed similar muscle activation of the PL and NPL exercising at a relative workloads and, in accordance with such similarity, no difference in mechanical efficiency. It is important to note that in this investigation, the exercise workload utilized for the calculation of mechanical efficiency and the EMG evaluation of muscle activation was different between the PL and NPL. Specifically, Carpes et al. (11) adopted for PL and NPL relative workloads calculated from a percent of the 2nd ventilatory threshold measured in previous incremental bilateral cycling test. Therefore, a direct comparison of the submaximal mechanical efficiency and, more importantly, the EMG activity of the PL and NPL exercising at the same absolute and relative workloads was missing.

In contrast with this literature but in accordance with the Wakeling hypothesis (39, 40), our results suggest, at least for the leg extension exercise modality, a better neuromuscular control (lower iEMG) in PL compared with NPL and inverse correlations between η_{net} and the iEMG (Fig. 6). Although, the experimental conditions did not allow us to clearly and unambiguously separate absolute and relative exercise intensity, which could act as a confounding factor in the interpretations of the results, our findings suggest that this physiological phenomenon is primarily determined by the different muscle activation exhibited by the PL and NPL. Therefore, at least for the exercise involving knee extensors muscles, we can propose that the smaller amount of muscle fibers needed to be recruited in the PL likely resulted in a lower oxygen requirement to support the ATP resynthesis at a given mechanical workload. The greater isometric torque and the higher RFD of the PL, which has a thigh muscle mass similar to NPL, support the view of a superior neuromuscular control in PL.

Table 2. *Correlations between ηnet, central and peripheral factors*

	35 W	η_{net} PL 35 W R (P)		η_{net} NPL 35 W R (P)	50% W_{peak}	η_{net} PL 50%W_{peak} R (P)		η_{net} NPL 50%W_{peak} R (P)
$\dot{V}E$	PL	0.188 (0.500)	NPL	0.044 (0.877)	PL	0.348 (0.204)	NPL	0.010 (0.970)
[La⁻]	PL	0.191 (0.495)	NPL	0.136 (0.628)	PL	0.023 (0.936)	NPL	0.338 (0.217)
HR	PL	0.079 (0.779)	NPL	0.209 (0.454)	PL	−0.046 (0.869)	NPL	−0.378 (0.164)
CO	PL	0.351 (0.199)	NPL	0.024 (0.932)	PL	−0.108 (0.701)	NPL	0.543 (0.063)
MAP	PL	−0.071 (0.801)	NPL	0.353 (0.197)	PL	0.044 (0.874)	NPL	−0.021 (0.941)
FBF	PL	−0.094 (0.737)	NPL	0.072 (0.797)	PL	−0.137 (0.624)	NPL	−0.127 (0.650)
VC	PL	−0.033 (0.907)	NPL	−0.046 (0.870)	PL	−0.119 (0.673)	NPL	0.141 (0.617)
[HHb]	PL	−0.382 (0.159)	NPL	0.117 (0.678)	PL	0.238 (0.393)	NPL	0.308 (0.264)
iEMG	PL	−0.838 (0.00009)	NPL	0.698 (0.00383)	PL	−0.824 (0.00001)	NPL	−0.799 (0.00034)
MVC	PL	0.033 (0.906)	NPL	0.241 (0.387)	PL	0.154 (0.583)	NPL	0.272 (0.327)
RFD_{50-100}	PL	−0.294 (0.286)	NPL	0.276 (0.319)	PL	0.029 (0.917)	NPL	0.189 (0.498)
$RFD_{100-200}$	PL	0.086 (0.760)	NPL	−0.248 (0.373)	PL	0.169 (0.547)	NPL	0.503 (0.253)

η_{net}, Net efficiency; CO, cardiac output; FBF, femoral blood flow; [HHb], near-infrared spectroscopy deoxyhemoglobin; HR, heart rate; iEMG, integrated electromyography; [La⁻], blood lactate concentration; MAP, mean arterial pressure; MVC, maximal isometric voluntary contraction; NPL, nonpreferred leg; PL, preferred leg; RFD_{50-100}, rate of force development of 50–100 ms; $RFD_{100-200}$, rate of force development of 100–200 ms; VC, vascular conductance; $\dot{V}E$, minute ventilation; 35 W, exercise executed at 35 Watts; 50% W_{peak}, exercise executed at 50% of the peak power output.

Physiological Considerations and Limitations

Two specific points require a further comment. First, there is a difference between cycling and DLE, as in the latter only the knee extensor muscles, i.e., the quadriceps, is involved, whereas in the former several limb muscles are called in action. Second, although cycling is an automatized motor skill for most people, not only cyclists, the DLE movement is not very usual and needs some learning and, possibly, greater cortical control. Therefore, it cannot be excluded that the learning process is faster or better in the PL than in NPL. Against this possibility, however, plays the observation that the RFD during an ordinary maximal isometric contraction is higher in PL than in NPL.

It is also important to mention that the exercise workloads utilized for the determination of the mechanical efficiency were chosen taking into account two specific physiological factors. Specifically, for a precise determination of the mechanical efficiency, it is particularly important that the $\dot{V}O_2$ reach a steady state, without a slow component of the $\dot{V}O_2$ kinetics. On the other hand, the calculation of mechanical efficiency is uncertain at very low exercise intensities, overestimating the efficiency. For these reasons, we have opted to measure the efficiency at workloads that, on the one hand, were below the accumulation of the blood lactate and consequently did not generate the $\dot{V}O_2$ slow component, and on the other hand were above the minimal workloads generating a sufficient $\dot{V}O_2$ response.

Moreover, a potential limitation of the current study was the analysis of the muscle EMG activity from the vastus lateralis instead of an integrated analysis from all muscles of the quadriceps muscles.

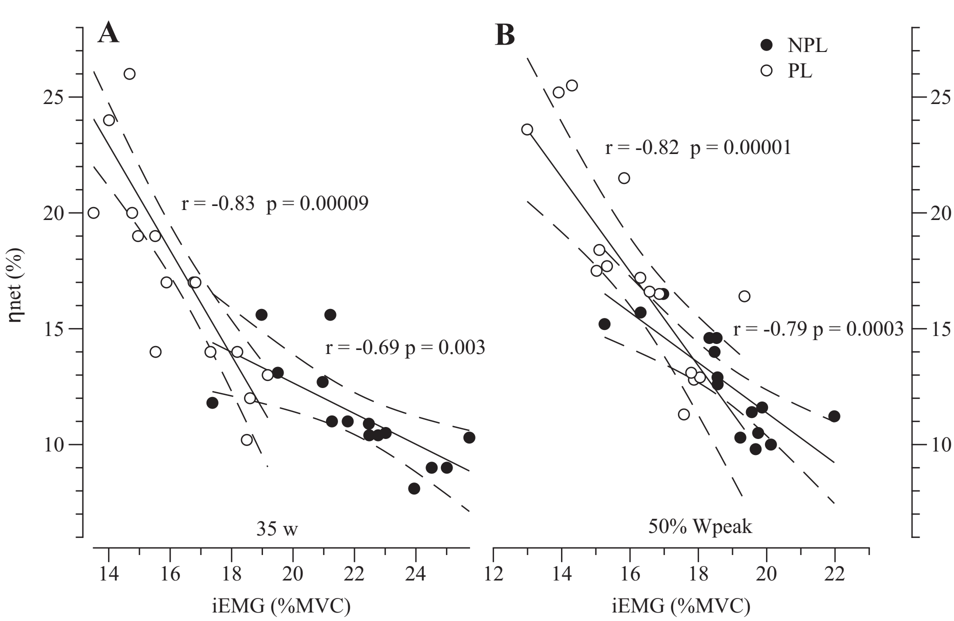

Figure 6. Correlations between muscle activation and net efficiency during exercise executed with preferred leg (PL; white circles) and nonpreferred leg (NPL; dark circles). *A* and *B*: represent the inverse linear correlation between net efficiency (η_{net}) and the integrated electromyography (iEMG) measured during a dynamic leg-extension exercise executed with the PL and NPL. *A*: represents the values recorded during dynamic leg-extension exercise executed at the same absolute workload (35 W). *B*: displays the data recorded during dynamic leg-extension exercises executed at the same relative workload [50% of the peak power output (50% W_{peak})].

Conclusions

In conclusion, this study has identified a critical role of submaximal mechanical efficiency in limb preference during single-leg extension exercise. Interestingly, the spectrum of the central cardio-respiratory and peripheral circulatory determinants of mechanical efficiency does not explain the difference between preferred and nonpreferred leg. In contrast, the lower level of muscle activation of the preferred leg, that was inversely correlated with mechanical efficiency, is likely a major determinant of this physiological phenomenon.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.V. and C.R. conceived and designed research; M.V., C.T., C.M., L.F., L.T., and C.R. performed experiments; M.V., C.M., and L.T. analyzed data; M.V., C.T., L.F., C.R., and F.F.S. interpreted results of experiments; M.V. prepared figures; M.V. drafted manuscript; M.V. and C.R. edited and revised manuscript; M.V., C.T., C.M., L.F., L.T., C.R., and F.S. approved final version of manuscript.

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