Muscle size, not quality, explains low passive skeletal muscle force in heart failure patients

Fausto A. Panizzolo[1], Andrew J. Maiorana[2,3], Louise H. Naylor[1], Lawrence Dembo[4], David G. Lloyd[1,5], Daniel J. Green[1,6], and Jonas Rubenson[1,7]

[1]The School of Sport Science, Exercise and Health, The University of Western Australia, Crawley, WA, Australia.

[2]Advanced Heart Failure and Cardiac Transplant Service, Royal Perth Hospital, Perth, WA, Australia.

[3]School of Physiotherapy and Exercise Science, Curtin University, Perth, WA, Australia.

[4]Envision Medical Imaging, Perth, Western Australia, Australia.

[5]Centre for Musculoskeletal Research, Griffith Health Institute, Griffith University, Gold Coast, QLD, Australia.

[6]Research Institute for Sport and Exercise Science, Liverpool John Moores University, Liverpool, United Kingdom.

[7]Biomechanics Laboratory, Department of Kinesiology, The Pennsylvania State University, University Park, PA, USA.

Corresponding author: Dr. Fausto A. Panizzolo

School of Engineering and Applied Sciences, Wyss Institute for Biologically Inspired Engineering,

Harvard University, 60 Oxford st, Cambridge, MA, United States.

Email: fpanizzolo@seas.harvard.edu

ABSTRACT

Background. Impaired skeletal muscle has been linked to the compromised exercise capacity characterizing chronic heart failure (CHF). However, how passive skeletal muscle force is affected in CHF is not clear. Understanding passive force characteristics in CHF can help further elucidate the extent to which altered contractile properties and architecture affect muscle and locomotor function. Therefore, the aim of this study was to investigate passive force in a single muscle for which non-invasive measures of muscle size are possible, the soleus (SOL), both in CHF patients and age- and physical activity-matched control participants.

Methods. Soleus muscle force and size were obtained by means of a novel approach combining experimental data (dynamometry, electromyography, ultrasound imaging) with a musculoskeletal model.

Results. We found reduced passive SOL forces (~30%) (at equivalent levels of muscle stretch) in CHF *vs.* healthy individuals. This difference was eliminated when force was normalized by physiological cross sectional area, indicating that reduced force output may be most strongly associated with muscle size. Nevertheless, passive force was significantly higher in CHF at a given absolute muscle length and likely explained by the shorter optimal muscle lengths measured in CHF compared to the control participants. This later factor may lead to altered performance of the SOL in functional tasks such gait.

Discussion. These findings suggest exercise rehabilitation targeting muscle hypertrophy, and for the calf muscles, exercise that promotes muscle lengthening.

INTRODUCTION

Growing evidence suggests that deficiencies in the skeletal muscle contributes to the limited functional capacity that characterizes chronic heart failure (CHF) and to the progression of the disease. For example, it is apparent that patients with CHF have a reduction in muscle size (*Mancini et al., 1992; Minotti et al., 1993; Anker et al., 1999; Fülster et al., 2013*) and strength (as determined by net joint moments) in the lower limbs (*Magnusson et al., 1994; Chua et al., 1995; Harrington et al., 1997; Sunnerhagen et al., 1998; Toth et al., 2006; Toth et al., 2010; Panizzolo et al., 2015*) compared to healthy age-matched individuals, and that these reductions are related to aerobic exercise capacity (*Volterrani et al., 1994*; *Harrington et al., 1997; Panizzolo et al., 2015).* It is still not clear, however, if the reduction in muscle and functional capacity are associated primarily with reduced muscle size that is known to occur in CHF (*Mancini et al., 1992; Fülster et al., 2013; Panizzolo et al., 2015*) or if size-independent characteristics- muscle quality- is an important determinant. Indeed, several studies that have measured both voluntary strength and muscle size in the quadriceps suggest that muscle size alone does not account for the loss of strength (*Harrington et al., 1997; Toth et al., 2006; Toth et al., 2010*). Resolving whether muscle size or quality is more closely linked to muscle function can prove important for guiding rehabilitation strategies in CHF.

Measurements of passive muscle forces and how they are related to muscle architecture can provide important information for understanding the mechanisms behind the alterations in skeletal muscle function associated with CHF. In particular, they can shed further light on whether motor deficits are related primarily to reductions in muscle size and the extent to which altered contractile properties and architecture affect *in vivo* function at a whole muscle level without introducing variability arising from voluntary and/or twitch contractions (*Princivero et al., 2000; Oskuei et al., 2003*). Passive forces are also functionally relevant as they influence normal (*Silder, Heiderscheit & Thelen, 2008*) and pathological (*Geertsen et al., 2015*) gait mechanics.

Our understanding of how passive skeletal muscle force is affected in CHF is currently unclear. Passive forces in cardiac muscle are altered in CHF (*Van der Velden, 2011*), as well as in diaphragm skeletal muscle (*Van Hees et al., 2010*). Surprisingly, as far as we are aware, only one study (*Van Hees et al., 2010*) has investigated passive forces in appendicular skeletal muscle in CHF and it has been conducted in a mouse model. This study reported unaltered passive forces in the soleus (SOL) muscle of CHF-affected mice, compared to a control group, when taking into consideration muscle size.

The aim of this study was to investigate the passive forces in the SOL muscle of CHF patients and age- and physical activity-matched control participants, as well as the relationship between muscle architecture [physiological cross sectional area (PCSA), muscle length, pennation angle] and passive force. The SOL was selected because it permits an estimation of passive force in a single muscle (*Rubenson et al., 2012; Tian et al., 2012*). Furthermore, SOL has been identified as a primary muscle in which muscle loss occurs in CHF (*Panizzolo et al., 2015; Green et al., 2016*) and its size is strongly correlated with the reduced exercise capacity present in CHF (*Panizzolo et al., 2015*) (more so than the gastrocnemius synergist) and thus is a muscle of choice for muscle-specific analysis. We hypothesized that there would be a reduction in passive force in CHF patients, compared to a healthy population. We further hypothesized that passive force would be similar after normalizing for the muscle PCSA, thus attributing any alteration to muscle size.

MATERIALS AND METHODS

Participants

Patients with CHF and age- and physical activity-matched control participants who were free from other musculoskeletal disorders and lower limb musculoskeletal injuries were recruited for this study. The CHF group included 12 participants (7 men, 5 women) in the class II-IV of the New York Heart Association (NYHA) classification with an ejection fraction of 30.5±9.6%. (For anthropometric

characteristics and exclusion criteria see Table 1). The control group was composed of 12 healthy participants recruited from the local community (8 men, 4 women). The CHF group underwent regular exercise activity 2-3 times per week for ~ 1 hour per session (treadmill walking and resistance weight training) as part of their standard patient care. The control participants underwent similar levels of weekly exercise. All participants read and signed an informed consent prior to participating in the study and all of the procedures were approved by the Human Research Ethics Committee at The University of Western Australia (approval ID: RA/4/1/2533) and Royal Perth Hospital (approval ID: 2011/019).

Passive force estimates

The procedures used to estimate passive and active SOL forces were similar to those adopted previously, with the exception that passive force was measured during continuous joint rotation (*Rubenson et al., 2012*). Passive moments were recorded with the participants sitting upright with their right foot and ankle positioned in a dynamometer (Biodex M3, Shirley, NY, USA) and with the knee positioned at 120° of flexion (0° knee fully extended) to mitigate the force contribution of the gastrocnemius muscles (*Maganaris, 2001*). The net passive ankle joint moment (M_p) was computed by subtracting the moment generated by the Biodex rig and the weight of the foot (*Rubenson et al., 2012*); the weight of the foot was expressed as a percentage of body mass. The M_p over a joint's range of motion passes through zero at an angle that approximates where passive muscle forces reach zero (*Silder et al., 2007*) (Figure 1). Moment data recorded by the dynamometer were filtered using 4th-order zero-lag 2 Hz low-pass Butterworth filter (MATLAB, The MathWorks Inc., USA). To detect the inflexion point in M_p where net dorsiflexion and plantarflexion moment converge on zero we first fitted the joint angle *vs.* M_p data with a 5th-order polynomial based on visual inspection of the data

and subsequently computed the first order derivative of this function (MATLAB, The MathWorks Inc., USA) (Figure 1).

In some instances the inflexion point was slightly above or below zero moment (<1.5 Nm or ~7% of the peak passive moment). This can occur if the weight of the leg transmits a small moment about the Biodex axis (i.e. small misalignment of ankle center of rotation) or if the moment predicted from weight of the foot has small errors. In these cases the passive moment data was corrected for the offset. Contribution from synergist muscles are minimal at the joint postures adopted (*Maganaris, 2001; Silder et al. 2007; Rubenson et al., 2012*). Passive force estimates from subject-specific scaled OpenSim models (version 2.0.2) further indicated that passive force from synergist muscles were minimal at the recorded knee and ankle postures.

The method described above does not account for passive moments arising from joint articulations and skin, but these are minimal compared to the passive moments arising from passive force in the Achilles tendon (*Costa et al., 2006*). In passive trials electromyography (EMG) from the tibialis anterior (TA), the medial and lateral gastrocnemius muscles (MG, LG, respectively) and the SOL were recorded (Noraxon wireless system, Scotsdale, AZ, USA, 2000 Hz) to ensure the muscles crossing the ankle remained inactive. For each trial, real-time root-mean-square (RMS) waves of the muscles' activity were computed from the EMG signals (incorporating DC offset; Spike2 V7 software; Cambridge Electronic Design, Cambridge, UK) (Rubenson et al. 2012). Soleus fascicle lengths and pennation angle were recorded using dynamic B-mode ultrasound (Telemed, EchoBlaster 128, Lithuania; 25 Hz capture rate; 7.5 MHz 60 mm linear array probe) following the placement and image analysis procedures outlined previously (*Rubenson et al., 2012; Panizzolo et al., 2013*). Simultaneous measurements of ankle joint flexion/extension angles were made using a portable 3D motion capture system (Optitrack, Corvallis, Oregon, US, 100 Hz). The net joint moment, EMG, ultrasound images and joint angles were recorded synchronously (Micro1401-3; Cambridge Electronic Design, Cambridge, UK; 2000 Hz) as the ankle was cycled through its full range of motion (the most plantarflexed and most dorsiflexed position tolerated by the participant) at a constant speed

of 5°/s over three consecutive cycles. Three initial warm-up cycles were performed prior the recording of any measurements. The SOL passive force ($F_{p_{SOL}}$) was computed continuously throughout the joint range of motion as the joint underwent dorsiflexion. Passive force was calculated as per (*Rubenson et al., 2012*) using the following equation:

$$F_{p_{SOL}} = \frac{M_p}{r * \cos\theta} \quad (1)$$

Where *r* represents the Achilles moment arm data and θ the SOL pennation angle. Participant-specific Achilles moment arm data were established experimentally on a separate testing day, following the method described previously in (*Manal, Cowder & Buchanan, 2010*). In this method B-model ultrasound (Telemed, Echo Blaster 128, Lithuania) was used to capture Achilles tendon images in the sagittal plane from the participants while their foot was cycled passively at an angular velocity of 5°/s across its range of motion in a Biodex dynamometer (M3, Biodex, Shirley, NY, USA). The ultrasound probe (7.5 MHz, 60 mm field of view, linear array probe, 50 Hz capture rate) was placed longitudinally above the Achilles tendon using a stand-off gel pad (Aquaflex, Parker, NJ, USA). Simultaneously, the trajectories of two retro-reflective markers mounted on the ultrasound probe were recorded by means of a 3D motion capture system (Optitrack, Corvallis, Oregon, US, 100 Hz). Additional anatomical landmarks (first metatarsal, calcaneus, medial malleoli and knee medial condyle) were tracked to calculate the ankle flexion/extension joint angle. A 2D customized graphical interface was developed in Matlab to display both the ultrasound images and the ultrasound probe and the medial malleoli markers in the same coordinate system. The line of action of the Achilles tendon was digitized in this common coordinate system and the moment arm was computed as the perpendicular distance between the tendon line of action and the medial malleoli, which was used as an estimate of the ankle joint center. This procedure was performed at 10 ankle joint angles that spanned the joint's range of motion. A 10-point moment arm-joint angle curve was obtained for each participant by using a polynomial fit of the moment arm-joint angle data.

We defined the fascicle slack length (L_{slack}) as the length where passive SOL forces are first generated, estimated as the point where the net passive dorsiflexion and plantarflexion moments converge on zero, and the fascicle length at the maximum tolerated dorsiflexion angle as the maximal fascicle length (L_{max}). Absolute and normalized passive SOL force-length (F-L) curves were established for each participant. Absolute passive F-L curves used the measured $F_{p_{SOL}}$ in Newtons and fascicle lengths (L) in mm. Normalized passive F-L curves were created by dividing each participant $F_{p_{SOL}}$ by their SOL PCSA (Equation 1) and by dividing L by L_{slack} (normalized length referred to here as L_{norm}). The PCSA was determined from underwater 3D ultrasound scans (Telemed, EchoBlaster 128, Lithuania; Stradwin, Medical Imaging Research Group, Cambridge University Engineering Department, UK) following (*Panizzolo et al., 2015*). To enable the comparison of absolute $F_{p_{SOL}}$ between groups, $F_{p_{SOL}}$ was determined at a percent fascicle stretch of 0%, 20%, 40%, 60%, 80% and 100% of the maximum fascicle stretch, where percent fascicle stretch was defined as $\left((L - L_{slack}) \div (L_{max} - L_{slack})\right) * 100$. The same procedure was done to compare passive moment data over both angle and muscle length ranges. Passive fascicle stiffness was computed for each participant as the slope of the absolute F-L curves between L_{slack} and 40% stretch (k_1) and between 60% - 100% stretch (k_2). In order to compare the normalized passive F-L curves we evaluated the normalized $F_{p_{SOL}}$ at a set of L_{norm} between 1.0 and 1.4 (i.e. strain of 0 - 40%) using intervals of 0.05. A peak L_{norm} was set to 1.4 as this represented the average maximum L_{norm} that the participants achieved at their end range of ankle dorsiflexion. The normalized $F_{p_{SOL}}$ was computed for each individual for the interval described above by fitting the normalized $F_{p_{SOL}}$ and L_{norm} data using a 1st-order exponential equation (*Gollapudi & Lin, 2009*). In some circumstances where the set range exceeded the experimental L_{norm} the normalized $F_{p_{SOL}}$ values were extrapolated from the exponential equation. Stiffness was computed between L_{norm} of 1.0 and 1.2 (k_{1norm}) and 1.2 and 1.4 (k_{2norm}).

Active forces estimates

As an ancillary comparison of the muscle lengths, we also analyzed peak active muscle forces at different ankle angles (and thus muscle lengths) to generate an active force-length relationship. The optimal muscle length coinciding with maximal peak active force (L_0) is known to correspond well with L_{slack}, both in human and non-human studies (*Azizi & Roberts, 2010*), including the human SOL (*Rubenson et al., 2012*) and can thus serve as an additional test for differences in fascicle lengths between groups. The protocol used in this study to obtain predictions of moments and force generated by the SOL (as well as the moments and force generated by synergist muscles and by the co-contraction of dorsiflexor muscles) expands on the procedures established in (*Rubenson et al., 2012*). It uses a combination of experimental net moment measurements from dynamometry, ultrasound fascicle imaging, electromyography and a scaled participant-specific musculoskeletal model in OpenSim 2.0.2 (*Delp et al., 2007*). Predictions were performed with the knee in a flexed position (>120°) and over a range of ankle angles from ~ -30° dorsiflexion to 30° plantarflexion (the ankle range of motion varied between individuals). The muscle length that corresponded with the maximal peak active force was designated as L_0.

First, a generic lower-limb model (*Arnold et al., 2010*) was scaled using each participant's joint axes and centers determined via motion capture data (8-camera VICON MX motion capture system, Oxford Metrics, UK; 100 Hz) from participants in a standing posture as well as dynamic joint motions (*Besier et al., 2003*). From these trials, an inverse kinematics algorithm was run on the position of 26 retroreflective spherical markers placed on anatomical landmarks and on functionally determined joint centers (*Besier et al., 2003*), that minimized the distance between the OpenSim model markers and the retroreflective and the functionally determined markers.

The moment generated by the plantarflexors (M_{plant}) during the maximal voluntary isometric plantarflexion contractions (MVC_{plant}) was calculated as:

$$M_{plant} = M_{peak} - \Delta M_p + M_{dorsi} \quad (2)$$

where M_{peak} is the peak net ankle joint moment (calculated as the difference between the Biodex recorded moment during MVC_{plant} and the moment at rest), ΔM_p represents the difference in the estimated passive SOL moment during the MVC_{plant} and the passive SOL moment at rest prior to the contraction, and M_{dorsi} is the moment generated by the co-contraction of the dorsiflexors muscles. ΔM_p was calculated as:

$$\Delta M_p = \left(F_{p_{SOL}}^{contr} * \cos\theta^{contr} * r^{contr}\right) - \left(F_{p_{SOL}}^{rest} * \cos\theta^{rest} * r^{rest}\right) \quad (3)$$

where $F_{p_{SOL}}$ was obtained for both the fascicle length at the MVC_{plant} and the fascicle length during the rest period just prior to contraction using a linear interpolation of the passive F-L relationship (*rest* and *contr* superscripts designate rest or MVC_{plant}, respectively). r^{contr} was estimated by increasing the value predicted from the experimental Achilles moment arm- joint angle equation (described above) by 20% to take in account the increase in moment arm distance reported during MVC_{plant} with respect to length at rest (*Maganaris et al., 1998*).

The M_{dorsi} was predicted by the participant-specific OpenSim model. First, the OpenSim maximal isometric forces of all the dorsiflexors (tibialis anterior, extensor digitorum longus, extensor hallucis longus, peroneus tertius) were adjusted by the same percentage increase or decrease so that the predicted model's peak isometric dorsiflexion moment at 100% activation (MVC_{dorsi}) matched that of the participant's experimental maximum M_{dorsi} recorded in the Biodex dynamometer at 10° plantarflexion, the angle that corresponds approximately to optimal dorsiflexion moments (*Silder et al., 2007*). The MVC_{dorsi} were performed only at this joint angle to reduce the total numbers of contractions performed and time spent in the experimental protocol by each participant. This was an important consideration because of the general high fatigability of CHF patients. In this procedure, the OpenSim model was positioned to match the participant's optically recorded ankle and knee joint posture. In subsequent measurements of MVC_{plant} the M_{dorsi} was predicted by the OpenSim model by prescribing an activation to all of the dorsiflexors equal to the ratio of the TA's peak EMG (linear

envelope) during the MVC_{plant} to its peak EMG (linear envelope) from the MVC_{dorsi} trial; i.e. this assumed the same activation level for all dorsiflexors.

To take into account the contribution of synergist muscles we predicted the relative percentage contribution of each plantarflexors muscle to the total plantarflexor moment in OpenSim (M_{Syn}) by prescribing the recorded ankle and knee angles and 100% activation of all plantarflexor muscles (peroneus longus, peroneus brevis, flexor hallucis, tibialis posterior, flexor digitorum, MG, LG and SOL). The percent contribution of the OpenSim SOL to the total predicted moment was applied to the experimental MVC_{plant} to define the moment generated by the participant's SOL ($M_{a_{SOL}}$). Lastly, peak voluntary active SOL force production ($F_{a_{SOL}}$) was calculated as:

$$F_{a_{SOL}} = \frac{M_{a_{SOL}}}{r^{contr} * \cos\theta^{contr}} \quad (4)$$

These active force trials were performed only by the participants that were able to tolerate a prolonged protocol (n = 7 and n = 8, for control and CHF participants, respectively).

Statistical analysis

Differences in the absolute (non-normalized) passive moment-angle, moment-length and F-L curves were assessed by testing if $F_{p_{SOL}}$ were different between groups (CHF and control), and if passive joint angles and/or fascicle lengths were affected, by using a two-way (CHF/control) repeated measures (0% 20%, 40%, 60%, 80% and 100% of angular excursion or muscle stretch, respectively) ANOVA, with Bonferroni *post hoc* tests. Similar two-way repeated measures ANOVAs were also performed on the normalized F-L curves using the L_{norm} set range (1.0 - 1.4). A two-tailed unpaired Student's t-test with significance level of $p < 0.05$ was used to determine significant differences in the $L_{slack,}$ L_{max} , the maximal fascicle stretch, and L_0, as well as in the passive fascicle stiffness (k_1, k_2, k_{1norm} and k_{2norm}) between the groups. Statistical analysis was performed in SPSS (IBM, Statistics 21, USA).

RESULTS

No main effect of group was found in the joint angle between the CHF and control groups (p = 0.42) (Figure 2). A main effect of group on net passive ankle joint moment was found (p = 0.014) with lower passive moment in the CHF group compared to the control group at equivalent levels of angular excursion and fascicle stretch, although no statistically significant interaction effect was found (p = 0.398) between group and moment (Figure 2).

A main effect of group on absolute $F_{p_{SOL}}$ (N) was found (p = 0.027) with lower absolute $F_{p_{SOL}}$ in the CHF group compared to the control group at equivalent levels of fascicle stretch, although no statistically significant interaction effect was found (p = 0.11) between group and level of stretch. No differences were found in k_1 and k_2 between the groups (p = 0.32; ES = 0.51 and p = 0.85; ES = 0.09) (Figure 3a). The L_{max} was significantly shorter in the CHF group compared to the control group (p = 0.046; ES = 0.96), although no statistically significant differences were found in L_{slack} (p = 0.11; ES = 0.76) and in the maximal fascicle stretch ($L_{max} - L_{slack}$) (p = 0.34; ES = 0.44) (Table 2) or maximal fascicle strain (p = 0.7; ES = 0.09).

No main effect was found in the PCSA-normalized $F_{p_{SOL}}$ (N cm^{-2}) between the CHF and control groups when using the L_{norm} strain range of 1.0-1.4 (p = 0.46) (Figure 3b), nor was there an interaction effect between the PCSA-normalized $F_{p_{SOL}}$ and normalized lengths (p = 0.52). Normalized passive fascicle stiffness (k_{1norm} and k_{2norm}) were not significantly different between the groups (p = 0.42; ES = 0.44 and p = 0.54; ES = 0.33) (Figure 3b).

L_0 determined from the active force-length data was significantly shorter (~22%) in the CHF group compared to the control group (p = 0.039; ES = 0.96) (Table 2). The voluntary forces were derived at a range of ankle joint angles, and therefore over a range of fascicle lengths. The maximal $F_{a_{SOL}}$ and corresponding L_0 occurred at approximately 10° dorsiflexion. The $F_{a_{SOL}}$ at both shorter and longer fascicle lengths relative to L_0 decreased, characteristic of the muscle force-length relationship

297 (Figure 4). L_0 was not significantly different from L_{slack} in either the control or CHF groups (p =
298 0.33 and p = 0.39, respectively; Table 2).
299

300 ## DISCUSSION

301 The present study provides, to the best of our knowledge, the first estimate of *in vivo* passive human
302 skeletal muscle force-length properties in CHF. As predicted, higher absolute M_p and $F_{p\,SOL}$ were
303 produced in the control group for a given amount of muscle stretch (Figure 2, 3). Also in agreement
304 with our hypothesis, passive force is not different after normalizing by muscle PCSA, nor is passive
305 muscle stiffness affected, indicating that muscle size rather than intrinsic muscle properties is a major
306 factor influencing passive force and stiffness in CHF SOL muscle. This finding stands in contrast to
307 previous work reporting stiffer cardiac muscle due to alterations in the titin structure (*Wu, 2002*) or
308 decreased passive force of the diaphragm, due to titin loss (*Van Hees et al., 2010*) in CHF. On the
309 other hand, our results do corroborate data from passive skeletal muscle properties in the mouse SOL,
310 in which passive forces from CHF-affected animals were likewise not altered after normalizing to
311 muscle cross sectional area (*Van Hees et al., 2010*).

312 It was surprising, however, that for a given absolute muscle length, passive force was
313 significantly higher in CHF SOL compared to the control group. This unexpected finding stems from
314 the fact that over the same ankle range of motion the passive muscle lengths are shorter in CHF
315 patients, in particular at maximal stretch (Figure 2, 3). The result is that for the same absolute muscle
316 length (above L_{slack}) the CHF muscle has undergone greater strain, thus generating greater force in
317 titin and other passive load bearing muscle components. Previous experimental studies (*Azizi &*
318 *Roberts, 2010; Winters et al., 2011; Rubenson et al., 2012*) have shown agreement between the onset
319 of passive force generation (L_{slack}) and L_0 (optimal length for active force production). The estimate
320 of L_0 in the present study was similar to L_{slack} for both groups and significantly ($p < 0.05$) shorter in
321 the CHF group (Table 2). The shorter L_{slack} and L_0 in CHF patients indicates that the SOL has

undergone a loss of in-series sarcomere numbers, a contributing factor to the reduced muscle size (*Panizzolo et al., 2015*). It was also surprising that, despite their shorter muscle fascicles, CHF patients underwent the same ankle range of motion and a similar SOL muscle strain across this range of motion (Figure 2, Table 2). The Achilles moment arms were similar between the control and CHF group suggesting that greater Achilles strain might explain the similarity in joint and muscle excursions. This is partially supported by the smaller tendon cross sectional area reported in CHF (*Panizzolo et al., 2015*).

Functional implications

Our results are consistent with the observation that muscle size dictates functional deficits in CHF (*Magnusson et al., 1994*). Exercise that promotes hypertrophy should therefore be a focus for restoring functional capacity in leg muscles. Exercise prescription for CHF is becoming commonplace, but programs that include specifically designed lower limb resistance training might be especially promising (*Maiorana et al., 2000*).

Our results also offer insight into the gait mechanics of CHF patients (*Panizzolo et al., 2014*). The combination of the shorter SOL muscle fascicles in CHF patients and their greater dorsiflexion during mid-stance of gait (*Panizzolo et al., 2014*) may cause significantly greater SOL strain. This might lead to the muscle operating on to the descending limb of the F-L curve where large passive forces develop (*Rassier, MacIntosh & Herzog., 1999; Rubenson et al., 2012*). In this scenario CHF patients would rely more on their passive forces to support the plantarflexion moment during walking, which has the benefit of reducing metabolically expensive active force development. This may help explain why CHF patients rely proportionately more on their ankle for powering walking as speed and metabolic demand increases (*Panizzolo et al., 2014*). However, whilst metabolically advantageous, this mechanism might lead to greater lengthening-induced muscle damage. The muscle's F-L operating range depends on multiple factors, including tendon stiffness, and a detailed understanding will require further *in vivo* analyses.

CONCLUSION

This work suggests that a primary factor leading to lower passive forces in the SOL is likely a reduction in muscle size. However, shorter muscle fascicles in CHF results in greater passive forces for a given absolute muscle length, and might be linked to changes in CHF gait (*Panizzolo et al., 2014*). Exercise that promotes calf muscle hypertrophy and serial sarcomerogenesis may prove particularly beneficial in CHF patients.

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