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Energy Utilization and Fatigue in Frail Older Women in Relation to Walking

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ABSTRACT

Background and Objectives: Fatigue is one of the characteristics defining frailty. However, the mechanisms leading to fatigue are still poorly understood. Our objectives were to assess the efficacy of energy utilization (EU) during walking in frail older persons and their level of fatigue. Research Design and Methods: Clinical study of a convenient sample of frail older women. 10 healthy (H; 77 ± 4 year, BMI: 25 ± 3 kg/m^2, MMSE: 29 ± 1) and 10 frail elderly women (F; 83 ± 6 year, 26 ± 5 kg/m^2, 27 ± 3) were compared for their usual level of fatigue and changes in perceived fatigue and EU before and after walking. A 10 cm Visual Analogue Scale (VAS) prior to and following a 6-Minute Walk Test (6MWT) served to measure fatigue. EU was based on VO_2 consumption adjusted for walking distance and measured using a portable Cosmed K4b^2 indirect calorimeter. Participants underwent body composition measurements by DXA and venous blood sampling.

Results: Groups had similar body composition and blood parameters. At rest, there were no differences in VO_2 or energy expenditure, but the frail group had a lower heart rate. During 6MWT, between group differences were found for distance VO_2, HR and EU. There were VAS changes in fatigue and a moderate correlation between the VAS of general fatigue and hsCRP.

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Discussion and Implications: Compared with their healthy counterparts, frail older women exhibited lower physical performance, efficacy of EU, and perceived more fatigue with activity. Inflammation was significantly correlated with subjective fatigue but did not characterize frailty.

KEYWORDS: frailty; fatigue; metabolism; physical performance; energy expenditure; six-minute walk test

INTRODUCTION

Aging is known to derive from an accumulation of detrimental changes in cells and tissues thereby increasing the risk of disease and death in an individual. These changes are more pronounced in frail elderly persons who are also more likely than their healthy counterparts to suffer from functional impairment [1]. Frailty has been defined in several ways: a biologic syndrome of decreased reserve and resistance to stressors, secondary to cumulative declines across multiple physiologic systems [2,3]; an impairment of the normal homeostatic mechanisms of the organism with aging, also known as "homeostenosis" [4]; a clinical condition characterized by both increased levels of pro-inflammatory cytokines such as interleukin (IL-6) and immunosenescence [5].

In accordance with the above observations, Fried *et al.*, using data from the Cardiovascular Health Study, proposed an operational definition of frailty that includes fatigue [3]. Fatigue is a major symptom in seniors [6] and its presence can be associated with or be the cause of three other criteria of frailty, namely the reduction in speed, strength and physical activity [7]. Moreover, fatigue in accomplishing activities of daily living is a strong predictor of onset disability and mortality in non-disabled elderly persons [8]. However, even though fatigue is considered a major component of the frailty syndrome, the pathophysiological mechanism underlying this symptom is still unclear. Fatigue has been defined as an unpleasant feeling disproportionate to the level of exertion that persists during rest [9]. Fatigue has been found to mediate the maximal power in sustained work [8], and thus is related to the individual's energy reserves and level of fitness. Since fatigue is mainly manifested with activity, the study of energy expenditure while performing a standardized physical performance test such as the 6-Minute Walk Test (6MWT) may assist in a better understanding of the pathophysiological basis of fatigue associated with frailty. Previous work has shown that elderly women with advanced solid tumor malignancies experienced a greater inflammatory load that could be associated with a lower 6MWT performance [10]. The inflammatory state may also contribute to fatigue, as elevated levels of IL-6 were associated with weakness and fatigue in community-dwelling elderly men [11]. Inflammation may impair mitochondrial function or be the manifestation of its dysfunction, and since mitochondria play an important role in energy metabolism, relating fatigue with markers of

inflammation and energy expenditure might be of interest in elucidating fatigue [12].

The aims of this study were to assess the level of perceived fatigue in healthy and frail elderly women after performing a 6MWT, as compared to rest, and to measure their energy expenditure to determine if fatigue was related to an impairment of energy utilization. We wish also to evaluate whether the pro-inflammatory and pro-oxidative states were contributors to the level of perceived fatigue in an attempt to unravel factors explaining fatigue. The original hypothesis for this study was that the subjective fatigue perceived by the frail elderly is associated with a reduced efficacy in energy utilization during activity.

MATERIALS AND METHODS

Subjects

Only women were included as they represent higher proportion of senior population [13] and, it would reduce sex-related variability. Community-dwelling women (>70 years; 10 healthy and 10 frail) were recruited: frail women from participants of the McGill University Health Centre (MUHC)-Geriatric Day Hospital, and healthy women from the community through ads. Frail women had fatigue as an obligatory variable, were living independently and could perform activities of daily living (ADL), with the exception that they could be receiving help for bathing. In addition, 9 out of the 10 frail participants required the use of either a cane (n = 4) or walker (n = 5) for mobility. Based on the Clinical Frailty Scale [14], all frail participants were determined to belong in categories 4, 5, or 6, whereas healthy participants were in categories 2 or 3 and none presented the fatigue phenotype. The exclusion criteria for all subjects were as previously reported [15]. All participants signed a consent form approved by the Ethics Review Board of the MUHC.

Overview of the Experimental Protocol

The study was conducted over two (2) visits, the first for screening procedures and to become acquainted with the equipment and the second to perform the walking protocol. Participants were brought to the MUHC for different measurements. During the first visit, subjects gave informed consent, and then completed the MMSE [16] and the Geriatric Depression Scale [17] for memory and mood status. They also indicated the impact of their perceived level of fatigue while preforming their ADLs by placing a vertical line on a 10 cm visual analogue scale (VAS) [18]. Thereafter, they underwent anthropometric measurements and a dual-energy x-ray absorptiometry (DXA) scan. Subjects were then familiarized with a portable closed-circuit Cosmed K4b^2 indirect calorimeter (COSMED s.r.l., Rome, Italy) in order to measure energy expenditure (EE).

For the second visit, participants came in the fasting state to have 50 mL of venous blood drawn. Plasma and serum were frozen at −80 °C for

further analyses. Resting energy expenditure (REE) was then measured with the Cosmed K4b^2 unit for 30 min in a supine position. Afterwards, each subject performed a specific VAS questionnaire (pre-exercise) that asked "How fatigued do you feel at this moment?" in order to measure their level of fatigue and the same was applied again after the 6MWT (post-exercise). Their EE was continuously measured by the Cosmed K4b^2 during the 6MWT, completed under standard conditions, in a pre-determined continuous 30-m long course.

Indirect Calorimetry and Heart Rate

Exhaled pulmonary gases were collected by the portable COSMED K4b^2 unit. The flow meter was attached to a flexible snug-fitting mask that the participants were required to wear for the 30-minute REE and 6MWT. During REE, subjects were quiet and resting in a supine position under thermo-neutral environmental conditions. Using the COSMED [19], the exchange of pulmonary gases was analyzed breath-by-breath during the REE and 6MWT as reported [10]. Heart rate (HR) was recorded using the Polar heart rate monitor and the measured VO_2 and VCO_2 values were used in the Weir equation to calculate REE [20] assuming a nitrogen excretion of 1.2 and 0.9 g kg^{-1}·day, for healthy and frail groups, respectively [21]. REE was normalized for weight and lean body mass and oxygen uptake was calculated (mL O_2 kg^{-1}·min). Averages for HR and for oxygen uptake were also calculated between the 3rd and 6th min of the metabolic steady-state period of the 6MWT. Energy utilization was defined as the average oxygen per meters walked (mL O_2 kg^{-1}·min·m). At the beginning of testing days, O_2 and CO_2 sensors were calibrated using gases containing 16% O_2 and 4% CO_2, respectively.

Six-Minute Walk Test

The 6MWT is a useful assessment tool to measure the exercise capacity of elderly persons [22,23]. Subjects walked a 30-meter long course and were encouraged to walk as fast as they could while maintaining a walking pace. Subjects were allowed to use their walking aid during the test. The total distance walked in 6 minutes was measured to the nearest 0.1 meter, and walking speed (m/s) was calculated.

Anthropometric and Body Composition Measurements

Height was measured to the nearest 0.5 cm and weight was measured to the nearest 100 g. Body mass index (BMI) was then calculated (kg/m^2). Anthropometric measurements were performed using standard techniques [24]. For the determination of total lean tissue, fat tissue and appendicular muscle mass, a total body DXA (Lunar Prodigy Advance™, GE Healthcare, Madison, WI, USA) scan was completed and analyzed using Advance's enCORE™ 2006 software (GE Healthcare, Madison, WI, USA) as in [25].

Assays

Plasma glucose was measured with the glucose oxidase method (GM7 Micro-stat, Analox, Lunenberg, MA, USA) and serum insulin by radioimmunoassay (Linco Research, St-Charles MO, USA) with the homeostasis model assessment (HOMA-IR), calculated as an index of insulin resistance [26]. Plasma FFAs were measured by spectrophotometry using a specific color reagent (NEFA C test kit, Waco chemicals, Waco, TX, USA). Serum interleukins (e.g., IL-1β, IL-6, and IL-10) and TNF-α were analyzed by ELISA using commercially available capture and detection antibody pairs (BD Pharmingen, Franklin Lakes, NJ, USA) following manufacturer's instructions. Serum TAS levels were determined using the Trolox equivalent antioxidant capacity assay [27]. The MDA level, a product of lipid peroxidation was measured by fluorimetric-liquid chromatographic determination [28]. Plasma vitamin E was assayed as α-tocopherol by reversed-phase-HPLC with electrochemical detection and UV detection at ε = 292 nm as previously described [29]. Complete blood count, FT4, albumin, pre-albumin, triacylglycerol, total cholesterol, HDL and LDL-cholesterol, and hsCRP were measured at the MUHC laboratory using standard procedures.

Statistical Analysis

Mean differences between groups were compared using independent *t*-tests and with ANCOVA with age as a covariate for those variables that correlated with age. When normality of the data was not present, non-parametric tests were applied. For the independent *t*-tests, homogeneity of variance was tested using the Levene test. Pearson correlation coefficient was used to analyze the relationships between variables. Results are presented as mean ± SD. Values were considered significant at $p < 0.05$. Statistical analyses were performed with SPSS Statistics (version 15.0.1 Chicago, IL, USA).

RESULTS

Subjects

Frail women were older than their healthy counterparts and their anthropometric characteristics revealed that they were shorter with less triceps skinfold thicknesses and arm circumferences. Both groups were similar for BMI and body composition measurements specified in Table 1.

Blood Parameters, Oxidative Stress and Inflammatory Markers

There were no significant differences in our comprehensive panel of blood parameters (Table 2), although higher levels of IL-10 reached borderline significance in the healthy group ($p = 0.05$).

Table 1. Patient Characteristics.

Characteristics	Healthy (*n* = 10)	Frail (*n* = 10)	*p*-value
Age (years)	77.1 ± 4.4	82.7 ± 5.7	0.024
MMSE Score	29.5 ± 1.0	27.4 ± 2.9	0.054
Chronic Diseases (*n*)	0.3 ± 0.5	4.2 ± 1.0	<0.001
Medications (n)	0.2 ± 0.4	4.5 ± 1.6	<0.001
Handgrip Strength (kg)	23.2 ± 5.9	10.8 ± 5.7	<0.001
Weight (kg)	62.2 ± 4.4	59.3 ± 13.2	0.529
Height (cm)	157.7 ± 4.2	150.3 ± 9.1	0.036
BMI (kg/m^2)	25.1 ± 2.5	26.2 ± 5.2	0.499 *
Triceps Skinfold Thickness (mm)	23.3 ± 4.4	18.3 ± 5.4	0.036
Arm Circumference (cm)	29.3 ± 2.5	26.1 ± 3.5	0.032
Waist Circumference (cm)	85.8 ± 7.2	86.8 ± 14.3	0.312 *
Lean Body Mass (kg)	36.1 ± 2.8	35.1 ± 3.8	0.510
Appendicular Muscle Mass (kg)	15.8 ± 1.3	14.8 ± 1.9	0.190
Total % Fat	38.0 ± 3.9	35.1 ± 11.7	0.471
Trunk Fat (kg)	11.4 ± 3.1	9.7 ± 6.2	0.436

* Adjusted for age. MMSE: mini-mental status examination; BMI: body mass index.

Table 2. Blood Parameters.

Parameters	Healthy (*n* = 10)	Frail (*n* = 10)	*p*-value
Hemoglobin (g L^{-1})	129.5 ± 8.1	121.8 ± 8.1	0.103
WBC (10^9 L^{-1})	5.4 ± 1.2	5.3 ± 1.3	0.859
Lymphocytes (10^9 L^{-1})	1.6 ± 0.4	1.5 ± 0.4	0.698
Albumin (g L^{-1})	39.6 ± 3.7	37.6 ± 3.4	0.900 *
Pre-albumin (g L^{-1})	0.24 ± 0.04	0.23 ± 0.04	0.651
hsCRP (mg L^{-1})	2.1 ± 1.5	7.6 ± 9.3	0.364
IL-1β (ρg mL^{-1})	33.2 ± 39.2	40.0 ± 30.8	0.343
IL-6 (ρg mL^{-1})	126.9 ± 39.3	151.4 ± 45.4	0.212
IL-10 (ρg mL^{-1})	108.4 ± 36.6	106.5 ± 80.3	0.050 *
TNF-α (ρg mL^{-1})	115.2 ± 282.4	179.8 ± 302.0	0.619
TAS (arbitrary units)	1.5 ± 0.1	1.5 ± .01	0.382
MDA (μmol L^{-1})	3.0 ± 0.6	3.1 ± 0.4	0.571
α-Tocopherol (μmol L^{-1})	15.1 ± 7.4	20.0 ± 6.8	0.176
HOMA-IR Score	2.8 ± 1.1	2.8 ± 1.3	0.933
Free-fatty acids (mmol L^{-1})	585.2 ± 232.6	623 ± 146.5	0.663
Total Cholesterol (mmol L^{-1})	5.7 ± 0.9	5.6 ± 1.1	0.867
Triacylglycerol (mmol L^{-1})	1.3 ± 0.6	1.3 ± 0.5	0.915
HDL-cholesterol (mmol L^{-1})	1.4 ± 0.2	1.4 ± 0.4	0.820
LDL-cholesterol(mmol L^{-1})	3.7 ± 0.9	3.6 ± 1.1	0.833
Total cholesterol/HDL	4.1 ± 0.8	4.1 ± 1.2	1.000
Free thyroxin (ρmol L^{-1})	11.3 ± 1.6	11.4 ± 2.4	0.881

*Adjusted for age. WBC: white blood cells; hsCRP: high sensitive C-reactive protein; HOMA-IR: homeostasis model assessment of insulin resistance; IL: interleukin; TNF-α: tumor necrosis factor-α; TAS: total antioxidant status of serum; MDA: malondialdehyde; HDL: high density lipoprotein; LDL: low density lipoprotein.

Resting Energy Measurements

During the resting state, groups were similar for O_2 consumption, CO_2 production and RQ, as well as for their REE expressed as total or corrected for body weight and LBM (Table 3). Frail women had a lower resting heart rate (p = 0.005) when compared to the healthy group.

Table 3. Metabolic and Functional Performance Measurements.

Performance Measurements	Healthy (n = 10)	Frail (n = 10)	p-value
Resting State			
VO_2 (mL min^{-1})	161.3 ± 49.6	164.3 ± 23.9	0.866
VCO_2 (mL min^{-1})	127.3 ± 41.5	125.1 ± 22.4	0.880
Oxygen uptake (mL O_2 kg^{-1}·min)	2.6 ± 0.7	3.0 ± 0.5	0.201
REE (kcal day^{-1})	1093 ± 346	1114 ± 163	0.866
REE/BW (kcal kg^{-1})	18.5 ± 4.9	19.3 ± 3.5	0.358
REE/LBM (kcal kg^{-1})	29.9 ± 7.5	31.7 ± 3.3	0.503
Heart rate (bpm)	65.4 ± 13.9	58.6 ± 10.8	0.005
Respiratory quotient	0.79 ± 0.07	0.77 ± 0.09	0.395
6-Minute Walk Test (6MWT)			
Distance (m)	472.2 ± 43.0	189.1 ± 67.8	<0.0001 *
Speed (m s^{-1})	1.3 ± 0.1	0.53 ± 0.2	<0.0001 *
6MWT Steady-state (min 3–6) Average			
Oxygen uptake (mL O_2 kg^{-1}·min)	14.0 ± 3.2	11.2 ± 2.8	0.049
EU (mL O_2 kg^{-1}·min·m)	0.030 ± 0.007	0.064 ± 0.02	<0.0001
Heart rate (bpm)	114 ± 18	92 ± 14	0.008
Respiratory quotient	0.83 ± 0.09	0.79 ± 0.08	0.390
Fatigue			
General VAS (cm)	2.9 ± 2.2	4.6 ± 1.7	0.078
Change Specific VAS (cm)	−0.1 ± 1.3	2.2 ± 2.6	0.024

*Adjusted for age. REE: resting energy expenditure; EU: energy utilization; VAS: visual analogue scale.

Six-Minute Walk Test

The distance walked was significantly shorter and the speed was slower in the frail women, even after taking into account the difference in age (Table 3). During the last 3 min of the steady-state test, frail women had a significant lower oxygen uptake, which after correcting for the distance walked disclosed higher energy utilization with a significantly lower average heart rate. The correlation between energy utilization and heart rate was significant (r = −0.44, p = 0.05). There were no differences observed in RQ between groups.

Measures of Fatigue

There was a trend for frail women to perceive more fatigue in their daily lives based on the general VAS (p = 0.078) and in response to the 6MWT, they experienced more fatigue during recovery when compared to

healthy women (p = 0.024). The general VAS measure correlated significantly with hsCRP (Figure 1). There were no differences between groups with regard to the pre and post VAS results (data not shown).

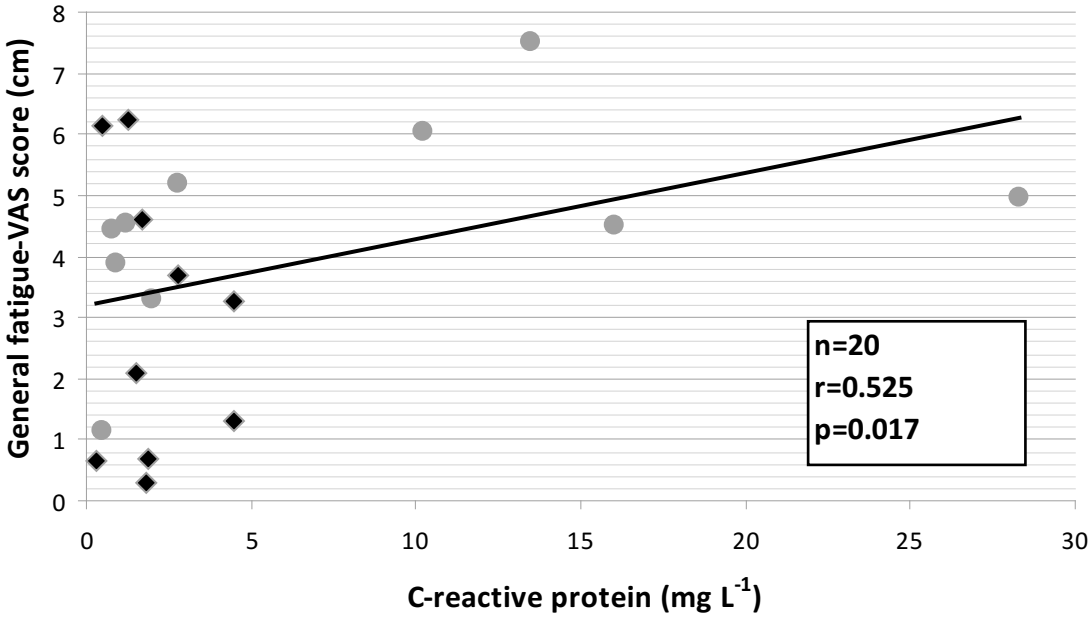

Figure 1. Correlation between general fatigue and C-reactive protein. Gray circle dots: Frail women. Black diamond dots: Healthy women.

DISCUSSION

This study showed that frail elderly women spend more energy per meter of distance walked, which is an important measure of energy utilization (EU). Furthermore, they perceived more fatigue in response to exercise which could account for the shorter distance walked. These findings indicate a decrease in efficiency of EU in frail elderly women, which might contribute to their often reported fatigue, although we were unable to show a correlation between EU and any of the fatigue VAS assessments.

Energy Utilization (EU)

We added to a commonly employed walking test in elderly persons, 6MWT [23,30], a measure of energy expenditure. In a similar study design of elderly women with or without solid malignancies [10], those with cancer covered shorter distances at slower walking speeds and trended toward an increase in energy utilization. The higher EU per unit of distance walked can be largely explained by two reasons: frail elderly may require more energy to accomplish the same task (=lower energy efficiency) than their healthy counterparts or may need more energy to accomplish a greater task than their healthy counterparts would require. In our frail population, both components are implicated since it is known that the level of physical fitness enables one to perform for longer periods and to remain below the threshold of fatigue when performing sub-maximal

exercise [31]. It is likewise recognized that frail individuals, due to gait disturbances related to muscle weakness and balance problems, deploy a greater usage of muscle groups as a means of compensating for their walking inadequacy, which is both inefficient and energy costly [32]. The slower gait speed observed in our frail sample may be an indication of this challenge. Another aspect, independent from the physiology of frailty, that might explain the greater EU in our frail women, is their use of assistive devices. Although the relationship between greater EU and use of assistive devices has been reported [33], it is also known that slow gait speed without devices is associated with increased EU [34]. Of note is that the average gait speed of elderly participants using assistive devices in the study by Protas *et al.* (2007) was near 1.2 m/s, closer to normal as in our healthy group whereas the average gait speed in our frail group was 0.53 m/s. At this low speed and level of gait impairment it is almost impossible for frail persons to walk safely without a cane or a walker. Therefore, it is predicted, that had our frail elderly women not used their walking aids, their EU would have been greater. The 6MWT results are also influenced by many other factors, including, number of chronic diseases [35], the latter likely mediated through impairment of EU, as in lung and cardiac conditions [36,37]. Our subjects had similar weight, fat mass and appendicular muscle mass and thus their difference in walking speed cannot be explained based on body composition. The discrepancy in walking speed greater than two-fold between groups cannot be attributed to their age or height differences (Table 1). Rather, a more likely explanation lies in the muscle mass quality leading to weakness or dynapenia [38], although physical capacity also depends on factors such as balance and an intact neurological system, to name a few [39]. In support of muscle weakness forcing the frail group to recruit more muscle groups and therefore explaining higher EU, is the handgrip data showing significantly higher handgrip strength in the healthy compared with the frail group (Table 1). At rest, there was no difference observed in O_2 uptake and energy expenditure between groups, but with activity it is clear that the frail women are less capable of producing the same degree of work. One of the landmarks of frail aging is reduced physiological reserves, which becomes apparent under stress and performance conditions, as we have demonstrated.

Fatigue

Despite a difference in the fatigue perceived between groups after the 6MWT, there was no correlation found between the VAS measures of fatigue and the EU. Fatigue is a concept that includes both objective and subjective components and we were probably under powered to demonstrate such a relation because many factors interfere with this perception [9]. In a larger study of 46 younger patients suffering from multiple sclerosis, the energy cost of walking was increased only in those with low gait speed, but as in the present study, no relation was found

between EU and perception of fatigue [34]. Measures of fatigue have been related to gait speed in a large sample of community-dwelling older persons [40]. Fatigue was found to predict not only disability and mortality outcomes, but also to mediate the effects of comorbidity and maximal power in sustained work on these two outcomes [8], and associated with poor muscle endurance in nursing home residents, and is related to both impaired mobility [41] as well as disability [42]. Our results complement the above findings relating fatigue with decreased performance.

Inflammation

In this study, hsCRP is correlated with the general fatigue VAS measure, which is in keeping with other studies relating markers of inflammation with fatigue and muscle weakness [43]. However, both hsCRP and pro-inflammatory cytokine levels did not differ between the healthy and frail groups. Therefore, from our data we can confirm that readily available hsCRP is a good proxy measure for more sophisticated, but less clinically applicable markers of inflammation such as the cytokines. Despite their state of frailty, no measures of increased inflammation (CRP, Il-1β, IL-6, TNF-α) or redox status (TAS and MDA) were different in the frail compared with the healthy group. Nevertheless, Il-10, a cytokine recognized for having anti-inflammatory properties was significantly higher (p = 0.05) in the healthy group. Furthermore, we have obtained some statistically significant results which may help to better clarify the underlying pathophysiology of fatigue in elderly people.

CONCLUSIONS

This study has potential limitations: including only women may limit the generalizability of our findings, although it enables us to determine significant differences due to reduced variability related to sex in performing the 6MWT. The age differences between groups could be perceived as being responsible for some of the differences in the results. However, the performance in the 6MWT is an indication that a 6-year age variation cannot account for these differences; the use of assistive walking devices might have created a bias in favor of increasing the EU during the walking test; we likely lacked power to ascertain relationships between fatigue or EU with other variables, including our panel of blood parameters. Using the VAS gives a rough measure of fatigue and we may have had more significance had we used a more precise scale, such as the Fatigue Severity Scale [44], but we opted for simplicity in applying the VAS immediately after the 6MWT.

In conclusion, frail elderly persons often report fatigue during activity, which might be related to a decreased efficiency of EU with physical activity. The findings of our experimental protocol have relevance to our geriatric population since it indicates that one should aim at improving their gait performance through whatever means required to reach this goal since it might contribute to reduce the energy cost of the effort

required to walk and thus their perceived fatigue. The findings of this study are especially relevant to the geriatric population where the prevalence of frailty and decline in physical ability is quite pronounced; therefore, the resulting goals should be in maintaining muscle strength and gait performance to delay the onset of increased EU and the imminent increase in perceived fatigue.

AUTHOR CONTRIBUTIONS

Study concept and design: JAM and TF. Acquisition of data: BT, JAM. Analysis and interpretation of data: JAM, RDK, AV. Drafting of the manuscript: GHB, KJJ, JAM, RDK. Critical revision of the manuscript for important intellectual content: GHB, KJJ, TF, AK, IJD, DT, BT, RDK, AV, JAM.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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