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# Handgrip fatiguing exercise can provide objective assessment of cancer-related fatigue: a pilot study

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## Abstract

**Purpose** As a subjective symptom, cancer-related fatigue is assessed via patient-reported outcomes. Due to the inherent bias of such evaluation, screening and treatment for cancer-related fatigue remains suboptimal. The purpose is to evaluate whether objective cancer patients' hand muscle mechanical parameters (maximal force, critical force, force variability) extracted from a fatiguing handgrip exercise may be correlated to the different dimensions (physical, emotional, and cognitive) of cancer-related fatigue.

**Methods** Fourteen women with advanced breast cancer, still under or having previously received chemotherapy within the preceding 3 months, and 11 healthy women participated to the present study. Cancer-related fatigue was first assessed through the EORTC QLQ-30 and its fatigue module. Fatigability was then measured during 60 maximal repeated handgrip contractions. The maximum force, critical force (asymptote of the force-time evolution), and force variability (root mean square of the successive differences) were extracted. Multiple regression models were performed to investigate the influence of the force parameters on cancer-related fatigue's dimensions.

**Results** The multiple linear regression analysis evidenced that physical fatigue was best explained by maximum force and critical force ( $r=0.81$ ;  $p=0.029$ ). The emotional fatigue was best explained by maximum force, critical force, and force variability ( $r=0.83$ ;  $p=0.008$ ). The cognitive fatigue was best explained by critical force and force variability ( $r=0.62$ ;  $p=0.035$ ).

**Conclusion** The handgrip maximal force, critical force, and force variability may offer objective measures of the different dimensions of cancer-related fatigue and could provide a complementary approach to the patient reported outcomes.

**Keywords** Breast cancer · Neuromuscular fatigue · Force · Physical activity · Quality of life

## Introduction

Cancer-related fatigue (CRF) is a prevalent and disabling symptom experienced by both cancer patients and cancer survivors. It has been defined as a distressing, persistent, and subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning [1]. CRF is multifaceted and at its worst is an extreme physical, emotional, and/or cognitive fatigue ongoing exhaustion that limits one's ability to enjoy life, do activities, and not improved by rest [2]. CRF is by far the most frequent, common and feared adverse effects reported in oncology patients [3]. It often persists beyond

remission, profoundly disrupts the quality of life, is considered a dose-limiting toxicity for some treatments [4], and can decrease survival [5].

As a subjective symptom, CRF is typically assessed via self-report questionnaires (i.e., patient-reported outcomes) [6]. CRF screening may be performed through several single items or multidimensional scale measures [7]. It allows to grade fatigue and its dimensions with score between 0 and 100. For example, the European Organization for Research and Treatment Quality of Life Questionnaire (EORTC QLQ-C30) [8] and its specific fatigue scale module (FA12) [9] are considered as optimal instruments for CRF screening [7]. However, the accuracy of retrospective

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symptoms such as fatigue can suffer of bias possibly due to the distortion of the cognitive heuristics during patients' recalls [10]. Furthermore, specific oncology patient-related barriers exist with fatigue communication. This may underestimate CRF due to several identified reasons including for example bdesire on the patient's part to treat fatigue without medications^ or bnot wanting to complain about it to the doctor^ [11]. Thus, despite this degree of distress and functional loss associated with CRF, screening, evaluation, and treatment for CRF in clinical settings remain suboptimal [12].

Because CRF presents important functional outcomes, a handful of studies tried to find objective physical measures to overcome the patient-reported outcome limitations. Hence, inspiratory muscle strength [13], lean body mass [13], mid-arm circumference [4], or skin-fold thickness [14] have been investigated as surrogate markers of CRF with no to limited correlations. The handgrip maximal strength has been shown to reflect consistently the overall strength capacity [15] and has been widely used in various chronic diseases as a global functional indicator [16–18]. Unfortunately, no [19, 20] or only weak [13, 20, 21] correlations have been evidenced between handgrip maximal strength and CRF. All the attempts to evaluate the CRF through objective functional measurements remain for now, at best, limited. Surprisingly, no study, to our knowledge, tried to correlate the CRF to the acute fatigue experienced when exercising.

Indeed, the term fatigue also refers to the failure to maintain the required or expected force/power output [22, 23]. In this case, fatigue is an acute reduction of a quantifiable neuromuscular performance (e.g., force or power production) in response to contractile activity [24]. This phenomenon may arise from many sites along the neuromuscular system, i.e., from the initiation of the motor drive to the cross bridge cycle [25]. Most studies distinguish the central fatigue, a decrease in neural activation of the muscle due to numerous spinal and supra-spinal factors [26], from the peripheral fatigue, an attenuated contractile response to neural input induced by biochemical changes at the myocyte level [27–29]. In order to distinguish these different concepts, accordingly to Kluger et al. [30], we will use the term fatigue to refer to subjective sensations (i.e., perceived fatigue) and fatigability to refer to objective changes in performance (i.e., neuromuscular fatigue). Since the deteriorated resistance to acute exercise may partly explain the fatigue subjectively felt in cancer populations [31], several experiments recently focused on fatigability alterations in fatigued cancer survivors. Some studies reported that during sustained [32–34] or intermittent [35] submaximal isometric contraction of the elbow flexors until volitional task failure, cancer survivors stopped sooner in comparison to age- and sex-matched healthy controls. However, other studies did not evidence different maximal

voluntary force decrease [36, 37] nor endurance time [36] after sustained contractions between fatigued and non-fatigued cancer survivor [37] or control participants [36]. The discrepancies observed may arise from the intensity chosen based on a percentage of an individual's maximum voluntary contraction (MVC) since it has been well-established that a percentage of MVC is not related to metabolic exercise intensity domains and thus fatigue development [38, 39]. A potential alternative approach would be to identify the critical force (i.e., the matching concept of critical power when performing isometric contractions of single agonist muscle groups [40]). Indeed, the critical force corresponds to the maximal exercise intensity that still results in a metabolic steady state [40–43]. In other words, it allows identifying a threshold above which the fatigability is critically developed [40]. To the best of our knowledge, there are no reports still date that have examine the relationship between the magnitude of the chronic fatigue experienced by oncology patients and the extent of their acute neuromuscular fatigability. Moreover, we are unaware of a study that has assessed the critical force as a fatigue threshold in relation to chronic fatigue. Therefore, the aim of the current study was to analyze through multiple linear regression models, the link between CRF and objective fatigability measures (i.e., maximal voluntary force, critical force, force variability) assessed during a single-bout forearm critical force test [39]. We hypothesized that exercise fatigability and especially the critical force as a fatigue threshold will correlate to CRF.

## Materials and methods

### Participants

Fourteen women ( $53.0 \pm 11.0$  years;  $1.63 \pm 0.08$  m;  $69.1 \pm 12.7$  kg; body mass index,  $26.0 \pm 4.4$  kg.m<sup>-2</sup>; mean  $\pm$  SD) with history of breast cancer participated in the study (CG, cancer group). Eligible patients were adults under chemotherapy at the time of the experimentation or who had received chemotherapy within the preceding 3 months. Eleven healthy women without a cancer history and with no known neurological, muscular, and skeletal disorders or other conditions that would influence their sensorimotor performance also have volunteered (HG, healthy group;  $51.4 \pm 10.1$  years;  $1.65 \pm 0.07$  m;  $64.1 \pm 8.6$  kg; BMI,  $23.4 \pm 2.2$  kg.m<sup>-2</sup>). Neither age nor anthropometrical differences were evidenced between both groups. All participants had a professional

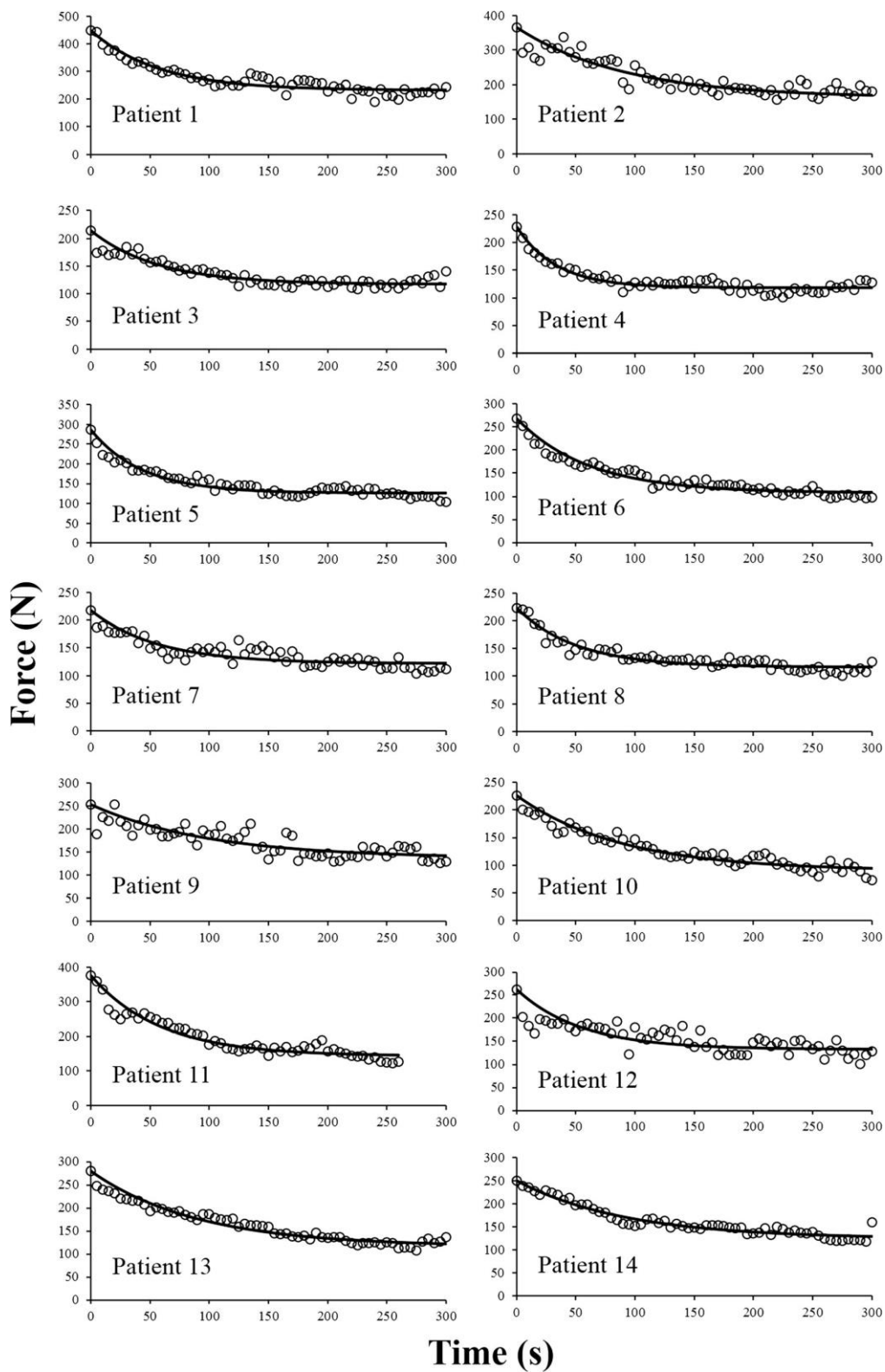


Figure 1 Peak force decrease over time for each participant of the cancer group. Each dot represents the peak force of a handgrip maximal voluntary contraction. The fitting procedure (exponential decay) is described in the text and is represented by the black line. Patient 11 voluntarily stopped the test before the end (due to pain) but sufficient data were recorded to model the force decrease over time

activity except for one in the CG and two in the HG (i.e., retired). For all participants, exclusion criteria were psychological disorders, effort contraindication, and any criteria influencing or preventing from responding autonomously to the questionnaires or to perform the experimental protocol. Furthermore, participants were not recruited if the oncologist who referred patients identified comorbidities. The protocol was approved by the institutional review board at the investigative site and we obtained written informed consent from each patient before study initiation. The study was conducted according to the declaration of Helsinki.

## Protocol

Participants of the CG responded to two self-assessment questionnaires about quality of life (EORTC QLQ-C30) [8] and CRF (FA12) [9] prior to a single experimental session. Participants responded to the questionnaires while they were alone, at home in a quiet place and following the subsequent instructions: "Please answer all questions yourself by circling the number that best applies to you. There are no right or wrong answers. The information that you provide will remain strictly confidential." The HG did not respond to these questionnaires, which are not relevant to assess the quality of life and fatigue in healthy population.

A typical experimental session lasted about 30 min and was conducted as follows: (i) a maximal handgrip force testing in order to determine the warm up intensity; (ii) standardized warm up (ten contractions performed at 25% of the pre-warm up maximum force, six at 50% maximal voluntary contraction (MVC) and 10 at 25%, recovery between sets was 30s); (iii) three maximal handgrip force tests; (iv) 3 min of recovery; (v) handgrip fatiguing exercise; and (vi) spontaneous physical activity assessment.

The finger flexor muscles force was measured with a handgrip dynamometer (Map 80K1S, Kern & Sohn, Germany). During all the testing procedure, participants were seated and their tested elbow by their side and flexed to a right angle while the wrist was at a neutral position in order to limit the involvement of peripheral muscles. Prior to the handgrip fatiguing exercise, participants were asked to perform three maximum voluntary contractions interspersed by 1 min of rest. Only the best trial was considered and normalized to body mass (MVC in N/kg). The fatiguing exercise consisted of repeating 4-s maximal handgrip contractions with the dominant hand interspersed by 1 s for up to 5 min (i.e., 60 contractions). In order to follow the duty cycle, a smartphone's application displayed a red color for contraction and green for recovery with an according audio signal. Participants were asked to perform each contraction at their maximum and were strongly verbally encouraged by the experimenter although they were unaware of the precise duration of the test or the

remaining time in order to avoid pacing strategies [44]. The peak force ( $F_{\text{peak}}$ ) was monitored for each contraction.

The spontaneous physical activity was estimated from the bactivity recall method [45]. The experimenter conducted an interview and invited participants to recall their daily activities (or weekly activities when pertinent, e.g., dancing, gardening). For the CG, two estimates were done, one for the situation before cancer and another for the actual situation (i.e., with cancer). Each type of physical activity was assigned to a metabolic equivalent task (MET) according to the compendium of physical activities [46] and classified as inactive (< 2.5 METs) and active (> 2.5 METs). Each activity was also categorized as daily living, professional, leisure or sport activity.

## Data analysis

EORTC QLQ-FA12 scores ranged from 0 to 100, with higher levels indicating greater degree of fatigue. Non-linear regression techniques were used to fit the kinetics of  $F_{\text{peak}}$  (expressed in percentage of MVC) over time for each participant (Eq. 1) [47]. Fittings were performed via non-linear least-squares procedures with Matlab 2016a (The MathWorks, Natick, MA, USA), i.e., an iterative process was used in order to minimize the sum of squared error between the fitted function and the observed values.

$$F_{\text{peak}} = F_{\text{Cr}} \left( 1 - e^{-t/\tau} \right) \quad (1)$$

where  $F_{\text{Cr}}$  is the critical force expressed in percentage of the MVC;  $t$  the time of contractions;  $\tau$  the curvature constant in number of contraction.  $F_{\text{Cr}}$  corresponds to the force-time asymptote relationship and  $\tau$  can be considered as the rate of the force decrease.

Kent-Braun et al. [48] estimated the force variability from the mean squared difference between the peak force measured and the value predicted by the non-linear model at the same point. Because the meaning of this variable is not easy-to-understand (unit is  $N^2$ ), we chose to use the values of the root mean squared of the successive differences (RMSSD), often used as a variability indicator (e.g., heart rate variability) [49]. RMSSD can be interpreted as the mean force variability in Newton between two contractions. In this aim, we subtracted the value of the model to the measured  $F_{\text{peak}}$  in order to remove the fatigue effect and then calculated the RMSSD.

## Statistical analysis

All data were analyzed with Statistica 8.0 Software (StatSoft Inc., Tulsa, OK, USA) and expressed as means  $\pm$  standard deviations. The normality of the error distribution was examined with the Lilliefors test. Homogeneity of variance was verified using Levene's test. With the assumption of normality and homogeneity of variance

Table 1 Mechanical parameters of the neuromuscular fatigability

	Healthy group	Cancer group
MVC (N kg <sup>-1</sup> )	6.0 ± 0.9	4.0 ± 0.9 *
F <sub>Cr</sub> (%)	40.3 ± 8.7	50.7 ± 7.3 *
F <sub>Cr</sub> (N kg <sup>-1</sup> )	2.4 ± 0.5	1.9 ± 0.4 *
τ (s)	73.9 ± 34.5	63.9 ± 24.1
RMSSD (N)	14.3 ± 3.3	13.8 ± 7.6

MVC, handgrip maximum force capacity; F<sub>Cr</sub>: critical force (i.e., asymptote of the force-time relationship); τ, curvature constant of the force-time relationship; RMSSD, root mean squared of the successive differences (i.e., force variability); \*significantly different from the Healthy Group

confirmed, a student t-test was performed to compare the CG and HG on MVC, F<sub>Cr</sub>, τ, RMSSD, and spontaneous physical activity/energy expenditure. Forward stepwise multiple linear regression analyses were performed to verify the influence of MVC, F<sub>Cr</sub>, τ, and RMSSD on the three dimensions of the CRF evaluated by the FA12 (i.e., physical, emotional, and cognitive fatigue) and the different type of spontaneous physical activities and their intensities. The coefficients of correlation (*r*) were calculated for each regression analysis. Correlation coefficient values of 0.0 to 0.19, 0.20 to 0.39, 0.40 to 0.59, 0.60 to 0.79, and greater than 0.79 were classified as very weak, weak, moderate, strong, and very strong, respectively, as proposed by Evans [50]. Finally, the normalized beta coefficients for the predictor variables (β\*) were estimated to assess the relative predictive power of each of the predictor variables. An alpha level of 0.05 was selected to determine if predictor variables would be included in the final equation and for determining the significance of the model in predicting the response variable.

## Results

### Cancer-related fatigue

For the CG, the CRF score evaluated by the QLQ C30 fatigue item was 64 ± 26 (ranging from 22 to 100). The physical, emotional, and cognitive fatigue scores of the CG evaluated through the FA12 were respectively 55 ± 27 (from 27 to 100), 31 ± 27 (from 0 to 78), and 23 ± 33 (from 0 to 100).

### Neuromuscular fatigability

All the patients' force-time relationship significantly fit with the exponential decay function (all *p* < 0.05; Fig. 1). The mechanical parameters of the neuromuscular fatigability are presented in Table 1. The MVC normalized to body mass was about one third less for the CG compared to HG (*p* < 0.001) despite non-different anthropometrical characteristics. The relative F<sub>Cr</sub> to MVC was 10% lower for HG (*p* = 0.004) but critical force in Newton per body mass remained significantly lower for CG (*p* = 0.03). The curvature constants of the force-time relationship and the force variability were not statistically different between both groups (respectively *p* = 0.40 and *p* = 0.89).

### Spontaneous physical activity

The distribution of types and intensities of spontaneous physical activities over a typical day are presented in Fig. 2. No difference was evidenced between the HG and CG before cancer. During cancer, professional activity was totally stopped. For the CG, the low intensity (≤ 2.5 METs) daily activities and leisure time increased respectively by 5 ± 2 and 3 ± 2 h.

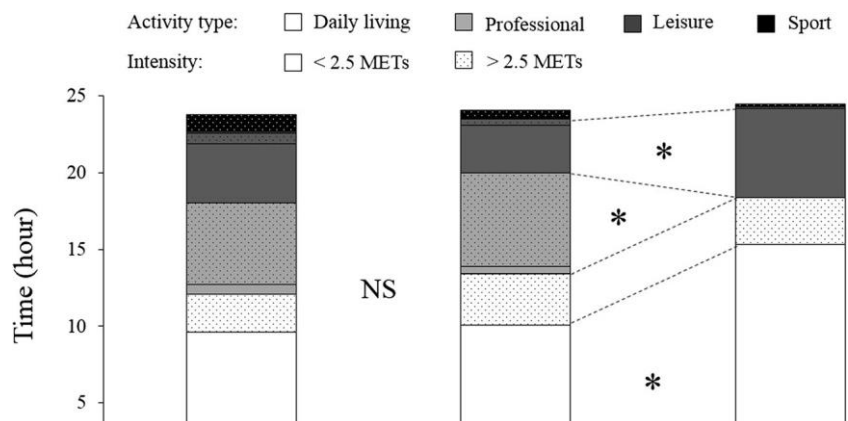


Figure 2 The repartition of spontaneous daily physical activities classified depending on types (daily living, professional, leisure and sport) and intensities (< or > 2.5 METs). HG healthy group, CG cancer group. NS non significant difference, \*significant difference between before cancer and with cancer

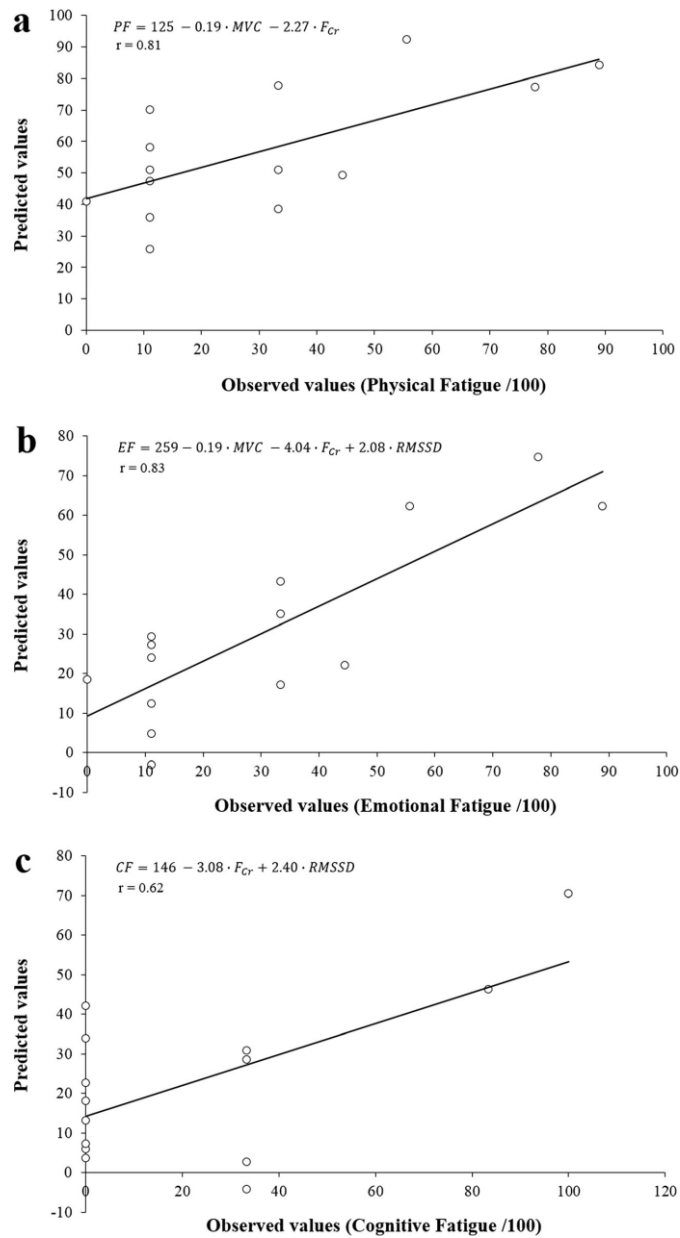


Figure 3 Predicted vs. observed values for physical fatigue (PF, a), emotional fatigue (EF, b), and cognitive fatigue (CF, c). The equations and coefficients of correlation ( $r$ ) of the multiple linear models are presented on each panel

### Linear regression models

The multiple linear regression analysis evidenced that physical fatigue was best explained by a model including both MVC ( $\beta^* = -0.27$ ) and  $F_{Cr}$  ( $\beta^* = -0.62$ ;  $p = 0.029$ ;

Fig. 3a). The emotional fatigue was best explained by a model including MVC ( $\beta^* = -0.46$ ),  $F_{Cr}$  ( $\beta^* = -1.08$ ) and RMSSD ( $\beta^* = 0.58$ ;  $p = 0.008$ ; Fig. 3b). The cognitive fatigue was best explained by a model including  $F_{Cr}$  ( $\beta^* = -0.72$ ) and RMSSD ( $\beta^* = -0.63$ ;  $p = 0.035$ ; Fig. 3c). Furthermore, the

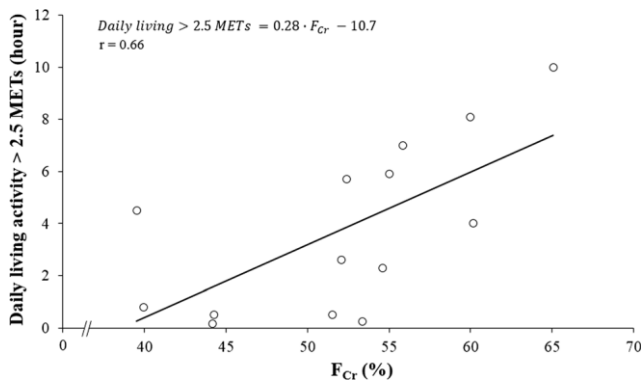


Figure 4 Relationship between the time spent to active daily living activities (i.e., intensity > 2.5 METs) and the Critical Force ( $F_{Cr}$ , expressed in percentage of maximal voluntary force)

daily time spent in medium intensity daily living activities was positively correlated to  $F_{Cr}$  ( $r = 0.66$ ;  $p = 0.009$ ; Fig. 4).

## Discussion

The aim of the present study was to evaluate whether objective mechanical parameters extracted from a fatigable handgrip exercise may correlate to the cancer-related fatigue as classically assessed by validated questionnaire's scores in oncology patients. The results evidenced strong multiple linear regression models between the physical, emotional, and cognitive dimensions of CRF, and several neuromuscular fatigability objective indicators (maximal force, critical, force and force variability). Especially, the critical force that can be considered as a muscle fatigue threshold had the highest regression weight for each fatigue dimension and also correlates with the spontaneous physical activity intensity.

The maximum handgrip strength normalized to body mass was one-third lower for the CG compared to the HG. Such decreased muscle strength is typically observed in patients due to muscle wasting in cancer [51, 52]. Although maximum force is a function of the cross-sectional area, muscle typology, and motor recruitment, it cannot represent the metabolic demand or oxygen delivery [53, 54]. Thus, the sole maximum handgrip strength cannot provide powerful information about muscle fatigability. That is why the present study focused on the critical force concept. Mathematically, it is the asymptote of the intensity-duration relationship, with intensity being frequently power although such a relationship has been shown to be consistent across all neuromuscular performance outputs such as velocity, torque, or force [40]. Physiologically, it provides demarcation between the heavy and very heavy intensity [55]. In other words, the critical force can be considered as an intensity threshold above which fatigue develops drastically [56]. Interestingly, the critical force expressed in Newton normalized per kilogram of body mass was 20% lower for the CG compared to the HG (Table 1). These patients

may thus often exceed their critical force even during daily living activities which may contribute to the development and persistence of chronic fatigue. One can note that, relatively to maximum force capacity, the CG had a significantly highest critical force than the HG (Table 1). This may be surprising since oncology patients generally present lower functional capacities than healthy individuals. However, the maximal voluntary force in CG probably underestimates their maximum muscle force capability because of a known reduced voluntary activation prior to any exercise [35, 57]. The critical force relative to MVC may thus not be pertinent to compare oncology patients to a healthy population. In the same way, the curvature constant ( $\tau$ ) of the force-time relationship and the force variability (RMSSD) were not statistically different between both groups (Table 1). Similar force variability has previously been observed between CRF patients and a control group [33] indicating that this mechanical parameter does not allow discriminating the neuromuscular function of individuals suffering from cancer to healthy ones.

To our knowledge, this is the first study to explore associations between the different dimensions of CRF and fatigability parameters on an individual data basis. In this context, a strong multiple linear correlation has been evidenced between the physical dimension of CRF (dependent variable) and both MVC and  $F_{Cr}$  (predictor variables; Fig. 3). Thus, the more patients reported physical fatigue, the lower MVC and  $F_{Cr}$  were found. Moreover, the normalized beta coefficients allow estimating the relative weight of each independent variable within the model. Hence,  $F_{Cr}$  seems to influence more the physical fatigue than MVC ( $\beta^*$  was two times greater). This may explain why a handful of studies previously examined the association between CRF and handgrip maximal strength evidencing no [19, 20] or only weak [13, 20, 21] correlations. Considering emotional fatigue, it was strongly correlated to MVC,  $F_{Cr}$ , and RMSSD (Fig. 3b), while the cognitive fatigue was strongly correlated to  $F_{Cr}$  and RMSSD only (Fig. 3c). Once again, the  $F_{Cr}$  standardized beta coefficient was the highest suggesting that this parameter is in close relationship with the CRF as a whole. Interestingly, the peak force variability assessed through the RMSSD value was positively correlated to both emotional and cognitive fatigue. Unfortunately, the only study which recorded the force variability in CRF patients did not analyze it in the light of the magnitudes and the dimensions of CRF [33] making no possible comparison. Nevertheless, it has been previously evidenced that weakest older adults have greater peak force variability [40] due to their decreased strength [58]. The present results did not highlight any correlation between the MVC and the RMSSD. Furthermore, the strongest HG had the same mean force variability than the weakest CG. Hence, the force variability seems to be independent of the strength level in cancer patients. Lorist et al. evidenced interaction between cognitive functions and the central mechanisms driving motor



behavior during fatiguing exercise [59]. When a cognitive task was performed during a submaximal sustained contraction, the force variability drastically increased [59]. We can hypothesize that the impaired mental (i.e., cognitive and emotional) status due to CRF induced similar perturbations of the motor drive increasing the peak force variability. The precise nature of this interference and at what level this interaction takes place is still unknown. However, the force variability has been hypothesized to have significant implications for functional performance [60, 61] and thus could be an interesting objective measure of mental fatigue in CRF patients.

We also evaluated the spontaneous physical activity as a potential functional outcome of the CRF. Mortimer et al. recently evidenced a negative correlation between CRF and the total energy expenditure after a chemotherapy treatment [62]. The present results are in line with this since a reduced spontaneous physical activity, mainly due to the stop of professional, has been observed (Fig. 2). Indeed, for the CG, almost 80% of the daytime is dedicated to daily living vs. ~ 50% for the HG or CG before the cancer (not statistically different). To go further, we also examined the relationship between daily living activity intensities and the critical force. Very interestingly, the active daily living activities (i.e., > 2.5 METs; e.g., food shopping, house cleaning, walking activities in general) were positively correlated to  $F_{Cr}$  ( $r = 0.66$ ;  $p = 0.009$ ; Fig. 4). As previously hypothesized, the reduced fatigue threshold (i.e.,  $F_{Cr}$ ) may be exceeded easily during mild intensity to vigorous daily life activities. Then it could trigger acute fatigue which may accumulate over the days/weeks and possibly contribute to the chronically perceived fatigue [31]. A low  $F_{Cr}$  could also lead a patient to reduce its spontaneous physical activity intensity in the aim not to overpass this threshold inducing a feeling of discomfort, which can, in turn, accelerate the neuromuscular deconditioning [63].

The present study is a pilot experimentation that provides interesting information about the possible links between CRF and neuromuscular fatigability but it is worth noting that there are limitations. First of all, the sample size was relatively small. Nevertheless, the multiple linear regression models observed were strong and allow us to take into consideration and discuss these preliminary results. Furthermore, participants were all women suffering from breast cancer and coming from the same care center. Although the chemotherapy treatment protocols for breast cancer are standardized, this restricts the generalization of the results. It might also be useful to include measures of major symptoms associated, but distinct to CRF such as sleep disturbance, depressed mood or pain in order to adjust the explaining models of CRF by neuromuscular fatigability. Nonetheless, such adjustment could only enhance the models that are already qualified as strong in the present study. Further studies should aim to perform similar analysis with a greater population from several care center and considering confounding symptoms to clarify the mechanisms between objective measures of the neuromuscular fatigue and CRF.

To our knowledge, this is the first study to explore associations between the different dimensions of CRF and exercise fatigability on an individual data basis. The present results provide evidence that exercise fatigability during a handgrip critical force testing may offer objective measures of the different dimensions of CRF. Especially, although a bunch of studies failed to demonstrate at least moderate links between functional measurements and CRF, this study evidenced that the critical force, a fatigability threshold, strongly correlates to the physical, emotional, and cognitive fatigue experienced by oncology patients. Moreover, the force variability could be an interesting objective measure of mental fatigue in CRF patients.

This may offer to clinician objective measurement procedures as a complementary approach to the patient reported outcomes in order to enhance the screening of CRF. Furthermore, this suggests a link between the subjective fatigue and the acute exercise fatigability that needs to be further investigated to better understand the possible mechanisms of the chronic fatigue's development and persistence.

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## Compliance with ethical standards

The protocol was approved by the institutional review board at the investigative site and we obtained written informed consent from each patient before study initiation. The study was conducted according to the declaration of Helsinki.

**Conflict of interest** The authors declare that they have no conflicts of interest.

**Disclaimer** The authors have full control of all primary data and agree to allow the journal to review these data if requested.

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