Supportive Care in Cancer (2019) 27:2617–2623
https://doi.org/10.1007/s00520-018-4542-1

ORIGINAL ARTICLE

Clinical utility of portable electrophysiology to measure fatigue in treatment-naïve non-small cell lung cancer

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Received: 12 July 2018 / Accepted: 4 November 2018 / Published online: 22 November 2018

Abstract

Purpose Cancer-related fatigue (CRF) biology remains poorly understood. Responsible mechanisms may be central or peripheral and originate anywhere from the brain to muscle fiber. Objective measurement is complex and previously limited to specialized laboratories. Portable electroencephalography (EEG) and electromyography (EMG) may enhance objective measurement. This study evaluated the feasibility and acceptability of portable EMG-EEG in CRF assessment.

Methods A prospective observational feasibility study compared ten outpatients with inoperable, treatment-naïve non-small cell lung cancer and CRF to ten healthy volunteers. All completed a sustained isometric hand-grip contraction at 30% maximal level until self-perceived exhaustion. 128-channel EEG and 2-channel EMG signals of forearm muscles were recorded. Device acceptability was evaluated by questionnaire.

Results The task was evaluated in two stages; first and last 20 s. CRF cohort perceived exhaustion earlier than volunteers (mean 137 ± 76 s vs 208 ± 51 s). As fatigue progressed, EMG amplitude increased significantly (CRF $p = 0.02$; volunteers: $p = 0.04$) in both groups as did EMG beta band power (CRF $p = 0.008$; volunteers: $p = 0.006$). The increase was significantly less in CRF (amplitude $p = 0.032$; beta power: $p = 0.014$). EEG beta band power in the contralateral motor cortex increased significantly (CRF $p = 0.03$; volunteers: $p = 0.019$) in both cohorts but to greater extent ($p = 0.024$) in CRF. One hundred percent device acceptability was reported.

Conclusions A laboratory-based evaluation was successfully adapted to the outpatient setting during routine visits. High acceptability supports clinical utility. In CRF, a higher degree of cortical activation was required to drive a much lower level of muscle performance. This suggests impairment of both central and peripheral mechanisms in CRF.

Keywords Cancer-related fatigue · Electroencephalography · Electromyography · Feasibility · Lung cancer · Objective measurement

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00520-018-4542-1) contains supplementary material, which is available to authorized users.

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Introduction

Cancer-related fatigue (CRF) is the most common cancer symptom [1]. It is defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment" [2]. Unlike normal fatigue, it is disproportional to activity and unrelieved by rest [2]. Prevalence ranges from 25 to 99% [2]. Although experienced across the cancer continuum [3], CRF remains under-recognized [4]. Greater understanding of the pathophysiology is necessary to improve diagnosis and treatment [5]. Possible mechanisms include neuromuscular function abnormalities [6] with impaired communication between the central nervous system (CNS) and functioning muscle [4, 7–10].

Motor units comprise a motor neuron, its axon and the muscle fibers innervated. Muscle force is determined by the number and firing rate of recruited motor units [11]. Fatigue leads to loss of force during a task [5]. Task failure can originate anywhere from the cerebral cortex to muscle fiber [5] and be either central or peripheral [12]. Central fatigue is CNS-driven [5]; loss of voluntary muscle activation originates proximal to the neuromuscular junction (NMJ). Peripheral fatigue results from failure of the muscle excitation-contraction mechanism [5, 7]. In CRF, central fatigue may be more significant [5, 7–10, 13–15]. Lower muscle fatigue (than healthy volunteers) observed during and after sustained contraction supports this hypothesis [7].

Fatigue assessment

Subjective evaluation provides limited insight into pathophysiology [4]. Objective evaluations like surface electromyography (EMG) and electroencephalography (EEG) enhance our knowledge of muscle and cortical function [5, 11]. EMG detects the sum of action potentials propagated through muscle motor units. Increased EMG amplitude reflects increased firing rate, additional motor unit recruitment, or both [16], with fatigue progression [9, 13]. EEG non-invasively records electrical potentials on the scalp surface. It offers excellent temporal resolution of central activity [17]. Voltage frequencies measured from lowest to highest (delta, theta, alpha, beta, gamma bands) provide information about cortical drive [17].

Objective CRF neuromuscular assessment has focused on EMG [7–10]; few studies have incorporated cortical activity through EEG [13, 15]. In previous studies, EMG-EEG was confined to specialized hospital laboratories [7–10, 13, 15]. Such investigations are impractical for seriously ill patients. Objective bedside evaluation has been limited. Modern mobile technology could potentially revolutionize symptom assessment in cancer and other illnesses. The evolution of portable EMG-EEG systems could facilitate bedside assessment of previously under-evaluated CRF. This feasibility study determined the clinical utility of bedside EMG-EEG. As those most fatigued with advanced cancer may be least able to undergo investigation, newly diagnosed, treatment-naïve patients with CRF were evaluated in the first instance.

Methods

This prospective observational study examined the feasibility of portable EMG-EEG to evaluate CRF. Ethical approval was granted by St Vincent's University Healthcare Group (SVHG) Ethics and Medical Research Committee and Tallaght Hospital/St James's Hospital (SJH) Joint Research Ethics Committee. Two cohorts were recruited. Healthy staff volunteers (Our Lady's Hospice & Care Services and Trinity Centre for Bioengineering) were initially recruited to a pilot study to test the protocol. As this was a feasibility study, volunteers were not age or gender matched. Ten consecutive newly diagnosed, inoperable, treatment-naïve non-small cell lung cancer (NSCLC) participants were subsequently recruited in SVHG and SJH between November 2014 and June 2015. Written consent was obtained from all participants. Participants were eligible if over 18 years with no previous cancer diagnosis, right hand dominant, and reported a subjective fatigue score greater than 3 on a 0–10 Numerical Rating Scale. Exclusion criteria included life-expectancy less than 7 days, Eastern Cooperative Oncology Group (ECOG) performance score greater than 2, dementia, Bedside Confusion Scale score of 2 or more [18], oxygen dependence or saturation less than 90%, a paraneoplastic condition affecting muscle function, or a previous wrist injury. Concurrent stimulant and sedative medications were also recorded.

Prior laboratory-based methodology [7, 13, 15] was adapted for portable use. Subjective fatigue was evaluated by the Brief Fatigue Inventory (BFI), a validated 9-item questionnaire to assess fatigue severity (0–10 scale) over the previous 24 h [19]. A higher score indicated more severe fatigue. Participants performed a motor fatigue task while EMG and EEG were recorded simultaneously. Two researcher-designed questionnaires captured (a) participant acceptability (Online Resource 1) and (b) researcher-perceived feasibility of study devices and procedures (Online Resource 2).

Study devices

A multi-unit data acquisition system (EMG, EEG, and handheld dynamometer) was custom-developed and configured as a single unit to record time-locked signals. EEG was measured at a sampling frequency of 2048 Hz using an ActiveTwo BioSemi 128-electrode system (BioSemi B.V., Amsterdam, Netherlands). Two-channel surface EMG, at a sampling rate of 2048 Hz, was recorded from the right forearm flexor muscles, flexor carpi radialis (FCR) and flexor carpi ulnaris

(FCU). EMG was digitized by a National Instruments (NI) Data Acquisition system (DAQ) [16-Bit, 250 kS/s] (National Instruments Corporation Ltd., Austin, Texas), connected to a laptop (Aspire, Acer Inc., Taiwan) running NI LabVIEW interface [version 2013, SP1 32-bit] (National Instruments Corporation Ltd., Austin, Texas). A forearm support, with elbow joint positioned at a 90° angle, stabilized the wrist in the neutral position. A grip force transducer recorded force data (PowerLab 26 T®, AD Instruments (ADI) Pty Ltd., New South Wales) utilizing ADI LabChart software which also provided real-time visual feedback to the participant through a Graphical User Interface (GUI).

Motor fatigue task

An isometric sustained right hand-grip contraction was performed. Maximum voluntary contraction (MVC) was measured three times. A target force (S-30) was set at 30% of the highest amplitude MVC. Participants matched S-30 through sustained contraction until subjective exhaustion (1–5 min). When the exerted force dropped > 10% of S-30 for > 3 s, the task was terminated. Exerted force, endurance time (ET), EEG, and EMG were recorded throughout.

Data analysis

Data was analyzed with Matlab® (Matlab and Statistics Toolbox 2014a, Mathworks®, Massachusetts, USA). FCR and FCU EMG signals were analyzed separately. All data was high- and low-pass filtered to ensure all valuable signal content was captured. EEG pre-processing was performed in FASTER (Fully Automated Statistical Thresholding for EEG artifact Rejection) [20]. Data was re-referenced to an average of all electrodes. EMG and EEG signals were resampled from 2048 to 256 Hz. ET was the duration from achieved target force (S-30) to contraction termination. Individual and mean ET and mean MVC for both cohorts were calculated and compared.

Two segments of the EMG data from FCU and FCR were examined; the first and last 20 s of each task. For analysis, segment length was determined by the participant with the shortest ET (40 s). The first segment represented mild fatigue (stage 1), and the second severe (stage 2). Amplitude was calculated from the root-mean-square (RMS) of EMG segments and normalized to individual MVC. Amplitude change and percentage gain were calculated for mild and severe fatigue. As the EMG beta frequency band (15–35 Hz) is important in motor tasks [16], mean EMG power was calculated for the beta band and normalized to total power.

EEG electrodes were divided into five scalp areas: left, right, central, frontal, and parietal [13, 17]. Ten electrodes overlying each area were analyzed. The first (mild fatigue) and last (severe) 20 s of EEG signals during the task were again analyzed. Mean EEG power was calculated in each scalp area, for both mild and severe fatigue, within alpha (10–14 Hz) and beta (15–35 Hz) frequencies and normalized to total power. Left scalp beta frequency power changes were of primary interest as this represents right forearm motor cortex activity [21]. Alpha power was included as an indirect measure of concentration.

Statistical analysis

Data were analyzed with SPSS-22 Software (IBM Corporation, New York). Independent *t* tests evaluated significance of mean BFI scores, ET, MVC, and fatigue effect on EMG (volunteers compared to CRF participants). A 5 × 2 repeated measures ANOVA evaluated EEG parameters. A one-way MANOVA was utilized to evaluate the significance of cohorts and different fatigue parameters. p values < 0.05 were considered statistically significant.

Results

Twenty-one CRF patients were screened; 13 were eligible, two could not participate before treatment and one declined. Demographic characteristics are in Table 1. Ten participants were recruited (4 male; 6 female); mean participant age was 64 ± 12 years. Ten healthy volunteers were recruited (7 male; 3 female) with mean age 28 ± 8 years. Mean BFI scores were significantly (p = 0.043) higher in CRF (3.4 ± 2) than volunteers (1.6 ± 1.8).

Feasibility

Laboratory-based techniques were adapted for outpatient use. A portable multi-unit system was successfully developed with recordings completed at three clinical locations. All participants completed the motor task with valid data. Key requirements achieved included the following: (1) system portability, (2) a tailored GUI for real-time feedback, and (3) time-locked triggers to facilitate synchronous EMG-EEG comparisons. Device development, data collection, and analysis required specialist engineering input. The multi-unit system and forearm support was perceived as cumbersome by the researchers. Preparation time which included system assembly and verification (60 min) and participant preparation (20–30 min) was considerably longer than the fatigue task itself (10–15 min).

Acceptability

A high level of device acceptability was reported in the CRF cohort. 2/10 reported mild EEG cap or chin strap discomfort. No participant expressed concerns for future device use in similar patients.

Table 1 Demographic characteristics of cancer-related fatigue cohort

Characteristics	$N = 10$	Mean ± SD
Sex		
Male	4	
Female	6	
Age		64 ± 12
41–50	2	
51–60	3	
61–70	1	
71–80	4	
Lung cancer histology		
Adenocarcinoma	6	
Squamous cell carcinoma	4	
Metastatic disease		
Yes	8	
No	2	
Performance status: ECOG		1 ± 0
0	1	
1	8	
2	1	
Stimulant medications		
Yes	0	
No	10	
Sedative medications		
Yes	0	
No	10	
Brief Fatigue Inventory scores		3.4 ± 2
0–3	4	
3.1–6	5	
6.1–10	1	

Objective fatigue measures

In the CRF cohort, there was significantly lower mean MVC (222 ± 93 vs 379 ± 123 newtons; $p = 0.0025$). ET was also significantly shorter (137 ± 76 vs 208 ± 51 s; $p = 0.007$).

Electromyography

During the task, as expected, 8/10 volunteers significantly increased EMG amplitude in both FCR and FCU as fatigue progressed (FCR $p = 0.015$; FCU $p = 0.04$). Similarly, in 9/10 CRF participants, EMG amplitude increased significantly in both muscles (FCR $p = 0.02$; FCU $p = 0.02$). Inter-cohort comparison (Fig. 1) showed no significant amplitude difference in mild fatigue (FCU $p = 0.114$; FCR $p = 0.361$). However, in severe fatigue, a greater EMG amplitude increase was noted in volunteers in both muscles, but this was only significant in FCU (FCU $p = 0.032$; FCR $p = 0.134$).

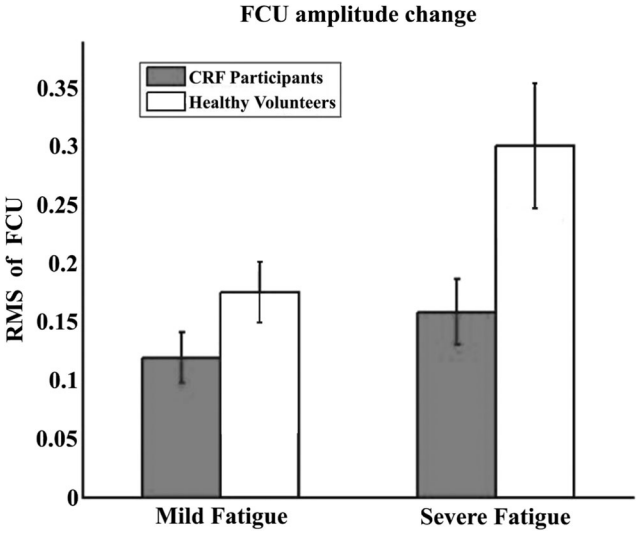

Fig. 1 EMG amplitude change compared between cancer-related fatigue participants and healthy volunteers

A significant EMG beta band power increase was noted in both cohorts with fatigue progression apart from one CRF participant (volunteers: FCR $p = 0.007$, FCU $p = 0.006$; CRF: FCR $p = 0.038$, FCU $p = 0.008$). On inter-cohort comparison (Fig. 2), in severe fatigue, EMG power increased significantly more in volunteers in both muscles (FCR $p = 0.018$; FCU $p = 0.014$).

Electroencephalography

In both volunteers and CRF participants, 8/10 had increased EEG power in both alpha and beta bands in all five scalp areas. On inter-cohort comparison (Fig. 3), severe fatigue showed a significantly greater increase within the beta power band in the

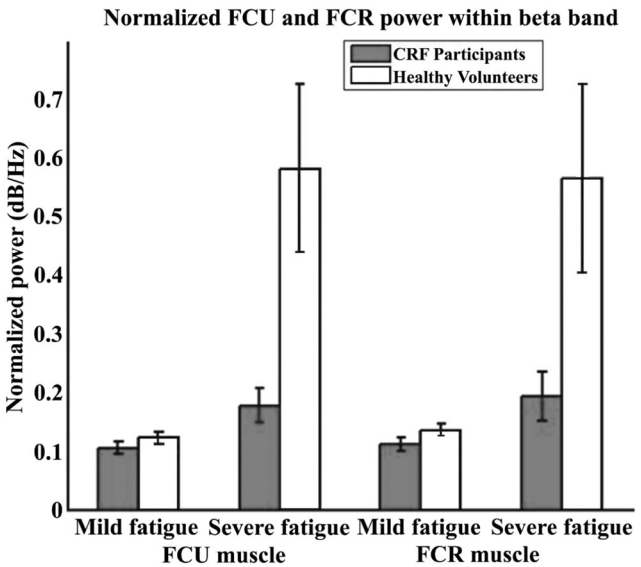

Fig. 2 Electromyography beta band power change compared between cohorts

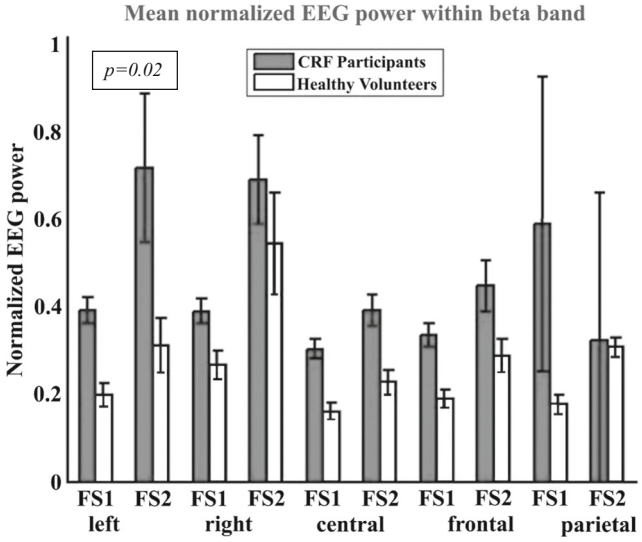

Fig. 3 EEG power within beta band compared between cohorts

left hemisphere in CRF ($p = 0.02$). No significant alpha power band difference was noted.

Discussion

This study demonstrated the feasibility of mobile technology in the clinical environment. EMG-EEG was effectively transferred from the laboratory to the outpatient setting to investigate CRF during routine hospital visits. We observed evidence of both central and peripheral fatigue in newly diagnosed, treatment naïve NSCLC patients.

A novel approach was necessary to adapt the research methodology [13–15]. Although equipment limitations were evident, we confirmed system efficacy. The CRF participants were age-representative of the cancer population. Despite the CRF cohort being treatment-naïve, with good performance status and low fatigue scores, neurophysiological abnormalities were evident. These fatigue-related alterations were consistent with the literature [7, 13, 15]. More extensive changes may be evident in a frailer population. Specialized engineering input was necessary for system design, development, and data analysis; this had both time and financial implications. However, given the economic impact of CRF [22, 23], this seems minor. Future studies should optimize the system for routine clinical use, e.g. combined EMG-EEG system. A key priority was ease of technology use and acceptability by the cancer cohort. Poor acceptability in newly diagnosed lung cancer patients would almost certainly preclude device use in those with more advanced cancer and worse fatigue. Participants reported a positive experience with no concerns expressed. Previous evaluation of technology in cancer symptom assessment supports this [24, 25]. Acceptance by end-users is critical to longevity of a medical device [26].

MVC is a direct measure of fatigue [27]. CRF participants were weaker; they sustained significantly lower MVC for a significantly shorter time. EMG amplitude increased with muscle fatigue in both cohorts but a significant difference was noted in severe fatigue. While both equally engaged their muscles to start, the CRF cohort failed to engage their muscles to the same degree as the task progressed. A laboratory-based assessment reached similar conclusions; lower muscle recruitment and limited muscle contractile change in cancer compared to age and gender-matched volunteers [7–10]. Our findings suggest impaired peripheral neuromuscular function in CRF compared to volunteers.

EEG power increased in both cohorts with fatigue progression. Left motor cortex activity controls right forearm function. Power increased more in CRF, particularly in the left hemisphere, so greater activation of the left motor cortex was required to maintain the same force. In previous cancer studies of EMG and muscle twitch force, lower muscle function in CRF was interpreted as reduced central drive [7–10]. EEG adds a new dimension. Our results revealed greater than expected central activation. As fatigue progressed, higher cortical activation was required for lower muscle performance. Unlike previous studies [7–10, 15], this indicates both central and peripheral dysfunction. The problem may arise along the motor control pathway and suggests impaired NMJ transmission. In NMJ dysfunction, central signals are inefficiently transmitted with incomplete muscle recruitment and so shorter ET [7]. Impaired NMJ function could also increase central fatigue in the motor cortex through negative feedback mechanisms [7] like radiation-induced CRF in prostate cancer [28].

A study strength was the close collaboration between bioengineers and clinician end-users. Study limitations include the small sample size which may limit the generalizability of results. The volunteers were a younger and more active cohort. Both age-related changes and cancer are associated with muscle atrophy [5]; however, no age-adjusted standards are available. Future studies should recruit age, sex, and body mass index-matched controls for direct comparison. EMG-EEG was not correlated with objective clinical measures of function (such as physical activity and endurance capacity) or performance status. Future studies should explore this relationship to further evaluate the clinical meaning of these findings.

The identification of neuromuscular fatigue markers facilitates both surveillance of the natural history of CRF and the impact of cancer treatments and therapeutic fatigue interventions. Further technology refinement is possible. The contralateral motor cortex should be the primary focus; fewer electrodes would reduce participant preparation time, data volume, and equipment cost. Inclusion of other methods like functional magnetic resonance imaging or transcranial magnetic stimulation is also important. This methodology could also be applied to other fatigue-associated chronic illnesses.

Conclusions

We successfully utilized portable electrophysiology to identify objective CRF measures in the outpatient setting during routine hospital appointments. During a fatigue task, CRF participants sustained a weaker contraction for a shorter time than healthy volunteers. Portable EMG-EEG showed abnormal CRF-related central and peripheral mechanisms. Greater EEG beta band power increase suggested central dysfunction. Lower EMG amplitude and power increase indicated impaired peripheral response. Therefore, in newly diagnosed, treatment-naïve, NSCLC CRF participants with a good performance status, higher cortical activation was needed for lower muscle performance. High participant acceptability supports wider use of this type of technology in CRF.

Acknowledgements We gratefully acknowledge the participation of patients at St Vincent's University Hospital and St James's Hospital, Dublin as well as the medical teams who supported recruitment. We also thank the healthy volunteers from Our Lady's Hospice and Care Services and Trinity Centre for Bioengineering for their involvement. We thank Ms. Pauline Uí Dhuibhir and Ms. Ciara O'Higgins for their assistance with data collection.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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