*Original Article*

# Lack of Muscle Contractile Property Changes at the Time of Perceived Physical Exhaustion Suggests Central Mechanisms Contributing to Early Motor Task Failure in Patients With Cancer-Related Fatigue

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## Abstract

**Context.** Fatigue is one of the most common symptoms reported by cancer survivors, and fatigue worsens when patients are engaged in muscle exertion, which results in early motor task failure. Central fatigue plays a significant role, more than muscle (peripheral) fatigue, in contributing to early task failure in cancer-related fatigue (CRF).

**Objectives.** The purpose of this study was to determine if muscle contractile property alterations (reflecting muscle fatigue) occurred at the end of a low-intensity muscle contraction to exhaustion and if these properties differed between those with CRF and healthy controls.

**Methods.** Ten patients (aged $59.9 \pm 10.6$ years, seven women) with advanced solid cancer and CRF and 12 age- and gender-matched healthy controls (aged $46.6 \pm 12.8$ years, nine women) performed a sustained contraction of the right arm elbow flexion at 30% maximal level until exhaustion. Peak twitch force, time to peak twitch force, rate of peak twitch force development, and half relaxation time derived from electrical stimulation-evoked twitches were analyzed pre- and post-sustained contraction.

**Results.** CRF patients reported significantly greater fatigue as measured by the Brief Fatigue Inventory and failed the motor task earlier, $340 \pm 140$ vs. $503 \pm 155$ seconds in controls. All contractile property parameters did not change significantly in CRF but did change significantly in controls.

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**Conclusion.** CRF patients perceive physical exhaustion sooner during a motor fatigue task with minimal muscular fatigue. The observation supports that central fatigue is a more significant factor than peripheral fatigue in causing fatigue feelings and limits motor function in cancer survivors with fatigue symptoms. J Pain Symptom Manage 2012;44:351–361. 

***Key Words***
*Cancer-related fatigue, central fatigue, peripheral fatigue, twitch contractile properties, biceps brachii*

## *Introduction*

Cancer-related fatigue (CRF) is a common and disabling symptom experienced by many cancer survivors. The etiology and risk factors for CRF are multifactorial and poorly understood. Knowledge of the pathophysiology of CRF is important to develop helpful strategies for prevention and treatment of the symptom. An understanding of the etiology of CRF and factors limiting muscle force production and the ability to perform everyday motor tasks that require endurance are essential for the development of safe and effective therapies for improving overall fatigue. It has been reported that exercise programs could reduce fatigue at different stages of disease and treatment in cancer subpopulations.[1] Exercise programs improve motor neuron firing rates and synchrony before improving muscle mass.[2]

Motor fatigue with CRF involves interactions of several physiological and psychological mechanisms that influence early motor task failure (inability to continue physical activity normally accomplished by healthy individuals). Symptoms of CRF associated with early motor task failure suggest involvement of both central and peripheral mechanisms, although recent studies[3,4] suggest that CRF is predominantly a central fatigue with mechanisms involving the motor neuron or proximal to the motor neuron. Although mechanisms that contribute to CRF have been proposed by many investigators,[3,5–9] the contribution of muscle contractile failure to motor fatigue in CRF is not well known. Symptoms related to skeletal muscles, such as muscle soreness, fatigability, skeletal muscle atrophy/weakness, electrolyte disturbance (calcium, magnesium, phosphorus), and altered skeletal muscle metabolism,[7] are prominent in patients with CRF. Bruera et al.[10] found that patients with advanced breast cancer have abnormal muscle electrophysiology that may be a major contributor to fatigue. Furthermore, selective atrophy of Type II fibers has been noted in animal models[11] and patients with cancer,[12] which could potentially change contractile properties of evoked twitch in CRF patients. Understanding contractile properties could provide insights into muscular adaptations in CRF as well as help recognize the contributions of central and peripheral fatigue mechanisms to early motor task failure in patients with CRF. A direct measure of peripheral (muscle) fatigue is the change in force response to electrical stimulation following fatigue exercise relative to the same stimulated force before the fatigue exercise (Fig. 1). It reveals loss of force-generating capability by the muscle as a result of fatigue and also shows alterations in contractile properties such as fatigue-induced slowing of contraction and relaxation times.[13]

The purpose of this study was to determine fatigue-related muscle contractile properties (a frequently examined physiological parameter for evaluating muscle fatigue) in cancer survivors with CRF. We hypothesized that patients would experience less fatigue-related muscle contractile property alterations (compared with healthy controls), indicating a greater contribution of central fatigue to early motor task failure.

## *Methods*

### *Subjects*

Ten middle-aged patients (aged 59.9 ± 10.6 years; body mass 74.7 ± 13.1 kg; height 169 ± 10 cm; body mass index [BMI] 26.4 ± 5.8; seven