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Effects of exercise on soleus in severe burn and muscle disuse atrophy

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ABSTRACT

Background: Muscle loss is a sequela of severe burn and critical illness with bed rest contributing significantly to atrophy. We hypothesize that exercise will mitigate muscle loss after burn with bed rest.

Materials and methods: Male rats were assigned to sham ambulatory (S/A), burn ambulatory (B/A), sham hindlimb unloading (S/H), or burn hindlimb unloading (B/H). Rats received a 40% scald burn or sham and were ambulatory or placed in hindlimb unloading, a model of bed rest. Half from each group performed twice daily resistance climbing. Hindlimb isometric forces were measured on day 14.

Results: Soleus mass and muscle function were not affected by burn alone. Mass was significantly lower in hindlimb unloading (79 *versus* 139 mg, $P < 0.001$) and no exercise (103 *versus* 115 mg, $P < 0.01$). Exercise significantly increased soleus mass in B/H (86 *versus* 77 mg, $P < 0.01$). Hindlimb unloading significantly decreased muscle force in the twitch (12 *versus* 31 g, $P < 0.001$), tetanic (55 *versus* 148 g, $P < 0.001$), and specific tetanic measurements (12 *versus* 22 N/cm^2, $P < 0.001$). Effects of exercise on force depended on other factors. In B/H, exercise significantly increased twitch (14 *versus* 8 g, $P < 0.05$) and specific tetanic force (14 *versus* 7 N/cm^2, $P < 0.01$). Fatigue index was lower in ambulatory (55%) and exercise (52%) *versus* hindlimb (69%, $P = 0.03$) and no exercise (73%, $P = 0.002$).

Conclusions: Hindlimb unloading is a significant factor in muscle atrophy. Exercise increased the soleus muscle mass, twitch, and specific force in this model. However, the fatigue index decreased with exercise in all groups. This suggests exercise contributes to functional muscle change in this model of disuse and critical illness.

1. Introduction

Severe burn is accompanied by a hypermetabolic state resulting in the loss of body mass [1]. Studies of protein kinetics and DEXA imaging after severe burn have shown that protein catabolism and the resulting loss of lean muscle mass continues after wound healing and can persist 9–12 mo after injury [2]. Severe muscle loss can increase the risks of sepsis

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and mortality, cause prolonged recovery times, lead to longer hospitalizations, and increase costs [3]. Given limitations in movement typically present in severe burn, most patients are initially bed bound, which also has been shown to contribute to muscle atrophy [4]. Studies in healthy volunteers have demonstrated that muscle loss during bed rest is exacerbated by elevated serum cortisol, a physiological response to burn; this suggests that the effects of bed rest could be worse in burn [5]. An animal model was recently created to mimic bed rest after burn by placing severely burned rats in a tail suspension system to cause hindlimb unloading. The animals are able to move around the cage freely without bearing weight on their hindlimbs, leading to disuse. This investigation found that hindlimb disuse had an additive effect on muscle atrophy with decreased muscle mass and muscle function [6]. This experiment was the first to closely model the prolonged metabolic changes with muscle atrophy and resultant decrease in function similar to the changes observed in humans after severe burn [6,7]. This newly developed model of bed rest in burn has created the opportunity to closely study treatments aimed at diminishing muscle atrophy and loss of muscle function after severe burn.

It is well established that disuse muscle atrophy can be mitigated with concurrent resistance exercise training [4,5,8–13]. Initiation of resistance exercises at the start of bed rest in healthy volunteers was shown to be protective against loss of muscle protein synthesis [12]. The use of exercise training in burn patients is variable and incompletely evaluated. Practice patterns in the rehabilitation of burn patients typically focus on range of motion, manual muscle testing, and quality of life with less emphasis on exercise training [14]. It has been documented that a combination of aerobic and resistance exercise training improves lean muscle mass in pediatric burn patients [15–17]. A study of burned adults randomized into control groups or exercise groups with supervised isokinetic leg exercise three times per week demonstrated a significant increase in strength [18]. These investigations of exercise training in burn patients have only evaluated its efficacy after recovery from the acute phase, typically as outpatients or 6 mo after injury. No studies have evaluated the effects of exercise training during the initial acute phase of recovery. We hypothesize that early initiation of resistance training in burn with bed rest will mitigate muscle atrophy due to disuse. The aim of this study was to evaluate the effects of exercise on muscle mass and function in an animal model of burn with hindlimb unloading.

2. Materials and methods

Approval was granted for all procedures from the Institutional Animal Care and Use Committee at the University of Texas Health Science Center at Houston. All animal procedures were performed at this location. Forty-eight adult male Sprague-Dawley rats (Harlan Labs, Houston, TX) were assigned to four groups ($n = 12$) as follows: sham ambulatory (S/A), burn ambulatory (B/A), sham hindlimb unloading (S/H), or burn hindlimb unloading (B/H). Animals were assigned to groups randomly after weight matching for a block design to allow for an even distribution of body mass between groups. These groups were then subdivided into exercise or no exercise ($n = 6$) for a total of eight groups. At the time of injury, animals were approximately 300 g. Animals were placed in standard cages on arrival and were then housed in specialized metabolic cages (144 in^2 of usable floor area) with a traction system for hindlimb unloading [11] for 5 d before burn procedures. Animals were fed a powder diet (Harlan Teklad #2018, Houston, TX) *ad libitum* and housed in a reversed 12-h light–dark cycle to allow for exercise training during the animal's dark phase. Room temperature was maintained at $26 \pm 2°C$, with a relative humidity of 30%–80% to simulate, as closely as possible, the ambient temperature maintained in a standard burn unit.

2.1. *Thermal injury*

All animals were anesthetized with isoflurane (2%–3% in 100% O_2). Each rat was shaved on the dorsal and ventral surface. Rats randomly assigned to the burn treatment groups (B/A or B/H with and without exercise) received a full-thickness scald burn of 40% total body surface area as previously described [19]. The burned animals were resuscitated intraperitoneally with 20 mL of lactated Ringer's [20]. Animals randomized to the sham treatment groups (S/A or S/H with or without exercise) were submerged in room temperature water after shaving. All animals were given buprenorphine (0.05 mg/kg subcutaneous) immediately after shaving and at 8 hours after injury for analgesia after burn.

2.2. *Hindlimb unloading*

Immediately after injury, animals randomized to the S/H or B/H (with and without exercise) groups were placed in a tail harness and attached to a hindlimb unloading system described by Morey-Holton and Globus [11]. After animals fully recovered from anesthesia, the harness was attached to a hook and pulley traction system on top of the cage with a fish-line swivel device. The rats were positioned at a 30° head-down angle from the floor unloading the hindlimbs only. The system rides along two parallel sides of the cage and allows the animals to have 360° access within the cage and to move on an x–y axis. Rats were able to freely access food and water without their hindlimbs contacting the walls of the cage. Animals were observed for signs of distress immediately after unloading and several times a day throughout the study period. Animals in the ambulatory groups were housed in similar cages but without hindlimb unloading.

2.3. *Exercise*

All animals were pretrained 10 d before injury. Animals were trained to climb 1 meter at an 80° incline. The 6-inch climbing lanes were covered in ½ inch plastic mesh. During the pretraining period, rats were trained daily (AM only) for the first 6 d and then twice daily (AM/PM) once acclimated. Each session consisted of five climbs from bottom to top with a 10-s rest between repetitions. On the day of injury, rats were randomly assigned to exercise groups, with the exclusion of rats that outright refused to climb ($n = 14$) during the pretraining period. After injury, weights in a plastic bag were