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PI Name:	Wolfe, Robert R. Ph.D.		
Project Title:	Nutritional countermeasures to ameliorate losses in muscle mass and function		
Division Name:	Human Research		
Program/Discipline:	NSBRI Teams		
Program/Discipline--Element/Subdiscipline:	NSBRI Teams--Nutrition, Physical Fitness, and Rehabilitation Team		
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Space Biology Special Category:	None		
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Comments:			
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No. of Bachelor's Candidates:	0	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
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COI Name (Institution):	Fitts, Robert (Marquette University) Ferrando, Arny (University of Arkansas for Medical Sciences)		
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	1. We examined muscle amino acid and protein kinetics over 24 hour periods, with and without accompanying hypercortisolemia, before and at the end of bed rest and demonstrated that: An amino acid/carbohydrate supplement stimulates net muscle protein synthesis during the two-hour period immediately following ingestion. The normal anabolic effect of meals was not be affected by prior ingestion of an amino acid and carbohydrate supplement. The post-absorptive nadir in net muscle protein synthesis was no greater in subjects receiving supplementation than in control subjects. In response to these findings, we investigated the effects of 28d of hypercortisolemia alone and demonstrated a much		

Task Description:	greater loss in lean body mass and a dramatic decline in muscle insulin sensitivity. 2. We have completed the study in which 7 subjects received an essential amino acid/carbohydrate supplement (EAA group) and 6 subjects received a placebo (Placebo group). The findings indicate that supplementation with EAA maintained lean body mass (LBM) throughout 28 days of bed rest, while a placebo group experienced a loss of LBM. The EAA supplement maintained LBM by stimulating net muscle protein synthesis to a much greater extent than meal ingestion alone. Although this stimulation is diminished with increased inactivity, the net gain in muscle protein is still significantly greater than that produced by meals alone. In other words, even though the anabolic response to the EAA supplement decreases after 28d of bed rest, it is still capable of producing a significant increase in net muscle protein synthesis. Though EAA supplementation is capable of maintaining LBM, it does not fully maintain muscle strength. While the loss of muscle strength was twice as great in the placebo group, the EAA group also lost leg muscle strength after 28d of bed rest despite the preservation of leg lean mass. These findings demonstrate that the maintenance of LBM alone is insufficient to fully maintain muscle function. In a concurrent investigation we also demonstrated that ingestion of an amino acid and carbohydrate supplement does not results in a subsequent compensatory nadir in net phenylalanine balance and does not affect the normal anabolic response to ingestion of a nutritionally mixed meal. Our findings also demonstrate that an EAA supplement is capable of stimulating net protein synthesis during an acute and chronic periods of hypercortisolemia; a model mimicking the stress response to spaceflight. We noted that hypercortisolemia amplifies the loss of muscle protein during the post-absorptive state both before and after 28 days of bedrest. Though the EAA supplement can slow this loss, it only does so temporarily, such that within 1-2 hours after the supplement, the muscle protein balance is again negative. After 28 days of inactivity, the response to a meal during elevated cortisol is further diminished, such that the muscle is dramatically catabolic. The EAA supplement is not capable of eliciting an anabolic response in the muscle after 28 of bed rest. On the contrary, when the supplement is given without the presence of cortisol, the net effect is muscle anabolism over the study time period. We have also investigated the effects of 28 days of bedrest and hypercortisolemia, on lean mass and skeletal muscle protein metabolism. Our findings indicate that with elevated cortisol, the loss in muscle mass is almost 3-fold greater than with inactivity alone. In addition, the presence of elevated cortisol induces insulin resistance. After 28 days of inactivity and elevated cortisol, the effectiveness of insulin on skeletal muscle glucose uptake and protein metabolism is greatly diminished. 3. Our findings demonstrate that the anabolic response to a meal diminishes with prolonged inactivity and a stress challenge. The stimulation of net muscle protein synthesis immediately following each EAA supplement translates to a maintenance of muscle protein over a 24 hr period, and in turn, over the 28 days of bed rest. However, the maintenance of LBM does not entirely translate to maintenance of muscle strength. The interaction of inactivity and stress exacerbates the ineffectiveness of ordinary meals. Though the EAA supplement can offset muscle catabolism during the stress state, the response is transient and incapable of ameliorating the overall loss of muscle protein. Taken together, these findings indicate that a nutritional supplement alone can reduce the muscle atrophy associated with space flight. However, whereas muscle mass can be maintained with a specified nutritional intervention, other modalities are required to preserve muscle function. The catabolic interaction of inactivity and hypercortisolemia is particularly applicable to a patient population where trauma or major surgery results in prolonged inactivity and a stress response. This combination is particularly deleterious to skeletal muscle resulting in a dramatic loss of muscle mass and function, in great part due to the accompanying insulin resistance. 4. We have completed this project and are currently studying the effects of chronically elevated cortisol and hypocaloric diet throughout 14 days of bed rest on muscle protein, LBM, and muscle function. As of this writing, we have completed 10 subjects. Preliminary evidence indicates that combined elevation of cortisol and a hypocaloric diet throughout bed rest increases muscle resistance to the action of insulin and increases the loss of lean body mass. This investigation is relevant to both clinical and astronaut populations, as both are prone to under-nutrition during a stress state. Further, we intend to investigate nutritional and exercise countermeasures with this model to determine an optimal operational countermeasure that can be economically (in terms of crew time and payload) utilized to ameliorate muscle loss during prolonged space flight.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Prolonged inactivity is inherent to trauma, serious injury, or major surgery. These events represent a significant stress to the patient such that the resultant muscle loss and weakness impairs subsequent rehabilitation. Studies reveal that the requirement for hospital intensive care often entails hypocaloric intake in the patient, thus further exacerbating the deleterious results of stress. This project is designed to investigate countermeasures which will maintain muscle mass during periods of prolonged inactivity, hypocaloric intake, and stress. The proposed interventions are primarily nutritional, and are of unique design and composition so as to have a maximal benefit on a gram per gram basis. Thus, these investigations will be directly applicable and translatable to a patient population.
Task Progress:	Based on our previous investigation on the protein-sparing effects of EAA during 28 days of hypercortisolemic bedrest, we decided to pursue a smilar dosing regimen (3 x 15g EAA) during a subsequent study. In this ongoing study, we have modified the supplement slightly to include a higher proportion of the amino acid leucine in hopes of stimulating net muscle protein synthesis to a greater degree. This is particularly relevant since we have chosen a clinically and space-relevant paradigm of hypercortisolemia with a hypocaloric diet. Our preliminary evidence indicates that hypercortisolemia + hypercaloric diet further exacerbates the loss of LBM, while the EAA supplement is only moderately effective in offsetting this loss. We are currently finishing the EAA supplement group.
Bibliography Type:	Description: (Last Updated: 10/23/2019)

Articles in Other Journals or Periodicals	Paddon-Jones D, Sheffield-Moore M, Cree MG, Hewlings SJ, Aarsland A, Wolfe RR, Ferrando AA. "Impaired muscle protein synthesis and atrophy during prolonged inactivity and stress." Journal of Clinical Endocrinology and Metabolism. In Press, June 2006. , Jun-2006
Articles in Peer-reviewed Journals	Paddon-Jones D. "Interplay of stress and physical inactivity on muscle loss: Nutritional countermeasures." J Nutr. 2006 Aug;136(8):2123-6. Review. PMID: 16857828 , Aug-2006
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