Mathematical Model for Blood Flow Restriction Exercise Stimulates mtorc1 Signaling in Older Men

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Abstract- The loss of skeletal muscle mass during aging, sarcopenia, increases the risk for falls and dependence. Resistance exercise (RE) is an effective rehabilitation technique that can improve muscle mass and strength however older individuals are resistant to the stimulation of muscle protein synthesis (MPS) with traditional high-intensity RE.

We use the stochastic model we found the effect of an acute bout of low-intensity resistance exercise with BFR o mTORC1 signaling and muscle protein synthesis in older men. We hypothesized that a single bout of low-intensity resistance exercise with reduced muscle blood flow would enhance mTORC1 signaling and stimulate muscle protein synthesis in older men.

Index Terms- chrf,cortisol,GH,BFR,mTORC1,MPS

I. INTRODUCTION

Generalized continuous univariate distributions which have been extensively used for analyzing and modeling data in many applied areas such as lifetime analysis, engineering, economics, insurance and environmental sciences. Resistance exercise training has been shown to be a beneficial intervention to protect against the effects of sarcopenia, with training studies showing increases in muscle protein synthesis and mass in both the old and young (24, 33). However, the training studies often show a more robust muscle protein synthetic and strength response in the young than in the elderly. This may be due to an inability of older individuals to lift an amount of weight sufficient to induce hypertrophy or an inability of aging muscle to respond to resistance exercise. The mechanisms responsible for how resistance exercise induces muscle hypertrophy are not completely understood; however, it does appear that activation of a key cell growth pathway, the mammalian target of rapamycin complex 1, is an important regulatory mechanism of muscle hypertrophy.

II. APPLICATION

There were no significant differences in plasma glucose or lactate between groups at baseline (Table 1). Plasma lactate increased significantly ($P < 0.05$, Table 1) in both groups in during the exercise bout ($P < 0.05$), remained elevated in the BFR group for 45 min after exercise, and was also higher compared with Ctrl for 30 min after exercise. Plasma lactate values returned to baseline in the Ctrl group after exercise. Plasma glucose increased significantly after exercise for 45 min in the BFR group compared with baseline and was higher than the Ctrl group ($P < 0.05$; Table 1), which did not change after exercise.

Cortisol concentrations were elevated only in the BFR group for 2 h after exercise from baseline values ($P < 0.05$; Fig. 2) and then returned to near-resting values ($P > 0.05$). After exercise, cortisol values were significantly higher than those in the Ctrl group during the first 90 min after exercise in the BFR group ($P < 0.05$). Serum cortisol concentrations did not change during or after exercise in the Ctrl group ($P < 0.05$).

Serum GH concentrations increased significantly 15 min after exercise and remained elevated for 30 min after exercise in the BFR group compared with baseline ($P < 0.05$; Fig. 2). Serum GH concentration in the BFR group was also higher than the Ctrl group for 30 min after exercise ($P < 0.05$; Fig. 2). GH concentration did not change after exercise in the Ctrl group ($P > 0.05$).

Table. 1 Plasma lactate and glucose measurements before and after resistance exercise

			Post exercise, Minutes					
	Baseline	Exercise	15	30	45	60	120	180
Lactate, mmol/1								
BFR	1.2±0.1	2.7±0.6*	3.3±0.4*#	2.4±0.4*#	1.8±0.3*	1.7±0.2	1.0±0.1	0.9±0.1
Ctrl	1.3±0.2	2.9±0.6*	1.7±0.2	1.3±0.2	1.2±0.1	1.1±0.1	0.9±0.1	0.9±0.1
Glucose, mmol/l								
BFR	5.3±3.2	5.3±3.2	6.0±3.6#	5.7±3.9#	5.6±3.7#	5.5±3.2	5.2±2.3	5.2±2.4
Ctrl	5.3±3.8	5.3±3.0	4.9±5.5	4.8±5.9	5.1±2.2	5.0±2.2	5.0±2.2	4.9±1.9

*Significantly different from baseline (P< 0.05); #Significantly different from Ctrl at same time point ($P < 0.05$).

III. MUSCLE BLOOD FLOW RESTRICTION EXERCISE IN AGING

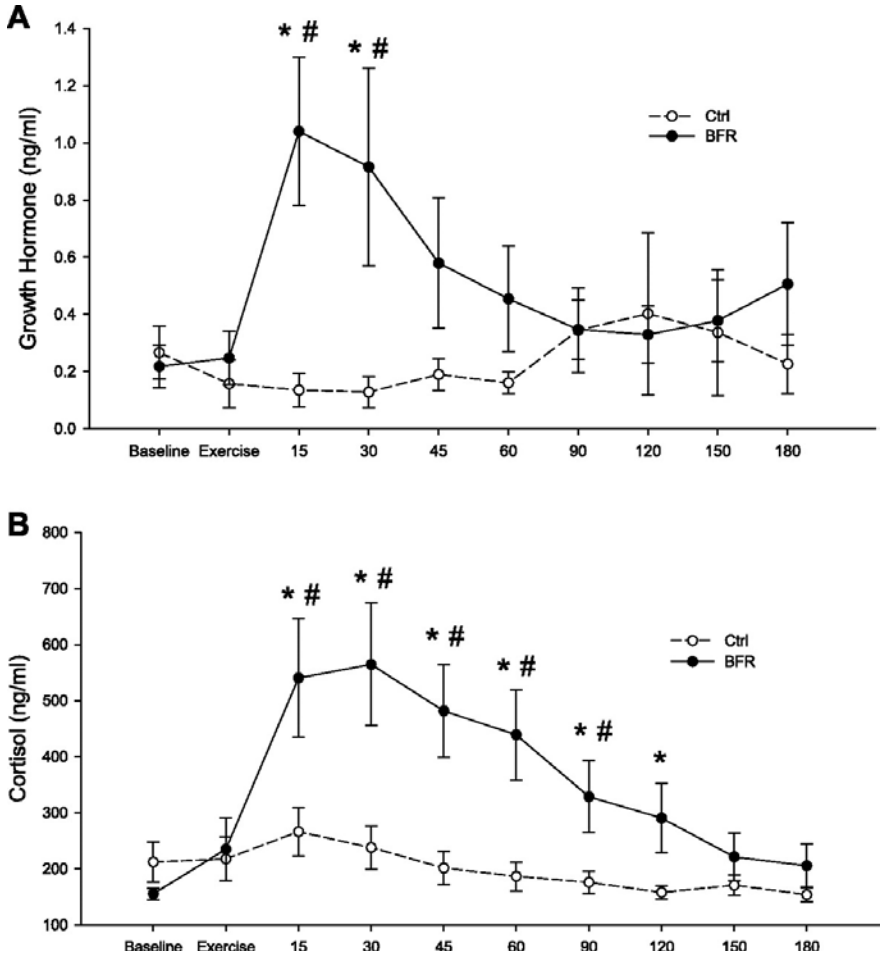

Fig. 2 Peripheral vein serum hormone concentrations. Samples were obtained from BFR and control (Ctrl; no BFR) subjects before and during exercise and for 3 h after exercise. A: serum growth hormone (ng/ml) B: serum cortisol (ng/ml). *Significantly different from baseline (P <0.05); # Significantly different from Ctrl subjects at corresponding time point (P < 0.05).

IV. MATHEMATICAL MODEL

The cdf of the MOFr is given (for x > 0) by

$$G(x,\alpha,\beta,\sigma) = \frac{e^{-(\frac{\sigma}{x})^{\beta}}}{\alpha+(1-\alpha)e^{-(\frac{\sigma}{x})^{\beta}}}, \quad (1)$$

whereσ> 0 is a scale parameter and α and β are positive shape parameters.

The corresponding probability density function (pdf) is given by

$$g(x,\alpha,\beta,\sigma) = \frac{\alpha\beta\,\sigma^{\beta}x^{-(\beta+1)}e^{-(\frac{\sigma}{x})^{\beta}}}{(\alpha+(1-\alpha)e^{-(\frac{\sigma}{x})^{\beta}})^{2}}, \quad (2)$$

Consider a baseline cdf G(x) and pdf g(x). Then, the cdf and pdf of the T-G family of distributions are respectively, defined by

$$F(x;\lambda) = G(x)\,[\,1 + \lambda - \lambda G(x)] \quad (3)$$

and

$$f(x;\lambda) = g(x)\,[\,1 + \lambda - 2\lambda G(x)], \quad (4)$$

where$|\lambda| \le 1$

The cdf of TMOFr (for x > 0)

$$F(x) = \frac{e^{-(\frac{\sigma}{x})^{\beta}}}{\alpha+(1-\alpha)e^{-(\frac{\sigma}{x})^{\beta}}}\left[1 + \lambda - \frac{\lambda e^{-(\frac{\sigma}{x})^{\beta}}}{\alpha+(1-\alpha)e^{-(\frac{\sigma}{x})^{\beta}}}\right], \quad (5)$$

Whereas its pdf can be expressed, from (1), (2) and (4) as

$$f(x) = \frac{\alpha\beta\,\sigma^{\beta}x^{-(\beta+1)}e^{-(\frac{\sigma}{x})^{\beta}}}{\left(\alpha+(1-\alpha)e^{-(\frac{\sigma}{x})^{\beta}}\right)^{2}}\left[1 + \lambda - \frac{2\lambda e^{-(\frac{\sigma}{x})^{\beta}}}{\alpha+(1-\alpha)e^{-(\frac{\sigma}{x})^{\beta}}}\right] \quad (6)$$

Whereσ> 0 is a scale parameter, α and β are positive shape parameters and $|\lambda| \le 1$.

A physical interpretation of the cdf of TMOFr is possible if we take a system consisting of two independent components functioning independently at a given time. So, if the two components are connected in parallel, the overall system will have the TMOFrcdf with

λ =-1.

The rf, hrf, reversed-hazard rate function (rhrf) and Cumulative hazard rate function (chrf) are, respectively given by

$$R(x)=\frac{\alpha^2+\left(\alpha-\alpha\lambda-2\alpha^2\right)e^{-\left(\frac{\sigma}{x}\right)^\beta}+\left(\alpha^2+\alpha\lambda-\alpha\right)e^{-2\left(\frac{\sigma}{x}\right)^\beta}}{\left[\alpha+(1-\alpha)e^{-\left(\frac{\sigma}{x}\right)^\beta}\right]^2}$$

$$h(x)=\frac{\alpha\beta\sigma^\beta x^{-(\beta+1)}e^{-\left(\frac{\sigma}{x}\right)^\beta}}{[\alpha+(1-\alpha)e^{-\left(\frac{\sigma}{x}\right)^\beta}]}\{\alpha(1+\lambda)-[\lambda(\alpha+1)+\alpha-1]\,e^{-\left(\frac{\sigma}{x}\right)^\beta}\}$$

$$X\{\alpha^2+[\alpha(1-\lambda-2\alpha)+(\alpha^2-\alpha\lambda-\alpha)e^{-\left(\frac{\sigma}{x}\right)^\beta}]e^{-\left(\frac{\sigma}{x}\right)^\beta}\}^{-1}$$

$$r(x)=\frac{\alpha\beta\sigma^\beta x^{-(\beta+1)}\{\alpha(1+\lambda)-[\lambda(\alpha+1)+\alpha-1]\,e^{-\left(\frac{\sigma}{x}\right)^\beta}\}}{\left[\alpha(1+\lambda)-(\alpha\lambda+\alpha-1)\,e^{-\left(\frac{\sigma}{x}\right)^\beta}\right]\left[\alpha+(1-\alpha)\,e^{-\left(\frac{\sigma}{x}\right)^\beta}\right]}$$

and

$$H(x)=\ln\{\frac{\left[\alpha+(1-\alpha)e^{-\left(\frac{\sigma}{x}\right)^\beta}\right]^2}{\alpha^2+\left(\alpha-\alpha\lambda-2\alpha^2\right)e^{-\left(\frac{\sigma}{x}\right)^\beta}+\left(\alpha^2-\alpha\lambda-\alpha\right)e^{-2\left(\frac{\sigma}{x}\right)^\beta}}\}$$

Theorem : 1

Let X :Ω→(0,∞) be a continuous random variable and let

$$h(x)=[1+\lambda-\frac{\lambda e^{-\left(\frac{\sigma}{x}\right)^\beta}}{\alpha+(1-\alpha)e^{-\left(\frac{\sigma}{x}\right)^\beta}}]^{1-b}$$

and $g(x)=h(x)[\alpha+(1-\alpha)e^{-\left(\frac{\sigma}{x}\right)^\beta}]^{-1}$ for x > 0. The random variable X belongs to TMOFr family (6) if and only if the function ηdefined in Theorem A has the form

$$\eta(x)=\frac{1}{2}\{1+[\alpha+(1-\alpha)e^{-\left(\frac{\sigma}{x}\right)^\beta}]^{-1}\},\ x>0.$$

Proof. Let X be a random variable with density (6), then

$$(1\text{-}F(x)\ \ E[h(x)|X\geq x]=\frac{1}{1-\alpha}\{[\alpha+(1-\alpha)e^{-\left(\frac{\sigma}{x}\right)^\beta}]^{-1}\text{-}1\},\ x>0$$

and

$$(1\text{-}F(x)\ E\ [g(x)|X\geq x]=\frac{1}{2(1-\alpha)}\{[\alpha+(1-\alpha)e^{-\left(\frac{\sigma}{x}\right)^\beta}]^{-2}\text{-}1\},\ x>0$$

and finally

$$\eta(x)\,h(x)-g(x)=\frac{1}{2}h(x)\{1-[\alpha+(1-\alpha)e^{-\left(\frac{\sigma}{x}\right)^\beta}]^{-1}\}>0$$

for x > 0.

Conversely, if η is given as above, then

$$S'(x)=\frac{\eta'(x)h(x)}{\eta(x)h(x)-g(x)}=\frac{-(1-\alpha)\beta\sigma^\beta e^{-\left(\frac{\sigma}{x}\right)^\beta}[\alpha+(1-\alpha)e^{-\left(\frac{\sigma}{x}\right)^\beta}]^{-2}}{x^{\beta+1}\{1-[\alpha+(1-\alpha)e^{-\left(\frac{\sigma}{x}\right)^\beta}]^{-1}\}},$$

x>0

and hence

$$s(x)=-\ln\{\{1-[\alpha+(1-\alpha)e^{-\left(\frac{\sigma}{x}\right)^\beta}]^{-1}\}\},\ x>0.$$

Theorem : 2

Let X :Ω→ (0,∞) be a continuous random variable. Then for α = 1, the pdf of X is (6) if and only if its hazard function $h_f(x)$ satisfies the differential equation.

$$h'_F(x)+(\beta+1)x^{-1}h_F(x)=\beta x^{-(\beta+1)}\frac{d}{dx}\{\frac{e^{-\left(\frac{\sigma}{x}\right)^\beta}[1+\lambda-2\lambda\,e^{-\left(\frac{\sigma}{x}\right)^\beta}]}{1+[\lambda e^{-\left(\frac{\sigma}{x}\right)^\beta}-(1+\lambda)]\,e^{-\left(\frac{\sigma}{x}\right)^\beta}}\},\qquad(7)$$

with the boundary condition $\lim_{x\to\infty}h_F(x)=0$.

Proof. If X has pdf(6), then clearly (7) holds, Now, if (7) holds, then

$$\frac{d}{dx}\{x^{\beta+1}h_F(x)\}=\frac{d}{dx}\{\frac{\beta e^{-\left(\frac{\sigma}{x}\right)^\beta}[1+\lambda-2\lambda\,e^{-\left(\frac{\sigma}{x}\right)^\beta}]}{1+[\lambda e^{-\left(\frac{\sigma}{x}\right)^\beta}-(1+\lambda)]\,e^{-\left(\frac{\sigma}{x}\right)^\beta}}\},$$

or , equivalently,

$$h_F(x)=\{\frac{\beta x^{-(\beta+1)}e^{-\left(\frac{\sigma}{x}\right)^\beta}[1+\lambda-2\lambda\,e^{-\left(\frac{\sigma}{x}\right)^\beta}]}{1+[\lambda e^{-\left(\frac{\sigma}{x}\right)^\beta}-(1+\lambda)]\,e^{-\left(\frac{\sigma}{x}\right)^\beta}}\},$$

GRAPH : 1

x	0.9	1.8	2.6	3.5	4.3	5.2	6	6.9	7.8	8.7
$h_F(x)$	0.0188	0.0332	0.0316	0.0216	0.0155	0.0115	0.0088	0.0068	0.0052	0.0045

x	0.9	1.8	2.6	3.5	4.3	5.2	6	6.9	7.8	8.7
s(x)	0.2538	0.2667	0.2941	0.3231	0.3491	0.3774	0.4016	0.4276	0.4523	0.4759

GRAPH : 2

x	0.9	1.8	2.7	3.6	4.5	5.4	6.3	7.2	8.1	9

$h_F(x)$	0.0776	0.0850	0.0621	0.0453	0.0342	0.0268	0.0217	0.0177	0.0150	0.0128

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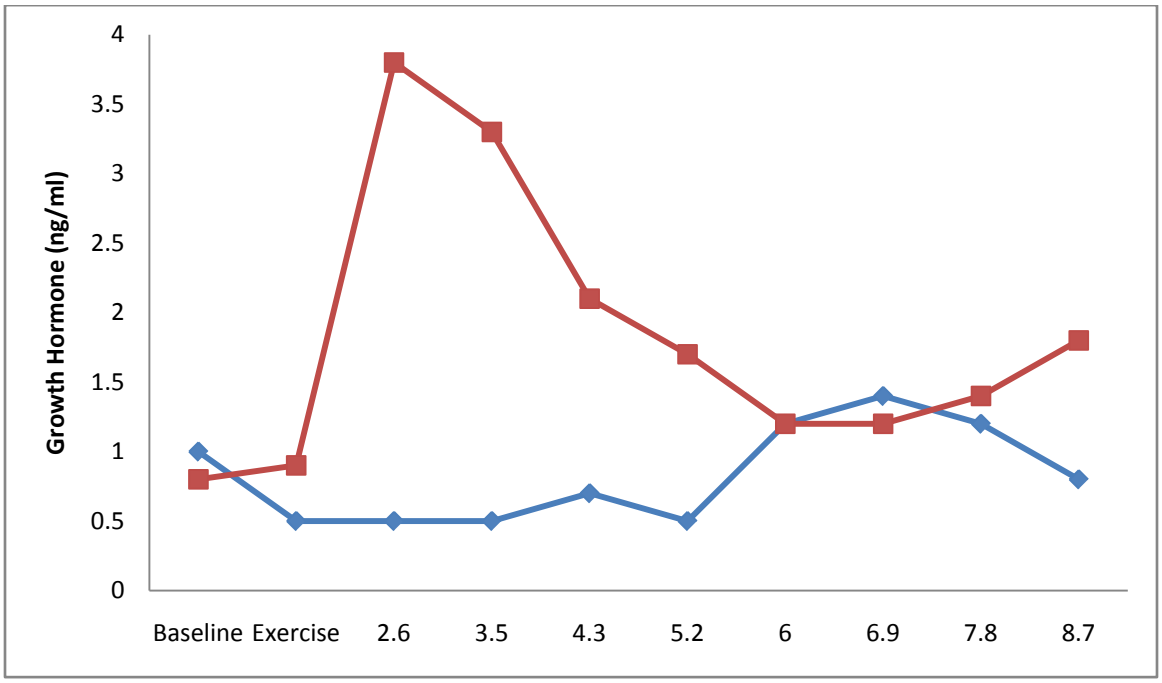
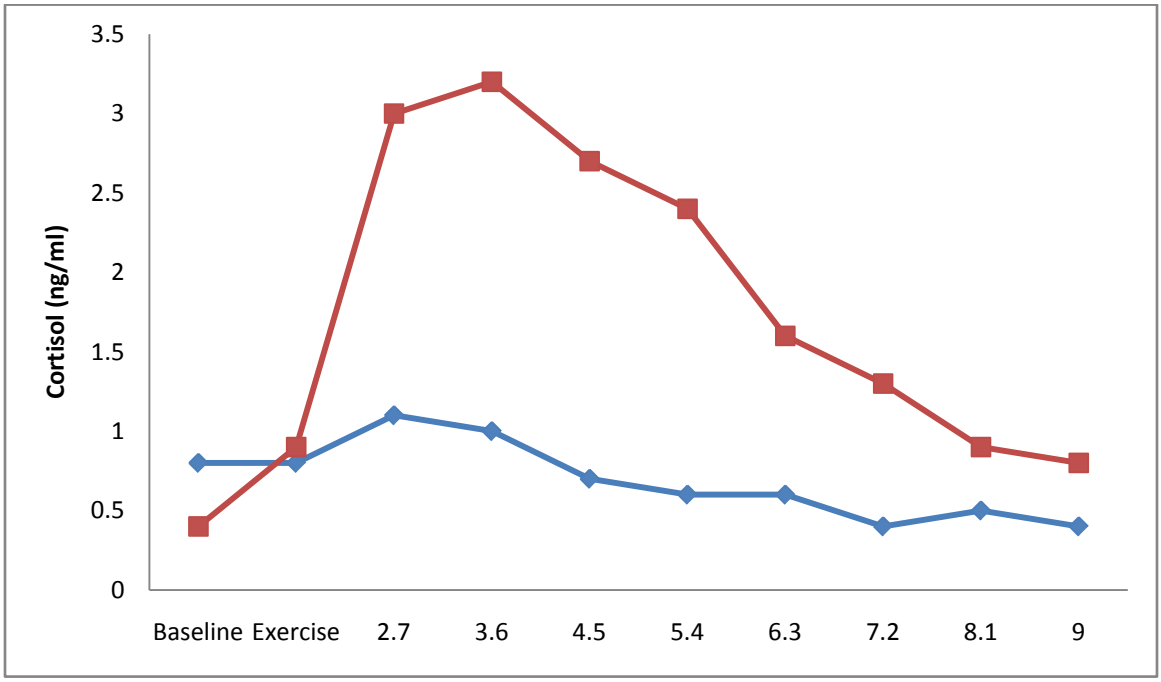
x	0.9	1.8	2.7	3.6	4.5	5.4	6.3	7.2	8.1	9
s(x)	0.1751	0.1987	0.2291	0.2598	0.2895	0.3178	0.3445	0.3699	0.3940	0.4168

GRAPH : 1



GRAPH : 2



Graph : 1

x	0.9	1.8	2.6	3.5	4.3	5.2	6	6.9	7.8	8.7
y1	1	0.5	0.5	0.5	0.7	0.5	1.2	1.4	1.2	0.8
y2	0.8	0.9	3.8	3.3	2.1	1.7	1.2	1.2	1.4	1.8

Graph: 2

x	0.9	1.8	2.7	3.6	4.5	5.4	6.3	7.2	8.1	9
y1	0.8	0.8	1.1	1	0.7	0.6	0.6	0.4	0.5	0.4
y2	0.4	0.9	3	3.2	2.7	2.4	1.6	1.3	0.9	0.8

V. CONCLUSION

Low-intensity RE in combination with BFR enhances mTORCl signaling and MPS in older men. BFR exercise is a novel intervention that may enhance muscle rehabilitation to counteract sarcopenia.

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