Link between blood flow and muscle protein metabolism in elderly adults

Hirofumi Zempo1,2*, Mitsuaki Isobe3 and Hisashi Naito2

1 Japan Society for the Promotion of Science, Kojimachi Business Center Building, 5-3-1 Kojimachi, Chiyoda-ku, Tokyo 102-0083, Japan
2 Graduate School of Health and Sports Science, Juntendo University, 1-1 Hiraga-gakuen-dai, Inzai, Chiba 270-1695, Japan
3 Department of Cardiovascular Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan

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Abstract

The mechanism which causes sarcopenia, a loss of muscle mass and strength with aging, remains unclear. Muscle mass is controlled by the net balance between protein synthesis and breakdown; however, net balance differences in the basal state do not contribute to sarcopenia. On the other hand, anabolic resistance, a reduction in muscle protein synthesis in response to protein intake, does seem to be involved in sarcopenia. Muscles which are subject to anabolic resistance do not show incremental blood flow volume during the fed-state. Because the vascular system transports amino acids and other nutrients that are essential for muscle protein synthesis, blood flow volume may be a regulator of anabolic resistance. There is some evidence of a link between blood flow and muscle protein metabolism. In addition, a combination of resistance training and amino acid supplementation promotes a positive net protein balance. Resistance training improves, and detraining reduces blood flow volume; therefore, blood flow volume may be involved as a background mechanism for sarcopenia. Moreover, previous studies have shown that sodium nitroprusside, a vasodilatory nitric oxide donor, enhances muscle protein synthesis. Conversely, angiotensin II, a major vasoconstrictive peptide, induces skeletal muscle protein breakdown. In this review, we discuss a possible role for blood flow in skeletal muscle protein metabolism in elderly adults. The regulation of blood flow may prove to be a beneficial treatment for sarcopenia.

Keywords: aging, skeletal muscle, protein synthesis, insulin, vascular flow

Introduction

Elderly populations are growing around the world with increasing life expectancy. The United Nations reported that the number of people over 60 years old in 2050 is projected to more than double its size in 2015, reaching nearly 2.1 billion1. Japan has entered the “super-aged society” stage, with the elderly population constituting more than 26% of the population, higher than any other country in the world5. In this situation, independent living for elderly people is very important, not only for maintaining their quality of life, but also to reduce care insurance. Prevention of sarcopenia, a loss of muscle mass and strength with advancing age8, can contribute to the independent living of elderly people. Some causative mechanisms for sarcopenia have been suggested7. Although reduction in the quality and number of satellite cells was a leading hypothesis for the sarcopenia mechanism, a recent animal study demonstrated that depression of satellite cells in adults did not facilitate sarcopenia9. Age-dependent mitochondrial dysfunction and cumulative oxidative stress was also a hypothesis for the sarcopenia mechanism; however, it is not key regulator of sarcopenia10. Moreover, a recent study showed that serum albumen concentration, which is an indicator of systemic malnutrition, was not associated with sarcopenia in Japanese11. Thus, the mechanism of sarcopenia remains unclear. Many sarcopenia and muscle atrophy studies focused only on skeletal muscle or the nervous system. However, the vascular system transports energy and amino acids that are essential for muscle protein synthesis, and blood flow volume and capillary number diminish with aging12. Therefore, changes in the circulatory system may be involved in sarcopenia. In this review, we discuss the possible role of blood flow on skeletal muscle protein metabolism in elderly adults.

Loss of skeletal muscle mass with aging

Skeletal muscle mass decreases by about 0.5-0.6% per year with aging12,13. Additionally, in elderly people who need nursing care, decrement of thigh muscle volume accelerates by up to 4% per year14. The characteristics of sarcopenia are type II (fast twitch and forceful contraction) muscle fiber-specific15,16, and affect the lower body...
with greater severity than the upper body\cite{17}. Therefore, sarcopenia leads to reduced activities of daily living (ADL), mainly resulting in reduced walking ability and an increased risk of falling\cite{3}. Moreover, recent findings showed that sarcopenia is a risk factor for several diseases and is linked to mortality\cite{18-28}. On October 1st, 2016, sarcopenia was given the code “M62.84” in the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM)\cite{27,28}, recognizing it as an independent clinical condition. Hence, understanding and research on sarcopenia should be accelerated in the future.

Muscle mass is controlled by the net balance between protein synthesis and breakdown\cite{29}. Many studies have shown that there is no difference in muscle protein synthesis in the basal state between the elderly and young people\cite{30-36}, although a few studies reported lower synthesis in the elderly\cite{37,38}. The IGF1-Akt-mTOR-FoxO signaling pathway, which is the main signaling pathway known to control protein turnover in skeletal muscle, does not change with aging in humans\cite{39}. Muscles are in the basal state for the majority of each day; however, if muscle protein synthesis is lower in the elderly than in the young in basal state, it will be difficult to detect such a phenomenon, because the protein net balance decreases by only 0.0016% per day (0.6% per year). Moreover, muscle protein breakdown in the basal state has shown no difference between elderly and young people\cite{31,40}. Thus, it remains possible, that the net balance in the basal state is not involved in the loss of skeletal muscle mass with aging. On the other hand, it has been shown that an increment in muscular protein synthesis in the fed state, or after insulin stimulation, is attenuated in elderly people compared to young people\cite{33,35,41}; a phenomenon known as “anabolic resistance”\cite{42}. However, amino acid absorption does not change with age\cite{43}. As will become apparent below, blood flow volume may be involved in anabolic resistance in elderly people.

Both resistance exercise and adequate nutrition can enhance muscle protein synthesis. Resistance training promotes muscle hypertrophy, even in elderly people, and a bout of resistance exercise can increase protein synthesis. However, the net balance remains negative or zero after a bout of resistance exercise in the absence of amino acid intake\cite{44-47} due to the simultaneous increment of protein breakdown\cite{45}. Although essential amino acid intake enhances muscle protein synthesis\cite{48,49}, it cannot maintain a positive net balance in the long run\cite{31}; not even leucine-rich amino acid supplements, which are known to increase protein synthesis\cite{50}, can do such. Moreover, a recent review concluded that leucine, as a stand-alone nutritional intervention, is not effective in the prevention of muscle wasting and sarcopenia\cite{51}. Also, many other intervention studies have shown that nutritional supplementation alone does not increase muscle mass\cite{52-55}. On the other hand, protein supplementation increases the fat-free mass during resistance training\cite{56,57}. Other papers have provided more detailed reviews discussing the link between exercise, nutrient intake, and muscle mass in the elderly\cite{58,59}. They concluded that a combination of resistance exercise and leucine supplementation is best to produce a positive net balance. However, the percentage of elderly people reporting frequent exercise remains low, and that exercise is usually limited to walking. Therefore, a habitual increase in resistance exercise is needed.

### Loss of blood flow volume with aging

Blood flow volume is directly proportional to the fourth power of the vascular radius and is deftly controlled mainly by resistance vessels. Vascular tone is regulated by neural activity and the concentration of circulating hormones (e.g., adrenalin and insulin), autacoids [e.g., angiotensin II, endothelin-1, and nitric oxide (NO)], and metabolites (e.g., adenosine, ATP, CO₂, H₂O₂, and K⁺). Vasoconstriction is enhanced by high neural activity, noradrenalin, angiotensin II, and endothelin, amongst other factors that lead to increased blood pressure. On the other hand, insulin, NO, and some metabolites promote vasodilation that leads to increased blood flow volume. The muscle blood flow represents only 15-20% of the resting cardiac output, but during maximal exercise increases to approximately 85% of total cardiac output. With aging, neural activity\cite{60-62} and endothelin-1 concentration\cite{63} increase, while endothelial function\cite{64-66}, aortic distensibility\cite{67}, and capillary number decrease\cite{6-11}. Moreover, erythrocyte-mediated ATP release, which mediates vasodilation during conditions of erythrocyte deoxygenation, decreases with aging\cite{68}. These changes induce a lowered blood flow volume with aging.

![Hypothetical mechanisms of sarcopenia. Lower blood flow volume-induced anabolic resistance may partially lead to sarcopenia. VEGF, vascular endothelial growth factor.](image)
Effect of blood flow volume on skeletal muscle protein metabolism

As described above, anabolic resistance may be a cause of sarcopenia. Recently, Rasmussen et al. reported that there is a strong correlation (r = 0.90) between changes in blood flow volume and changes in muscle protein synthesis due to the anabolic action of insulin that was stimulated after a meal in humans. Moreover, in this study, no increase in leg blood flow due to insulin was observed in elderly people, compared to young people. Mitchell et al. also showed that an incremental increase in postprandial microvascular blood volume is observed in young men, but not in elderly men. These findings suggest that attenuation of insulin-induced vasodilation in elderly people may be involved in anabolic resistance. Indeed, sodium nitroprusside, a vasodilatory NO donor, ameliorates the muscle protein anabolic effect and net balance induced by insulin or amino acids in older adults. Also, a previous study showed that the amino acid concentration in plasma is more important for mediating protein synthesis than the intramuscular concentration. These results suggest that amino acids in blood are initiators of protein synthesis, and amino acid volume in blood (product of blood flow volume and amino acid concentration) may be an important factor for protein synthesis.

Insulin is a key factor in anabolic resistance. Insulin is a vasodilatory factor and has the dual effect of enhancing muscle protein synthesis and inhibiting breakdown. Insulin promotes net muscle protein anabolism primarily by inhibiting protein breakdown, rather than by stimulating protein synthesis. In addition, insulin appears to have a permissive role in protein synthesis in the presence of elevated amino acid levels, and plays a clear role in reducing protein breakdown independent of amino acid availability. However, insulin does not promote a positive net balance in elderly people, because due to impaired suppression of protein breakdown by insulin stimulation. Therefore, attenuation of insulin responses including vasodilation and switch of net balance induce anabolic resistance. On the other hand, vasoconstrictors inhibit protein synthesis and enhance protein breakdown. We have previously shown that suppression of the angiotensin II type 1a receptor, a vasoconstrictive receptor, enhances skeletal muscle development in mice. Although, many of the studies that investigated the effect of angiotensin II on skeletal muscle focused on atrophic factors, it may also be involved via blood flow.

A decrease in capillary numbers contributes to blood flow volume loss in the elderly. Capillary number to muscle fiber ratio strongly correlates with muscle fiber radius (R² = 0.948) and cross-sectional area (R² = 0.864). In younger humans, the cross-sectional area of skeletal muscle fiber is comparable in type I and II muscle. However, the characteristics of sarcopenia are type II muscle fiber-specific, and a reduction of muscular capillary density in the elderly is only observed around type II muscle fibers. Moreover, myonuclear apoptosis had been thought to be the root cause of sarcopenia; even though the fact remains that 70-80% of apoptosis in aged skeletal muscle occurs in capillary endothelial cells. A decrease in vascular endothelial growth factor (VEGF) production by elderly skeletal muscle may be an underlying mechanism. Moreover, in glucose metabolism, skeletal muscle capillary density correlates well with insulin sensitivity, and blood flow affects insulin sensitivity. Thus, there is a strong possibility of a cause-effect relationship between capillary reduction and anabolic resistance. Taken together, Fig. 1 shows our hypothetical mechanisms of sarcopenia.

Resistance training improves blood flow volume in elderly people. In contrast, detraining reduces blood flow volume within two weeks. Additionally, type II muscle fiber capillarization at baseline is a critical factor in muscle fiber hypertrophy during resistance exercise training in older men. These data suggest that blood flow volume are linked to muscle protein metabolism both during and after resistance training. Nevertheless, conflicting data exist. A recent study showed increased fed-state muscle blood flow volume after resistance training; however, this did not enhance net protein balance in elderly men. Further studies are needed to explain these differences.

Prospects

In this review, we have discussed the possibility of a role for blood flow in the regulation of muscular protein metabolism. Nevertheless, some problems remain to be solved. Firstly, a thorough analysis of the relationship between blood flow and muscle protein metabolism, and investigation of a causative mechanism, are required. Secondly, we need to elucidate the effects of inhibitory factors on vasodilation in elderly people. Thirdly, investigations in situations closer to daily life are required; most cases started with an overnight fasting state, a condition that may have affected the study results. Lastly, longitudinal studies are needed to better understand the bigger picture.

To conclude, we would like to borrow the words of Thomas Sydenham (1624-1689) who said “A man is as old as his arteries.” Vascular aging might indeed contribute to sarcopenia.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.
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