Skeletal Muscle Hypertrophy Induced by Low-Intensity Exercise with Heat-Stress in Healthy Human Subjects

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ABSTRACT
Effects of low-intensity exercise (LIE) combined with or without heat-stress on muscle hypertrophy were investigated. Nine healthy men were subjected to 10 weeks of LIE for elbow flexor muscles (4 days/wk at less than 30 repetition maximum (RM), 3 sets (30 repetitions) of flexion-extension exercise of elbow joints). The 60-min heat-stress was applied to only non-dominant arm, which performed LIE during the last 30-min period, by using a heat- and steam-generating sheet (heating area was set for 430 cm², Kao Corporation, Tokyo, Japan). The dominant arm was subjected to only LIE. Maximum isometric force in flexion of the heated non-dominant, not the unheated dominant, arm significantly increased (18.4%) after 10-week LIE (p<0.05). However, the maximum isometric torque in extension of both arms was not improved. Mean cross-sectional area of biceps brachii muscles in the non-dominant, not the dominant, arm was significantly increased by LIE combined with heat-stress for 10 weeks (7.5%, p<0.05). It was strongly indicated that exercise training at an intensity even lower than 50% 1 RM could be effective in increasing of muscle strength associated with hypertrophy, when the training was combined with heating. These results suggest that heat-stress might be a useful countermeasure for prevention of muscular atrophy during space flight and/or long-term bed rest. Its application could be also extended to rehabilitation.

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Key words : heating sheet, muscle hypertrophy, low-intensity exercise, human

INTRODUCTION
It is well-known that mechanical loading, such as stretch, is one of the primary factors regulating the synthesis and degradation of proteins in skeletal muscles. Increased loading on skeletal muscles stimulates protein synthesis and often results in hypertrophy. In contrast, decreased loading during the exposure to space or simulated microgravity environment causes a loss of muscular protein and atrophy, and then results in a decreased force generation. Therefore, the establishment of a countermeasure for prevention of muscle atrophy caused by space flight is essential. It is generally considered that the mechanical stretch is one of the useful tools as the
countermeasure. However, the muscle atrophy during space flight is not completely prevented by mechanical stretch as well as heavy resistant exercise. Effective and/or useful countermeasure for muscle atrophy is not developed yet.

Recently, it is reported that heat-stress could partially prevent the unloading-related muscular atrophy. Heat-stress stimulates the synthesis of heat shock protein 72 (HSP72) in muscular cells. We have also shown that the application of heat-stress at 41°C for 60 min could facilitate the stretch-induced muscle hypertrophy and loading-induced muscle re-growth. Heat-stress could also induce muscle hypertrophy in cultured skeletal muscle cells and animal models. Evidences obtained in our previous studies strongly suggested that the application of heat-stress may be useful as a countermeasure for muscle atrophy. However, there is a technical problem that the heating at 41°C for 60 min is difficult to apply for human skeletal muscles.

In human, it is impossible to increase the body temperature up to 41°C by heat-stress. However, it has been confirmed that heat-stress at ~38°C for 30-40 min could induce muscle hypertrophy in rats. Therefore, this heating condition may be applicable to human in order to induce muscle hypertrophy, although there is no evidence regarding the effects of heat-stress on skeletal muscle in human subjects. Therefore, this study was performed to investigate the effects of exercise training at low intensity combined with heat-stress on muscle hypertrophy.

MATERIALS AND METHODS

Subjects

Nine healthy men (age: 38.2 ± 5.8 years old (mean ± SD), height: 171.8 ± 4.2 cm, body weight: 67.8 ± 5.0 kg) participated in the 10-week study. All experimental procedures were conducted in accordance with World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects). The study was also approved by the Bioethics Committee at St. Marianna University School of Medicine. All subjects were informed about the possible risks in this study, and a signed informed consent was obtained from each subject.

Application of heat-stress

A heat- and steam-generating sheet (heating area is set for 430 cm², Kao Corporation, Tokyo, Japan) was placed on only the non-dominant upper arm, not the dominant arm. The sheet produces high heat flux and warms the skin more widely and deeply than the heat-generating sheet without steam. The detail for the heat- and steam-generating sheet is described elsewhere. Briefly, the sheet contains the powder of iron and a small amount of water. The powder of iron in the sheet reacts with atmospheric oxygen in the air, and then heat and steam are produced. Each subject also wore supporter on forearm and gloves in both hands to depress the heat radiation. The heating was applied for 60 min and exercise was performed during the last 30-min period 4 days a week for a period of 10 weeks. Skin temperature under the sheet at 30 and 60 min after the initiation of heating was approximately 40°C.

Measurement of muscular temperature

At a depth of 15 mm below the skin surface, the temperature of midbelly region of biceps brachii muscle of five of nine subjects was measured by using a digital thermometer (PTC-201, Unique Medical, Tokyo) equipped with a needle thermo-sensor (TOG203-143B, Unique Medical) immediately before, and 30 and 60 min after the initiation of heating.

Low-intensity exercise

All subjects performed flexion-extension exercise of elbow joint in both the non-dominant and the dominant arms between 30 and 60 min after the initiation of heating procedure. The exercise sessions were consisted of 3 sets (30 repetitions) of exercise against a resistance at less than 30 repetition maximum (RM) with 3 min of rest between each set and were performed 4 days a week for a period of 10 weeks. Low-intensity exercise (LIE) training was performed by the non-dominant arm, which was also heated. On the other hand, only LIE was subjected for the dominant arm.

Measurements

The measurements of isometric torque and the cross-sectional muscle size by computed tomography (CT) were
performed in both arms 1 week before the initiation of study and 3 days after the termination of 10-week training.

Isometric torque: Isometric torque measurements of both hands were performed by using Biodex-System (Biodex Medical Systems, Shirley, NY). Subjects performed a maximum voluntary contraction at 90° of elbow flexion twice, and then extension twice. Each contraction was performed for 5 seconds with 5-second interval.

CT analyses: The CT images were acquired by using Asteion Multi Slice CT (Toshiba Medical Systems Corporation, Otawara, Tochigi, Japan). This measurement was done in both upper arms. Four cross-sectional images with 5-mm thick were obtained at the mid-portion of upper arm with the maximum circumference (100 mm-proximal position from olecranon, 120 kv and 30 mA). The CT images were used for the measurement of cross-sectional area (CSA) of biceps brachii muscle. The CSA was calculated by using SCION image.

Statistical analyses
All data were presented as means±SD. Statistical significance was examined by using one-way ANOVA followed by Scheffe’s post hoc test for muscular temperature and by paired t-test for the maximum isometric torque and CSA. Differences were considered significant at the 0.05 level of confidence.

RESULTS

Muscle temperature
Figure 1 shows the changes in the temperature of biceps brachii muscles in 5 subjects. The mean muscle temperature increased from ~36 to 38°C 30 min after the initiation of heating \((p<0.05)\) and was maintained during the remaining 30-min period.

Maximum isometric torque
The mean maximum isometric torque of biceps brachii muscle in nine subjects is indicated in Figure 2. The mean increase of the maximum isometric torque during the arm flexion in the heated non-dominant arm was 18.4±11.0% after 10-week LIE \((p<0.05)\). However, the maximum isometric torque during flexion did not increase significantly in the unheated dominant arm \((11.5±20.5\%, p>0.05)\). There was no significant increase in the maximum isometric torque during extension in both heated and unheated arms.

Cross-sectional area
Figure 3 showed the representative CT images obtained before and after training in the same subject. Increase in the CSA of biceps brachii muscle in non-dominant arm, with both exercise training and heat-stress, was observed in eight out of nine subjects (Fig. 4). There was no change in one subject, who had the largest CSA of biceps among
Fig. 3. Representative images of the computed tomography obtained from one subject before and after 10-week low-intensity exercise training combined with heat-stress. Hypertrophy of biceps brachii muscle (*) was observed. Abbreviations are the same as in Fig. 2.

Fig. 4. Changes in the cross-sectional area of biceps brachii muscle in each subject in response to the 10 weeks of low-intensity exercise training combined with heat-stress. Abbreviations are the same as in Fig. 2.

Fig. 5. Mean cross-sectional area of biceps brachii muscles. Values are means ± SD. n=9 per group. Abbreviations are the same as in Fig. 2. *: p<0.05.

subjects. Significant increment of the CSA of biceps brachii muscles in the heated non-dominant arm was observed following 10-week LIE (Fig. 5, 7.5±5.5%, p<0.05). However, there was no change in the CSA of the unheated dominant arm (+0.3±4.8%, p>0.05).

DISCUSSION

This study clearly showed that LIE combined with heat-stress induced an increase in the maximum isometric torque and CSA in biceps brachii muscle of human subjects. Evidences strongly indicated that exercise training at the intensity even less than 50% 1 RM could be effective in gaining muscular size and strength when heat-stress is combined. To our knowledge, there is no report regarding the increase of muscle temperature induced by using a heating and steam-generating sheet. The present study demonstrated that the temperature of biceps brachii muscles was increased up to ~38°C by the heating procedure. It is well-known that heat-stress causes an increase in the expression of HSP72. The HSP72 expression in cells is also stimulated by ischemia, protein degeneration, and/or hypoxia. This phenomenon, so-called the heat shock response, could be induced in most cells. The HSP72 may have some protective roles against cellular stress as molecular chaperons. The HSP72 also plays an important role as chaperoning nascent peptides during
translation, in cellular protein transport, and in stability of cellular proteins\textsuperscript{11}. It has been reported that muscle hypertrophy was induced in response to heating at 38°C for more than 45 min in rats\textsuperscript{9}. Further, exercise training generally causes an increase of core body temperature\textsuperscript{11} and of the expression of HSP72 in skeletal muscles\textsuperscript{5,6,25–27}. Therefore, it is suggested that a part of the heat-stress-associated muscle hypertrophy might be dependent on the chaperoning actions of HSP72\textsuperscript{5,14,29}.

On the other hand, it has been also reported that there was no up-regulating of HSP72 expression in skeletal muscles with the colonic temperature in rats at less than 38°C\textsuperscript{8}. It has been generally considered that the up-regulation of HSP72 in cells is induced, when the body temperature is elevated by 3–5°C\textsuperscript{8,12}. However, the muscular temperature might be still less than the threshold for stimulation of HSP72 expression, even if the environmental temperature is elevated to 38°C for 60 min. In the present study, there was no information regarding the up-regulation of HSP72 expression, because it was not investigated. It has been also suggested that the up-regulation of HSPs may not play the key role for the heat-stress-associated muscle hypertrophy induced by exposure to 38°C\textsuperscript{9}.

Effectiveness of LIE in this study disagrees with the established principle for programming resistance exercise, because it has been generally believed that an intensity lower than 65% 1 RM is not useful for gaining muscular size and strength\textsuperscript{17}. The present study also confirmed that no significant increases in the maximum isometric torque in flexion and mean CSA of biceps brachii muscle were induced by LIE alone (Figs. 2 and 5). Muscle size (CSA of biceps brachii muscle) and strength (maximum isometric torque) were significantly increased following LIE combined with heat-stress. Hypertrophy of cultured muscle cells was also observed when both stretch and heat-stress were applied\textsuperscript{5,20}. It has been also reported that heat stress–related enhancement of muscle weight was due to the increased protein contents\textsuperscript{20}, because there was no change in the water contents. Heat stress–associated muscle hypertrophy may also be caused by the increments in the CSA of each muscle fiber\textsuperscript{20}. The data suggested that the heat-stress stimulated the exercise-induced intracellular signaling(s) contributing the protein synthesis.

Effect of heat-stress or LIE alone on muscular size and strength was not investigated in the present study. Therefore, it is unclear whether the increases in the maximum isometric torque and CSA in the trained non–dominant upper arm were due to LIE and/or heat-stress per se. However, LIE with heat-stress clearly caused the increase of muscular size and strength. These observations suggest that heat–stress may enhance the exercise–induced muscular hypertrophy by activating the protein synthesis.

CONCLUSION

The LIE combined with heat-stress induced an increase in the maximum isometric torque and CSA of biceps brachii muscle of human subjects. Evidences obtained from this study strongly suggest that heat-stress might be a useful countermeasure for prevention of muscular atrophy during space flight and/or long-term bed rest. Its application could be also extended to rehabilitation.

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