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Low-Intensity Exercise with Blood Flow Restriction Increases Muscle Strength without Altering hsCRP and Fibrinogen Levels in Healthy Subjects

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Abstract

Strengthening exercise combined with blood flow restriction potentially increases muscle strength. This type of exercise does not require heavy weight liftings and is a feasible method to be performed by persons suffering illnesses. However, strengthening exercise may induce inflammatory responses due to muscle and vascular endothelial damage. This study aimed to investigate alterations of high-sensitivity C-reactive protein (hsCRP) and fibrinogen levels in healthy subjects after five weeks of low intensity resistance training (LIRT) with blood flow restriction (BFR) on increasing strength in comparison with high intensity resistance training (HIRT) and LIRT alone, and to evaluate aspects related to the relative safety of LIRT + BFR. Eighteen healthy subjects were randomized into 3 groups. The HIRT group: 70% of One-Repetition Maximum (1-RM); LIRT + BFR group: 30% of 1-RM with BFR (a modified 13-cm wide cuff was used); LIRT group: 30% of 1-RM. The peak torque of isokinetic contraction of the left elbow flexor in each subject was measured before and after 5 weeks of resistance exercises to determine any increases in the left biceps brachii muscle strength. Blood markers of homeostasis (fibrinogen) and inflammation (hsCRP) were also measured before and after five weeks of training. Significant increases of strength were demonstrated between the five weeks of resistance exercises in the HIRT group ($P = 0.003$) and the LIRT + BFR group ($P = 0.001$). Peak torque of isokinetic contraction of the left flexor elbow joint at 60° per second angular velocity showed that the LIRT + BFR group produced the greatest peak torque increase than the HIRT group. There were no significant changes in the hsCRP levels in all the groups ($P > 0.05$) after five weeks of intervention. No significant differences of fibrinogen levels were found in the HIRT group ($P = 0.500$) and the LIRT + BFR group ($P = 0.405$), but significant decreases were found in the fibrinogen levels in the LIRT group ($P = 0.017$). The LIRT + BFR increases in the muscle strength were as significant as in HIRT without altering the fibrinogen and hsCRP levels in the healthy subjects. In this study, LIRT + BFR showed increase muscle strength without any vascular problems.

Key Words: blood flow restriction, fibrinogen, hsCRP, muscle strength, resistance training

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Introduction

Resistance exercise is recommended to prevent age-induced muscular degeneration that could reduce activities of daily living (ADLs). According to the guideline of American College of Sports Medicine, training intensity greater than 70% of the one-repetition maximum load (1-RM) can generate muscular adaptation (4). However, high-intensity resistance exercises should be prescribed carefully, especially for the elderly and patients with chronic diseases, particularly cardiovascular diseases. It has been reported that high-intensity resistance training (HIRT) (>65% 1-RM) markedly increases both the systolic and diastolic systemic blood pressure and amplifies the risk of injury (4, 16). Furthermore, aerobic training alone cannot maintain muscle volume and strength. Hence, resistance exercise is recommended to prevent the degenerative loss of skeletal muscle along with age advancement and metabolic syndrome.

A 2005 study originally developed by Yoshiaki Sato showed that low-intensity exercise, when applied with restriction of muscle blood flow, induced muscle hypertrophy and led to strength increase (10). Almost all of the studies on low-intensity resistance training (LIRT) combined with the application of blood flow restriction (BFR) used pneumatic cuff with a 3-cm width for upper extremities and 5 cm for lower extremities. This type of exercise has been widely used in healthy subjects and athletes and has also been applied to conditions such as orthopedic diseases, obesity and diabetes.

Further evidence has revealed that BFR training leads to muscle hypertrophy and strength increase as effectively as does high-intensity resistance exercise, but little attention has been given to impact of BFR training on vascular function (4). Several studies reported that the pressurization of blood vessels may cause the formation of thrombus, and may, thus, induce microvascular occlusion even after releasing the blood flow restriction, resulting in muscle-cell damage and necrosis (6, 10). Detailed reports on the side effects of Kaatsu training have not been available, and evidence establishing a relationship between resistance training and inflammation is limited. Park and Lakata and Yasuda *et al.* reported that low-intensity squatting and knee extension with BFR in thirty women aged 61-86 years showed gains in quadriceps MRI-measured muscle cross-sectional area (CSA) and strength, while no decrease in vascular function was found (11, 18). On the other hand, another study reported that acute elevation of blood pressure during resistance exercise altered the arterial structure, resulting in arterial stiffness due to the increased damage caused by reactive hyperemic blood flow (18). However, another study reported that resistance exercise does not affect flow-mediated dilation (FDM) but increases brachial artery vessel diameter and post-occlusion blood flow (4). It is still unclear and controversial whether resistance exercise increases arterial stiffness and diminish endothelial function.

Fibrinogen and high-sensitivity C-reactive protein (hsCRP) are novel risk factors which strongly predict the risk of cardiovascular diseases (1). Fibrinogen is a soluble glycoprotein that acts as a precursor of the fibrin monomer, the primary fibrillar protein involved in clot formation. Fibrinogen is also an important mediator of atherosclerosis. It is produced in the liver, binds to GP1b and GP2b/3a receptors of platelets and stimulates adhesion and aggregation of platelets (1, 2, 17). C-reactive protein is an acute phase protein, which induces expression of pro-inflammatory cytokines including intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6), and decreases the expression of nitric oxide synthase. Inflammatory response stimulates the transfer of fibrinogen and fibrin molecules to the intima (3, 14).

Several studies have demonstrated that LIRT + BFR walking dramatically leads to muscle hypertrophy and strength gain that equal to those of high intensity training although the effects on vascular functions are still unclear (4). There is not enough research on the chronic effects of resistance exercises on levels of fibrinogen and hsCRP. A concern of thrombosis has been suggested because resistance exercise is performed with restricted venous blood flow and pooling of blood in extremities (14, 16). Therefore, to discover side effects of resistance exercise, we measured not only the strength but also the blood coagulation and inflammation markers.

The objective of this study is to investigate the alteration of hsCRP and fibrinogen level in healthy subjects after five weeks of LIRT + BFR on increasing strength in comparison with HIRT and LIRT alone. We aimed to test the hypothesis that there is no alteration of hsCRP and fibrinogen levels after five weeks of training in all groups.

Materials and Methods

Participants

Eighteen untrained healthy men aged 26-45 year-old were randomly assigned into three groups: the HIRT, LIRT + BFR and LIRT groups. All participants were selected based on the inclusion crite-

ria of having a normal body mass index (18.5-24.9 kg/m^2), had systolic blood pressure between 110-130 mmHg and diastolic blood pressure between 70-80 mmHg, and were willing to voluntarily participate as subjects. The exclusion criteria were as follows: having done resistance training routinely within at least the past eight months; had a medical history of ischemic heart disease, deep vein thrombosis, and/or peripheral artery disease. All participants were assessed through medical history briefing, physical examination and Ankle Brachial Index (ABI) measurement to screen for peripheral arterial disease (PAD). All participants were asked to avoid intense physical exercise three days before the initial session. Before starting the resistance exercise, all subjects were required to sign a written informed consent form. This research plan was approved by the Ethics Committee, Dr. Soetomo General Hospital, Surabaya.

Exercise Protocols

An isotonic resistance exercise of the left biceps brachii muscle was done using an isotonic pulley machine (EN-TreeM, NR: 0410.301, serial NR: 01343, Enraf-Nonious, Holland) for biceps curl movement. The subjects in the HIRT group were assigned to do a 70% one-repetition maximum (1-RM) intensity exercise, and performed 3 sets of 12 repetitions in each set, and were allowed 2 min of rest period between each set. The exercise intensity for the LIRT group was 30% 1-RM, with 4 sets of 30 repetitions in the first set and 15 repetitions in each second until the fourth set, and a 30-second rest period between each set. The LIRT + BFR group were assigned to the similar exercise intensity as the LIRT group, with a modification of pressured adult sphygmomanometer cuff application on the proximal portion of the exercised limb, 2 fingers below the axilla, during the exercise. A 13-cm wide adult sphygmomanometer cuff was used because the 3-cm wide pneumatic cuff was difficult to obtain in Indonesia. Fifty-mmHg pressure was maintained during the whole exercise including the rest periods between each set. One-RM was determined automatically by the isotonic pulley machine (EN-TreeM).

Resistance exercises were done twice a week for five weeks with at least one day off between each exercise. In order to determine any increase in the isokinetic muscle strength of the left biceps brachii muscle, peak torque of isokinetic contraction of the flexor left-elbow joint in each subject was measured with an isokinetic dynamometer (Cybex®, serial no: A 7718, Henley Healthcare) before the start of the whole exercise regimen and after completion of 5 weeks of resistance exercise.

Twenty-four h before and after completing the 5 weeks of experiments, blood samples were taken from the left brachial vein. To measure fibrinogen levels, blood samples were collected in tubes containing trisodium citrate anticoagulant solution and were incubated at 37°C for 2 min. After adding the Fibri-Pretest Automate reagents, plasma fibrinogen levels were determined by the clotting method of Clauss. Human CRP (hsCRP) levels were determined using an immunoturbidimetric assay, which was composed of human CRP agglutinates with latex particles coated with monoclonal anti-CRP antibodies (CRPHS test with COBAS system).

Statistical Analysis

Results are reported as mean ± standard deviation (SD). The data were analyzed using Shapiro-Wilk normality test. Parametric statistical analyses were performed if the data were normally distributed and non-parametric analyses were performed if the data were abnormally distributed. Two-way ANOVA was used to evaluate the training effects for all dependent variables. *Post hoc* test was performed if any significant main effect was observed. The statistical significance threshold was set at $P < 0.05$.

Results

The characteristics of the subjects of this study are shown in Table 1. There were no significant differences ($P > 0.05$) among all the three groups with regard to age, body mass index (BMI), left ABI, systolic and diastolic blood pressure.

There were increased peak torques of isokinetic contraction observed on the left flexor elbow joint at 60°/s angular velocity in the HIRT group (5.50 ± 2.59 ft-lbs; 27.27%; $P = 0.003$) and the LIRT + BFR group (8.33 ± 2.07 ft-lbs; 2.07%; $P = 0.001$) (Table 2).

There were significant differences in the increase of peak torque between the HIRT and LIRT groups (mean difference 6.95 ft-lbs; $P = 0.001$), between the LIRT + BFR and the HIRT groups (mean difference 2.27 ft-lbs; $P = 0.042$), and between the HIRT with BFR and the LIRT groups (mean difference 9.23 ft-lbs; $P = 0.001$) (Table 3).

There were no significant changes in the hsCRP levels ($P > 0.05$) in all three groups over the duration of intervention (Table 4). However, after the intervention, there were significant differences in the hsCRP levels between the LIRT and HIRT groups (mean difference -2.45 mg/l; $P = 0.004$) and between the LIRT and the LIRT + BFR groups (mean

Table 1. Characteristics of subjects.

Characteristics	HIRT (n = 6)	LIRT + BFR (n = 6)	LIRT (n = 6)	*P* value
Age (years)	33.33 ± 3.14	33.00 ± 3.10	31.00 ± 2.20	0.334
BMI (kg/m^2)	22.57 ± 1.48	23.25 ± 0.80	20.98 ± 1.67	0.090
Ankle Brachial Index	1.11 ± 0.58	1.13 ± 0.60	1.11 ± 0.61	0.801
Systolic blood pressure (mmHg)	120.83 ± 2.04	120.83 ± 2.04	118.33 ± 4.08	0.284
Diastolic blood pressure (mmHg)	78.33 ± 4.08	79.17 ± 2.04	75.00 ± 5.48	0.268

HIRT, high intensity resistance raining; LIRT, low intensity resistance training; BFR, blood flow restriction.

Table 2. Peak torque of isokinetic muscle contraction of left flexor elbow joint at 60°/s angular velocity before and after 5 weeks of resistance exercise.

Exercise groups	Before RE (ft-lbs)	After RE (ft-lbs)	Increase of peak torque (ft-lbs)	*P* value
HIRT	20.17 ± 5.95	25.67 ± 7.06	5.50 ± 2.59[a]	0.003*
LIRT + BFR	17.50 ± 6.25	25.83 ± 5.23	8.33 ± 2.07[b]	0.001*
LIRT	16.67 ± 2.58	17.33 ± 2.58	0.67 ± 1.75[c]	0.394

RE, resistance exercise; HIRT, high intensity resistance raining; LIRT, low intensity resistance training; BFR, blood flow restriction; ft-lbs, foot-pound. *$P < 0.05$.

Table 3. Comparison of the increase of left elbow joint peak torque 60°/s angular velocity among the 3 groups.

Group	HIRT (ft-lbs)	LIRT + BFR (ft-lbs)	LIRT (ft-lbs)
HIRT	-	-2.27 (P = 0.042*)	6.95 (P = 0.001*)
LIRT + BFR	2.27 (P = 0.042*)	-	9.23 (P = 0.001*)
LIRT	-6.95 (P = 0.001*)	-9.23 (P = 0.001*)	-

See footnote to Tables 1 & 2. *$P < 0.05$.

Table 4. hs-CRP levels before and after 5 weeks of resistance exercise.

	hs-CRP (mg/l) before RE	hs-CRP (mg/l) after RE	hs-CRP level difference (mg/l)	*P* value
HIRT	1.65 ± 1.30	2.87 ± 2.47	1.22 ± 1.41	0.088
LIRT + BFR	9.35 ± 11.16	1.58 ± 0.78	-7.77 ± 10.43	0.128
LIRT	3.15 ± 3.93	2.17 ± 2.17	-0.98 ± 1.89	0.075

See footnote to Tables 1 & 2. hs-CRP, high-sensitivity C-reactive protein.

Table 5. The difference of hs-CRP levels after 5 weeks of resistance exercise among the 3 groups.

Group	HIRT (mg/l)	LIRT + BFR (mg/l)	LIRT (mg/l)
HIRT	-	0.16 (P = 0.777)	2.45 (P = 0.004*)
LIRT + BFR	-0.16 (P = 0.777)	-	2.29 (P = 0.005*)
LIRT	-2.45 (P = 0.004*)	-2.29 (P = 0.005*)	-

See footnote to Tables 1 & 2. *P < 0.05.

Table 6. Comparison of hsCRP levels difference before and after resistance exercise among the 3 groups.

Group	HIRT (mg/l)	LIRT + BFR (mg/l)	LIRT (mg/l)
HIRT	-	9.21 (P = 0.066)	-0.94 (P = 0.864)
LIRT + BFR	-9.21 (P = 0.066)	-	-10.16 (P = 0.084)
LIRT	0.94 (P = 0.864)	10.16 (P = 0.084)	-

See footnote to Tables 1 & 2.

Table 7. Fibrinogen levels before and after 5 weeks of resistance exercise.

	Fibrinogen levels before RE (ng/ml)	Fibrinogen levels after RE (ng/ml)	Fibrinogen levels difference	P value
HIRT	339.67 ± 37.33	323.33 ± 67.86	-16.33 ± 57.88	0.500
LIRT + BFR	306.50 ± 112.43	258.83 ± 63.40	-47.67 ± 128.54	0.405
LIRT	306.83 ± 43.90	266.67 ± 24.50	-40.17 ± 28.16	0.017*

See footnote to Tables 1 & 2. *P < 0.05.

Table 8. Comparison of fibrinogen levels difference before and after resistance exercise among the 3 groups.

Group	HIRT (ng/ml)	LIRT + BFR (ng/ml)	LIRT (ng/ml)
HIRT (ng/ml)	-	29.59 (P = 0.575)	-1.36 (P = 0.983)
LIRT + BFR (ng/ml)	-29.59 (P = 0.575)	-	-30.95 (P = 0.621)
LIRT (ng/ml)	1.36 (P = 0.983)	30.95 (P = 0.621)	-

See footnote to Tables 1 & 2.

difference -2.29 mg/l; P = 0.005) (Table 5). However, there were no significant differences in the comparison of changes of the hsCRP levels before and after intervention among the three groups (Table 6).

Fibrinogen levels were not affected in the HIRT (P > 0.05) and LIRT + BFR groups (P > 0.05), but a significant decrease was observed in the LIRT group (-40.17 ng/ml ± 28.16; 13.09%; P = 0.017) (Table 7). The changes of fibrinogen levels were not significant between groups (Table 8). Figure 1 showed significant changes were observed in peak torque of HIRT and LIRT + BFR groups. No significant decrease was observed in fibrinogen levels

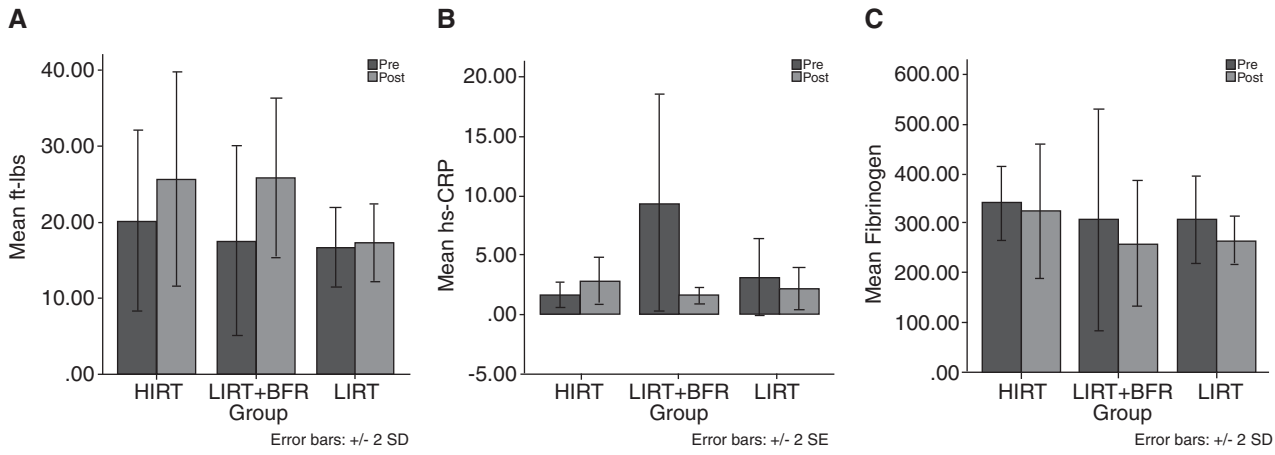

Fig. 1. Changes in peak torque of isokinetic muscle contraction (A), hs-CRP levels (B) and fibrinogen levels (C). Values depicted are data from before (dark colour bars) and after 5 weeks (light colour bars) of the experiments with RCT pre and post designed study.

in LIRT group, but no significant changes in HIRT and LIRT + BFR groups.

Discussion

This study showed that applying BFR during LIRT yielded strength increase in the left biceps brachii muscle in healthy subjects as satisfactorily as HIRT alone did. In addition, this study showed that LIRT combined with BFR increased muscle strength better than LIRT alone. To apply the compression, 50 mmHg-pressured cuffs were used that had less effects on arterial blood flow. Our data are consistent with the report of Kubota *et al*. that 50 mmHg external compression alone without resistance exercise, performed five sets twice a day for 14 days in the lower extremity, reduced muscular weakness (7).

Previous studies have reported that the accumulation of intramuscular stress metabolites such as depletion of phosphocreatine, an increase in inorganic phosphate and lactate, decrease in muscle pH, and also reactive hyperemic blood-induced anabolic signaling muscle hypertrophy (18). Sugiarto *et al*. reported that HIRT and LIRT + BFR induced biceps muscle hypertrophy and increased muscle strength (15). Furthermore, LIRT + BFR may stimulate the mammalian target of rapamycin complex 1 (mTORC1) and mitogen-activated protein kinase (MAPK)-mediated anabolic signaling (4, 12, 13). Evidence suggests that the hypoxic environment created during BFR may increase the activation and proliferation of myogenic stem cells, thus enhancing the hypertrophic response (13, 18).

In a clinical RCT study, Sumide *et al*. reported the results of exercise regimen that consisted of 20% 1-RM of straight leg-raising and hip-joint adduction, and maximum intensity of abduction training, which were all performed three times a week over an 8-week period; the total muscle work increased significantly in the 50 and 150 mmHg pressure groups ($P < 0.05$ and $P < 0.01$, respectively) (16). Cuff pressure may occlude venous return and causes the blood flow to become turbulent, resulting in the enhanced metabolic stress and fast-twitch fiber recruitment in skeletal muscle. In this study, both HIRT and LIRT + BFR increased the muscle strength but it is currently not known whether the mechanisms of strength increase in both groups are the same until further investigation is conducted. Both the HIRT and LIRT + BFR subjects in this study increased the muscle strength without altering the hsCRP levels, in line with the study reported by Clark *et al*. with BFR applied to the upper leg muscle (2). Madarame *et al*. also reported that applying BFR during LIRT in stable ischemic heart disease patients did not affect exercise-induced changes in markers of haemostasis (D-dimer and FDP) and inflammation (hsCRP) (9). In this study, three experimental sessions were carried out, separated by at least one week between each session. The subjects performed four sets of bilateral knee extension exercise with a load of 20% 1-RM and compression were applied at 200 mmHg using 5 mm-width elastic cuffs. Another cross-sectional study in 2012 demonstrated an inverse relationship between regular physical activity and the serum concentrations of inflammatory markers, and reported that the effects of exercise training on CRP varied with the type of exercise (14).

Hemostatic and inflammatory responses are major concerns for patients with cardiovascular diseases regarding performing strenuous exercise. This study shows that in healthy subjects, HIRT

and LIRT + BFR lead to strength increase without inducing changes in fibrinogen levels. Ischemic reperfusion induced by cuff deflation at the end of BFR stimulates shear stress, followed by greater vasodilatation and enhanced blood flow.

Another study by Madarame *et al.* reported that low-intensity leg press exercise (30% 1-RM) with BFR were insufficient to activate coagulation and markers of the coagulation system (9). In accordance with the previous study, the experiments in this study were also insufficient to elevate fibrinogen levels. However, there is not enough research on the chronic effects of LIRT + BFR on levels of fibrinogen.

An interesting result of this study is that LIRT affected the synthesis of coagulation markers and significantly decreased fibrinogen levels. A previous study reported that LIRT + BFR had not been shown to yield changes in creatine kinase levels as a marker of muscle injury (9). We deduced that low-intensity resistance exercise did not induce enough muscle injury to induce fibrinogen synthesis leading to the observed significant reduction of the fibrinogen levels.

The subjects of this study were male adults that were under no specific medications during the study period. However, these criteria were not extended to the population with higher risk, which included elderly, patients with cardio-respiratory disease, neuromuscular and musculoskeletal problems. Although the results indicated no changes in several markers of coagulation and inflammation, the findings in this study were based on experiment conducted in that population. It is also to be noted that the pre-intervention hsCRP levels were not homogenize so that there were significant differences in the post-intervention hsCRP levels between the LIRT and HIRT groups, and between the LIRT and LIRT + BFR groups although the differences of pre- and post-intervention hsCRP levels were not significant among all groups.

In conclusion, we observed that there was significant increase in muscle strength with 5 weeks of LIRT + BFR in healthy subjects without alteration in variables associated with vascular problems. Future researches are needed to determine whether LIRT + BFR might be used as a prospective alternative strategy for patients who have contraindications to perform HIRT in rehabilitation settings.

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Conflict of Interest

The authors declared no conflict of interest.

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