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Haemostatic and inflammatory responses to blood flow-restricted exercise in patients with ischaemic heart disease: a pilot study

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Summary

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Low-intensity resistance exercise can effectively induce muscle hypertrophy and increases in strength when combined with moderate blood flow restriction (BFR). As this type of exercise does not require lifting heavy weights, it might be a feasible method of cardiac rehabilitation, in which resistance exercise has been recommended to be included. Although previous studies with healthy subjects showed relative safety of BFR exercise, we cannot exclude the possibility of unfavourable effects in patients with cardiovascular disease. We therefore aimed to investigate haemostatic and inflammatory responses to BFR exercise in patients with ischaemic heart disease (IHD). Nine stable patients with IHD who were not taking anticoagulant drugs performed four sets of knee extension exercise at an intensity of 20% one-repetition maximum (1RM) either with or without BFR. Blood samples were taken before, immediately after and 1 h after the exercise session and analysed for noradrenaline, D-dimer, fibrinogen/fibrin degradation products (FDP) and high-sensitive C-reactive protein (hsCRP). Plasma noradrenaline concentration increased after the exercise, and the increase was significantly larger after the exercise with BFR than without BFR. On the other hand, increases in concentrations of plasma D-dimer and serum hsCRP were independent of the condition. However, increases in D-dimer and hsCRP were no longer observed after plasma volume correction, suggesting that hemoconcentration was responsible for these increases. Plasma FDP concentration did not change after the exercise. These results suggest that applying BFR during low-intensity resistance exercise does not affect exercise-induced haemostatic and inflammatory responses in stable IHD patients.

Introduction

Accumulating evidence suggests that low-intensity resistance exercise can effectively induce muscle hypertrophy and increases in strength when combined with moderate blood flow restriction (BFR) of the exercising muscle [reviewed in (Loenneke & Pujol, 2009; Manini & Clark, 2009; Wernbom *et al.*, 2008)]. As this type of exercise does not require lifting heavy weights, it might be a feasible method of cardiac rehabilitation, in which resistance exercise has been recommended to be included (Balady *et al.*, 2007; Pollock *et al.*, 2000).

Safety as well as efficacy is especially important for individuals who have health problems when performing an exercise. A large-scale questionnaire survey in Japan has shown that serious side effects of BFR exercise are extremely rare (Nakajima *et al.*, 2006). In addition, safety issues of BFR exercise, such as muscle damage (Umbel *et al.*, 2009), cardiovascular (Renzi *et al.*, 2010) and haemostatic/inflammatory (Clark *et al.*, 2011) responses, have been studied experimentally in recent years (Loenneke *et al.*, 2011). Most studies, however, were performed with healthy young subjects.

Haemostatic and inflammatory responses are major concerns for patients with cardiovascular disease (CVD) when performing an exercise, because these responses might be related to cardiovascular events observed during and after strenuous exercise (Womack *et al.*, 2003). A single bout of BFR exercise has been shown to evoke favourable responses in healthy individuals, increases fibrinolytic potential (Clark *et al.*, 2011; Nakajima *et al.*, 2007) without affecting coagulation (Clark *et al.*, 2011; Fry *et al.*, 2010; Madarame *et al.*, 2010a; Nakajima *et al.*, 2007) and inflammatory (Clark *et al.*, 2011) activities.

However, we cannot exclude the possibility of unfavourable responses in patients with CVD. Increased coagulation activity and/or decreased fibrinolytic activity (Bounameaux *et al.*, 1992; Hamouratidis *et al.*, 1988; Held *et al.*, 1997), as well as enhanced inflammatory activity (Held *et al.*, 1997; Kop *et al.*, 2008), have been previously reported after cycle ergometry or treadmill exercise in patients with CVD.

We therefore aimed to investigate haemostatic and inflammatory responses to BFR exercise in patients with CVD. Blood markers of haemostasis [D-dimer and fibrinogen/fibrin degradation products (FDP)] and inflammation [high-sensitive C-reactive protein (hsCRP)] were measured before and after a single bout of low-intensity resistance exercise either with or without BFR in patients with ischaemic heart disease (IHD).

Methods

Patients

Nine stable IHD patients (seven men, two women) who were not taking anticoagulant drugs volunteered to participate in this study. Their mean age, height and body mass were 57 ± 6 years, 165·9 ± 6·7 cm and 67·7 ± 13·7 kg, respectively. Seven of nine patients had been treated with percutaneous coronary intervention (PCI), and the other two had been treated with coronary artery bypass grafting (CABG). The mean elapsed time from surgery was 4 ± 1 years, and none of the patients had organic stenosis after the surgery. They were fully informed about the purpose and experimental procedures of the study and gave their written informed consent prior to participation. This study was approved by the ethics committee of the University of Tokyo Hospital.

Experimental procedure

The patients participated in three experimental sessions separated at least by 1 week. In the first session, one-repetition maximum (RM) of bilateral knee extension exercise was estimated by the 10RM method (Baechle *et al.*, 2000) using a weight stack machine (VR1 13050 Leg Extension; Cybex International Inc., Medway, MA, USA), and a load of 20% 1RM was determined for the second and third sessions. In the second and third sessions, the patients performed four sets of bilateral knee extension exercise with a load of 20% 1RM either with or without BFR. The order of these two conditions was randomly assigned, and five of nine patients exercised with BFR first, whereas the other four exercised without BFR first. In each exercise session, one set of 30 repetitions was followed by three sets of 15 repetitions with 30-s rest between each set (Rossow *et al.*, 2011; Yasuda *et al.*, 2011). The patients were instructed to maintain a cadence of a 1-s concentric phase and a 1-s eccentric phase. Percutaneous oxygen saturation (SpO2) and heart rate were monitored (Onyx I; Nonin Medical Inc., Plymouth, MN, USA) throughout the exercise session by experienced cardiologists. There were no warning signs or symptoms of cardiovascular events, and SpO2 was maintained $\geq$ 94% in all patients (neither a condition × time interaction nor a main effect of time was observed for SpO2). All patients completed the exercise protocol.

When the patients performed the exercise with BFR, the proximal portions of their thighs were compressed at the pressure of 200 mmHg by 50 mm width elastic cuffs (Kaatsu Master; Sato Sports Plaza Co., Ltd., Tokyo, Japan) to restrict venous blood flow. The cuff pressure of 200 mmHg was determined according to previous studies demonstrating endocrine responses (Madarame *et al.*, 2010b; Takarada *et al.*, 2000) or muscle hypertrophy (Takarada *et al.*, 2002) after knee extension exercise with BFR. The cuffs were applied with an initial pressure of 40 mmHg and then inflated to 200 mmHg immediately prior to the start of the exercise. The compression was kept throughout the session including rest periods between sets and was released immediately after the session.

Blood sampling and analysis

The patients rested in a supine position for 30 min before pre-exercise blood collection. Blood samples were obtained before, immediately after and 1 h after the exercise through an indwelling catheter inserted into an antebrachial vein and collected into test tubes with EDTA-2Na, 3·2% sodium citrate, serum separator and EDTA-2K. Test tubes with EDTA-2Na, 3·2% sodium citrate and serum separator were centrifuged (4°C, 1006 **g**) for 10 min, and removed plasma and serum were stored at −80°C until analysis. Test tubes with EDTA-2K were stored at 4°C until analysis.

Blood samples were analysed for haemoglobin (Hb), haematocrit (Hct), noradrenaline, D-dimer, FDP and hsCRP. Hb (g/100 ml) was measured by the cyanomethemoglobin method (Coulter Hemoglobinometer; Beckman Coulter Inc., Brea, CA, USA), whereas Hct was measured by micro-haematocrit using ultracentrifugation. Plasma concentrations of noradrenaline, D-dimer, FDP and serum hsCRP concentration were measured at a commercially available laboratory (SRL Inc., Tokyo, Japan). Plasma noradrenaline concentration was measured from EDTA plasma by high-performance liquid chromatography (HPLC) (Tosoh Corporation, Tokyo, Japan). To reduce the volume of blood drawn, plasma noradrenaline concentration was not measured for 1 h after the exercise. Previous studies with similar protocols have shown that plasma noradrenaline concentration increases immediately after the exercise and returns to pre-exercise value within 30 min (Madarame *et al.*, 2008, 2010b). Plasma D-dimer concentration was measured from 3·2% sodium-citrate plasma by latex turbidimetric immunoassay (LTIA) (LATECLE D-dimer; Kainos Laboratories, Inc., Tokyo, Japan). Plasma FDP concentration was measured from 3·2% sodium-citrate plasma by LTIA (Nanopia P-FDP; Sekisui Medical Co., Ltd., Tokyo, Japan). Serum hsCRP concentration was measured by LTIA

(N-Latex CRP II CardioPhase hsCRP; Siemens Healthcare Diagnostics Inc., Tokyo, Japan). The total coefficients of variation for assays were 8·0% for noradrenaline, 2·0% for D-dimer, 3·4% for FDP and 2·2% for hsCRP. Per cent changes in blood volume (BV) and plasma volume (PV) were derived from the following equation (Dill & Costill, 1974):

$$BV_B/BV_A = Hb_A/Hb_B$$

$$\%\Delta PV = 100 * (Hb_B/Hb_A) * ((1 - Hct_A * 10^{-2})/(1 - Hct_B * 10^{-2})) - 100$$

where *A* is the value at rest (Pre) and *B* is the value after the exercise.

Statistical analysis

Statistical analysis was performed with R 2.12.2 for Windows (R Development Core Team, 2011). Box and whisker plots were used to display the data. The central line of the box represents the median value, whereas the bottom and top of the box represent the 25th and 75th percentiles. Whiskers indicate the lowest and highest values within 1·5 interquartile ranges (IQR). Markers beyond the whiskers are outliers. The data were analysed with a two-factor (condition × time) repeated-measures ANOVA. $P \leq 0{\cdot}05$ was considered significant.

Results

Figure 1 shows heart rate measured at pre-exercise and immediately after each set of the exercise. Although not statistically significant, there was a trend for a condition × time interaction ($F = 2{\cdot}59$, $P = 0{\cdot}055$). In addition, there was a significant main effect of condition ($F = 11{\cdot}96$, $P<0{\cdot}01$) as well as a main effect of time ($F = 27{\cdot}73$, $P<0{\cdot}001$).

Changes in plasma noradrenaline concentration are shown in Fig. 2. Values with uncorrected (a) and corrected (b) for PV changes are shown. There was a significant main effect of time (PV uncorrected: $F = 43{\cdot}15$, $P<0{\cdot}001$; PV corrected: $F = 42{\cdot}85$, $P<0{\cdot}001$) as well as a condition × time interaction (PV uncorrected: $F = 12{\cdot}84$, $P<0{\cdot}01$; PV corrected: $F = 10{\cdot}80$, $P<0{\cdot}05$). Postexercise noradrenaline concentration was significantly higher after the exercise with BFR than after the exercise without BFR (mean difference, 1·04 nmol l^{-1}; 95% confidence interval, 0·37–1·71 nmol l^{-1}; $P<0{\cdot}05$).

Although there was no condition × time interaction ($F = 2{\cdot}09$, $P = 0{\cdot}16$), there was a significant main effect of time for plasma D-dimer concentration ($F = 7{\cdot}80$, $P<0{\cdot}01$) before PV correction (Fig. 3a). Postexercise concentration was significantly higher than pre-exercise concentration independent of the condition (mean difference, 0·07 μg ml^{-1}; 95% confidence interval, 0·04–0·10 μg ml^{-1}; $P<0{\cdot}001$) (Fig. 3a). However, no statistical significance was observed (condition × time interaction: $F = 1{\cdot}20$, $P = 0{\cdot}33$; main effect of time: $F = 0{\cdot}19$, $P = 0{\cdot}83$) after PV correction (Fig. 3b).

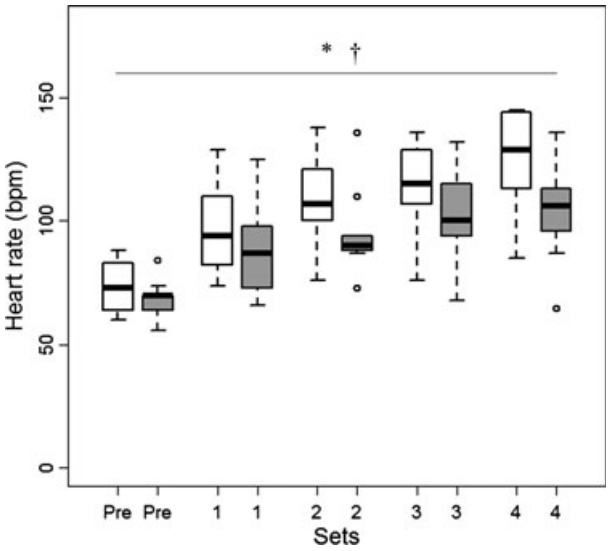

Figure 1 Heart rate measured at pre-exercise and immediately after each set of the exercise with (white box) and without (grey box) blood flow restriction. The central line of the box represents the median value, whereas the bottom and top of the box represent the 25th and 75th percentiles. Whiskers indicate the lowest and highest values within 1·5 interquartile ranges (IQR). Markers beyond the whiskers are outliers. *Main effect of time ($P<0{\cdot}001$). †Main effect of condition ($P<0{\cdot}01$).

Neither a condition × time interaction (PV uncorrected: $F = 1{\cdot}89$, $P = 0{\cdot}18$; PV corrected: $F = 1{\cdot}60$, $P = 0{\cdot}23$) nor a main effect of time (PV uncorrected: $F = 1{\cdot}24$, $P = 0{\cdot}32$; PV corrected: $F = 0{\cdot}42$, $P = 0{\cdot}67$) was observed for plasma FDP concentration (Fig. 4).

For serum hsCRP concentration, although there was no condition × time interaction ($F = 1{\cdot}10$, $P = 0{\cdot}36$), there was a significant main effect of time ($F = 11{\cdot}30$, $P<0{\cdot}001$) before PV correction (Fig. 5a). Postexercise concentration was significantly higher than pre-exercise concentration independent of the condition (mean difference, 51·3 ng ml^{-1}; 95% confidence interval, 28·1–74·6 ng ml^{-1}; $P<0{\cdot}001$) (Fig. 5a). However, these significant differences were no longer apparent (condition × time interaction: $F = 0{\cdot}83$, $P = 0{\cdot}46$; main effect of time: $F = 1{\cdot}95$, $P = 0{\cdot}17$) after PV correction (Fig. 5b).

Discussion

This study showed that applying BFR during low-intensity resistance exercise did not affect exercise-induced changes in markers of haemostasis (D-dimer and FDP) and inflammation (hsCRP) in patients with IHD, although heart rate and plasma noradrenaline concentration were increased. This result suggests that low-intensity resistance exercise with BFR would be relatively safe for patients with IHD, at least in terms of haemostatic and inflammatory responses.

In this study, D-dimer concentration increased significantly after the exercise independent of the condition (with or without BFR). This increase, however, is no longer observed after PV

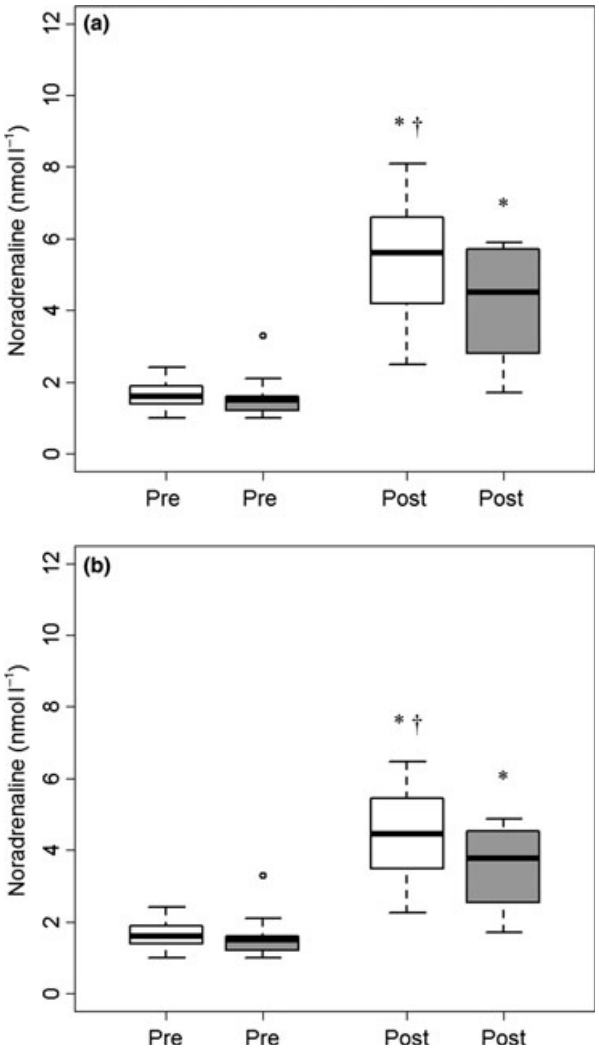

Figure 2 Plasma noradrenaline concentration measured before (Pre) and after (Post) the exercise with (white box) and without (grey box) blood flow restriction. Values with uncorrected (a) and corrected (b) for plasma volume changes are shown. The central line of the box represents the median value, whereas the bottom and top of the box represent the 25th and 75th percentiles. Whiskers indicate the lowest and highest values within 1·5 interquartile ranges (IQR). Markers beyond the whiskers are outliers. *Significantly different from pre-exercise ($P<0·001$). †Significantly different from the other condition ($P<0·05$).

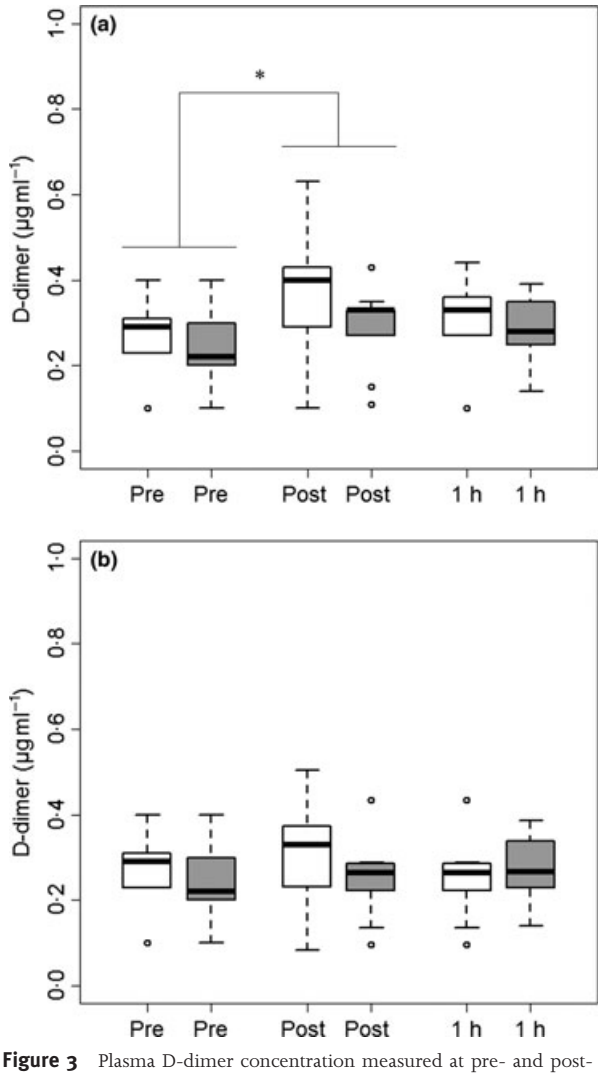

Figure 3 Plasma D-dimer concentration measured at pre- and post-exercise, and 1 h after the exercise with (white box) and without (grey box) blood flow restriction. Values with uncorrected (a) and corrected (b) for plasma volume changes are shown. The central line of the box represents the median value, whereas the bottom and top of the box represent the 25th and 75th percentiles. Whiskers indicate the lowest and highest values within 1·5 interquartile ranges (IQR). Markers beyond the whiskers are outliers. *Significant difference between pre- and postexercise, independent of the condition ($P<0·001$).

correction (Dill & Costill, 1974), so that increase would be attributed to hemoconcentration (Fall *et al.*, 2011). It is therefore unlikely that intravascular clot formation was stimulated by the exercise in this study. In addition, even if PV correction was not performed, the values of D-dimer concentration were still within a clinically normal range. This result is in line with previous studies reporting that plasma D-dimer concentration was not affected by low-intensity resistance exercise with BFR in healthy young (Clark *et al.*, 2011; Madarame *et al.*, 2010a; Nakajima *et al.*, 2007) and elderly (Fry *et al.*, 2010) subjects.

Statistical outliers should not be ignored especially when assessing clinical safety. For example, although FDP concentration did not change statistically, one of the patients showed a fourfold increase in FDP concentration after the exercise with BFR. In this patient, however, the increase in D-dimer concentration was slight, and D-dimer/FDP ratio decreased from 0·2 to 0·06. This indicates that the FDP increase was not due mainly to secondary fibrinolysis (breakdown of an intravascular clot) but to primary fibrinolysis (breakdown of fibrinogen) (Sato *et al.*, 1995), because the FDP assay detects both fibrinogen and fibrin degradation products, whereas the D-dimer assay is specific for cross-linked fibrin (Boisclair *et al.*, 1990; Levi & Meijers, 2011), the main component of the intravascular clot. In fact, low-intensity

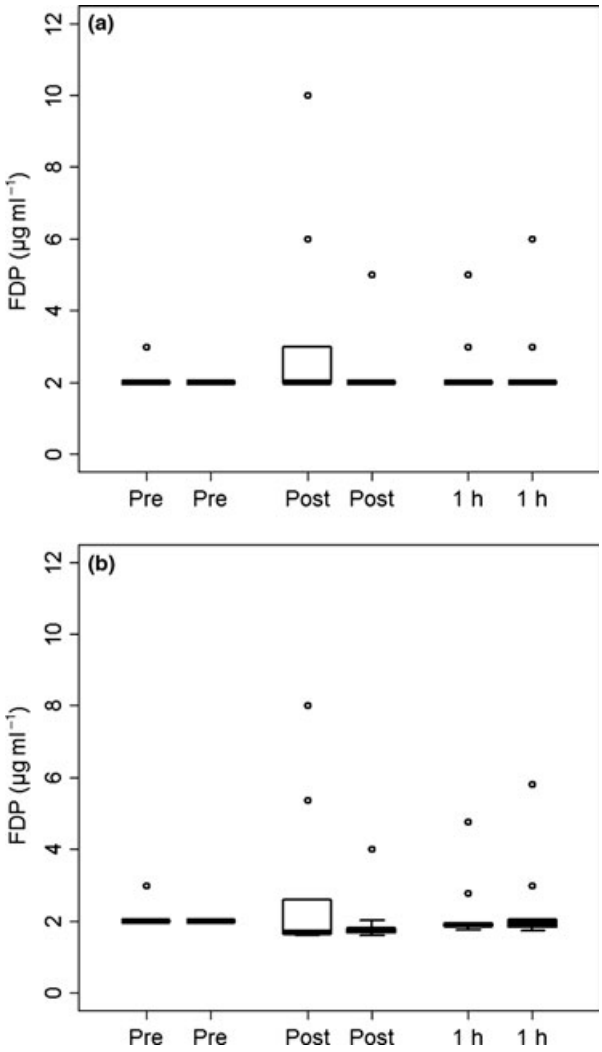

Figure 4 Plasma fibrinogen/fibrin degradation products (FDP) concentration measured at pre- and postexercise, and 1 h after the exercise with (white box) and without (grey box) blood flow restriction. Values with uncorrected (a) and corrected (b) for plasma volume changes are shown. The central line of the box represents the median value, whereas the bottom and top of the box represent the 25th and 75th percentiles. Whiskers indicate the lowest and highest values within 1·5 interquartile ranges (IQR). Markers beyond the whiskers are outliers.

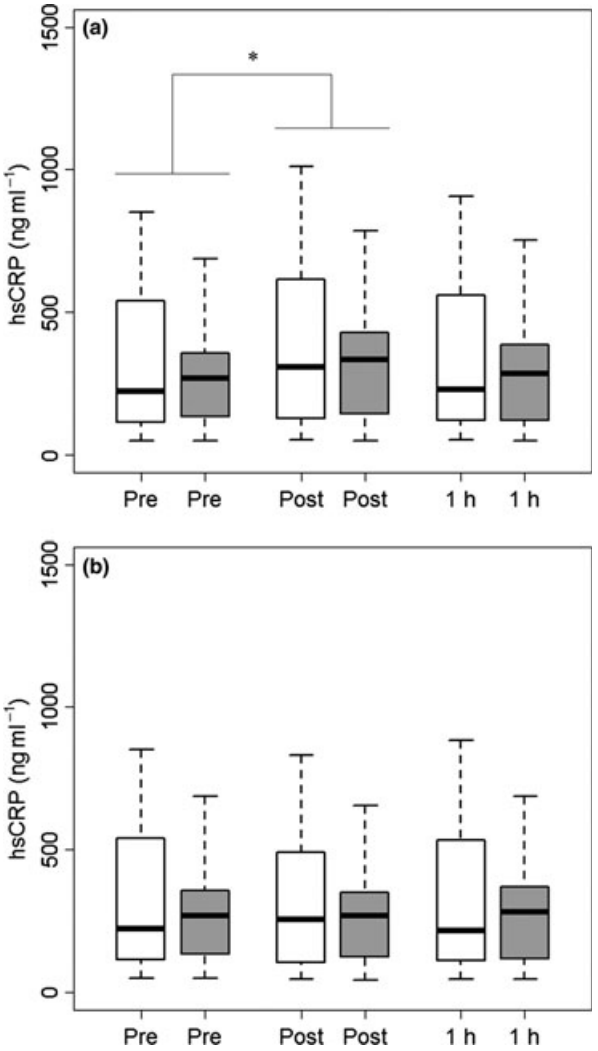

Figure 5 Serum high-sensitive C-reactive protein (hsCRP) concentration measured at pre- and postexercise, and 1 h after the exercise with (white box) and without (grey box) blood flow restriction. Values with uncorrected (a) and corrected (b) for plasma volume changes are shown. The central line of the box represents the median value, whereas the bottom and top of the box represent the 25th and 75th percentiles. Whiskers indicate the lowest and highest values within 1·5 interquartile ranges (IQR). Markers beyond the whiskers are outliers. *Significant difference between pre- and postexercise, independent of the condition ($P<0·001$).

resistance exercise with BFR has been shown to enhance fibrinolytic potential, assessed by tissue plasminogen activator (tPA) activity, without affecting the coagulation activity in healthy subjects (Clark *et al.*, 2011; Nakajima *et al.*, 2007).

Although serum hsCRP concentration increased significantly after the exercise independent of the condition, the increase was no longer apparent after PV correction. This observation was similar to that in the plasma D-dimer concentration, and we also assume that hemoconcentration was responsible for the hsCRP increase. This result along with the previous study in healthy subjects (Clark *et al.*, 2011) suggests that low-intensity resistance exercise with BFR does not acutely stimulate CRP production in healthy individuals or patients with IHD. However, these studies might fail to detect changes in serum hsCRP concentration because of the timing of blood collection (up to 1 h after the exercise). For example, Mendham *et al.* (2011) reported that plasma hsCRP concentration increased 24 h after a single bout of whole-body resistance exercise. In that study, they also reported that plasma concentration of interleukin-6 (IL-6), the principal regulator of CRP synthesis (Ganapathi *et al.*, 1991; Volanakis, 2001), increased immediately after the exercise (Mendham *et al.*, 2011). Although IL-6 was not measured in the present and previous (Clark *et al.*, 2011) studies, plasma IL-6 concentration has been shown to

be increased by a single bout of low-intensity resistance exercise with BFR (Takarada *et al.*, 2000). However, this increase in IL-6 might be due to an increased demand for energy from muscle cells, because it has recently been suggested that muscular IL-6 is related to metabolism rather than to inflammation and works as an energy sensor (Pedersen, 2012).

This study indicates a relative safety of low-intensity resistance exercise with BFR in patients with IHD. However, there are limitations to this study which must be considered in interpreting the results. First, the amount of restricted blood flow might be different between patients. In this study, all patients were applied the same cuff pressure of 200 mmHg according to previous studies (Madarame *et al.*, 2010b; Takarada *et al.*, 2000, 2002). However, the degree of BFR would be affected by several factors such as blood pressure and the amount of tissue surrounding the vasculature. In fact, a recent study has shown that thigh circumference is the largest determinant of arterial occlusion pressure (Loenneke *et al.*, 2012). Second, this study is only a pilot study with a small number ($N = 9$) of stable IHD patients. The result of this study cannot be transferred to unstable IHD patients. In addition, this study along with previous studies shows that BFR increases cardiac work (Abe *et al.*, 2006; Renzi *et al.*, 2010) and/or plasma noradrenaline (Madarame *et al.*, 2008; Takano *et al.*, 2005) during and after a single bout of exercise. Therefore, it should still be cautious to prescribe BFR to patients with IHD.

In conclusion, this pilot study demonstrated that applying BFR during low-intensity resistance exercise did not affect exercise-induced changes in markers of haemostasis (D-dimer and FDP) and inflammation (hsCRP) in stable IHD patients, although heart rate and plasma noradrenaline concentration were increased. This result suggests that low-intensity resistance exercise with BFR would be relatively safe for stable IHD patients, at least in terms of haemostatic and inflammatory responses.

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