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DOES FOUR LIMB COMPRESSION MIMIC THE EFFECTS OF EXERCISE?

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ABSTRACT

DOES FOUR LIMB COMPRESSION MIMIC THE EFFECTS OF EXERCISE? **Tom R. Thomas, Danny Whiteman, John Q. Zhang, Kevin L. Fritsche, Heidi L. Messimer, Richard H. Cox, Darla B. Hess, Bryan K. Smith, Thomas P. Lafontaine.** JEP^{online}. 2002;5(1):32-41. In order to assess the cardiovascular response to four limb compression, 12 healthy middle-aged men and women and eight cardiac patients undertook compression treatment for 15 days. The two groups responded similarly to both a single session of compression and 15 days of compression therapy. Heart rate and cardiac output were not significantly affected by either a single session or 15 days of compression treatment. Systolic and diastolic blood pressure were increased during a compression session, and nitric oxide concentration was decreased. Blood pressure and prostacyclin decreased after 15 days of compression therapy, but nitric oxide and fibrinolytic markers were not affected. These results suggest that the blood pressure response to limb compression is similar to mild exercise. Nitric oxide and prostacyclin change in opposite directions with compression compared to that previously shown with exercise.

Key Words: Cardiovascular, Heart Rate, Blood Pressure, Nitric Oxide

INTRODUCTION

The application of external compression to the limbs has been used for many years to improve cardiovascular function (1,2,3,4). Researchers and clinicians have used pneumatic compression instruments to apply intermittent pressure to the limbs to improve hemodynamics and to prevent deep vein thrombosis after surgery (1,2). Intermittent pneumatic compression has been sequenced such that the pressure was applied from the distal to the proximal parts of the limb. The wave-like action elicited higher peak venous velocities over the standard compression technique (3). In general, the authors of previous studies have shown improved cardiodynamics using compression (1,2,3).

More recently, the mechanism of the thrombolytic effect of intermittent limb compression has been evaluated.

For example, using 90 second phases of inflation and deflation, Tarnay et al. (2) reported that euglobulin lysis time decreased. Jacobs et al. (4) confirmed the euglobulin lysis time effect and also found that tissue plasminogen activator increased suggesting greater thrombolysis with compression (4). This improved thrombolysis also has been demonstrated with a session of moderate exercise (5).

Another potential effect of limb compression is the stimulation of vasoactive substances from the endothelium caused by the increased shear stress. Results from exercise studies suggest that sheer stress can increase prostacyclin (PGI₂) and nitric oxide (NO) production (6,7). Data from Guyton et al (8) demonstrated that in surgical patients a session of single limb compression with inflation durations of 12 s increased the plasma concentration of the PGI₂ metabolite, 6-keto-prostaglandin F1alpha, (6-keto-PGF_{1α}). This response suggested that similar to shear stress induced by exercise, the sheer stress from limb compression also causes the release of vasoactive substances from the endothelium. On the other hand, Kessler et al. (9), found little change in 6-keto-PGF_{1α} following 13 weeks of sequential compression treatment using 11 second inflation cycles. No published studies were found in which NO was measured with compression treatment in humans. It is possible that the increased blood flow found with limb compression could mimic the effect of exercise on NO activity.

Although numerous studies have used compression in patients with heart disease, the purpose for this treatment was to prevent coagulation or angina symptoms (1,10). However, this population may at times be unable to exercise, and limb compression may serve as a short-term substitute for exercise therapy. Therefore, the purpose of this study was to assess the acute and chronic effect of intermittent, sequential compression on cardiac, thrombolytic, and vasoactive parameters in apparently healthy men and women, and in cardiac patients. We hypothesized that limb compression would improve indices of cardiac and vasoactivity function to a lesser degree than previously reported with exercise, and that the effect of compression would be magnified in the cardiac patients vs. controls.

METHODS

Subjects

Twenty subjects were recruited for this study including eight middle-aged subjects with previous coronary artery disease (4 females and 4 males), and 12 healthy controls (7 females and 5 males), with a mean age of 59.8±6.9 years and ranging from 47 to 70 years (Table 1). The cardiac subjects had normal left ventricular function with an ejection fraction of 55% or higher, and no significant valve-related regurgitant lesions. Patients with significant stenotic lesions or prosthetic valves were not included. Members of the cardiac group had a previous myocardial infarction or had undergone coronary artery bypass surgery or percutaneous coronary intervention. The mean time since an infarction and/or surgery for the cardiac subjects was 25.5 months. Neither controls or cardiac patients were on any anti-coagulant or vasodilating drugs, except most patients were taking coated aspirin daily. Subjects were also free from painful arthritic conditions. All cardiac patients were taking a β-receptor blocker.

Table 1. Subject characteristics.

	<i>Females</i>	<i>Healthy Females</i>	<i>Cardiac Females</i>	<i>Males</i>	<i>Healthy Males</i>	<i>Cardiac Males</i>	<i>All Subjects</i>
<i>Age (y)</i>	57.6±7.3	54.7±5.8	62.8±7.5	62.4±6.2	60.0±7.5	65.5±2.4	59.8±7.1
<i>Weight (kg)</i>	69.5±17.7	72.7±20.8	64.0±10.7	87.7±16.6	95.2±18.8	78.3±6.9	77.7±19.1
<i>Height (cm)</i>	164.2±6.2	166.4±4.6	160.3±7.4	177.3±6.7	181.4±6.1	172.3±3.0	170.1±9.2

For control subjects, individuals were recruited who were apparently healthy, non-smokers, with no history of cardiovascular disease (Table 1). All subjects in both groups were performing mild to moderate aerobic

exercise 3-4 times/week.

Limb Compression

Each subject underwent 15 consecutive days of compression treatment using a compression instrument (Noninvasive Circulation Enhancer, Inc., Riverdale, NY). The subject sat in the instrument in a semi-reclining position, and plastic cuffs were placed on the entire length of the arms and legs. The compression cycle consisted of inflation and deflation cycles of 2 lbs/in² (approximately 100 mmHg). The cycles alternated between starting the inflation cycle in the arms or in the legs. For example, when the inflation cycle began with the legs, the cuffs in the legs inflated and then after 20 seconds, the arm cuffs inflated. Then both remained inflated for another 65 seconds. At that time, the leg and arm cuffs deflated and remained deflated for 20 seconds, and the cycle began again starting with the arms. Each participant received 45 min of compression treatment each day for 15 days. On days 1 and 15, data was collected on each subject before compression and near the end of the session (cardiac parameters), or after the session (blood parameters) of compression treatment.

Testing protocol

Prior to testing, each subject completed health history, medical, and activity questionnaires. The project was approved by the University Health Science Center Institutional Board, and each subject provided informed written consent.

Each subject was instructed to avoid caffeine, aspirin, and exercise the day of the testing. Electrodes were placed at the root of each side of the neck, and on each side of the thorax even with the xiphoid at the mid-axillary line, according to manufacturer instructions. The electrodes were used with a thoracic bioelectrical impedance analysis recorder (BioZ version 1.54, CardioDynamics Corp., San Diego CA) to measure heart rate (HR) and cardiac output (CO). This procedure has been validated previously and compared favorably to the Fick method (11). The subject then rested for 10 minutes, after which blood pressure was measured using a wrist digital blood pressure monitor (Omron, Vernon Hills, IL).

Following the rest period, blood was collected by vena puncture into a vacutainer containing sodium citrate which was used to measure prothrombin time, activated partial thromboplastin time, and fibrinogen. The samples were centrifuged at 7,500 rev/min for 3 min and plasma extracted. A second vacutainer contained EDTA and was collected for use in measuring 6-keto-PGF_{1 α} and NO. Indomethacin was added to the blood used to measure 6-keto-PGF_{1 α} in order to inhibit any further synthesis of PGI₂. The samples were centrifuged at 1,500 g for 15 min to separate plasma, which was subsequently stored in a -70°C freezer until analysis.

After resting data collection, the compression treatment began. HR, and CO data were collected throughout the 45 minutes treatment and the mean of the last 15 min used as the late compression values. At 40 min, one of the arm compression sleeves was removed from the subject, and blood pressure was measured during a compression cycle. Immediately at the end of the 45 min, the compression was stopped, and blood was drawn in the previously described manner. The compression treatments on days 2 through 14 were conducted without data collection.

Blood analysis

The fibrinolytic measures (prothrombin time, partial thromboplastin time, and fibrinogen) were analyzed in the coagulation lab at the University Hospital using an automated analyzer (model STA, Diagnostica Stago, Asnieres France). This instrument measures clotting times based on changes in plasma viscosity following various additives to the plasma: rabbit cerebral thromboplastin for prothrombin, cephalin and silica for thromboplastin, and human calcium thrombin for fibrinogen.

NO was measured using a commercially available kit (Oxford Biomedical Research, kit number NB 88, Oxford, MI). Briefly, cadmium beads were used to convert nitrate into nitrite, and after deproteination of the plasma by

zinc sulfate, Griess reagent was added, causing the sample to turn a purple shade in the presence of nitrite which allowed for the colorimetric measurement. Prostacyclin was measured by its stable metabolite, 6-keto-PGF_{1α}, using a commercially available enzyme immunoassay kit (Cayman Chemical, kit number 515211, Ann Arbor, MI). Briefly, a known amount of acetylcholinesterase-labeled 6-keto-PGF_{1α} was added as a tracer, and the sample was placed in a rabbit antiserum coated well in which both the labeled and plasma 6-keto-PGF_{1α} bind with the antiserum. Ellman's reagent was added, which contains the substrate for acetylcholinesterase. The product of this enzymatic reaction was measured on a spectrophotometer.

Statistical analysis

Statistical analysis was conducted on each of the parameters using a four way analysis of variance, group x gender x days (1 and 15) x time (pre and post) with repeated measures on days and time using the software program Statistical Analysis System (SAS Institute, Cary NC). These analyses allowed the determination of any acute changes by comparing the pre and post results combined from day 1 and day 15 and also the examination of the chronic changes by comparing results of day 1 to results of day 15. All values are presented as mean±standard deviation (SD).

RESULTS

Cardiac Variables

Except for partial thromboplastin time, there were no gender differences for any of the variables and thus the genders were combined for the presentation of the data. Over all times, CO was not different between the two groups (healthy and cardiac) (Table 2). The patient group tended to have lower HR during the treatment than did the healthy group (p=0.06). The cardiac group did not respond differently to the treatment than the healthy group, i.e., there were no group x time interactions. Acute compression treatment (pre vs. post in session 1 and session 15) caused no significant change in HR or CO, although CO tended to be higher in late compression (p=0.07) (Table 2). Only HR exhibited a chronic effect as it tended to be lower on day 15 vs. day 1 (62.6±10.4 vs 69.0±14.5) (p=0.06).

Table 2: Cardiac output for healthy and cardiac patients.

<i>Cardiac output (l/min)</i>					
	<i>Day 1</i>		<i>Day 15</i>		
	Pre Comp	Late Comp	Pre Comp	Late Comp	All Times
<i>Healthy</i>	7.1±2.8	7.4±2.9	7.2±3.1	7.7±3.2	7.4±3.1
<i>Cardiac</i>	5.3±1.2	5.3±1.1	4.9±1.0	4.9±1.0	5.1±1.2
<i>All subjects</i>	6.3±2.4	6.5±2.5	6.2±2.7	6.5±2.9	
<i>Heart Rate (bpm)</i>					
	<i>Day 1</i>		<i>Day 15</i>		
	Pre Comp	Late Comp	Pre Comp	Late Comp	All Times
<i>Healthy</i>	72.3±14.5	75.4±15.9	66.1±12.2	68.3±10.3	70.5±13.2
<i>Cardiac</i>	61.0±10.6	66.7±17.0	57.3±7.3	55.8±4.3	60.0±9.8
<i>All subjects</i>	67.4±13.8	71.6±16.4	62.4±11.0	62.9±10.2	

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were not different between groups, nor did the groups respond differently to the acute or chronic treatment. However, acute treatment did cause a significant increase in both pressures (Table 3). In addition, chronic compression treatment caused attenuation in both blood pressures in both groups (Table 3).

Table 3: Blood pressure in healthy and cardiac patients

Systolic Blood Pressure					
	Day 1		Day 15		All Times
	Pre Comp	Late Comp	Pre Comp	Late Comp	
Healthy	124.6±20.1	146.7±33.9	121.7±23.3	130.4±21.6	130.9±24.7
Cardiac	113.2±8.7	124.8±5.3	105.8±5.8	115.8±6.2	114.9±6.5
All subjects	119.3±16.4	136.6±26.8*	114.4±18.8 ^t	123.7±17.5* ^t	

Diastolic Blood Pressure					
	Day 1		Day 15		All Times
	Pre Comp	Late Comp	Pre Comp	Late Comp	
Healthy	71.1±10.8	82.7±13.0	68.0±8.3 ^t	74.6±12.9	74.1±11.3
Cardiac	68.2±7.3	71.0±6.1	57.3±9.3	68.2±5.6	66.2±7.1
All subjects	69.8±9.1	77.3±11.7*	63.1±10.1 ^t	71.6±10.3* ^t	

* Indicates significant difference between pre comp and late comp, $p < 0.05$. ^t Indicates significant difference between day 1 and day 15, $p < 0.05$.

Blood Parameters

Overall, there were no differences between the cardiac group and the healthy group on any blood parameters. Acute or chronic compression had no effect on partial thromboplastin time, prothrombin time, or fibrinogen (Table 4).

Table 4: Thrombolytic Parameters in Healthy and Cardiac Patients

Partial Thromboplastin Time (seconds)					
	Day 1		Day 15		All Times
	Pre Comp	Post Comp	Pre Comp	Post Comp	
Healthy	28.0±3.1	27.5±3.0	27.9±3.0	27.9±2.6	27.8±2.9
Cardiac	27.0±2.1	27.1±2.1	27.1±1.9	26.3±1.9	26.9±1.6
All subjects	27.6±2.7	27.3±2.7	27.6±2.6	27.3±2.4	

Prothrombin Time (s)					
	Day 1		Day 15		All Times
	Pre Comp	Post Comp	Pre Comp	Post Comp	
Healthy	12.8±0.4	12.9±0.5	12.9±0.4	13.0±0.6	12.9±0.04
Cardiac	12.6±0.6	12.8±0.6	12.9±0.3	13.0±0.4	12.8±0.4
All subjects	12.8±0.5	12.8±0.6	12.9±0.4	13.0±0.5	

Fibrinogen (mg/100 mL)					
	Day 1		Day 15		All Times
	Pre Comp	Post Comp	Pre Comp	Post Comp	
Healthy	366.0±61.1	357.8±60.6	353.4±66.3	346.6±70.1	356.0±62.3
Cardiac	372.4±63.6	376.4±64.9	381.5±73.7	350.8±66.6	368.0±54.2
All subjects	368.6±60.5	361.6±60.6	364.7±68.9	348.3±67.0	

Acute compression caused a significant decrease in NO (Figure 1) and also a tendency to decrease PGI₂ pre to post on both days (Figure 2). There was a significant time x day interaction indicating that the decrease in NO during the session was attenuated following the 15 day treatment. Compression therapy caused a significant reduction in PGI₂ when comparing day 1 to day 15 (Figure 2).

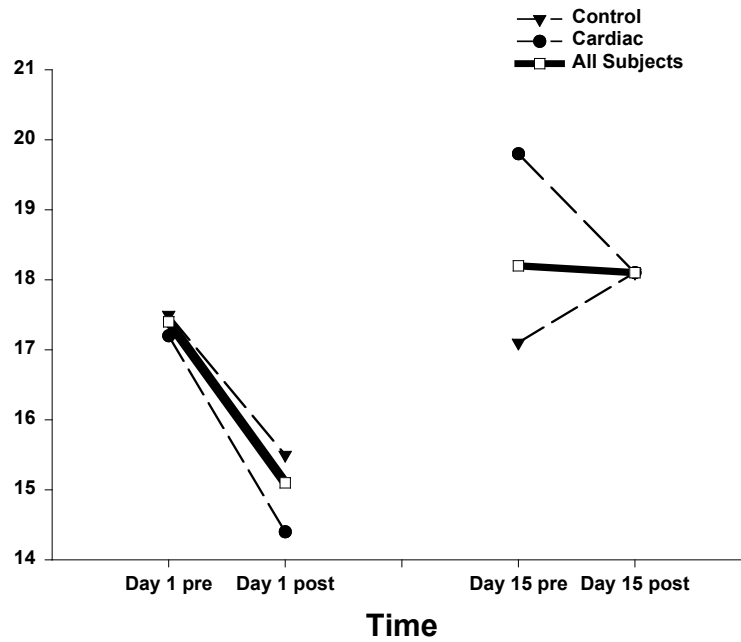


Figure 1. Response of nitric oxide to one session and 15 sessions of limb compression. NO was reduced following a session of compression, day 1 and day 15 combined (pre vs. post), $p < 0.05$.

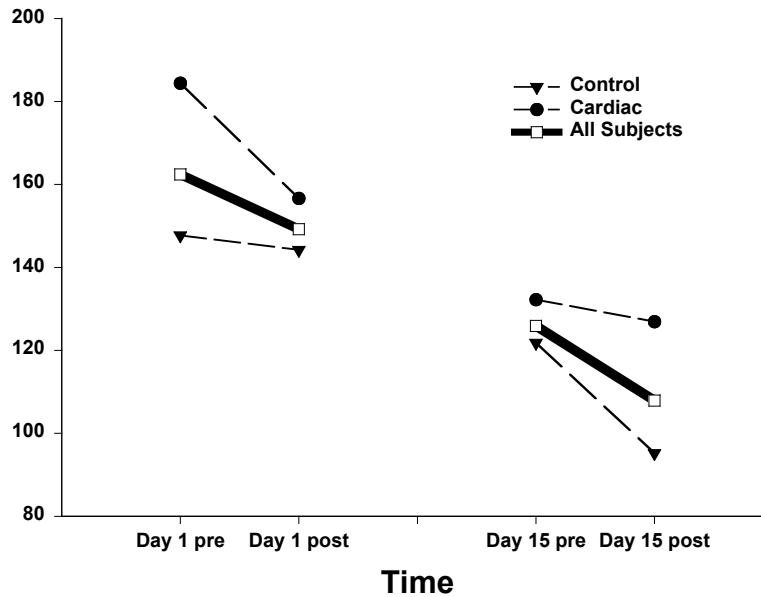


Figure 2. Response of prostacyclin (as 6-keto-PGF_{1α}) to one session and 15 sessions of limb compression. Day 15 values were significantly lower than Day 1 values, $p < 0.05$.

DISCUSSION

These results suggest that intermittent sequential compression can affect blood pressure, PGI₂, and NO. In contrast, a session of compression had little effect on HR or CO although there was a tendency for CO to increase from pre to late compression ($p < 0.06$) (Table 2). Power analysis (0.80, $p < 0.05$) indicated that 61 subjects would be necessary to achieve statistical significance for this CO comparison. Compression training for 15 days did not significantly affect the cardiac parameters, although HR tended to be lower after the 15 day

treatment ($p=0.06$) (Table 2). Power analysis indicated that 65 subjects would be necessary to achieve statistical significance for the treatment effect on HR. Surprisingly very few of the previous studies using intermittent pneumatic compression have measured HR or CO. In contrast, even mild exercise on a treadmill or cycle is known to increase HR, stroke volume, and CO (12).

One of the most important findings of the present study was the effect of compression on systolic and diastolic blood pressures. In the previous literature, only Kern et al. (13) reported increased mean arterial pressure with intermittent compression in cardiac patients. Our results confirm these previous findings, and further suggest that intermittent pneumatic compression has similar effects on both SBP and DBP. The increase at the end of a compression session was substantial, averaging about 8 mmHg for both pressures. The increased blood pressure coupled with the increase in venous return and resulting subendocardial perfusion has been suggested as the mechanism by which enhanced external counterpulsation therapy reduces anginal symptoms (10).

A session of mild exercise also has been shown to increase SBP; a magnitude of 8 mm Hg corresponding to an exercise session of 20% VO_2 max (14) in aerobic exercise or 40% one repetition maximum (1RM) in resistance exercise (15). A session of rhythmic aerobic exercise typically does not cause a change in DBP (16). On the other hand, resistance exercise was reported to increase DBP in normal subjects (17) and cardiac patients (15). Haslam et al. (15) observed that DBP was increased at 60 % 1RM in cardiac patients using the double leg press but not at 20 or 40% 1RM. Thus, the four limb compression technique may mimic the DBP response associated with moderate resistance exercise.

In contrast, short-term compression treatment over 15 days caused a significant reduction in both SBP and DBP. We could find no previous reports in the literature in which the chronic effect of intermittent compression on blood pressure was assessed. We cannot rule out that the reduction in blood pressure was due to reduced anxiety on day 15, but this explanation is unlikely since all subjects were thoroughly habituated to the instrumentation and testing procedures prior to the pre-test. The lowering of blood pressures after 15 days of compression treatment is especially intriguing in that this may provide a strategy for hypertension therapy.

The effect of short term aerobic exercise training on resting blood pressure is controversial, but the majority of studies indicate reduced resting SBP and DBP following an aerobic training program (18). In addition, after 6 days of aerobic training, SBP was lower during vigorous aerobic exercise but not moderate exercise, and DBP was unaffected by the training program (16). Meredith et al (19) observed decreases in both SBP and DBP after only 4 sessions of aerobic training at 60-70% maximum, a result which parallels the rapid decreases in SBP and DBP observed with compression treatment in the present study.

Resistance exercise training has not been shown to decrease resting SBP or DBP, but may reduce blood pressure during resistance exercise at the same weight (17). Isometric training at 30% maximum for four weeks caused comparable reductions in SBP and DBP as observed in the present study (20). Thus, four limb compression appears to produce comparable changes in SBP as mild aerobic training or mild isometric training and changes in DBP similar to mild isometric training.

Clotting indices including PT, PTT, and fibrinogen were generally unchanged by a single compression session or 15 days of treatment. None of the important comparisons were close to significant, $p=0.19-0.72$. These results were unexpected since others have reported decreased euglobulin lysis time, an indicator of increased fibrinolysis, with compression (2,4). Previous studies have used various inflation and deflation cycle durations, and so the compression/deflation cycle does not appear to be the reason for the discrepancy. Perhaps the blood flow changes induced by our compression procedure were inadequate to stimulate thrombolysis.

A session of exercise has been shown to decrease euglobin lysis time and PTT; however, exercise induced changes in other markers of fibrinolysis, such as PT and fibrinogen are less consistent (5). The effects of

training on fibrinolysis also are controversial. Aerobic training has been associated with decreased euglobin lysis time (21) and PTT (22). Others have not observed aerobic training to change markers of fibrinolysis. In fact, Suzuki et al (23) observed that 30 days of training in cardiac patients actually increased PTT but decreased fibrinogen, responses which would have the opposite effect on fibrinolysis. Worsonu et al. (24) also observed decreased fibrinogen as a result of an aerobic cardiac rehabilitation program, while resistance exercise did not affect markers of thrombolysis. Thus, a session of exercise appears to affect fibrinolysis in contrast to our compression treatment. However, exercise training appears to produce equivocal effects on markers of fibrinolysis, a finding which parallels our results with 15 days of compression therapy.

Perhaps the most surprising result of the present study was the decrease in endothelium derived NO and 6-ketoPGF_{1 α} , the stable metabolite of PGI₂, as a result of compression. Both of these compounds are vasodilators, and we hypothesized that compression would increase endothelium production as is observed in exercise (6,7). In contrast to our results, Guyton et al. (8) previously observed an increase in the PGI₂ metabolite following a compression session. In that study, the inflation phase was 12 s, much shorter than our compression phase, and this may explain the discrepancy in results.

Weksler (25) suggested that pulsatile flow caused an increase in PGI₂ production. It seems reasonable to speculate that our compression technique using 60 s inflation periods produced a prolonged partial obstruction of blood flow which had the opposite effect of pulsatile flow; i.e., inhibition of PGI₂ synthesis or release. The prolonged decreased flow also may have diminished the uptake of arginine and arachidonic acid, the precursors for synthesis of NO and PGI₂, respectively. Others have observed decreased endothelium derived plasminogen activator following repeated days of venous occlusion, suggesting the possibility of depletion of endothelium derived substances (26). In our study, the compensatory increase in blood flow during the deflation phase apparently did not completely counteract the effects of occlusion.

Our results confirmed the finding of Kessler et al (9) who also observed decreased PGI₂ metabolite following a compression session in vascular patients and hypothesized that this group of subjects had endothelium damage which could account for the decreased production of PGI₂. Likewise, in our protocol the prolonged inflation period may have caused transient damage to the endothelium, temporarily inhibiting the production of PGI₂.

The effect of a session of exercise on PGI₂ is controversial, with studies showing increases (6) or no change (27) with exercise. On the other hand, exercise has been shown to increase the secretion of NO by the endothelium. Exercise training also increases NO production (7). Training induced increases in NO production may be important to the cardiac patient because the vasodilation caused by NO can be important to the delivery of blood to the cardiac tissue. While acute exercise and training stimulate NO production, four limb compression seems to have the opposite effect. This paradox could relate to the differences in shear stress between the two therapies or the compression mechanisms discussed above. Future studies might use more rapid inflation/deflation cycles to increase shear stress and perhaps magnify the effects on endothelium derived substances.

In summary, the results of this study suggest that intermittent, sequential compression can have marked effects on blood pressure, NO, and PGI₂ in cardiac patients as well as apparently healthy individuals. Specifically, a single session of compression increased DBP and SBP decreased NO. In addition, 15 days of compression treatment decreased blood pressure and PGI₂ concentration. Overall, these results indicate that this compression technique has a generally favorable effect on the cardiovascular parameters assessed, but mimics mild exercise only in the blood pressure response.

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REFERENCES

1. Kierkegaard A, Norgren L. Graduated compression stockings in the prevention of deep venous thrombosis in patients with acute myocardial infarction. **Eur Heart J** 1993;14:1365-1368.
2. Tarnay TJ, Rohr PR, Davidson AG, Stevenson MM, Byars EF, Hopkins GR. Pneumatic calf compressing, fibrinolysis, and the prevention of deep venous thrombosis. **Surgery** 1980;489-496.
3. Janssen H, Trevino C, Williams D. Hemodynamic alterations in venous blood flow produced by external pneumatic compression. **Cardiovasc Surg** 1993;441-447.
4. Jacobs DG, Piotrowski JJ, Hoppensteadt DA, Salvator AE, Fareed J. Hemodynamic and fibrinolytic consequences of intermittent pneumatic compression: preliminary results. **J Trauma** 1996;40:710-716.
5. El Sayed MS. Effects of exercise on blood coagulation, fibrinolysis, and platelet aggregation. **Sports Med** 1996;22:282-298.
6. Boger RH., Bode-Boger SM, Schroder EP, Tsikas D, Frolich JC. Increased prostacyclin production during exercise in untrained and trained men: effect of low-dose aspirin. **J Appl Physiol** 78:1832-38, 1995.
7. Kingwell, BA. Nitric oxide as a metabolic regulator during exercise: effects of training in health and disease. **Clin Exp Pharm Physiol.** 2000;27:239-250.
8. Guyton DP, Khayat A, Husni EA, Schreiber H. Elevated levels of 6-Keto-prostaglandin-F_{1α} from a lower extremity during external pneumatic compression. **Surg Gynecol Obstet.** 1988;166:338-342.
9. Kessler CM, Hirsch DR, Jacobs H, MacDougall R, Goldhaber SZ. Intermittent pneumatic compression in chronic venous insufficiency favorably affects fibrinolytic potential and platelet activation. **Blood Coag Fibrinol** 1996;7:437-446.
10. Arora RR, Chou TM, Jain D, Fleishman B, Crawford, L, McKiernan T, et al. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. **J Am Coll Cardiol.** 1999;33:1833-1840.
11. Salandin V, Zussa C, Risica G, Michielon P, Paccagnella A, Cipolotti G, Simini G. Comparison of cardiac output estimation by thoracic electrical bioimpedance, thermodilution, and fick methods. **Critical Care Medicine** 1988;16:1157-1158.
12. Miles DS, Critz JB, Knowlton RG. Cardiovascular, metabolic, and ventilatory responses of women to equivalent cycle ergometer and treadmill exercise. **Med Sci Sports Exerc** 1980;12(1):14-19.
13. Kern MJ, Henry RH, Lembo N, et al. Effects of pulsed external augmentation of diastolic pressure on coronary and systemic hemodynamics in patients with coronary artery disease. **Am Heart J** 1985;110:727-735.
14. Niederberger M, Bruce RA, Kusumi F, Whitkanack S. Disparities in ventilatory and circulatory responses to bicycle and treadmill exercise. **Brit Heart J** 1974; 36:377-382.
15. Haslam DRS, McCartney N, McKelvie RS, MacDougall JD. Direct measurements of arterial blood pressure during formal weightlifting in cardiac patients. **J Cardiopulm Rehab** 1988;8:213-225.

16. Rogers MA, Yamamoto C, Hagberg JM, Martin WH, Ehsani AA, Holloszy JO. Effect of 6 d of exercise training on responses to maximal and sub-maximal exercise in middle-aged men. **Med Sci Sports Exerc** 1988;20(3):260-264.
17. Sale DG, Moroz DE, McKelvie RS, MacDougall JD, McCartney N. Effect of training on the blood pressure response to weight lifting. **Can J Appl Physiol** 1994;19(1):60-74.
18. Kelley G, Vu Tran, Z. Aerobic exercise and normotensive adults: a meta-analysis. **Med Sci Sports Exerc** 1995;27(10):371-1377.
19. Meredith IT, Jennings GL, Esler MD, Dewar EM, Bruce AM, Fazio VA, Korner PI. Time-course of the antihypertensive and autonomic effects of regular endurance exercise in human subjects. **J Hypertens** 1990;8:859-866.
20. Wiley RL, Dunn CL, Cox RH, Hueppchen NA, Scott MS. Isometric exercise training lowers resting blood pressure. **Med Sci Sports Exerc** 1992;24:749-754.
21. Watts, EJ. Haemostatic changes in long-distance runners and their relevance to the prevention of ischaemic heart disease. **Blood Coag Fibrinol** 1991;2:221-225.
22. Handa K, Terao Y, Mori T, Tanaka, Kiyonaga A, Matsunaga A., et al. Differing coagulability and fibrinolytic activity during exercise depending on exercise intensities. **Thromb Res** 1992;66:613-616.
23. Suzuki T, Yamauchi K, Yamada Y, Furumichi T, Furui H, Tsuzuki J, et al. Blood coagulability and fibrinolytic activity before and after physical training during the recovery phase of acute myocardial infarction. **Clin Cardiol** 1992;15:358-364.
24. Wosornu D, Allardyce W, Ballantyne D, Tansey P. Influence of power and aerobic exercise training on hemostatic factors after coronary artery surgery. **Br Heart J** 1992;68:181-186.
25. Weksler BB. Prostaglandins and vascular function. **Circulation** 1984;70 (suppIII):63-71.
26. Keber D, Stegnar M. exhaustion of arm fibrinolytic potential after repeated venous occlusions and local exercise. **Thromb Res** 1982;55:693-704.
27. Todd MK, Goldfarb AH, Boyer BT. Effect of exercise intensity on 6-keto-PGF_{1 α} , TXB₂, and 6-keto-PGF_{1 α} /TXB₂ ratios. **Thromb Res** 1992;65:487-493, 1992.