Eur J Appl Physiol (2012) 112:2375–2379
DOI 10.1007/s00421-011-2210-y

SHORT COMMUNICATION

Vascular inflammation and blood pressure response to acute exercise

Mark Hamer · Andrew Steptoe

Received: 6 September 2011 / Accepted: 11 October 2011 / Published online: 25 October 2011

Abstract Exaggerated blood pressure (BP) response to exercise is a strong predictor of cardiovascular disease, although the mechanisms remain unknown. The purpose was to examine the association between systemic markers of vascular inflammation and exercise blood pressure (BP) responses. Participants were 191 healthy men and women (aged 45–59 years). Blood pressure was measured at baseline and during 8 min of steady state cycling ergometry exercise (at 50 W). Markers of vascular inflammation (fibrinogen, von Willebrand factor antigen, tumour necrosis factor-α, interleukin-6 [IL-6], C-reactive protein [CRP]) were measured at baseline together with other traditional risk factors including central adiposity, smoking, alcohol, and habitual physical activity. CRP ($\beta = 0.30$, $p < 0.001$), IL-6 ($\beta = 0.25$, $p = 0.001$), and fibrinogen ($\beta = 0.14$, $p = 0.04$) were associated with exercise systolic BP. The association with CRP remained significant after adjustment for age, sex, resting BP, and other risk factors. Other independent predictors of exercise BP included resting BP, female gender, waist–hip ratio, lower employment grade, and low physical activity level. In summary, central adiposity and vascular inflammatory processes may underlie exaggerated BP responses to acute exercise.

Keywords Blood pressure · Central obesity · C-reactive protein · Exercise · Inflammation · Interleukin-6

Communicated by Susan Ward.

M. Hamer (✉) · A. Steptoe
Department of Epidemiology and Public Health,
University College London, 1-19 Torrington Place,
London WC1E 6BT, UK
e-mail: m.hamer@ucl.ac.uk

Introduction

Exaggerated systolic blood pressure (BP) response to exercise is a strong independent predictor of hypertension and cardiovascular disease (Singh et al. 1999; Mundal et al. 1994; Jae et al. 2006a, b). A potential underlying reason for excessive BP responses to exercise is an impaired vasodilatation response (Stewart et al. 2004) due to endothelial dysfunction, which may be linked to vascular inflammatory processes (Hingorani et al. 2000). Indeed, heavy physical exertion has been shown to trigger the onset of acute myocardial infarction in sedentary individuals (Mittleman et al. 1993), possibly due to rupture of vulnerable plaque and activation of thrombogenic risk factors (Willich et al. 1993). Various biomarkers, such as fibrinogen, von Willebrand factor antigen (vWF), and interleukin (IL)-6, have been implicated in vascular inflammatory processes and are also independent predictors of cardiovascular risk (Danesh et al. 2004). It is unclear whether vascular inflammatory processes underlie exaggerated exercise BP responses. The purpose of this study was, therefore, to examine whether vascular inflammatory markers are associated with exercise BP independently of traditional risk factors in healthy middle-aged participants.

Methods

Participants

One hundred and ninety-one men and women were drawn from the Whitehall II epidemiological cohort (Marmot and Brunner 2005) for a sub-study. The criteria for entry into the study included no history or objective signs of coronary heart disease, no previous diagnosis or treatment for

hypertension, inflammatory diseases, or allergies. Selection was stratified by grade of employment to include higher, intermediate, and lower status participants. In addition participants were prohibited to use any anti-histamine or anti-inflammatory medication 24 h before testing and were rescheduled if they reported colds or other infections on the day of testing. Participants gave full informed consent to participate in the study and ethical approval was obtained from the UCLH committee on the Ethics of Human Research.

Anthropometry, cardiovascular, and health related measures

Anthropometric data, including weight, height, and waist and hip measures were collected from participants in light clothing. Body weight was measured to the nearest 0.1 kg and height was measured to the nearest mm using the Frankfort plane to standardize the measurement. Waist circumference was measured with a metal anthropometric tape midway between the lower rib margin and the iliac crest and hip circumference was measured at the level of the great trochanters. Following the insertion of a venous cannula, participants rested for 30 min before the collection of blood for the assessment of vascular inflammatory markers and lipids. Blood pressure was measured continuously using a Portapres-2 device (Finapres Medical Systems, Amsterdam, The Netherlands) and an average from the last 5 min of the rest period was calculated. Heart rate was assessed using an impedance based Ambulatory Monitoring System (VU-AMS, Free University, Amsterdam, The Netherlands). Participants reported how many times a week they engaged in vigorous physical activity (defined as activity that "makes you feel out of breath"), their weekly alcohol intake (units/week), and smoking habits. Grade of employment was used as an indicator of socioeconomic status.

Exercise stress test

Following the collection of baseline data two 5-min mental stress tasks were administered (not reported here) followed by a 45-min recovery period. Participants were then required to undergo a sub-maximal exercise test that was performed on a cycle ergometer (Monark, Model 864, Sweden) for 8 min at a constant work load of 50 W. Heart rate and BP were measured continuously during the exercise period and an average from the last 2 min was calculated. Participants were required to hold onto the handlebars with their dominant hand whilst blood pressure was assessed continuously from the finger of their non-dominant hand that was supported on a foam cushion.

Biological assays

Peripheral blood was collected in EDTA coated tubes and spun at room temperature. All blood samples were frozen at −20°C until assay. The analysis of plasma CRP, IL-6 and tumour necrosis factor (TNF)-α was performed using high sensitivity ELISA (R & D Systems, Oxford, UK). The limit of detection was 0.09 pg/ml, and the intra and inter-assay coefficients of variation were 5.3 and 9.2%, respectively. Von Willebrand factor antigen (vWF) was determined using a double sandwiched antibody enzyme linked immunoassay (DakoCytomation Ltd, UK) and fibrinogen by an automated Clauss assay in a MDA-180 coagulometer (Organon Teknika, Cambridge, UK) using the manufacturer's reagents and the International fibrinogen standard (Gaffney and Wong 1992). Analysis of total and high-density lipoprotein (HDL) cholesterol was measured using enzymatic colorimetric methods.

Data analysis

A log transformation was performed on CRP and vWF data to normalize the distribution. Linear regression analyses were employed to examine the relationship between exercise BP (dependent variable) and markers of vascular inflammation, adjusting for age, sex, waist-to-hip ratio (WHR), employment grade, smoking, alcohol intake (units/week), vigorous physical activity (categorised into tertiles), total/HDL cholesterol ratio, and resting BP. Various definitions have used to describe exaggerated BP responses to exercise, including greater than the 95th percentile (e.g, Singh et al. 1999) and also fixed values such as systolic BP greater than 210 mmHg (e.g, Manolio et al. 1994). Since our analyses employed the continuous exercise BP measures in a linear regression model we chose not to specifically define "exaggerated BP responses".

Results

Participants were of white European origin (43% female), aged 45–59 years, lived in the London area, and were in full-time employment. Participants displayed normal resting systolic BP (115.6 ± 0.9 mmHg), body mass index (25.6 ± 3.7 kg/m^2), and 55% of the sample reported participation in regular vigorous exercise whilst only 7.8% reported currently smoking. There was, on average, a significant heart rate and BP response to the sub-maximal exercise test (see Table 1).

In univariate analysis CRP ($\beta = 0.30$, $p < 0.001$), IL-6 ($\beta = 0.25$, $p = 0.001$), and fibrinogen ($\beta = 0.14$, $p = 0.04$) were associated with exercise systolic BP. In further multivariate models, the association between IL-6 and exercise

Table 1 Cardiovascular responses to sub-maximal exercise testing

Data are mean ± SEM with range in brackets

Variable	Rest	Exercise
Heart rate (bpm)	64.9 ± 0.6 (40.8–94.8)	82.3 ± 1.2 (43.0–130.0)
Systolic blood pressure (mmHg)	115.6 ± 0.9 (82.7–159.0)	147.3 ± 1.4(109.0–216.0)
Diastolic blood pressure (mmHg)	70.3 ± 0.7 (49.5–97.0)	81.0 ± 0.9 (58.0–172.0)

Table 2 Regression of interleukin-6 and traditional risk factors on exercise systolic blood pressure

Variable	Model 1	Model 2	Model 3[†]
Interleukin-6	0.25*	0.15*	0.10
Gender	0.03	0.19*	0.32*
Age	−0.09	−0.05	−0.06
Resting systolic BP	–	0.52**	0.46**
WHR	–	–	0.20*
Employment grade	–	–	0.15*
Smoking	–	–	−0.07
Alcohol	–	–	0.07
Physical activity	–	–	−0.13*
Total/HDL cholesterol	–	–	0.06

Data presented as standardized coefficients

Model 1, adjusted for age and sex; Model 2, adjusted for age, sex, and resting systolic BP; Model 3, adjusted for age, sex, resting systolic BP, waist-to-hip ratio (WHR), smoking, alcohol, regular physical activity (tertile), employment grade (high/medium/low), total/HDL cholesterol ratio

** $p < 0.001$; * $p < 0.05$

[†] $R^2 = 0.366$, adjusted $R^2 = 0.335$

Table 3 Regression of C-reactive protein and traditional risk factors on exercise systolic blood pressure

Variable	Model 1	Model 2	Model 3[†]
CRP	0.29**	0.23**	0.14*
Gender	0.03	0.18*	0.30*
Age	−0.07	−0.03	−0.06
Resting systolic BP	–	0.52**	0.47**
WHR	–	–	0.18*
Employment grade	–	–	0.14*
Smoking	–	–	−0.07
Alcohol	–	–	0.07
Physical activity	–	–	−0.12*
Total/HDL cholesterol	–	–	0.04

Data presented as standardized coefficients

Model 1, adjusted for age and sex; Model 2, adjusted for age, sex, and resting systolic BP; Model 3, adjusted for age, sex, resting systolic BP, waist-to-hip ratio (WHR), smoking, alcohol, regular physical activity (tertile), employment grade (high/medium/low), total/HDL cholesterol ratio

** $p < 0.001$; * $p < 0.05$

[†] $R^2 = 0.387$, adjusted $R^2 = 0.356$

systolic BP persisted in analyses adjusted for age, sex, and resting systolic BP, although did not remain significant after adjustment for further risk factors (see Table 2). However, the association between CRP and exercise systolic BP persisted after full adjustment for all other risk markers (see Table 3). Other significant predictors of exercise systolic BP included resting BP, female gender, WHR, lower employment grade, and a low self-reported physical activity level. Systolic BP was approximately 11 mmHg higher in participants in the highest compared with the lowest WHR tertile, after adjustment for baseline BP. Weaker associations were observed between inflammatory markers and exercise diastolic BP (for example, age and sex adjusted associations for IL6; $\beta = 0.19$, $p = 0.01$).

Discussion

In a sample of healthy middle-aged men and women we have demonstrated that several markers of systemic vascular inflammation were associated with exaggerated BP during mild exercise, independently from resting BP. In addition, WHR remained one of the strongest predictors of exercise BP, which suggests central adiposity may be an important underlying risk factor.

In a previous study Jae and colleagues (Jae et al. 2006a, b) demonstrated an association between exaggerated BP responses to exercise and white blood cell count, although not with CRP. However, given that we employed a steady state sub-maximal exercise protocol in comparison with their graded test to exhaustion, it is difficult to make direct comparisons between the two studies. Physical activity, inflammation and health are linked together in a complex fashion. Cytokines are produced and secreted by exercising muscle (termed "myokines") although regular physical activity has been consistently associated with lower levels of systemic inflammatory markers (Hamer 2007). Once released transiently into the blood stream, myokines are thought to mediate some of the systemic and beneficial effects of exercise in non-muscle tissue (Handschin and Spiegelman 2008). Paradoxically, chronically elevated serum IL-6 levels have been associated with various disease processes, and in particular cardiovascular dysfunction. Thus, heavy physical exertion may only trigger the onset of acute myocardial infarction in sedentary individuals, whilst habitual physical activity is linked with

beneficial effects in coronary patients (Hamer and Stamatakis 2009).

A potential underlying reason for excessive BP responses to exercise is an impaired vasodilatation response (Stewart et al. 2004) due to endothelial dysfunction, which may be linked to vascular inflammatory processes (Hingorani et al. 2000). However, whether inflammation is the cause or consequence of vascular dysfunction remains uncertain. Exaggerated BP responses to exercise can be attenuated through regular exercise training. In patients with severe hypertension, 16 weeks of low to moderate aerobic exercise resulted in significantly lower exercise BP at maximal and absolute sub-maximal exercise workloads (Kokkinos et al. 1997). Although the mechanisms for a reduction in exercise BP remain unknown, a crucial training adaptation might involve a decrease in low-grade inflammation and restoration of endothelial function.

Exaggerated exercise BP has previously been associated with a clustering of metabolic syndrome factors, including elevated cholesterol, lipids, body mass index, and glucose intolerance (Mundal et al. 1998). Obesity is also a determinant of impaired endothelial function (Steinberg et al. 1996) and tends to cluster with other risk factors including a pro-inflammatory state (Kapiotis et al. 2006), which might explain our findings relating to WHR and exercise BP. Central adiposity has been shown to impact upon cardiovascular function in the absence of obesity and appears to represent a higher potential health risk than peripheral fat depots (de Simone et al. 2005). There is also a particularly strong correlation between visceral obesity and inflammation that is related to the unique properties of visceral fat which distinguish it from other fat depots (Greenberg and Obin 2006).

Limitations

The present study was cross-sectional thus we were unable to demonstrate causality or determine the direction of the association. Although we did not collect direct measures of BP, the Finapres device provides measures of arterial pressure based on the volume clamp method and uses Modelflow modelling to derive hemodynamic parameters from pressure data, which have been previously validated using a range of stressors (Wesseling 1995; Wesseling et al. 1993). The advantage of using this device is that it captures the full contour of the BP response, as opposed to taking discrete measures using the conventional approach. We employed a fixed exercise work load as it was not feasible to perform tests of maximal capacity in the present sample of older, sedentary participants. Thus, in order to address the possible influences of different relative workloads, we adjusted the analysis for levels of habitual vigorous exercise as a proxy marker of physical fitness, although the results were not altered.

In summary, heightened BP during exercise is a risk marker for cardiovascular health. Central adiposity and vascular inflammatory processes may underlie exaggerated BP responses to acute exercise.

Ethical standards the authors declare that the present experiment complies with the current research ethics laws of the country it has been performed in. The experimental protocol has been approved by the institution's Ethical Committee in Research and all of the subjects have signed an informed consent.

Acknowledgments This research was supported by the Medical Research Council, UK, and the British Heart Foundation. We acknowledge the contributions of Dr Sabine Kunz-Ebrecht, Dr Pamela Feldman, Dr Gonneke Willemsen, Dr Natalie Owen and Bev Murray to data collection, and Dr Vidya Mohamed-Ali to the cytokine analyses.

Conflict of interest The authors declare that they have no conflict of interest.

References

Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V (2004) C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 350:1387–1397

de Simone G, Devereux RB, Kizer JR, Chinali M, Bella JN, Oberman A, Kitzman DW, Hopkins PN, Rao DC, Arnett DK (2005) Body composition and fat distribution influence systemic hemodynamics in the absence of obesity: the HyperGEN Study. Am J Clin Nutr 81:757–761

Gaffney PJ, Wong MY (1992) Collaborative study of a proposed international standard for plasma fibrinogen measurement. Thromb Haemost 68:428–432

Greenberg AS, Obin MS (2006) Obesity and the role of adipose tissue in inflammation and metabolism. Am J Clin Nutr 83:461S–465S

Hamer M (2007) The relative influences of fitness and fatness on inflammatory factors. Prev Med 44:3–11

Hamer M, Stamatakis E (2009) Physical activity and mortality in men and women with diagnosed cardiovascular disease. Eur J Cardiovasc Prev Rehabil 16:156–160

Handschin C, Spiegelman BM (2008) The role of exercise and PGC1alpha in inflammation and chronic disease 2008. Nature 454:463–469

Hingorani AD, Cross J, Kharbanda RK (2000) Acute systemic inflammation impairs endothelium-dependent dilatation in humans. Circulation 102:994–999

Jae SY, Fernhall B, Heffernan KS, Kang M, Lee MK, Choi YH, Hong KP, Ahn ES, Park WH (2006a) Exaggerated blood pressure response to exercise is associated with carotid atherosclerosis in apparently healthy men. J Hypertens 24:881–887

Jae SY, Fernhall B, Lee M, Heffernan KS, Lee MK, Choi YH, Hong KP, Park WH (2006b) Exaggerated blood pressure response to exercise is associated with inflammatory markers. J Cardiopulmon Rehab 26:145–149

Kapiotis S, Holzer G, Schaller G, Haumer M, Widhalm H, Weghuber D, Jilma B, Roggla G, Wolzt M, Widhalm K, Wagner OF (2006) A proinflammatory state is detectable in obese children and is accompanied by functional and morphological vascular changes. Arterioscler Thromb Vasc Biol 26:2541–2546

Kokkinos PF, Narayan P, Fletcher RD et al (1997) Effects of aerobic training on exaggerated blood pressure response to exercise in African-Americans with hypertension treated with indapamide, verapamil and enalapril. Am J Cardiol 79:1424–1426

Manolio TA, Burke GL, Savage PJ, Sidney S, Gardin JM, Oberman A (1994) Exercise blood pressure response and 5-year risk of elevated blood pressure in a cohort of young adults: the CARDIA study. Am J Hypertens 7:234–241

Marmot M, Brunner E (2005) Cohort profile: the Whitehall II study. Int J Epidemiol 34:251–256

Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE (1993) Triggering of acute myocardial infarction by heavy physical exertion Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. N Engl J Med 329:1677–1683

Mundal R, Kjeldsen SE, Sandvik L, Erikssen G, Thaulow E, Erikssen J (1994) Exercise blood pressure predicts cardiovascular mortality in \ men. Hypertension 24:56–62

Mundal R, Kjeldsen SE, Sandvik L, Erikssen G, Thaulow E, Erikssen J (1998) Clustering of coronary risk factors with increasing blood pressure at rest and during exercise. J Hypertens 16:19–22

Singh JP, Larson MG, Manolio TA, O'Donnell CJ, Lauer M, Evans JC, Levy D (1999) Blood pressure response during treadmill testing as a risk factor for new-onset hypertension. The Framingham heart study. Circulation 99:1831–1836

Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD (1996) Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. J Clin Invest 97:2601–2610

Stewart KJ, Sung J, Silber HA, Fleg JL, Kelemen MD, Turner KL, Bacher AC, Dobrosielski DA, DeRegis JR, Shapiro EP, Ouyang P (2004) Exaggerated exercise blood pressure is related to impaired endothelial vasodilator function. Am J Hypertens 17:314–320

Wesseling KH (1995) A century of non-invasive arterial pressure measurement: from Marey to Penaz and Finapres. Homeostasis 36:50–66

Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ (1993) Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J Appl Physiol 74:2566–2573

Willich SN, Lewis M, Löwel H, Arntz HR, Schubert F, Schröder R (1993) Physical exertion as a trigger of acute myocardial infarction. Triggers and Mechanisms of Myocardial Infarction Study Group. N Engl J Med 329:1684–1690