LEADING ARTICLE

Sports Med 2006; 36 (2): 109-116
0112-1642/06/0002-0109/$39.95/0

The Anti-Hypertensive Effects of Exercise

Integrating Acute and Chronic Mechanisms

Mark Hamer

Department of Epidemiology and Public Health, University College London, London, England

Abstract

It is anticipated that hypertension will afflict up to a third of the worldwide population by the year 2025. Therefore, cost-effective treatment strategies are essential to control this disease. Exercise has been associated with anti-hypertensive benefits, but despite extensive research the optimal exercise dose (training frequency, intensity and time) required to lower blood pressure and maintain normotensive status remains unclear. This article explores the interrelationships between acute and chronic mechanisms that have been linked to the anti-hypertensive benefits of exercise and proposes that the optimal exercise dosage may depend on the interplay between these mechanisms and the effects of exercise on independent risk markers of hypertension. Therefore, the correct exercise dose for the treatment of hypertension should be prescribed on an individual basis. Future work should examine post-exercise hypotension effects in relation to exercise training in hypertensive populations and both acute and longitudinal training studies should be conducted that incorporate independent risk factors of hypertension as co-variables into their analysis on blood pressure effects.

An acute bout of exercise elicits a number of transient physiological and psychological responses, whereas accumulated bouts of acute exercise produces more permanent or chronic adaptations that may be termed the 'exercise training response'. Higher levels of physical activity and fitness are associated with a reduced incidence of hypertension that has been attributed to: (i) the effects of chronic exercise training on resting blood pressure (BP); and (ii) the immediate reductions in BP following a bout of acute exercise.[1] However, the underlying mechanisms of the anti-hypertensive effects of exercise remain unclear, especially in relation to the link between chronic and acute effects. For example, a meta-analysis that considered the separate effects of chronic exercise training and acute exercise on ambulatory BP demonstrated no significant difference in the chronic and acute BP lowering effects when adjusted for baseline BP.[2] One line of argument suggests that chronic training effects may merely reflect an acute phenomenon with sustained BP reductions accumulating from each bout of exercise. This line of evidence is supported by the fact that reductions in resting BP can be observed after only three sessions of aerobic activity[3-5] and BP returns to pre-exercise values within 1–2 weeks of detraining.[4] However, there are also grounds to suggest that the anti-hypertensive effects of exercise do not result from the influence of exercise itself, but from its effects on other risk factors, such as glucose homeostasis, blood lipids, abdominal adiposity, smoking and psychobiological processes. This is

supported by some evidence from epidemiological studies that show physical inactivity no longer contributes to the risk of hypertension after the adjustment of age, body mass index, waist-to-hip ratio, diabetes mellitus and smoking history.[6,7]

An understanding of how acute and chronic mechanisms influence the relationship between habitual physical activity and BP will lead to a better understanding of how to successfully implement exercise as a treatment and preventative measure of hypertension. Therefore, the aim of the current article is to discuss underlying mechanisms of the anti-hypertensive effects of aerobic exercise in relation to the interaction of acute and chronic mechanisms and suggest future areas of research. This is not intended to be an exhaustive review of the literature, but rather an analysis of the important issues and more recent work. Therefore, relevant literature was identified from recent reviews and meta-analyses[1,2,8-11] and a search on MEDLINE was performed for recent articles (since 2000) that examined the after effects of aerobic exercise and exercise training on BP and cardiovascular function.

1. Chronic Exercise

The most recent meta-analysis of 72 randomised controlled trials showed a significant effect of aerobic exercise training on BP, with net reductions of resting and ambulatory daytime systolic and diastolic BP of, respectively, 3.0/2.4 and 3.3/3.5mm Hg.[11] The anti-hypertensive effects of exercise are mostly considered to be due to a reduction in peripheral vascular resistance, which are possibly mediated through neurohumoral and structural adaptations.[1]

1.1 Neurohumoral Mechanisms

One of the most widely investigated anti-hypertensive mechanisms of exercise training is the reduction in sympathetic nerve activity (SNA), leading to attenuated peripheral vasoconstriction. However, whether exercise training lowers SNA in humans remains controversial[12] mainly due to the limitations in measurements. Central sympathetic nerve outflow can be measured directly by microneurography, although studies are limited to nerve activity from skeletal muscle beds or skin; studies that have measured plasma noradrenaline (norepinephrine) release are also confounded by measurement issues. However, findings that show an increase in baroreflex control of SNA after endurance exercise training appear to be more consistent.[12]

Chronic exercise-induced vascular adaptations have also gained significant attention. Although evidence exists in animals to show attenuation in α-adrenoceptor responsiveness to noradrenaline after training,[13-15] there is no available evidence in humans. Martin et al.[16] have also shown that β_2 adrenergic responsiveness, which mediates vasodilatation, is unaltered after 12 weeks of exercise training in healthy men. However, exercise training-induced effects on other vasoactive substances have been observed in humans. For example, endothelin-1, which is a potent vasoconstrictor, was reduced[17] and nitric oxide (NO), a potent vasodilator, was increased.[18,19]

1.2 Structural Adaptations

Exercise training-induced alterations in vascular structure that result in larger lumen diameter and improved compliance are expected to result in lower peripheral resistance. Cross-sectional studies and longitudinal training studies show that endurance-trained individuals display larger arterial lumen diameter in conduit arteries compared with untrained individuals.[20-22] Similarly, longitudinal and cross-sectional studies have demonstrated improvements in arterial compliance in healthy normotensive populations,[23-25] although more recent training studies in older hypertensive individuals have not.[26,27] It is possible that older hypertensive individuals may be more resistant to exercise-induced alterations because of the replacement of elastic fibres in the large arteries by less distensible collagen and calcium. Therefore, the anti-hypertensive mechanisms of chronic exercise are probably multifactorial and dependent on the individual.

2. Post-Exercise Hypotension

Post-exercise hypotension (PEH) is a term used to describe the immediate reduction in BP following a bout of acute exercise. Following acute exercise, the average ambulatory BP taken over 24 hours is reduced on average by 3.2 and 1.8mm Hg for systolic and diastolic BP, respectively.[2] However, reductions in average 24-hour ambulatory BP are mainly due to the substantial reductions in BP during the first few hours following exercise. This effect may have significant benefits for hypertensive patients by lowering their BP into normotensive ranges for certain periods of the day. A number of recently published reviews have examined the mechanisms of PEH[1,8,9] and concur that reductions in vascular resistance play a major role, although there is considerable disagreement as to whether changes in SNA may be involved. Recent work has thus focused on changes in vascular responsiveness that are associated with decreased transduction of sympathetic outflow and the release of local vasodilator substances that would facilitate post-exercise vasodilatation.

2.1 Sympathetic Vascular Regulation

Halliwill and colleagues[28] have conducted a series of studies to examine vascular responsiveness following acute exercise in relation to PEH. Their initial work indicated that sympathetic vascular regulation was impaired after a 60-minute bout of exercise and they suggested that the ineffective transduction of sympathetic outflow into vascular resistance may be the result of competing influences at the level of the arterial smooth muscle. Recent work has shown that α_1-adrenergic responsiveness does not appear to be blunted after acute exercise[29] but may be increased 24 hours following exercise in humans.[30] Also, conflicting findings exist regarding the effects of acute exercise on β_2 receptors, with no effects[16] and increased responsiveness[31] having been shown. A further possible neural mechanism is an increased sympatho-inhibitory input from cardiopulmonary (CP) baroreceptors post-exercise. Collins and DiCarlo[32] showed that PEH was reversed in rats after blocking CP afferents. Also, Bennett et al.[33] examined forearm vascular resistance (FVR) responses to lower body negative pressure (LBNP) before and after exercise, reporting greater increases in FVR during LBNP after exercise, suggesting that CP baroreceptors exert a greater inhibitory influence on the vasculature after exercise. However, the mechanism by which the CP baroreceptors are activated may be different immediately following exercise, when there is significant hypovolaemia, compared with 24 hours after exercise, when hypervolaemia is commonly induced. That is, the CP baroreceptors act to buffer the expected arterial BP change induced by increases in cardiac filling pressures. Thus, immediately following exercise, increases in cardiac contractility may be responsible for enhancing CP baroreceptor activity, whereas 24 hours after exercise, the mechanism may be central hypervolaemia. Convertino[34] has recently demonstrated this effect by showing that the increase in plasma volume 24 hours after a bout of maximal exercise resulted in a vasodilated cardiovascular system. Therefore, sustained hypervolaemia, as a result of regular bouts of vigorous exercise, may also be linked to the anti-hypertensive mechanisms of chronic exercise and may help explain why reductions in BP are apparent after only a short period of exercise training.

2.2 Vasodilator Substances

There has been substantial interest in vasodilator substances in relation to PEH, although recent work has provided mixed findings. For example, using pharmacological blockade, Halliwill's group have found no evidence to support mechanisms linked with NO[35] or prostaglandins,[36] although they recently showed that histamine contributes to PEH acting via H_1 receptors.[37] The H_1 receptors are primarily located on the vascular endothelial cells and cause vasodilatation via formation of local vasodilatators, such as NO. Thus, this finding corroborates with other recent data that have demonstrated sustained increases in endothelial-dependent flow-mediated vasodilatation following an acute bout of exercise in normotensive postmenopausal women.[38] The increase in endothelial function was

also highly correlated with post-exercise changes in total peripheral conductance and is therefore implicated as a mechanism of PEH. Given that NO production has been shown to increase in response to acute and chronic exercise stimulus[18,19] this suggests that endothelial-derived NO remains a potentially interesting mechanism in relation to the anti-hypertensive effects of exercise and also provides a link between acute and chronic mechanisms.

3. Interaction of Acute and Chronic Effects

There are a paucity of studies that have attempted to examine the link between PEH and the long-term anti-hypertensive adaptations associated with exercise training. Given that most of the literature documenting PEH comes from sedentary participants, the possibility remains that PEH is merely due to the effect of a novel stressor on a sedentary cardiovascular system and therefore plays no role in an anti-hypertensive training effect. Thus, Senitko et al.[39] examined the influence of exercise training status on PEH. Interestingly, after a 60-minute bout of exercise at an intensity of 60% maximal oxygen uptake ($\dot{V}O_{2max}$) there was no difference in the PEH response between endurance-trained and healthy sedentary individuals. However, in endurance-trained men, PEH was the result of a reduced cardiac output, whereas in sedentary men it was the result of vasodilatation. Although these findings suggest the intriguing possibility that training may alter the mechanism (but not the magnitude) of PEH, they may be confounded by the cardiovascular physiology of endurance-trained participants and more definitive longitudinal training studies should therefore be performed to examine the influence of exercise training on PEH. Nevertheless, this study demonstrates that PEH persists in healthy endurance-trained individuals and suggests that it is a specific acute physiological response to exercise. However, given that PEH is a function of baseline BP and greater for persons with hypertension than those with normal BP,[2] it is logical to suggest that PEH may diminish as training-induced reductions in baseline BP become greater. Thus, in hypertensive patients, exercise training may impact on the magnitude of PEH response, although further studies in hypertensive patients are needed to examine this issue.

One potential interaction between acute and chronic exercise is that exercise training increases the capacity of an individual exercise session in terms of intensity and duration that may magnify the acute response providing greater and longer lasting PEH. However, there appears to be considerable debate as to whether or not higher intensity exercise is more beneficial for PEH. For example, Pescatello et al.[40] recently demonstrated that a light intensity (40% $\dot{V}O_{2max}$) was as effective as a higher intensity bout of exercise (60% $\dot{V}O_{2max}$) in eliciting significant PEH over the course of a 9-hour ambulatory monitoring period. In contrast, Quinn[41] demonstrated more substantial and sustained PEH over a 24-hour period after a bout of higher intensity exercise (75% $\dot{V}O_{2max}$) compared with exercise at 50% $\dot{V}O_{2max}$. Nevertheless, given that the frequency or intensity of exercise training programmes in longitudinal studies does not appear to influence the BP lowering effect,[10] this does not support the notion that the anti-hypertensive benefits of exercise training may be derived from being able to perform more vigorous exercise sessions.

It is interesting to note that certain individuals termed 'non-responders' do not appear to sustain BP reductions after endurance training; Hagberg and Brown,[42] in fact, identified 25% of hypertensive participants as non-responders in a review of 47 studies. Pescatello and Kulikowich[2] have pointed out that some of these discrepancies may be due to methodological delimitations, although there may also be a genetic basis.[1] However, an intriguing question arises as to whether or not these same non-responders demonstrate PEH. If these individuals are equally unresponsive to the acute effects of exercise then this would lend support to a common mechanism of action. Therefore, future studies are needed that more closely examine non-responder groups in terms of their physiological responses to acute and chronic exercise and their genetic make-up.

4. Does Exercise Play a Causal Role?

4.1 Biological Risk Markers

The possibility remains that the relationship between hypotension and exercise is not causal but instead exercise affects a number of risk factors that directly impact on hypertension. Exercise is known to have a profound influence on the inflammatory cytokines with lower baseline levels of inflammatory markers found in individuals who are most physically active[43] and chronic exercise training interventions resulting in reduced circulating concentrations of these markers.[44,45] Given that inflammation is known to be an important independent predictor of hypertension[46,47] through causal pathways of endothelial dysfunction[48] and the proliferation of vascular smooth muscle,[49] it is likely that the anti-hypertensive effects of exercise are partially mediated through a reduction in inflammatory markers. However, epidemiological data and longitudinal training studies of exercise and hypertension have not previously considered inflammation as a co-variable in their final analyses.

Another important factor in the development of hypertension is abdominal obesity and insulin resistance that have been linked with several mechanisms including sympathetic hyperactivity, endothelial dysfunction, vascular stiffening and inflammation.[50] Given that some of the proposed anti-hypertensive mechanisms of exercise training are reductions in SNA and improvements in vascular responsiveness and arterial compliance, it is possible that that these effects are mediated through weight loss or improved insulin sensitivity. Indeed, a recent study in hypertensive patients demonstrated a close association between the reduction in resting BP and plasma noradrenaline and improved insulin sensitivity after 3 weeks of exercise training.[51] However, recent meta-analyses[10,11] have demonstrated that mean BP reduction following exercise training was predicted independently of any weight loss, although these conclusions were based on a small number of study groups. Nevertheless, in order to more fully examine the possible mediating effects of exercise on adiposity, future analysis should include a more accurate assessment of body composition such as abdominal adiposity, which is more closely related to hypertension risk.[46] For example, a recent exercise training study in hypertensive participants showed that a reduction in abdominal adiposity was a significant predictor of the training-induced reductions in systolic BP.[27] However, further studies are needed to confirm these findings.

4.2 Lifestyle and Psychobiological Processes

There are a number of important factors related to lifestyle that are independently associated with a greater risk of hypertension, including smoking,[46] and psychosocial factors,[52-56] which are also known to be affected by exercise.

Cigarette smoking was independently associated with the development of hypertension in a recently published 11-year follow-up study.[46] Recent work suggests that exercise may be a successful intervention for smoking cessation,[57] although longitudinal studies of exercise training and hypertension do not appear to have considered the impact of the training programme on smoking cessation or if this was related to BP reduction.

A number of psychosocial factors have been prospectively associated with hypertension development that include increased BP responses to acute psychological stress,[52,53] increased job strain[54] and depression.[55,56] Following acute exercise, and in physically active individuals, BP responsiveness to a psychosocial stressor is known to be reduced.[58,59] Therefore, reducing daily reactions to stressful situations may certainly be involved with the anti-hypertensive effects of exercise training. Similarly, exercise may blunt BP responsiveness to other pressor stimuli such as caffeine intake, which has been implicated in hypertension.[60] Exercise is also known to reduce symptoms of depression, although this relationship is sometimes observed in the absence of increases in cardiorespiratory fitness.[61] Thus, interaction with fitness instructors and the training environment, which may for example enhance social support and self efficacy, could play an important role in improving aspects of mood that is

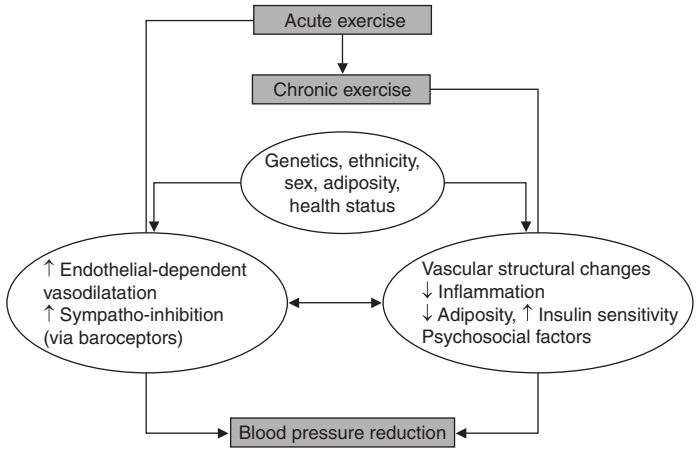

Fig. 1. The integration of acute and chronic anti-hypertensive mechanisms of exercise. ↓ indicates decrease; ↑ indicates increase.

likely to impact upon the anti-hypertensive effects of exercise training. This fact may partly explain why Whelton et al.[10] observed larger BP reductions in short-term exercise training studies that involved supervised training, compared with longer follow-up periods of unsupervised training. Inflammatory processes are also thought to be involved in the aetiology or symptomology of depression[62] and therefore exercise-induced reductions in inflammatory markers may be equally important. Lastly, recent work has suggested that serotenergic function is associated with positive mood,[63] which could provide an important link between PEH and mood given that serotonin has been implicated in PEH.[8]

5. Conclusions and Future Directions

The anti-hypertensive mechanisms of exercise appear to be multi-factorial, and may differ between individuals. This apparent diversity may explain the rather mixed and conflicting findings in this area of research over the last two decades. The close association between acute and chronic mechanisms is inevitable given that the chronic training effect stems from accumulated bouts of acute exercise. However, emerging evidence suggests that the effect of an acute bout of exercise on endothelial-dependent vasodilatation contributes to PEH and may also directly superimpose on the chronic training adaptations associated with BP reduction (see figure 1). The effect of exercise on structural adaptations to the vasculature and other risk factors such as inflammation, insulin resistance, abdominal adiposity, smoking, and psychosocial pathways are likely to play a more important role in relation to chronic training mechanisms. Given the complexity of the interaction between acute and chronic mechanisms, this explains why the American College of Sports Medicine have stated that "the optimal exercise dose (training frequency, intensity, and time) required to lower BP status remains unclear".[1] Given the difficulties associated with adherence to regular exercise, anti-hypertensive mechanisms of acute exercise may be potentially more relevant in relation to hypertension treatment. Therefore, the correct exercise dose for the treatment of hypertension should be prescribed on an individual basis that considers the patient's pre-existing risk factors, acute response to exercise, and genetic make-up.

Future studies that examine the link between PEH and the long-term anti-hypertensive effects of exercise will provide a better understanding of the optimal exercise dosage for the treatment and prevention of hypertension. These studies should include the examination of PEH in relation to exercise training in hypertensive populations, examination of non-responders, and acute and chronic training studies that incorporate independent risk factors of hypertension as co-variables into their analyses.

Acknowledgements

Dr Hamer is supported by a grant from the British Heart Foundation, UK.

References

1. Pescatello LS, Franklin BA, Fagard R, et al. American College of Sports Medicine position stand: exercise and hypertension. Med Sci Sports Exerc 2004 Mar; 36 (3): 533-53
2. Pescatello LS, Kulikowich JM. The aftereffects of dynamic exercise on ambulatory blood pressure. Med Sci Sports Exerc 2001 Nov; 33 (11): 1855-61
3. Jennings GL, Deakin G, Korner P, et al. What is the dose-response relationship between exercise training and blood pressure? Ann Med 1991 Aug; 23 (3): 313-8
4. Meredith IT, Jennings GL, Esler MD, et al. Time-course of the antihypertensive and autonomic effects of regular endurance exercise in human subjects. J Hypertens 1990 Sep; 8 (9): 859-66
5. Pescatello LS, Fargo AE, Leach CN, et al. Short-term effect of dynamic exercise on arterial blood pressure. Circulation 1991 May; 83 (5): 1557-61
6. Folsom AR, Prineas RJ, Kaye SA, et al. Incidence of hypertension and stroke in relation to body fat distribution and other risk factors in older women. Stroke 1990 May; 21 (5): 701-6
7. Haapanen N, Miilunpalo S, Vuori I, et al. Association of leisure time physical activity with the risk of coronary heart disease, hypertension and diabetes in middle-aged men and women. Int J Epidemiol 1997 Aug; 26 (4): 739-47
8. MacDonald JR. Potential causes, mechanisms, and implications of post exercise hypotension. J Hum Hypertens 2002 Apr; 16 (4): 225-36
9. Halliwill JR. Mechanisms and clinical implications of post-exercise hypotension in humans. Exerc Sport Sci Rev 2001 Apr; 29 (2): 65-70
10. Whelton SP, Chin A, Xin X, et al. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann Intern Med 2002 Apr 2; 136 (7): 493-503
11. Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. Hypertension 2005; 46 (4): 667-75
12. Narkiewicz K, Somers VK. Endurance training in mild hypertension: effects on ambulatory blood pressure and neural circulatory control. Blood Press Monit 1997; 2: 229-35
13. Chen HI, Li HT, Chen CC. Physical conditioning decreases norepinephrine-induced vasoconstriction in rabbits: possible roles of norepinephrine-evoked endothelium-derived relaxing factor. Circulation 1994 Aug; 90 (2): 970-5
14. Delp MD, McAllister RM, Laughlin MH. Exercise training alters aortic vascular reactivity in hypothyroid rats. Am J Physiol 1995 Apr; 268 (4 Pt 2): H1428-35
15. Spier SA, Laughlin MH, Delp MD. Effects of acute and chronic exercise on vasoconstrictor responsiveness of rat abdominal aorta. J Appl Physiol 1999 Nov; 87 (5): 1752-7
16. Martin WH, Spina RJ, Korte E, et al. Effects of chronic and acute exercise on cardiovascular beta-adrenergic responses. J Appl Physiol 1991 Oct; 71 (4): 1523-8
17. Maeda S, Miyauchi T, Kakiyama T, et al. Effects of exercise training of 8 weeks and detraining on plasma levels of endothelium-derived factors, endothelin-1 and nitric oxide, in healthy young humans. Life Sci 2001 Jul 20; 69 (9): 1005-16
18. Jungersten L, Ambring A, Wall B, et al. Both physical fitness and acute exercise regulate nitric oxide formation in healthy humans. J Appl Physiol 1997 Mar; 82 (3): 760-4
19. Kingwell BA, Sherrard B, Jennings GL, et al. Four weeks of cycle training increases basal production of nitric oxide from the forearm. Am J Physiol 1997 Mar; 272 (3 Pt 2): H1070-7
20. Huonker M, Halle M, Keul J. Structural and functional adaptations of the cardiovascular system by training. Int J Sports Med 1996 Nov; 17 Suppl. 3: S164-72
21. Wijnen JA, Kuipers H, Kool MJ, et al. Vessel wall properties of large arteries in trained and sedentary subjects. Basic Res Cardiol 1991; 86 Suppl. 1: 25-9
22. Dinenno FA, Tanaka H, Monahan KD, et al. Regular endurance exercise induces expansive arterial remodelling in the trained limbs of healthy men. J Physiol 2001 Jul 1; 534 (Pt 1): 287-95
23. Cameron JD, Dart AM. Exercise training increases total systemic arterial compliance in humans. Am J Physiol 1994 Feb; 266 (2 Pt 2): H693-701
24. Mohiaddin RH, Underwood SR, Bogren HG, et al. Regional aortic compliance studied by magnetic resonance imaging: the effects of age, training, and coronary artery disease. Br Heart J 1989 Aug; 62 (2): 90-6
25. Vaitkevicius PV, Fleg JL, Engel JH, et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults. Circulation 1993 Oct; 88 (4 Pt 1): 1456-62
26. Ferrier KE, Waddell TK, Gatzka CD, et al. Aerobic exercise training does not modify large-artery compliance in isolated systolic hypertension. Hypertension 2001 Aug; 38 (2): 222-6
27. Stewart KJ, Bacher AC, Turner KL, et al. Effect of exercise on blood pressure in older persons: a randomized controlled trial. Arch Intern Med 2005 Apr 11; 165 (7): 756-62
28. Halliwill JR, Taylor JA, Eckberg DL. Impaired sympathetic vascular regulation in humans after acute dynamic exercise. J Physiol 1996 Aug 15; 495 (Pt 1): 279-88
29. Halliwill JR, Dinenno FA, Dietz NM. Alpha-adrenergic vascular responsiveness during postexercise hypotension in humans. J Physiol 2003 Jul 1; 550 (Pt 1): 279-86
30. Convertino VA. Evidence for altered alpha-adrenoreceptor responsiveness after a single bout of maximal exercise. J Appl Physiol 2003 Jul; 95 (1): 192-8
31. Brownley KA, Hinderliter AL, West SG, et al. Sympathoadrenergic mechanisms in reduced hemodynamic stress responses after exercise. Med Sci Sports Exerc 2003 Jun; 35 (6): 978-86
32. Collins HL, DiCarlo SE. Attenuation of postexertional hypotension by cardiac afferent blockade. Am J Physiol 1993 Oct; 265 (4 Pt 2): H1179-83
33. Bennett T, Wilcox RG, Macdonald IA. Post-exercise reduction of blood pressure in hypertensive men is not due to acute impairment of baroreflex function. Clin Sci (Lond) 1984 Jul; 67 (1): 97-103
34. Convertino VA. Baroreflex-mediated heart rate and vascular resistance responses 24h after maximal exercise. Med Sci Sports Exerc 2003 Jun; 35 (6): 970-7
35. Halliwill JR, Minson CT, Joyner MJ. Effect of systemic nitric oxide synthase inhibition on postexercise hypotension in humans. J Appl Physiol 2000 Nov; 89 (5): 1830-6
36. Lockwood JM, Pricher MP, Wilkins BW, et al. Postexercise hypotension is not explained by a prostaglandin-dependent peripheral vasodilation. J Appl Physiol 2005 Feb; 98 (2): 447-53
37. Lockwood JM, Wilkins BW, Halliwill JR. H1 receptor-mediated vasodilatation contributes to postexercise hypotension. J Physiol 2005 Mar; 563 (Pt 2): 633-42

38. Harvey PJ, Morris BL, Kubo T, et al. Hemodynamic after-effects of acute dynamic exercise in sedentary normotensive postmenopausal women. J Hypertens 2005 Feb; 23 (2): 285-92

39. Senitko AN, Charkoudian N, Halliwill JR. Influence of endurance exercise training status and gender on postexercise hypotension. J Appl Physiol 2002 Jun; 92 (6): 2368-74

40. Pescatello LS, Guidry MA, Blanchard BE, et al. Exercise intensity alters postexercise hypotension. J Hypertens 2004 Oct; 22 (10): 1881-8

41. Quinn TJ. Twenty-four hour, ambulatory blood pressure responses following acute exercise: impact of exercise intensity. J Hum Hypertens 2000 Sep; 14 (9): 547-53

42. Hagberg JM, Brown MD. Does exercise training play a role in the treatment of essential hypertension? J Cardiovasc Risk 1995 Aug; 2 (4): 296-302

43. Abramson JL, Vaccarino V. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. Arch Intern Med 2002 Jun 10; 162 (11): 1286-92

44. Adamopoulos S, Parissis J, Kroupis C, et al. Physical training reduces peripheral markers of inflammation in patients with chronic heart failure. Eur Heart J 2001 May; 22 (9): 791-7

45. You T, Berman DM, Ryan AS, et al. Effects of hypocaloric diet and exercise training on inflammation and adipocyte lipolysis in obese postmenopausal women. J Clin Endocrinol Metab 2004 Apr; 89 (4): 1739-46

46. Niskanen L, Laaksonen DE, Nyyssonen K, et al. Inflammation, abdominal obesity, and smoking as predictors of hypertension. Hypertension 2004 Dec; 44 (6): 859-65

47. Sesso HD, Buring JE, Rifai N, et al. C-reactive protein and the risk of developing hypertension. JAMA 2003 Dec 10; 290 (22): 2945-51

48. Verma S, Yeh ET. C-reactive protein and atherothrombosis: beyond a biomarker: an actual partaker of lesion formation. Am J Physiol Regul Integr Comp Physiol 2003 Nov; 285 (5): R1253-6

49. Wang CH, Li SH, Weisel RD, et al. C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. Circulation 2003 Apr 8; 107 (13): 1783-90

50. Rahmouni K, Correia ML, Haynes WG, et al. Obesity-associated hypertension: new insights into mechanisms. Hypertension 2005 Jan; 45 (1): 9-14

51. Kohno K, Matsuoka H, Takenaka K, et al. Depressor effect by exercise training is associated with amelioration of hyperinsulinemia and sympathetic overactivity. Intern Med 2000 Dec; 39 (12): 1013-9

52. Carroll D, Ring C, Hunt K, et al. Blood pressure reactions to stress and the prediction of future blood pressure: effects of sex, age, and socioeconomic position. Psychosom Med 2003 Nov-Dec; 65 (6): 1058-64

53. Matthews KA, Katholi CR, McCreath H, et al. Blood pressure reactivity to psychological stress predicts hypertension in the CARDIA study. Circulation 2004 Jul 6; 110 (1): 74-8

54. Markovitz JH, Matthews KA, Whooley M, et al. Increases in job strain are associated with incident hypertension in the CARDIA Study. Ann Behav Med 2004 Aug; 28 (1): 4-9

55. Davidson K, Jonas BS, Dixon KE, et al. Do depression symptoms predict early hypertension incidence in young adults in the CARDIA study? Coronary Artery Risk Development in Young Adults. Arch Intern Med 2000 May 22; 160 (10): 1495-500

56. Jonas BS, Franks P, Ingram DD. Are symptoms of anxiety and depression risk factors for hypertension? Longitudinal evidence from the National Health and Nutrition Examination Survey I epidemiologic follow-up study. Arch Fam Med 1997 Jan-Feb; 6 (1): 43-9

57. Ussher M, West R, Taylor A, et al. Exercise interventions for smoking cessation. Cochrane Database Syst Rev 2005 Jan 25; (1): CD002295

58. Hamer M, Taylor A, Steptoe A. The effect of acute aerobic exercise on stress related blood pressure responses: a systematic review and meta-analysis. Biol Psychol 2006 Feb; 71 (2): 183-90

59. Crews DJ, Landers DM. A meta-analytic review of aerobic fitness and reactivity to psychosocial stressors. Med Sci Sports Exerc 1987 Oct; 19 (5 Suppl.): S114-20

60. Lane JD, Pieper CF, Phillips-Bute BG, et al. Caffeine affects cardiovascular and neuroendocrine activation at work and home. Psychosom Med 2002 Jul-Aug; 64 (4): 595-603

61. Dunn AL, Trivedi MH, O'Neal HA. Physical activity dose-response effects on outcomes of depression and anxiety. Med Sci Sports Exerc 2001 Jun; 33 (6 Suppl.): S587-97

62. Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychol Rev 1998 Jan; 105 (1): 83-107

63. Flory JD, Manuck SB, Matthews KA, et al. Serotonergic function in the central nervous system is associated with daily ratings of positive mood. Psychiatry Res 2004 Nov 30; 129 (1): 11-9

Correspondence and offprints: Dr *Mark Hamer*, Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London, WC1E 6BT, UK.
E-mail: m.hamer@ucl.ac.uk