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.\textsuperscript{[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\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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\textsuperscript{[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.\textsuperscript{[12]}

Chronic exercise-induced vascular adaptations have also gained significant attention. Although evidence exists in animals to show attenuation in \(\alpha\)-adrenergic responsiveness to noradrenaline after training,\textsuperscript{[13-15]} there is no available evidence in humans, Martin et al.\textsuperscript{[16]} have also shown that \(\beta_2\) 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\textsuperscript{[17]} and nitric oxide (NO), a potent vasodilator, was increased.\textsuperscript{[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.\textsuperscript{[20-22]} Similarly, longitudinal and cross-sectional studies have demonstrated improvements in arterial compliance in healthy normotensive populations,\textsuperscript{[23-25]} although more recent training studies in older hypertensive individuals have not.\textsuperscript{[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. 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 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 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 α1-adrenergic responsiveness does not appear to be blunted after acute exercise but may be increased 24 hours following exercise in humans. Also, conflicting findings exist regarding the effects of acute exercise on β2 receptors, with no effects and increased responsiveness having been shown. A further possible neural mechanism is an increased sympatho-inhibitory input from cardiopulmonary (CP) baroreceptors post-exercise. Collins and DiCarlo showed that PEH was reversed in rats after blocking CP afferents. Also, Bennett et al. 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. Conventino 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 hypovolaemia, 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 or prostaglandins, although they recently showed that histamine contributes to PEH acting via H1 receptors. The H1 receptors are primarily located on the vascular endothelial cells and cause vasodilatation via formation of local vasodilators, 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. 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 (\(\dot{VO}_{2\text{max}}\)) 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% \(\dot{VO}_{2\text{max}}\)) was as effective as a higher intensity bout of exercise (60% \(\dot{VO}_{2\text{max}}\)) 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% \(\dot{VO}_{2\text{max}}\)) compared with exercise at 50% \(\dot{VO}_{2\text{max}}\). 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 covariable 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 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.[66] 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.[56,59] 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 stressor 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
likely to impact upon the anti-hypertensive effects of exercise training. This fact may partly explain why Whelton et al. 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 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, which could provide an important link between PEH and mood given that serotonin has been implicated in PEH.

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 vasodilation 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”. 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.

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

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

References

62. Floey 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