Mechanisms and Clinical Implications of Post-exercise Hypotension in Humans

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INTRODUCTION

Recent studies in humans have demonstrated that immediately after a single bout of exercise, there are profound changes in the mechanisms that regulate and determine arterial pressure. These changes result in a post-exercise hypotension that lasts nearly 2 h in healthy individuals and may last beyond 12 h in hypertensive patients (9). Several reviews have documented many aspects of post-exercise hypotension, including early observations of post-exercise hypotension and the evidence that post-exercise hypotension is also observed in animal models (3,9,14). The primary purpose of this review is to integrate selected recent findings, from human and animal studies, that have contributed to either an enhanced understanding of the mechanisms or an appreciation of the potential clinical relevance of post-exercise hypotension. Recent work suggests that the cause of post-exercise hypotension is two-fold, involving both neural and local mechanisms (5,6). The clinical implications of post-exercise hypotension are only now being investigated in prospective studies, but post-exercise hypotension may contribute to some of the long-term adaptations associated with exercise training, such as amelioration of hypertension and plasma volume expansion.

OVERVIEW OF HEMODYNAMIC CHANGES

Numerous studies have confirmed the existence of post-exercise hypotension in normotensive and hypertensive individuals as well as in several animal models (e.g., spontaneously hypertensive rats) (9). In young healthy normotensive individuals, moderate-intensity dynamic exercise for 30–60 min will produce post-exercise blood pressure reductions on the order of 5–10 mm Hg in the supine position that last several hours. Typically, post-exercise hypotension is more apparent in hypertensive individuals, reaching 20 mm Hg and lasting up to 12 h (4,9). The magnitude of pressure reductions is exaggerated in the seated or standing positions (9).

In comparison with rest (e.g., pre-exercise), post-exercise hypotension is characterized by a persistent drop in systemic vascular resistance that is not completely offset by increases in cardiac output (5–7,9). On a simplistic level, this hemodynamic state can be seen as a transition between that occurring during large-muscle dynamic exercise and that of the resting state. With the termination of exercise, cardiac output declines from high exercising values more rapidly than systemic vascular resistance recovers. This imbalance in the two determinants of arterial pressure results in a hypotension that is maintained for hours. Several other aspects of the post-exercise hemodynamic state merit comments.

First, forearm and calf vascular resistance decreased in parallel with systemic vascular resistance by ~30% (5–7,9). Thus, the vasodilation that underlies post-exercise hypotension is not restricted to the sites of active skeletal muscles (i.e., the legs) but instead involves inactive regions as well (e.g., the arms). Second, the associated rise in arterial blood
inflow through the vasodilated regions contributes to an increase in venous pooling of blood. During exercise, the rhythmically contracting skeletal muscles in the leg reduce the degree of venous pooling by squeezing veins, in effect, pumping blood back to the heart. This "muscle pump" activity is absent during passive recovery from exercise. Third, the increase in venous pooling, in conjunction with the loss of plasma volume associated with exercise, leads to a reduction in central venous pressure (~ 2 mm Hg supine) and cardiac filling pressure (preload) (6). Fourth, despite this fall in cardiac preload, stroke volume is maintained due to the reduction in cardiac afterload and a probable increase in cardiac contractility (5,6). The net result of these influences on the blood vessels and heart is that cardiac output is elevated (heart rate is higher and stroke volume is unchanged compared with before exercise). Thus, it is generally accepted that in most persons, post-exercise hypotension is due to a persistent drop in systemic vascular resistance that is not completely offset by increases in cardiac output.

FACTORs THAT INFLUENCE POST-EXERCISE HYPOTENSION

Several factors have been identified either anecdotally or in prospective studies that can modify the magnitude or duration of post-exercise hypotension.

Exercise Modality, Duration, and Intensity

Post-exercise hypotension can be observed after several modes of large muscle mass dynamic exercise (e.g., cycling or running) (9). Although shorter or less vigorous exercise protocols elicit inconsistent changes in arterial pressure in normotensive individuals, post-exercise hypotension is consistently elicited after longer (30–60 min) bouts of moderate-intensity (50–60% Vo2peak) exercise. Shorter (< 30 min) and less intense bouts of exercise may readily produce post-exercise hypotension in hypertensive patients but not in normotensive individuals. It is unknown what effect exercise training has on these "dose-response" relationships to exercise.

Environmental Factors

Many of the environmental factors that have an impact on post-exercise hypotension can be predicted by understanding the fundamental hemodynamic changes outlined in Figure 1. It is expected that exercise in a hot environment will exacerbate post-exercise hypotension in two ways: a greater loss of plasma volume due to sweating and a greater drop in vascular resistance due to vasodilation of the cutaneous circulation. In contrast, fluid replacement may lessen post-exercise hypotension (2). Active recovery, by maintaining action of the muscle pump, would likely reduce post-exercise hypotension compared with passive recovery, but this has not been studied systematically. Orthostasis (e.g., seated upright or standing recovery from exercise) positions the major vasodilated vascular beds below heart level and exaggerates the magnitude of venous pooling. This could further reduce central venous pressure, cause cardiac output to fall, and result in reduced orthostatic tolerance.

Population Differences

Post-exercise hypotension has been observed in numerous populations, including young and older normotensive men...
MECHANISMS OF POST-EXERCISE HYPOTENSION

Recent research has focused on the mechanisms responsible for the sustained decrease in regional and systemic vascular resistances after a single bout of exercise. Findings indicate that this sustained vasodilation is associated with two alterations in sympathetic vascular regulation: what has been defined as a “neural” and a “vascular” component (5) (as shown in Figure 2). The neural component of this vasodilation is a reduction on the order of ~30% in the outflow of sympathetic vasoconstrictor nerve activity to skeletal muscle vascular beds (5,9). The vascular component refers to the attenuation of vascular responses to sympathetic vasoconstriction, as well as the potential influence of local and circulating vasodilator substances.

Sympathoinhibition After Exercise

Multiple studies have documented that the amount of activity in the sympathetic nerve fibers that control vasoconstriction in the leg is inhibited during post-exercise hypotension in humans (5,7,9) and in some animal models (10). Under resting conditions, muscle sympathetic nerve activity is under strong regulation by the arterial baroreflexes and cardiopulmonary receptor reflexes. During exercise, the baroreflex is “reset” to a higher operating point and sympathetic activity is increased. After exercise, these reflexes are reset to lower pressures such that sympathetic outflow from the central nervous system is lower than pre-exercise levels (3,5). Early studies in animals suggested that this sympathoinhibition might be the result of activation of endogenous opioid receptor pathways in the central nervous system (14). Although this was a popular notion, it does not appear to be the case during post-exercise hypotension, in that the blockade of opioid receptors with naloxone does not alter post-exercise sympathetic nerve activity or arterial pressure in humans (7), and the more recent research on this mechanism in animals has had inconsistent results (13). The central nervous system mechanisms involved in baroreflex resetting during exercise and post-exercise hypotension are unknown.

Vasodilator Substances

In addition to reductions in sympathetic outflow, vascular responsiveness to α-adrenergic receptor stimulation is impaired so that vascular resistance is reduced for a given level of nerve activity after exercise (3,5,12). The nature of this vascular component of post-exercise hypotension is unknown, but ineffective transduction of sympathetic outflow into vascular resistance could be the result of competing influences at the level of the arterial smooth muscle, such as the release of local vasodilator substances, or by modulation of the α-adrenergic pathway (e.g., either presynaptic or postsynaptic inhibition).

Factors associated with acute exercise, such as increases in blood flow, cyclic wall stress associated with pulsatile blood flow, and catecholamines, stimulate the release of nitric oxide from the vascular endothelium. In fact, studies in humans have suggested that nitric oxide production may be increased after acute exercise (11). It is also well established that nitric oxide attenuates the vasoconstrictor response to α-adrenergic receptor stimulation. Along these lines, evidence in animal models (3,12) suggests that
nitric oxide contributes to post-exercise hypotension by blunting vasoconstrictor responses. However, there are a number of other potential vasodilators that could potentially modify α-adrenergic responsiveness, as illustrated in Figure 3.

**Recent Observations**

Two recent studies attempted to address the importance of neural (sympathoinhibition) and vascular (vasodilator substances) effects in mediating post-exercise hypotension. First, a study by VanNess et al. (15) used a ganglionic receptor antagonist to block sympathetic outflow in rats. This intervention resulted in a > 85% reduction in post-exercise hypotension (from −9 to −1 mm Hg). In contrast, a study by Halliwill et al. (6) used an infusion of an α-adrenergic antagonist to block sympathetically mediated vasoconstriction in normotensive humans. This intervention did not alter post-exercise hypotension (Figure 4), although it appeared that ~ 30% of the drop in systemic vascular resistance could be attributed to loss of sympathetic vasoconstriction after exercise. The authors were unable to attribute any of the reductions in regional vascular resistance or arterial pressure to changes in sympathetic vasoconstriction. These results are perplexing and suggest that the role of sympathoinhibition in causing post-exercise hypotension is both complex and limited in normotensive humans. It is possible that the role of sympathoinhibition is more pronounced in patients with elevated levels of sympathetic activity (e.g., primary hypertension).

Recent work has also investigated the role of nitric oxide–mediated vasodilation after exercise. Halliwill et al. (6) tested the extent to which, in normotensive humans, systemic nitric oxide synthase inhibition can reverse post-exercise hypotension. They found that arterial pressure continues to be lower after exercise compared with a control day, even after the blockade of nitric oxide production (Figure 4). Thus, in contrast to animal studies, it does not appear that post-exercise hypotension is dependent on increased production of nitric oxide in normotensive humans. It must be noted that in this study, nitric oxide synthase inhibition was performed after α-adrenergic receptor blockade, to isolate the effects of humoral dilators from ongoing neural changes. As such, this study cannot exclude a role for nitric oxide in modifying α-adrenergic responses after exercise.

In this context, it is becoming evident that sympathoinhibition and changes in nitric oxide production cannot account for all of the vasodilation after exercise. It seems likely that some factor or factors are released by the exercised muscle (e.g., adenosine, prostaglandins) and continue to reduce vascular tone for an extended period of time after exercise ceases. Unfortunately, the identity of a single such substance is likely to remain elusive, and multiple substances may be involved. In summary, many of the earlier tenets regarding post-exercise hypotension in humans are being rewritten as our understanding of the phenomenon advances. A future area of research will be extending this understanding to why post-exercise hypotension is more pronounced in individuals with hypertension (i.e., what mechanism or mechanisms are augmented in that state?).

**Clinical Implications of Post-Exercise Hypotension**

Neither the physiological nor the pathophysiological consequences of post-exercise hypotension have been studied systematically, despite the demonstration of alterations in cardiovascular regulation after exercise. However, several important observations hint at the clinical significance of post-exercise hypotension.

**Orthostatic Hypotension and Syncope**

From the changes outlined in Figure 1, it can be inferred that post-exercise hypotension has many characteristics that would contribute to orthostatic hypotension and predispose toward syncope. The ability to defend against orthostatic stress is compromised by enhanced venous pooling, reduced venous return, and reduced sympathetic outflow.
more, the baroreflexes are reset to defend pressure at a lower level (6). Thus, orthostatic tolerance is often reduced in healthy individuals during the first hours after exercise, and syncopal episodes are not uncommon immediately after exercise. Studies have not identified what factors might influence the incidence of orthostatic intolerance after exercise or determined the extent to which post-exercise hypotension in the supine position would predict orthostatic intolerance after exercise.

Long-Term Adaptations and Hypertension

Hypertension is a major health issue in the United States. One in four adults in the United States (~50 million individuals) have hypertension. Thus, development and understanding of nonpharmacological treatment modalities for hypertension continue to deserve high priority. Along these lines, aerobic exercise has come to the forefront of nonpharmacological treatments for hypertension. The antihypertensive effects of aerobic exercise are poorly understood, but it is likely that the mechanisms that play a role in mediating post-exercise hypotension are linked to long-term adaptations that occur during exercise training and, thus, are important to understand. The extent to which the pressure-lowering effects of exercise training reflect the integration or carryover of the acute effects of exercise (i.e., post-exercise hypotension) remains unknown. To date, definitive studies linking post-exercise hypotension to the long-term antihypertensive adaptations associated with exercise training have yet to be conducted. Of note, several studies by Cléroux and co-workers have shown the effects of antihypertensive medications are often additive with post-exercise hypotension (1).

Changes in Fluid Balance

It is intriguing to speculate that post-exercise hypotension may serve some homeostatic purpose. One such purpose may be the newly identified role that post-exercise hypotension appears to play in the recovery of plasma volume after exercise. In a recent study by Hayes et al. (8), a phenylephrine (α-adrenergic agonist) infusion was used to prevent post-exercise hypotension during the first 90 min after exercise. When compared with a control day on which post-exercise hypotension was allowed to occur, the normal recovery of plasma volume was prevented by >50% when post-exercise hypotension was blocked. It is believed that increased plasma albumin contributes to the plasma volume recovery and subsequent volume expansion after exercise, and this mechanism may be linked to post-exercise hypotension by the pressure-dependent transcapillary escape rate of albumin. In other words, when pressure is lower (i.e., during post-exercise hypotension), more albumin stays in the intravascular space and more fluid is drawn into that space from the extravascular space. It remains to be seen whether post-exercise hypotension has a similar facilitative effect on the plasma volume expansion that occurs 24 h after a single bout of exercise.

SUMMARY

A review of the evidence indicates that post-exercise hypotension is common after moderate-intensity dynamic exercise in both normotensive and hypertensive individuals and that hemodynamic responses are greater in hypertensive patients. The hypotension results from persistent reductions in vascular resistance, mediated by the autonomic nervous system and vasodilator substances. Post-exercise hypotension may play an important role in recovery of plasma volume after exercise and may be linked to long-term adaptations to exercise training.

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References