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INVITED REVIEW

Blood pressure regulation XI: overview and future research directions

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Abstract While the importance of regulating arterial blood pressure within a 'normal' range is widely appreciated, the definition of 'normal' and the means by which humans and other species regulate blood pressure under various conditions remain hotly debated. The effects of diverse physiological, pathological and environmental challenges on blood pressure and the mechanisms that attempt to maintain it at an optimal level are reviewed and critically analyzed in a series of articles published in this themed issue of the *European Journal of Applied Physiology*. We summarize here the major points made in these reviews, with emphasis on unifying concepts of regulatory mechanisms and future directions for research.

Keywords Arterial baroreflex resetting · Cardiac output · Hemodynamic responses · Hypertension · Reactive oxygen species · Set-point theory · Operating point · Total peripheral resistance

Abbreviations

MAP	Mean arterial pressure
NTS	Nucleus tractus solitarii
ROS	Reactive oxygen species
NO	Nitric oxide
Ang II	Angiotensin II

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Introduction

The fundamental relationships between hemodynamics and regulation of arterial blood pressure are well established. For example, arterial blood pressure, or blood pressure, is positively related to cardiac output (heart rate × stroke volume) and total peripheral vascular resistance; with the latter being strongly influenced by sympathetically mediated vasoconstriction. The benefits of maintaining blood pressure at a 'normal' pressure are also widely appreciated. A decrease in blood pressure may decrease blood flow and oxygen delivery to peripheral tissues and potentially compromise cellular and organ system function. Conversely, an increase in blood pressure may cause devastating end-organ damage. In addition, the mechanistic role of the arterial baroreceptor reflexes in regulating the arterial blood pressure in a negative-feedback manner have been identified (Chapleau 2012). Other negative-feedback mechanisms including the renin-angiotensin system and the renal pressure natriuresis response contribute to arterial blood pressure regulation, albeit with a slower time course than the arterial baroreceptor reflexes. The fundamental relationships and concepts described above would suggest that the blood pressure is very tightly regulated around a 'set point' via adaptive changes in cardiac output, peripheral resistance, and blood volume. Examination of cardiovascular and autonomic nervous system responses to physiological, pathological and environmental challenges known to change blood pressure provides insights into the mechanistic nature of integrative blood pressure regulation.

In the introductory article of this themed issue, Joyner and Limberg (2014) clearly set the stage for the remaining articles. They show that the effectors that determine ones blood pressure (e.g., heart rate, cardiac output, sympathetic nerve activity, vascular responsiveness) vary in their contributions to the changes in blood pressure depending on age, sex and situation. Thus, the mechanisms regulating ones blood pressure are not constant but change under various conditions. The authors also provide illuminating examples of the marked changes in blood pressure that occur in healthy individuals during normal daily activities including: (1) the diurnal variation in an individual's blood pressure, (2) the wide range of resting blood pressures observed in healthy individuals, (3) the extremely high, yet regulated, blood pressures that occur during heavy weight lifting, and (4) the phenomenon of post-exercise hypotension. The question is raised that if blood pressure is the regulated variable why does the operating pressure (i.e., the regulated pressure) "reset" to a different blood pressure during different physiological and pathophysiological stressors? The results clearly demonstrate that blood pressure is not well regulated around a single, absolute 'set-point' blood pressure.

The authors emphasize that while redundant mechanisms help preserve maintenance of one's blood pressure at optimal pressures, other important regulated variables such as blood flow and/or oxygen delivery to the brain or contracting skeletal muscle may contribute to the blood pressure under different conditions. Thus, physiological adaptations to various challenges represent an integration of multiple control systems. We provide below a summary of the additional nine invited articles classified under four themes.

When one system must serve two (or more) masters

While blood pressure is clearly an important regulated variable, other regulated variables that may influence arterial blood pressure exist including blood flow and/or oxygen delivery to contracting skeletal muscle, skin and brain. Ichinose et al. (2014) provide a detailed description of the physiological challenge of providing sufficient blood flow and oxygen delivery to contracting skeletal muscle to meet the very high metabolic demand of performing near-maximal whole body exercise, with the excessive vasodilation potentially decreasing the resultant blood pressure. The authors discuss: (1) the influence of the major neural inputs (i.e., central command, mechano- and metabo-receptors within skeletal muscle, cardiopulmonary baroreceptors within the heart and adjacent vessels) on arterial baroreflex control of blood pressure and muscle sympathetic nerve activity; and (2) the interaction between the muscle mechano- and metabo-receptor afferent inputs in determining baroreflex control of muscle sympathetic nerve activty (MSNA) and vascular tone in contracting skeletal muscle. As noted by Joyner and Limberg (2014) in their interpretation of Calbet's et al. (2004) data, it could be argued that the delivery of oxygen to the exercising muscles is of more importance than regulating the blood pressure at a specific 'set point' because as the active muscle mass increases, the regulated mean arterial blood pressure decreases [see Fig. 6 in Joyner and Limberg (2014)]. Highly trained endurance athletes have been shown to tolerate lower blood pressures to enable higher blood flows to the active skeletal muscles during whole body exercise. The significance of needing to understand the mechanisms of blood pressure control during acute and chronic physical activity becomes manifest when the human has functional limitations because of metabolic, cardiopulmonary and/or musculo-skeletal disease. For example, a growing body of evidence identifies that exercise-induced hypertension and its increased risk of exertion related stroke and post-exercise sudden cardiac death may be a result of exacerbated signaling from the skeletal muscles, the renin-angiotensin system, cardiopulmonary baroreceptor loading and/or the central nervous system integration.

Kenney et al. (2014) provide a different view of the interaction that must occur between temperature regulation and blood pressure regulation during exercise in hot ambient temperatures. Since early times this interaction was approached as one of competition that would occur when high intensity exercise is performed in high ambient temperatures. The current thinking would require the central nervous system to make a hierarchical decision between the circulatory needs as to whether to regulate body temperature and reduce blood pressure and hence, reduce the delivery of oxygen to the working muscles, or vice versa. The authors summarize the central and peripheral circulatory adjustments and baroreflex regulation of blood pressure of young healthy humans at rest undergoing passive heating. They concluded, as did Rowell (1974), that at rest the blood pressure was well maintained under extreme heat conditions that demand large increases in skin blood flow. With the addition of high intensity dynamic exercise, the authors use more recently published data that indicate that the reductions in cutaneous blood flow because of actively diverting blood flow and oxygen to the active muscle does not impair heat loss mechanisms in young healthy humans. These circulatory adjustments are examples of "commensalism", i.e., in this case a sharing of the same cardiac output with one system (O_2 delivery to the active muscles) making major adjustments, while the function (temperature regulation) of the other circulation is unaffected. The authors point out that it is the inability of either the cutaneous or skeletal muscle blood flow to increase limitlessly that sets functional limits for both circulations to maintain

arterial blood pressure. However, there have been a number of high profile examples of elite endurance athletes exercising in the heat that demonstrate that the limits of "commensalism" can be surpassed resulting in impairment of neuromuscular function, especially when subjects are dehydrated.

Consequences of chronic changes in vascular pressures on cardiovascular structure and function

Chronic changes in intravascular pressures lead to structural and functional changes in the cardiovascular system with implications for blood pressure regulation. For example, loss of gravitational forces during exposure to microgravity during spaceflight or during extended periods of bedrest lead to redistribution of blood volume, cardiac and vascular structural/mechanical changes, and alterations in neurohumoral regulation. Chronic hypertension leads to cardiac and vascular hypertrophy, with the thick-walled arterioles amplifying vasoconstrictor responses. Norsk (2014) examines the effects of decreasing gravitational load (microgravity) on blood pressure regulation. He presents evidence that in space flights ranging from 2 weeks to 6 months in duration, arterial blood pressure of humans is regulated at the same pressure as that observed in the supine position at 1.0 G atmospheric pressure. However, the stroke volume and cardiac output are increased with an unchanged heart rate resulting in decreases in systemic vascular resistance. Norsk also reports that in-flight muscle sympathetic nerve activity is increased, vagal control of heart rate is diminished, and the heart rate, diastolic blood pressure and muscle sympathetic nerve activity responses to lower body negative pressure in-flight are augmented. Norsk hypothesizes that natriuretic peptides released from the distended cardiac chambers in microgravity cause vasodilation and decreased arterial blood pressure, with the latter resulting in baroreflex-mediated increases in sympathetic activity. However, in-flight measures of plasma natriuretic peptides have not been obtained. Other possible mechanisms include: (1) in-flight vascular remodeling resulting in a decreased myogenic tone; and/or (2) a decrease in vasoconstrictor responsiveness to circulating norepinephrine because of decreased alpha adrenergic receptor density or sensitivity.

Eiken et al. (2014) describe the adaptations of the pre-capillary blood vessels to sustained increases and decreases in intra-luminal pressure. The authors identify that smooth muscle adaptations are responses to sustained increases and decreases in blood pressure and the loading and unloading, respectively, on the blood vessel walls. However, the increases in the transient pulsating beat-to-beat pressures have little effect on the vessel's adaptive response. Furthermore, the adaptations are regulated by local mechanisms and the readiness by which the adaptations to pressure-distension stresses occur indicate that the pre-capillary wall stiffness is involved in blood pressure regulation. Because the human's daily activities occur in the upright posture, the blood vessels mainly affected by the increased intra-luminal pressures are in the gravity-dependent vessels of the legs. In conditions where dependent intra-luminal pressures are reduced (prolonged bed rest, space flight, water immersion, etc.) for sustained periods, orthostatic intolerance occurs.

Homeostatic physiological adaptations vs. pathological processes

Physiological adaptations to various stressors often lead to adaptive, beneficial changes, but may also lead to pathological processes, particularly in chronic states. Taylor and Tan (2014) raise the intriguing question as to whether the age-related increase in muscle sympathetic nerve activity is obligatory for an age-related increase in mean arterial blood pressure. The authors raise the question because not all middle-aged and older individuals that have high sympathetic activity have hypertension. In addition, the authors propose that the age-related changes in cardiac output, total peripheral vascular resistance and blood pressure can be explained as parallel phenomena rather than a deterministic outcome of physiological aging. Their argument is supported by identifying that although there is an age-related increase in sympathetic outflow there is evidence that its effect on peripheral vasoconstriction is diminished. The mechanism involved in the reduced sympathetically mediated peripheral vasoconstriction may be a function of diminished alpha-1 adrenergic receptor density in relation to available nitric oxide (NO) and/or beta-2 adrenergic receptor density providing more vasodilator capacity in response to circulating catecholamines. The authors conclude that the high sympathetic activity in the elderly is likely to be homeostatic in terms of maintaining normal mean BP, and is not a primary cause of increased total peripheral vascular resistance and hypertension.

Atkinson et al. (2014) address the well-documented "morning surge" in arterial blood pressure in terms of accuracy of measurement, reliability and clinical relevance. There are five main measurement methodologies, each with a standard deviation of test–retest differences of +11 mmHg. It was generally accepted that individuals with exacerbated morning surges in blood pressure were at risk for cardiovascular disease. However, a new study that normalized the morning blood pressure surge with the individual's nightly "dipping status" appeared to eliminate any correlation between the magnitude of morning blood pressure surge and cardiovascular disease. The

author's summary identifies that to date there is no precise link between the morning surge in blood pressure and an increased risk of cardiovascular disease.

Padilla et al. (2014) develop a novel postulate that a pro-atherogenic conduit artery cell phenotype results in part from the increased microvascular tone of the downstream skeletal muscle resistance arteries. This increased microvascular tone of the resistance arteries results in increases in upstream mean arterial blood pressure and oscillatory shear stress within the conduit arteries. These changes in blood pressure and shear stress patterns resulting from the increases in sympathetic nerve activity and/or NO availability modulate the skeletal muscle's microvasculature tone. Thus, this mechanism renders the conduit arteries more susceptible to atherosclerotic peripheral artery disease, especially in the presence of hypertension.

Cerebral autoregulation and post-exercise hypotension and syncope

Tzeng and Ainslie (2014) review the methods used to evaluate cerebral autoregulation during changes in blood pressure. With the development of Doppler ultra-sound technology and its use in measuring cerebral arterial blood velocities and internal carotid artery blood flows, along with magnetic resonance imaging and functional magnetic resonance imaging of metabolic brain activity, our understanding of the link between brain metabolism and cerebral blood flow regulation has advanced exponentially. However, despite these technological advances, the authors identify a number of measures of cerebral blood flow regulation that remain questionable because of a lack of understanding of the basic relationship between linear and non-linear analysis techniques and their physiologic interpretation. They present many examples of such confusion and conclude that the hemodynamic properties of cerebral autoregulation remain muddled, misinterpreted, and misunderstood. The authors conclude that there is a need to revisit the assumptions underlying the scientific characterization of cerebral autoregulation to clearly identify the physiological and pathophysiological differences between a healthy and a diseased cerebral circulation.

Halliwill et al. (2014) provide an in-depth analysis of the currently accepted mechanisms that form the basis of our understanding of post-exercise hypotension and reductions in cerebral perfusion that may or may not lead to neurogenic hypotension. The obligatory mechanisms include: (1) post-exercise baroreflex resetting and blunted transduction and resetting of the thermo-reflexes, and (2) post-exercise vasodilatation via pre-synaptic inhibition of sympathetic vasoconstrictor nerves and activation of H_1- and H_2-receptors in the exercised muscle (most important). In addition, the blood pressure regulation during recovery from exercise is affected by situational mechanisms that include: (1) fluid status, (2) an individual's heat balance with the environment; and (3) the presence or absence of gravitational stress. However, investigations into which of these mechanisms underlie the immediate onset of post-exercise syncope and/or sudden cardiac death would require more sophisticated measurement and analysis of cardiorespiratory data obtained at the off-response transition.

The authors follow this introduction by exploring the modes of exercise and environments that predispose one to post-exercise syncope, such as: (1) moderate exercise intensity of an hour or more, (2) high intensity exercise of short duration, (3) exercise in the heat, (4) exercise at altitude, and (5) resistance exercise. Subsequently the authors identify possible countermeasures to post-exercise syncope that include: (1) behavioral maneuvers, e.g., maintenance of skeletal muscle pump activity, use of inspiratory resistance breathing, cool water ingestion, assumption of the Trendelenburg position, or use of compression garments on legs, (2) administration of pharmacological agents, e.g., β_2-adrenergic and H_1- and H_2-receptor antagonists, and (3) mechanical interventions, e.g., placement of cardiac pacemaker.

Subsequently, we will attempt to provide the readers with a forward look into the new questions to be addressed with a primary focus on using our understanding of the physiological mechanisms of blood pressure regulation to identify pathologies of hypertension.

Unifying concepts of blood pressure regulation

Several conclusions can be drawn and unifying concepts developed from the material presented in this series of articles. Furthermore, the articles provide established and young investigators with a guide to a number of relevant questions that require further investigation. Answers to these questions are sure to expand our understanding of the physiological mechanisms involved in blood pressure regulation and the causes of impaired blood pressure regulation in disease. In answering these questions, the balance between the demand for blood flow (oxygen) and blood pressure regulation seems to be of major importance. Concepts and questions are listed below, with added discussion of relevant topics related to blood pressure regulation and future directions for research. Presumably, sensory nerve activity and humoral factors released into the blood signal the central nervous system of the ongoing physiological state. Central nervous system interactions of the various inputs differentially modulate regional autonomic nervous system outflows.

While mean arterial blood pressure is tightly regulated in the short term by the arterial and cardiopulmonary baroreflexes (and other mechanisms) under defined conditions, physiological demands/challenges evoke substantial changes in blood pressure. Thus, the absolute blood pressure is not rigorously maintained. However, the regulatory mechanisms appear to maintain blood pressure within a range of normal, thus minimizing the deleterious consequences of very low or very high-blood pressures (e.g., ischemia, end-organ damage, myocardial infarction, stroke, etc.). Cannon (1929) realized the importance of active regulation of blood pressure (and other variables) by the autonomic nervous system, naming the process "homeostasis", and recognized the presence of some variation in the regulated variables. However, we suggest the following questions need to be answered:

1. How much regulation is enough? Is the regulated blood pressure an absolute "set" pressure (homeostatic) or is it a more dynamic (homeokinetic) range of pressures?
2. Do sensory signals triggered by ischemia or end-organ damage define the limits of regulation?
3. Do repeated physiologically induced increases in blood pressure cause end-organ damage?
4. Are end-organs protected during exercise-induced increases in blood pressure? If so, what are the mechanisms?
5. Do high-blood flow states during exercise or between contractions confer protection?

During aerobic and resistance exercise, changes in blood pressure may occur because of influences of other important regulated variables affecting blood pressure. Examples of this competition include blood flow or oxygen delivery to exercising skeletal muscle, skin, or brain. High demand of blood flow to specific critical regions may require excessive vasodilation, thereby resulting in decreased arterial blood pressure or, in the case of resistance exercise mechanical constriction of blood vessles, increases in blood pressure. Tissues may compete for a limited share of the cardiac output and simultaneously limit the maximum cardiac output, exacerbating the situation. Adaptive regulatory responses may lead to pathological processes and disease, particularly when chronically engaged. For example, chronic activation of the sympathetic nervous system and/or the renin-angiotensin system often leads to chronic hypertension and heart failure. Furthermore, chronic increases in BP cause end-organ damage, which often exacerbates pathological processes that worsen the hypertension and/or lead to organ system failure (e.g., heart failure, kidney failure and stroke). Oxidative stress and inflammation have been causally implicated in chronic hypertension.

Therefore, we suggest a number of additional questions that need to be addressed:

1. How does the body know which tissues are most in need of blood flow and/or oxygen delivery?
2. How does it determine the optimal allocation of blood flow to various regions?
3. What is the relative role of adaptive homeostatic responses vs. pathological processes in causing chronic hypertension?
4. Is essential hypertension and/or exercise-induced hypertension a disturbance of normal blood pressure regulatory mechanisms or a pathological consequence of some other abnormality?

Evidence suggests that long-term blood pressure regulation is influenced by the renin-angiotensin system, the renal pressure natriuresis response, inflammation and, more recently, the arterial baroreceptor reflexes. Further characterization of the role of the renin-angiotensin and the renal pressure natriuresis response in the acute regulation of arterial blood pressure needs to be identified.

Future directions

In many conditions (e.g., exercise), changes in mean arterial blood pressure are accompanied by a resetting of the baroreceptor reflex function curve to higher (or lower) pressures, with preservation of baroreflex sensitivity to acute changes in blood pressure. Thus, blood pressure often continues to be regulated acutely at the new prevailing mean blood pressure ('operating point') required by the new 'set point'. The mechanisms responsible for changes in mean arterial blood pressure during physiological challenges may be adaptive with beneficial consequences. For example, increased blood pressure during isometric exercise may promote increased blood flow through mechanically compressed arteries in the contracted muscle. In other words, blood pressure may be regulated at the new prevailing 'set-point' pressure to optimize specific organ system functions. While negative-feedback mechanisms are usually emphasized when discussing blood pressure regulation, feed-forward mechanisms might be expected to drive changes in blood pressure toward a new 'set point'. When blood pressure is changed from rest, the mechanoreceptors within the walls of the arterial baroreceptors sense a change in blood pressure and the afferent nerve traffic to the NTS increases with hypertension and decreases with hypotension. These changes in afferent nerve traffic from the arterial baroreceptors are integrated with other sensory inputs within the NTS. One theory is that an error signal between

the operating pressure and a central 'set-point' pressure elicits an efferent reflex response to the heart and blood vessels to correct the operating pressure to reflect the 'set-point pressure'. In contrast to invasive measurements from exercising canines (Melcher and Donald 1981; Walgenbach et al. 1981), early measurement technologies used in humans to assess arterial baroreflex function during exercise indicated that the baroreflex was "turned off" (Bristow et al. 1971). However, in the past 20 years, the use of the non-invasive variable pressure neck collar modeling of heart rate and arterial baroreflex function curves has established that the baroreflex is reset to higher operating pressures directly and linearly related to workloads (Fadel and Raven 2012). Joyner and Limberg (2014) identify that the acute operating pressure resetting is a result of the integration between cardiac output and total peripheral resistance and that this adaptation is modulated by subject age, central blood volume and endurance training history. Flaws in the 'error signal/set point' concept in engineering-based models of physiological regulatory systems have been identified (Cannon 1929; Mekjavic and Eiken 2006). Can these flaws be resolved in studies of blood pressure regulation? An overview of some of the approaches used to model blood pressure regulation is provided in Korner (2007).

Current evidence indicates that during exercise there are four functional neural mechanisms involved in arterial blood pressure regulation, these being: (1) central command; (2) the exercise pressor reflex; (3) the arterial baroreflexes; and (4) the cardiopulmonary baroreflexes, all of which play important roles in determining the magnitude of acute baroreflex resetting and the new 'set-point' blood pressure (Fadel and Raven 2012). Central command is a primary feed-forward mechanism and the exercise pressor reflex is a primary feedback mechanism both of which integrate within the NTS and are modulated by the arterial and cardiopulmonary baroreceptor's afferent neural information regarding arterial pressure and central blood volume, respectively. These integrated inputs to the NTS are referenced against the 'set point' leading to reflex responses that change cardiac output and total peripheral resistance, and thereby 'reset' the operating arterial blood pressure around which the arterial baroreceptor reflex regulates the arterial blood pressure.

A variety of experimental approaches will be needed to answer the many unanswered questions. These include studies in animal models in which key sensory inputs to the brain are controlled in a precise manner during physiological challenges. In addition, integrative studies in humans in which cardiovascular reflexes can be characterized in a selective manner will be needed to demonstrate the applicability of the animal models. New technologies enabling selective optogenetic activation and/or silencing of specific cardiovascular regulatory regions of the brain and site-selective, inducible gene modification will provide insights into the central nervous system circuitry and underlying genetic and molecular determinants of the central integration of reflexes. The study of human subjects with defined characteristics and mutations in genes linked to autonomic regulation will enable translation of this information to the clinic.

However, resting pre-essential hypertensive and some normotensive patients have an exacerbated blood pressure response to exercise (Manolio et al. 1994; Matthews et al. 1998; Miyai et al. 2002; Pescatello et al. 2004), which even if related to an exacerbated exercise pressor reflex input to the NTS involves the ROS scavenging of NO (Leal et al. 2012, 2013). It is not unusual for a cardiology clinic population referred for evaluation of exertional chest pain to identify that 20–25 % of referrals having a negative EKG stress test will have a hypertensive response to exercise. Exercise-induced hypertension indicates an exacerbated resetting of the arterial baroreflex's operating point blood pressure and when this occurs at a young age identifies a 3- to 5-fold increased risk of progressing to essential hypertension at an older age. Chronic central oxidative stress is implicated in impaired autonomic regulation of cardiovascular function associated with aging (Monahan et al. 2004), hypertension (Grassi et al. 2004), chronic heart failure (Nightingale et al. 2003), and obstructive sleep apnea (Yamauchi and Kimura 2008). Central electron transport chain and Ang II linked ROS production scavenges NO resulting in an increased central sympathetic neural outflow (Aslan et al. 2001; Fisher and Fadel 2010; Jiang et al. 1996; Waki et al. 2008). The Ang II linked ROS production is recognized as a major mechanism involved in neurogenic hypertension (Paton and Waki 2009; Waki et al. 2011; Zubcevic et al. 2011). One caveat regarding the etiology of exercise-induced hypertension is related to age-related arterial blood vessel stiffening and subsequent increases in stroke ejection velocity increasing dependent blood vessel hypertrophy and hyperplasia, which is linked to hypertension (see review article BP regulation VIII Padillia et al. 2014). For a more in-depth review of the central ROS mechanisms involvement in hypertension and associated maladies that appear to be related to central sympathetic overactivity you are referred to a recent review by Fisher and Fadel (Fisher et al. 2009). Based on the identification of the possible central mechanisms, a number of innovative treatment strategies focused on reducing the central sympathetic overactivity have been initiated (Fisher and Fadel 2010).

Conclusion

Because many activities of daily living require us to engage in mild to heavy intensity exercise in a variety of

environmental conditions, a number of areas of investigation need to be addressed to identify if the effective treatments of hypertension at rest do not compromise blood pressure regulation during increases in physical activity. These include investigating: (1) behavioral modification (endurance exercise training, weight loss by diet and/or exercise and stress/relaxation therapy), (2) newly developed pharmacological treatments, (3) surgical treatments including renal denervation, chronic deep brain stimulation and carotid baroreflex stimulation.

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