Controls of Central and Peripheral Blood Pressure and Hemorrhagic/Hypovolemic Shock

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Abstract: The pressure exerted on the heart and blood vessels because of blood flow is considered as an important parameter for the cardiovascular function. It determines sufficient blood perfusion as well as transportation of nutrition, oxygen and other essential factors to every organ. Pressure in the primary arteries located near the heart and the brain, known as central blood pressure (CBP), while in peripheral arteries, known as peripheral blood pressure (PBP). Normally, CBP and PBP are correlated; however, cardiovascular disorders interfere their regulation and affect the blood flow in vital organs and accessory organs, differently. Therefore, understanding each of them in normal and disease conditions is essential for managing various cardiovascular disorders and increasing their treatment outcomes. In this review, we have described the control systems (neural, hormonal, osmotic and cellular) of the blood pressure and its regulation in hypovolemic shock using centhaquine (Lyfaquin®) as a resuscitative agent.

Keywords: Blood Pressure; Cardiovascular Disorder; Hypertension; Hypotension; Hypoxia; Baroreflex; Hypovolemic Shock; Vasopressors; Centhaquine (Lyfaquin®), Resuscitation; Sympathetic System; Parasympathetic System; and Adrenoreceptors.

Introduction:

Our circulatory system is a highly complex closed cardiovascular organ system equipped to transport essential substances required for survival, sustainability, and function of tissues / organs in the body [1]. It is one of the key organ systems, which develops as the first organ system during organogenesis and supports other organs for their survival and development[2-4]. From start to the end of an organism's life the circulatory system works continuously as a lifeline support. It is so critical that its function is highly controlled and regulated by multiple organs through various neuro-hormonal and osmotic mechanisms [5,6]. Structurally, heart as a pump and vessels as a transport system for blood / lymph, lungs (oxygen exchange) and kidneys (filtration) form the whole circulatory system in the body. The heart is at the center of the circulatory system where blood flow starts following its movement and leads to the aorta for distribution in the whole body through smaller arteries and capillaries and back to heart through veins [7,8]. The heart and aorta in association with some notable arteries and veins (pulmonary arteries, ascending aorta, coronary, primitive carotid, internal carotid, external carotid, cerebral and brachiocephalic arteries, superior vena cava, inferior vena cava, cardiac and pulmonary veins) constitute the central circulatory system, and rest of the vascular system is considered as the peripheral circulatory system. While the blood pressure measured in aorta or carotid arteries, which are in proximity of the heart and brain is known as central blood pressure (CBP), and the blood pressure in brachial or radial arteries is peripheral (PBP). The key physiological factors required for continuous blood flow through the closed vascular system include pressure gradient and pulsatile movement[9,10], which are highly modulated through the control centers according to the needs of specific organs, and in different pathophysiological conditions [11-14]. The control centers regulate blood pressure in both central as well as peripheral circulatory systems through various mechano- chemosensory mechanisms affecting the system for short and long terms[12].

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Maintenance of optimum blood pressure in both central as well as peripheral circulatory system is essential for efficient organ function. Dysregulation in blood pressure could cause increased blood pressure (hypertension) or decreased blood pressure (hypotension), which may be deleterious with varied pathological conditions related to the brain, kidneys, eyes, and heart or even multiorgan failure and ultimately death[15,16]. Hypertension is known as a silent killer because it is a major risk factor for cardiovascular diseases including stroke, heart attack, and heart failure; however, mostly it remains undetected due to its symptomless onset[17]. It is a highly prevalent disease in adults (18 yrs and older), according to a recent (2017-2018) survey by National Health and Nutrition Examination Surveys (NHANES) the age-adjusted prevalence of hypertension was 45.4% among adults in the USA. The survey also indicated that hypertension increases with age - 22.4% in the age group 18–39 yrs, 54.5% in the age group 40–59 yrs, and 74.5% in the age group 60 yrs and over[18]. On the other hand, hypotension is less prevalent, and risk factors for hypotension include age, serious conditions like shock, and use of some medicines [19,20]. Approximately, 10-20% of people older than 65 suffer from the most common type of hypotension; postural or orthostatic hypotension [21]. Serious conditions due to severe hemorrhage, sepsis, diabetes, dehydration, anaphylaxis, etc., which could lead to shock are also responsible for hypotension. While use of some of medicines such as alpha blockers, beta blockers, diuretics etc. are also known to cause hypotension [22]. The pathological condition either because of hypertension or hypotension could be serious and their management / treatment is required to avoid serious cardiovascular complications or deaths[23,24]. For hypertension, treatment plan varies patient to patient and may include only the lifestyle changes such as heart-healthy eating and exercise or one may need to take blood pressure medicines. There are different types of blood pressure medicines, which target intrinsic individual blood pressure control system in the body. These include - diuretics (including potassium-sparing, loop, thiazide, and thiazide-type diuretics), angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers (including dihydropyridines and nondihydropyridines), adrenergic blockers (including alpha, beta, alpha-beta, and peripherally acting blockers), and centrally acting alpha-agonists[25]. In patients, mostly one of these drug types could normalize the blood pressure efficiently; however, some patients need to take more than one types [26]. On the other hand, treatment strategy for hypotension depends upon the symptoms and etiology, for example hypotension without symptoms or with only mild symptoms rarely requires any treatment, while orthostatic hypotension in aged patients is treated with the drug fludrocortisone (boosts blood volume) or midodrine (reduces the ability of the blood vessels to expand)[27,28]. The hypotension due to shock (e.g., hemorrhagic, septic, or anaphylactic) is mostly critical, and quick response for its management through resuscitation with agents to increase blood pressure is necessary for survival of patients [29]. Since hypertension and hypotension in patients are determined based on the measurements of their arterial blood pressure, it is vital to decide whether central blood pressure or peripheral blood pressure should be addressed in a particular pathophysiological condition. In this review, we will describe central and peripheral blood pressure and various control systems for regulating blood pressure in central and peripheral circulatory systems. It will help us understanding the physiological control units of blood pressure in the whole cardiovascular system to facilitate advances in the prevention of blood pressure related anomalies in susceptible individuals, and treatment of patients suffering from cardiovascular diseases or shock.

1. Central and peripheral blood pressure:

The pressure exerted by the blood on the heart and the wall of blood vessels in the circulatory system is known as blood pressure, which is generated because of blood flow and vascular resistance during systolic and diastolic heart movements. The pressure measured during systole is systolic pressure and at the time diastole is diastolic pressure. Depending on the anatomical location of blood vessel, the blood pressure is also

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categorized into "central" (CBP) or "peripheral" (PBP) types. CBP is the blood pressure in the aorta, where the blood gets pumped first from the left ventricle of heart during its systolic movement. While on the other hand, blood pressure measured in the brachial artery (upper arm) or in radial artery (wrist) is known as PBP. CBP is known to reflect the blood pressure in the heart, brain, and other vital organs, hence it is considered as a key determinant of cardiovascular health and diseases[30]. However, measurement of PBP is in common practice by health professionals, and is measured with ease, quickly and in a non-invasive manner[31]. The PBP measurement in the upper arm is one of the oldest methods to measure blood pressure, which is subsequently also used for diagnosis of high blood pressure or hypertension. Nonetheless, recent studies in hypertensive patients and animal models have delineated the importance of CBP measurement over PBP in predicting heart disease and stroke[30,32,33] and concluded that CBP is more accurate and useful than PBP. One of the main reasons for the difference between CBP and PBP is the inherent pulsatile nature of blood flow. After ejection of blood from the heart into arterial system, blood flow, pressure and a propagating pulse along the arterial bed are generated. The property of the pulse is like a periodically oscillating wave and is known as pulse wave (PW) or pulse pressure (PP). PW travels from the heart toward the peripheral arteries, and in clinical settings, it is quantified as the variation in systolic and diastolic blood pressure at a distinct site of arterial tree (e.g., carotid artery, brachial artery, or radial artery). However, an increase in the whole amplitude of the PW also known as "PW amplification" or "PP amplification" is observed as it travels distally, which leads to "gradual widening" of PW as it travels away from aorta in the arterial bed. The analysis of PW amplification indicates that typically the diastolic and mean pressures change little but systolic pressure gets amplified significantly as the wave moves from the aorta to the periphery[34]. The amplification (A) of the PW is determined as the ratio of the amplitude of PP at proximal (PP1) to distal (PP2) location (A=PP2/PP1). The main point to be noted during the amplification of PP is that the wave amplification is without additional energy requirement in the arterial system; hence, it is more like a distortion than true amplification. In hypertensive patients this distortion is generally more intriguing and may lead to a condition where peripheral (brachial) systolic pressure doesn't reflect the status of the central (aortic) systolic pressure. For example, study by Kelly et al.,[35] on hypertensive patients showed that after nitroglycerin administration, aortic systolic pressure fell in all patients (~22 mmHg average decrease) whereas brachial systolic pressure remained unchanged or fell to a lesser degree (~12 mmHg average decrease). Thus, PP amplification may cause a condition of pseudo-hypertension in the peripheral vascular system, which may lead to overuse of hypertensive drugs and affect the coronary and cerebral blood flow severely[36]. Hence, measuring CBP could be more helpful in managing hypertension and avoiding the side effects of hypertensive medicines than PBP; however, more scientific research is needed to be carried out for validating its use.

2. Regulation of central and peripheral blood pressure:

Mechanistically, mean arterial blood pressure (MAP) is determined by the cardiac output (CO) and peripheral vascular resistance (PVR), also known as systemic vascular resistance (SVR)[37-39]. CO indicates the amount of blood ejected from the left ventricle in one minute, while PVR is the resistance to the blood flow in the arteries and arterioles. The equation of MAP = CO × PVR, which represents the interaction of two independent factors which are influenced by several cardiac activities and other physiological variables. CO is a derivative of heart rate (HR) and stroke volume (SV) and represented with equation, CO = HR × SV, where HR is beat per minute and the SV is the amount of blood ejected from the left ventricle with each contraction (beat). The SV is dependent on the preload, contractility, and afterload of the left ventricle. Hence, the overall equation of MAP could be represented as MAP = HR x SV x PVR. Knowledge of physiological variables affecting HR, SV and PVR is essential to understand the regulation of blood pressure,

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because these variables act as effectors / targets for blood pressure control systems in our body.

Factors which affect the chronotropy (conductance of sinoatrial node), dromotropy (conductance of artrioventricular node), and lusitropy (relaxation) of the myocardium can modulate HR, the positive chronotropy and dromotropy increase the HR, while positive lusitropy decreases HR, their effects are reversed when the factors affect them negatively[40,41]. Therefore, the resultant MAP could be increased with positive chronotropy and dromotropy but decreased with positive lusitropy. SV is determined by ventricular preload, inotropy (contraction) and afterload. Blood volume and compliance of veins are known to affect preload. Increased blood volume increases the preload, which increases SV. Positive inotropy also increases SV, while increase in afterload reduces the velocity of muscle fiber shortening and blood ejection velocity, which reduces the SV. Therefore, the resultant MAP could be increased with increased preload and positive inotropy, while it could be decreased with increased afterload. SVR is dependent on the radius and length of the blood vessels along with viscosity of the blood. However, the major change in SVR in the body is performed by regulation of vessel radius. Change in the radius leads to a dramatic change in resistance because resistance is inversely proportional to the fourth power of vessel radius. Therefore, slight decrease in arteriole diameter can result in large increase in SVR and vice a versa. Since vessel length is not subjected to change in the body, it has negligible effect on SVR. Viscosity is known to play a minor role in SVR and increase in hematocrit may increase the blood viscosity, which would increase SVR[42]. Hence, decrease in vessel radius increases SVR, which will cause increase in blood pressure, and the effect will be vice a versa with increase in the vessel diameter.

The blood pressure control systems in the body regulate these factors through various mechanisms involving neural signaling, hormonal, enzymatic, osmotic, and cellular effects to maintain / change the blood pressure according to the needs in normal as well as in disease conditions (**Figure 1**).

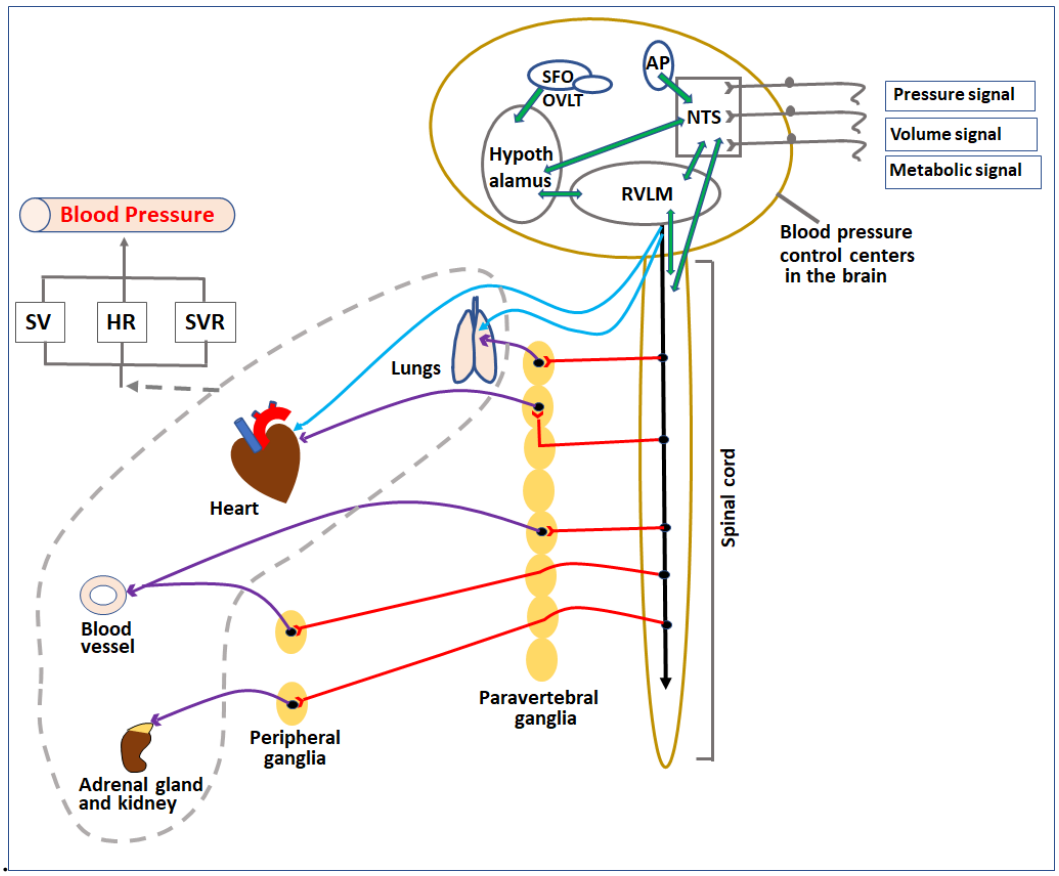

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Figure 1. Diagrammatic representation of control centers and organs involved in regulation of blood pressure. Pressure, volume, and metabolic signals are sensed by various receptors in the body and transferred to blood pressure control centers in the CNS directly or indirectly through afferent nerves. The signals are processed among various localized sub-centers present in the brain stem, circumventricular organs, and spinal cord. Based on the signals these centers release parasympathetic and sympathetic nerve impulses to regulate various cardiovascular organs (heart, lungs, kidneys, and blood vessels) as well as adrenal glands. The overall effect of the change in activities of these organs (indicated by broken blue line) affect the SV, HR and SVR, which in turn regulate the blood pressure.

2.1. Neural controls:

Blood pressure control in our body by neural system is highly complex. It involves coordination among peripheral autonomic nerves, spinal cord, and brain stem for sensing changes in baroreceptors and chemoreceptors for maintaining the homeostasis at normal condition or preparing body for fight or flight. Neural components are strategically arranged in the cardiovascular system to sense mechanical and chemical changes in the blood and send the signal to the cardiovascular control center (CCC) in the brain stem, where the signals are further processed and regulated by specific neuronal cells and relay either sympathetic or parasympathetic commands to related effector organs as compensatory measures (**Figure 2**). We will briefly describe each of the neural components and their roles in regulating the cardiovascular activities.

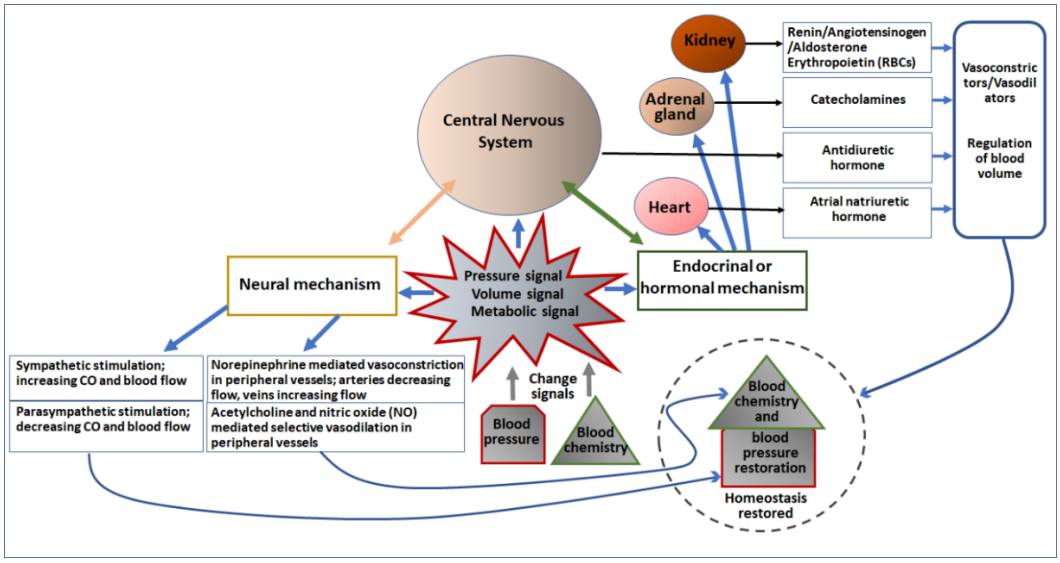

Figure 2. Diagrammatic representation of the effect of blood pressure and blood chemistry change signals on major cardiovascular organs and CNS and regulation of blood pressure. Pressure, volume, and metabolic signals generated due to change in blood pressure and chemistry primarily activate the neural as well as the endocrinal/hormonal mechanism of regulation. Both, neural and endocrinal/hormonal components are connected to the CNS, which initiates neural signaling to directly control the blood pressure as well as blood chemistry as depicted in the left portion of the figure. Moreover, CNS (the brain) also secrete anti-diuretic hormone to regulate blood volume and chemistry. The endocrine/hormonal signaling is also mediated by the heart (secretes atrial natriuretic hormone), adrenal gland (secretes catecholamines) and kidney (secretes renin, angiotensinogen, aldosterone, and erythropoietin). These secreted factors regulate both blood chemistry as well as blood pressure (depicted in the right portion of the figure).

2.1.1. Sensory receptors (baroreceptors and chemoreceptors)

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Baroreceptors are stretch receptors located on the terminal arborizations of afferent nerve fibers of the autonomic peripheral nervous system. They sense the stretch stimulus in the arterial wall and relay information to specialized parts of the central nervous system, which regulates the autonomic activities of the peripheral nervous system[43,44]. Based on their functional property they are categorized into two types, high-pressure arterial baroreceptors, and low-pressure volume receptors. Aortic arch and carotid sinus of circulatory system are equipped with high pressure arterial baroreceptors, while atria, ventricles, and lungs have low-pressure volume receptors, or cardiopulmonary receptors. The bioreceptors in the aortic arch and carotid sinus have stretch fibers which sense the stretch stimulus in the arteries and send electrical signals to solitary nucleus of the medulla via the vagus nerve (cranial nerve X) and glossopharyngeal nerve (cranial nerve IX), respectively. The arterial baroreceptors instantaneously provide information to the nervous system about beat-to beat stretch changes in the carotid and aortic arteries, which helps in sensing rapid changes in the blood pressure by CNS in day-to-day life. For example, postural changes alter stretching in the artery wall, which is sensed by these baroreceptors and signal is sent to CNS. CNS reflexly regulates activities through efferent (sympathetic and or parasympathetic) nerves and affect cardiac output, vasoconstriction, or vasodilation to change the SVR for blood pressure adjustment. Dysfunction in these baroreceptors compromise the blood pressure compensatory mechanisms and may lead to orthostatic hypotension, which is a common hypotensive disorder with aging[45]. The low-pressure volume receptors or cardiopulmonary receptors are mechanoreceptors that sense the changes in the blood volume and send signal to CNS through vagus afferent nerve. They are present in both lungs, both atria, and both ventricles, and are capable of modulating central sympathetic outflow. Clinical and experimental observation suggest that the receptors either in left ventricle or in atria are more important than other receptors for modulating cardiopulmonary reflexes[46]. In reflex to the afferent signal from these receptors, CNS initiates the compensatory mechanisms to normalize the blood volume. For instance, in the low volume state, CNS relays sympathetic activity to modulate renal activities for increasing salt and water resorption to increase the blood volume and helps in increasing the heart preload and SV[47]. The activity of mechanoreceptors is returned to the baseline after arterial pressure reaches homeostasis. Hence, they are essential for adjusting the short-term blood pressure[48]. However, seldom resetting of the baseline value of these receptors help them to operate over a higher range of MAP and sympathetic activity during exercise and stress. The advantage of such mechanoreflex resetting is that during physiologically advantageous behaviors (e.g., exercise or defensive behavior) where increased arterial pressure is required, they can effectively regulate the arterial pressure at the increased level[49]. Chemoreceptors - The chemoreceptors are present in the carotid and aortic arteries as peripheral chemoreceptors, while in medulla oblongata as central chemoreceptors. These specific chemoreceptors are activated primarily by a decrease in PaO_2 to a level of hypoxic condition or due to increased pCO_2 level (hypercapnia). Like the baroreceptors, the cranial nerves IX and X act as the afferent nerve for carotid and aortic chemoreceptors, respectively and send signal to the CNS. The selective hypoxia or hypercapnia condition of peripheral chemoreceptors produces bradycardia, increased respiratory rate and alveolar ventilation with concurrent decrease of blood flow in the peripheral tissue to conserve the available O_2[50,51]. On the other hand, the tachycardia and hypertension result from hypoxia or hypercapnia of the central chemoreceptors, which help to increase blood flow in the affected areas and thereby decrease PCO_2 or increase PO_2. These chemoreceptor reflexes are observed in adults; however, in the fetus the role of central and peripheral chemoreceptors is poorly understood[52]. Mostly, the net result of hypoxia or hypercapnia in fetus is bradycardia with hypertension. Nasopharyngeal receptors - Apart from above mentioned chemoreceptors, nasopharyngeal receptors also act to conserve the available O2 in all air-breathing vertebrates. The nasopharyngeal reflex is also known as diving reflex, which is particularly powerful in diving animals[53]. Activation of nasopharyngeal receptors leads to a reflex apnea, bradycardia, and intense peripheral vasoconstriction (except in the brain and heart). Also, in non-diving animals,

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in response to stimulation of nasopharyngeal receptors by noxious substances such as smoke, same pattern of respiratory and cardiovascular effects is evoked[54]. Cessation of ventilation and O_2 conservation increases the probability of survival. Besides the above-mentioned receptors there are some other receptors e.g., vestibular receptors, skeletal muscle receptors and skin nociceptors, which play some minor roles in the regulation of blood flow and pressure in specific vascular beds[55-58].

The complexity of reflexes exists because of the activation of reflexes from more than one type of bioreceptors in response to a particular challenge, in most of the situations. For example, in diving animals, the first reflex after submersion is the nasopharyngeal receptors mediated diving reflex, which causes apnea, bradycardia and vasoconstriction. The resultant hypoxia, in turn, triggers the chemoreceptor mediated reflex. Interaction of these two different reflexes reinforces the vasoconstriction and bradycardia, along with suppression of normal ventilatory response to chemoreceptors reflex by inputs from nasopharyngeal receptors[59]. Thus, the resultant effect of cardiovascular and respiratory activities depends on the interaction of several reflexes, which is determined to provide optimum adaptability in case of imminent challenges.

2.1.2. Peripheral nervous system (PNS)

The peripheral nervous system (PNS) consists of all the nerves branching out of the central nervous system (CNS), and their ganglia (a series of clusters of neurons linked by axonal bridges). Each nerve is consisted of a bundle of many nerve fibers (axons) and their connective tissue coverings, while each nerve fiber is an extension of a neuron whose cell body is either within CNS or within ganglia of the PNS. These nerves are the workhorse of the PNS and transmit impulses from sensory receptors to CNS and from CNS to effector organs. The nerves, which transmit impulses from sensory receptors/sense organs are known as afferent nerves. While the nerves that bring nervous information towards effector organs are known as efferent nerves. There are a total of 43 paired nerves forming the basis of the peripheral nervous system in our body. According to where they exit the CNS they are classified as 'cranial' (emerge from cranium or brain/brainstem) or 'spinal' (emerge from spinal cord), 12 pairs of them are cranial nerves and 31 pairs are spinal nerves[60]. The PNS can be divided into the autonomic nervous system (ANS) and somatic nervous system (SNS) based on their property of controlling involuntary and voluntary activities, respectively. The ANS is instrumental in homeostatic mechanisms in the body and mainly perform these activities through its two divisions, sympathetic division, and the parasympathetic division[61]. The first division is associated with the fight-or-flight response, and the second one is related to rest and digest like activities. Balance of these two divisions of ANS helps in establishing homeostasis in our body. The nerves emerging from the thoracic and upper lumbar spinal cord also referred to as the thoracolumbar system are important components of the sympathetic division. They influence various organ systems of the body through sympathetic activities[62]. Anatomically, nerves or neurons of these spinal regions are projected to the adjacent ganglia through the ventral spinal roots. Typically, there are 23 ganglia in the chain on either side of the spinal column (3 in the cervical region, 12 in the thoracic region, 4 in the lumbar region, and 4 in the sacral region)[62]. The cervical and sacral ganglia are not connected to the spinal cord directly through the spinal roots, but their connections are through the bridges within the chain. The nerve fiber, which projects from CNS to a sympathetic ganglion is referred to as a preganglionic fiber or neuron, and the nerve fiber projected from a ganglion to the target effector is referred as postganglionic fiber or neuron. The preganglionic fiber has output from the CNS to the ganglion, while postganglionic fiber has output from the ganglion to effector organs. The preganglionic sympathetic fibers are relatively short, and they are myelinated. The postganglionic sympathetic fibers are longer because they cover the distance from the ganglion to the target effector organ, and they are unmyelinated. There is one special preganglionic sympathetic fiber that does not terminate in a ganglion but directly project to the adrenal medulla[63]. The chromaffin cells in the adrenal

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medulla are in contact with the preganglionic fibers. These cells are neurosecretory in nature and release signaling molecules into the bloodstream. They develop from the neural crest along with the sympathetic ganglia, therefore adrenal medulla is also considered as a sympathetic ganglion. However, adrenal medulla uses signaling molecules, rather than using axons to communicate with target structures. As a response to a threat the sympathetic system increases heart rate and breathing rate and causes blood flow to the skeletal muscle to increase, while decreases blood flow in the digestive system. Increases sweat gland secretion, and thus it can execute an integrated response against a stimulus or threat. All these physiological changes are required to occur together in a highly synchronized manner involving activities of multiple organs at the same time for execution of a successful "fight or flight" response. These responses of sympathetic division are possible due to a wide diversion of the sympathetic nerve projections, which enable each preganglionic neuron to influence different regions of the sympathetic system very broadly by acting on widely distributed organs throughout the body[64-66]. Parasympathetic division – It is named parasympathetic because the central neurons of this division are located on either side of the thoracolumbar region of the spinal cord. Their preganglionic neurons are in nuclei of the brain stem and the lateral horn of the sacral spinal cord; therefore, it is also referred as the craniosacral system (or outflow)[61]. The preganglionic parasympathetic nerve fibers originated from the cranial region and the sacral region travel in cranial nerves and spinal nerves, respectively. The axons of these nerve fibers travel from the CNS to the terminal ganglia located in the proximity of (or into) the target effector. The postganglionic parasympathetic fibers project to target effector or to specific target tissue of an organ. The vagus nerve (cranial nerve X) is an important cranial component of the parasympathetic system involved in regulation of blood pressure by affecting heart activities directly with parasympathetic effects[67]. Neurons in the dorsal nucleus of the vagus nerve and the nucleus ambiguus (both situated in the brain stem) travel through the vagus nerve and project the terminal ganglia of the thoracic (primarily influencing the heart, bronchi, and esophagus) and abdominal (primarily influencing the stomach, liver, pancreas, gall bladder, and small intestine) cavities. Chemical signaling in the autonomic nervous system - Synapses of the autonomic system are classified as either cholinergic or adrenergic[61]. Acetylcholine (ACh) is released in the cholinergic synapses, while norepinephrine is released in adrenergic synapses after electrical signal is generated due to action potential in the nerve fiber. The cholinergic system has two classes of receptor: the nicotinic receptor and the muscarinic receptor, both bind to ACh and cause changes in the target cell[61]. However, their signaling could be different because nicotinic receptor is a ligand-gated cation channel, and the muscarinic receptor is a G protein–coupled receptor. The adrenergic system also has two types of receptors: the α-adrenergic receptors and β-adrenergic receptors, and both types are G protein–coupled receptors. The α-adrenergic receptor and β-adrenergic receptor are further sub-grouped into $\alpha 1$, $\alpha 2$, $\alpha 3$, and $\beta 1$, $\beta 2$, respectively. Besides the higher versatility in the receptors of adrenergic system than cholinergic system, it also has a second signaling molecule called epinephrine (or adrenaline)[61]. The chemical difference between norepinephrine and epinephrine is that latter has an additional methyl (CH_3) group (the prefix "nor-" refers to the missing methyl group). All sympathetic and parasympathetic preganglionic nerve fibers are cholinergic type and release ACh. While all ganglionic neurons, the targets of the preganglionic nerve fibers—have nicotinic receptors because they are ligand-gated cation channels and facilitate depolarization of the postsynaptic membrane. The parasympathetic postganglionic nerve fibers are also cholinergic and release ACh, but the receptors on their targets are muscarinic receptors, which are G protein–coupled receptors. While on the other hand sympathetic postganglionic nerve fibers are mostly adrenergic and release norepinephrine, except for fibers that project to sweat glands and to blood vessels associated with skeletal muscles, which are cholinergic type and release Ach[61].

2.1.3. Central Nervous System (CNS)

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The components of central nervous system, which are primarily involved in the regulation of blood pressure are spinal cord and the brain stem. CNS subserves the baroreceptor, chemoreceptor, and other reflexes to regulate the blood pressure and oxygenation by feedback (reflex) and / or feedforward (central command) mechanism[68]. These two general mechanisms are not, however, entirely autonomic but are modulated by central command signals from the forebrain or mid-brain[69]. The arterial baroreceptors located in the carotid sinus and aortic arch run into the glossopharyngeal nerve (cranial nerve IX) and vagus nerve (cranial nerve X), respectively. They terminate in the nucleus tractus solitarius (NTS) in the dorsomedial medulla of the brain stem. NTS in association with other brain centers e.g., nucleus ambiguus, caudal ventrolateral medulla (CVLM) and rostral ventrolateral medulla (RVLM) makes complex neuronal interconnections or (baro)reflex circuitry to control and regulate the efferent signals according to the requirement and challenging conditions. Second-order neurons of NTS can connect directly to cardiac vagal motoneurons in the nucleus ambiguus or to interneurons present in the CVLM. The interneurons of CVLM project to sympathetic premotor neurons in the RVLM. Sympathetic premotor neurons in RVLM are tonically active. They are critical for maintenance of the sympathetic vasomotor tone and resting arterial pressure. While on the other hand, the interneurons of CVLM are GABAergic neurons, which can inhibit the activity of sympathetic premotor neurons of RVLM[70]. Thus, the (baro)reflex circuitry can modulate the tonic activity of sympathetic premotor neurons and permit both reflex decrease and increase in sympathetic activity in response to altered input from the arterial baroreceptors. Moreover, some of the neurons within the baroreflex circuitry are known to receive inputs from nuclei at higher levels of the brain e.g., periaqueductal gray (PAG) of the midbrain, dorsomedial and paraventricular nuclei of the hypothalamus, central nucleus of the amygdala, medial prefrontal cortex, and insular cortex[49,71]. Although the precise role of these inputs has yet to be established, it is likely that they play an important role in resetting the baroreceptor reflex during different behaviors and conditions. The afferent nerves of chemoreceptors of carotid and aortic arteries also terminate on secondary interneurons in the NTS. The NTS secondary interneurons project to several targets e.g., respiratory neurons in the RVLM, the pre Bötzinger complex and dorsolateral pons[68]. The chemoreflex sympathetic excitation is mediated by the direct input from the NTS to RVLM sympathetic premotor neurons and by indirect inputs via neurons of the central respiratory network.

Inputs from a wide range of other receptors e.g., nasopharyngeal receptors, cardiopulmonary receptors, vestibular receptors, skeletal muscle receptors and skin nociceptors that reflexly affect cardiovascular function also project to the NTS, either directly or indirectly via other relay nuclei in the medulla oblongata. Moreover, inputs from some of these receptors can project directly to the RVLM bypassing the NTS[68]. However, the inputs from all the receptors ultimately reach to the sympathetic premotor neurons present in the RVLM. Thus, the RVLM acts as the major site at which interactions among different inputs from receptors regulating sympathetic activity occur. The RVLM is equipped with subgroups of sympathetic premotor neurons that preferentially or exclusively control different sympathetic outflows in a differential manner to various organs at the same time. For example, stimulation of baroreceptors causes reflex vasodilation in the vascular bed of the skeletal muscle with a modest vasodilator effect on the skin blood vessels, whereas stimulation of chemoreceptors evokes a powerful vasoconstrictor effect on skeletal muscle vascular beds but has a similar effect (modest vasodilation) on skin blood vessels[68]. Thus, the lower brainstem portion of the brain contains the structural centers for performing the central pathways subserving the reflexes described above. However, the regulatory centers for defending the body against a decrease in blood volume (because of hemorrhage or dehydration) are located in the forebrain as well as the lower brain stem. The circumventricular organs [organum vasculosum lamina terminalis (OVLT) and subfornical organ (SFO)] in the anterior wall of the third ventricle are equipped with specific neurons, which can sense the increased levels of osmolarity (Na^+), metabolites, pH and specific cytokines, peptides or hormones (e.g., angiotensin II) in the

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blood due to hemorrhage or dehydration. After sensing the signals, neurons in the OVLT and SFO relay the information to the hypothalamic supraoptic nucleus (SON) and paraventricular nucleus (PVN) using direct or indirect (via the median preoptic nucleus) connections. Collectively, OVLT, SFO, and median preoptic nucleus is also referred to as the lamina terminalis. In response to the low blood volume signals these neurons trigger an increase in drinking and lead to vasopressin release from the pituitary gland and increased sympathetic activity[72]. These compensatory responses help in increasing the fluid intake, minimizing fluid loss by kidneys (vasopressin increases water reabsorption in kidneys) and increasing blood pressure to restore fluid homeostasis. Similarly, leptin, a hormone derived from adipose tissue can bind to its receptors present in the SFO neurons and induce an increase in renal sympathetic nerve activity[73]. A high level of circulating proinflammatory cytokines in blood is also known to increase blood pressure, heart rate, and sympathetic activity mediated through the SFO[74]. However, the effects of circulating leptin or cytokines are not exclusively via the SFO but hypothalamic regions outside of the circumventricular organs are also involved[75]. Taken together, both OVLT and SFO circumventricular organs are critical sites, which sense the circulating factors indicating hypovolemia or dehydration and affect the cardiovascular function.

2.1.4. Spinal cord

The spinal cord act as an important integrative center of sympathetic responses essential for blood pressure control[76]. The effect of the sympathetic nervous system is highly crucial in regulating the blood pressure because postganglionic sympathetic nerves innervate blood vessels and affect the peripheral resistance by modulating vascular smooth muscle tone. At rest, the background level of sympathetic tone is the fundamental determinant for the long-term blood pressure control. This background level is set by a central autonomic network formed among the rostral ventrolateral medulla (RVLM), the nucleus of the solitary tract (NTS), the hypothalamus and the spinal cord. Moreover, the core sympathetic network is regulated by many classes of sensory afferent that project either to the NTS or to the spinal cord (somatic and sympathetic afferents detecting chemical factors, physical factors and metabolites during muscle stretch or tissue hypoxia)[77]. Although these characteristics of spinal cord indicate its potential roles in sympathetic background tone set up and regulating core sympathetic network, the spinal cord is often described as a mere relay station between the brainstem and the peripheral nervous system. Nonetheless, clinical and experimental evidence have suggested that intraspinal reflex circuits could directly and independently orchestrate reflex-mediated changes in the blood pressure, especially in patients with spinal cord injuries where descending inhibitory pathways were interrupted[78]. Moreover, inflammatory conditions involving the viscera, such as inflammatory bowel disease may cause hyperexcitability in the visceral spinal afferent[79]. While several studies have demonstrated an increased incidence of hypertension in patients with inflammatory bowel disease[80]. These observations indicate that spinal afferent hyperexcitability in these patients may contribute to hypertension via activation of the viscero-spinal sympathetic reflex circuitry. Supporting this notion, study by Jensen et al., have shown that the risk for developing hypertension was significantly reduced in patients who had surgical colectomy compared to patients had other surgical procedures[81]. Thus, the active roles of spinal cord in sympathetic regulation of blood pressure cannot be ignored; however, more conclusive future studies using animal models are required to prove the roles of spinal afferent fibers in development of systemic hypertension in diseases like inflammatory bowel disease.

2.2. Hormonal (endocrine) and enzymatic controls:

Hormones are required for managing and regulating blood pressure for short, mid as well as long term in the body. Various types of hormones are involved in regulating

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the blood pressure[82]. They influence the cardiovascular system directly to induce vasoconstriction and vasodilation for short-term blood pressure control, while they work with kidneys in managing blood volume required for mid-term control and affect generation of red blood cells (erythropoiesis) that changes the hematocrit volume as well as the oxygen carrying capacity of blood required for long-term blood pressure changes[83]. Thus, the hormone (endocrine) system plays critical role in establishing and maintaining appropriate blood pressures by sustainably responding to both decreases and increases in the blood pressure. Some of the important hormones that play in blood pressure control are as follows –

2.2.1. Catecholamines

Catecholamines are physiologically active molecules e.g., dopamine, norepinephrine, and epinephrine, which act both as neurotransmitters and hormones. They play vital roles in maintenance of blood pressure and homeostasis through the autonomic nervous system. Catecholamines are produced in the brain and in the sympathetic nerve endings and neuroendocrinal chromaffin cells of peripheral tissues (adrenal glands)[84]. They activate adrenergic receptors primarily located in multisystem smooth muscle and adipose tissue. They are well known for "fight or flight" response of the sympathetic nervous system, which results from quick multisystem action of catecholamines[85]. Norepinephrine is important for regulation of blood pressure because the adrenergic receptors (alpha-1 receptors) linked to blood vessels have great affinity for norepinephrine and induce constriction in smooth muscle cells of arteries [86]. Other remarkable functions of catecholamines related to muscular activities include beta-1 receptors mediated enhanced contraction of cardiac muscle, alpha-1 receptors mediated contraction of the pupillary dilator muscle and piloerection, and beta-2 receptors mediated relaxations of smooth muscle in the gastrointestinal tract, urinary tract, and bronchioles[87]. Epinephrine and norepinephrine are also involved in regulating metabolic activities in the body such as stimulating glycogenolysis, glucagon secretion (both via beta-2 receptors), lipolysis via beta-3 receptors and decreasing insulin secretion via alpha-2 receptors[88,89]. Moreover, epinephrine also controls type I hypersensitivity reactions[90]. Thus, catecholamines are important hormones which are essential for regulation of neurovascular, cardiovascular, and metabolic activities important for quick responses of body in presence of stimuli as well as for adaptation in a new environment.

2.2.2. Renin-angiotensin-aldosterone-antidiuretic hormone system (RAAAS)

While renin is commonly referred to as a hormone, it is functionally an enzyme and produced from conversion of prorenin by juxtaglomerular cells in kidneys[91]. Prorenin is also produced and secreted in blood circulation by adrenal gland and gonads. The amount of prorenin in circulation is about ten times higher than renin, which makes prorenin sufficiently available for conversion into renin[92]. The production and release of renin from juxtaglomerular cells is in response to multiple stimuli, including hypotension, decreased pulse amplitude, excessive urine production, or in response to sympathetic activity[93]. Circulatory renin in the blood acts on angiotensinogen; a pre-pro-hormone produced by the liver and converts it to angiotensin I (Ang I). That's why renin is also known as angiotensinogenase. Further, enzymatic conversion of Ang I to angiotensin II (Ang II) is carried out by angiotensin converting enzyme (ACE)[94]. ACE is found in the lungs and its activity depends on the amount of fluid passing through pulmonary tissues. Ang II is the most important hormone in the RAAAS as it is at the core of this system with multiple effects. It controls blood flow and blood pressure by promoting vasoconstriction. It stimulates aldosterone secretion by the adrenal cortex and induces the release of antidiuretic hormone (ADH) or vasopressin from pituitary gland[95]. It also stimulates thirst at the level of the hypothalamus to increase consumption of fluids and thus regulates blood volume. Moreover, Ang II can bind to AT1 receptors on juxtaglomerular cells and inhibits renin production by negative feedback mechanism[95]. Aldosterone is a steroid hormone

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produced in the mitochondria of cells in a distinct region of the adrenal cortex; zona glomerulosa[96]. Aldosterone is normally released at the basal level; however, in presence of signals from regulatory hormones its release rate is enhanced or inhibited. Ang II and high serum potassium are major aldosterone release stimuli[96]. Ang II binding to AT1 receptors on zona glomerulosa cells induces closure of potassium channels, which results in favoring the flow of ions that depolarize the membrane and causes opening of voltage-gated calcium channels. The calcium influx generated due to opening of the calcium channels initiates aldosterone secretion from zona glomerulosa cells. A breakdown product of Ang II, which is known as Ang III can also stimulate aldosterone release with equal efficacy to Ang II[97]. Sympathetic reflexes due to stress or from baroreceptors in the carotid artery due to low blood pressure are also known to increase the rate of aldosterone[98]. Once released, aldosterone can bind to its receptors on membrane surface and in the cytoplasm; however, generally it exerts its effects through cytoplasmic receptors by altering transcription[99]. Aldosterone involves multiple activities such as promoting sodium retention and inhibition of potassium retention by the kidneys, and the stimulation of sodium uptake by the colon. In the kidneys, it increases the reuptake of sodium in the thick ascending limb of the loop of Henle, in the distal convoluted tubule, and in the collecting duct by upregulating amiloride-sensitive sodium channels, the sodium-potassium-chloride cotransporter 2 (NKCC2)[96]. Amiloride-sensitive sodium channels assists the passive movement of sodium along its concentration gradient, while NKCC2 uses concentration gradient of sodium to transport sodium, potassium, and chloride from the filtrate into epithelial tubule cells exposed to the lumen of the nephron[100]. Aldosterone also increases the number and activity of sodium-potassium-ATPase pumps present in these tubule cells and helps in exchanging intracellular sodium for extracellular potassium and pumping sodium out into the interstitial fluid[101]. Chloride that entered the tubule cells via NKCC2 is also reach to interstitial fluid either through chloride channels or co-transported with potassium using the high intracellular concentration of potassium. From interstitial fluid sodium, chloride and potassium are reabsorbed by peritubular capillaries. Aldosterone also increases the expression of potassium channels on the apical membrane of epithelial tubule cells, which allow the accumulating intracellular potassium within these tubule cells. Thus, aldosterone facilitates the sodium reabsorption and decreases reabsorption of potassium in the kidney. Ang II also drives the secretion of ADH or vasopressin, which play an important role in water reabsorption in kidneys. It is secreted from the posterior pituitary, and its secretion is also governed directly by hypothalamus. ADH is secreted when high extracellular sodium is detected by hypothalamic osmoreceptors. Moreover, the hypothalamus can also induce ADH secretion when it receives signals of decreased arterial blood volume, even if plasma osmolarity is low (e.g., during a period of hyponatremia) [102]. ADH has no basal level of secretion, but it is released into open circulation only after induced by factors or signals. The central effects of ADH include promoting thirst to increase water consumption and raising the volume of water in blood, increasing water reabsorption in the kidneys, and minimizing water loss through urine. ADH targets epithelial cells lining the distal convoluted tubule as well as collecting duct in kidneys. It stimulates transcription and translocation of aquaporins to the apical membranes these epithelial cells[102]. Aquaporins increase the ability of water to flow from filtrate into the interstitial space along its osmotic gradient. ADH can also change the permeability of collecting duct to urea and helps in the osmotic gradient drawing water into the interstitial space. Water from the interstitial space is absorbed by peritubular capillaries and thus increasing the water volume in blood. Moreover, ADH enhances sodium reabsorption in the ascending limb of the loop of Henle by increasing the activity of NKCC2 through phosphorylation[103]. The increased sodium reabsorption enhances the osmotic gradient that enables water reabsorption.

Although Ang II regulates the release of both aldosterone and ADH, they operate independently; however, often synergistically. For example, aldosterone contributes to the osmotic gradient by promoting the retention of sodium in the kidneys, which helps ADH in water retention. While, in the case of hypernatremia the high osmolarity in the

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extracellular fluid drives the release of ADH without promoting the release of aldosterone. Thus, the RAAAS serves to raise sodium and water reabsorption in kidneys to increase blood volume and consequently blood pressure.

2.2.3. Natriuretic peptides

The body has another type of hormones known as natriuretic peptides, which have effects almost exactly opposite to aldosterone and ADH[104]. Mainly, they are of two types - atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), which have similar roles in blood pressure regulation. ANP is produced in the right atrium of the heart. Its production is induced upon overstretching of the atrium, or when baroreceptors in the aorta and carotid artery signal excessive hypertension. ANP inhibits aldosterone release and act as an inhibitor of ADH action in the kidneys, and hence decreases sodium and water retention in the kidneys. The lower sodium and water retention leads to lower blood volume and lower blood pressure. Moreover, ANP also affects the release of epinephrine and norepinephrine to reduce vasoconstriction and blood pressure. BNP is primarily released by the ventricles in response to stretching and has effects on blood volume and blood pressure similar to ANP[105].

2.2.4. Erythropoietin

In response to decreased blood pressure/volume, if the short-term and mid-term responses fail to sufficiently deliver process oxygen to tissues where it is needed, the kidneys begin a multi-week of increasing the number and longevity of red blood cells[106]. This is achieved through increased production of erythropoietin (EPO) by the kidneys in hypoxic condition. EPO is a hormone produced by the peritubular cells of the kidney that stimulates red blood cell production[107]. Normally, there is a basal release of EPO required for maintaining appropriate number of red blood cells in the blood and providing them an average life span of about 4 months. The upregulated production of EPO the kidney increases the number of RBCs in the blood, which increases both blood volume as well as its oxygen carrying capacity moreover, it also increases the average life span of RBCs[108]. Thus, by increasing the production of EPO in low oxygen condition, which could be due to low blood pressure the kidneys help in increasing the blood pressure by increasing blood volume and reduces hypoxic damage by increasing hematocrit.

2.3. Vascular endothelial cells mediated controls

Endothelial cells line all blood vessels and are critical regulators of vascular tone and blood pressure by releasing specific vasoactive factors e.g., nitric oxide, prostacyclin and endothelins[109]. Disruption of endothelial function can alter the release of these vasoactive factors and result in increased vascular tone and hypertension. Nitric oxide (NO) is released from endothelial cells, and also known as endothelium-derived relaxing factor (EDRF). It is a free radical gas with a very short half-life[110]. The level of NO release is changed in response to blood flow-induced shear stress and activation various receptors. In addition to vasodilatation, NO also affects myocardial contractility and has anti-thrombotic, leukocyte adhesion inhibition effects[111], which directly or indirectly influence the blood pressure. The pharmacological inhibition of NO causes an enhanced vasoconstrictor effect of Ang II, decreased cardiac output and an increase in systemic as well as pulmonary arterial blood pressure. Prostacyclin is a potent endogenous inhibitor of platelet aggregation by inhibiting platelet activation induced by various stimulants. It also acts as a potent vasodilator and inhibits the growth of vascular smooth muscle cells[112]. Endothelial cells produce 3 different types of endothelins (ET-1, ET-2 and ET-3). They are vasoactive polypetides and belong to the same family but each one is encoded by different genes. ET-1 is considered as one of the most potent vasoconstrictors ever isolated[113,114]. They can bind to two different types of ET receptors, ETARs and ETBRs and initiate different levels and categories of downstream activities. Activation of ETBRs leads to decreased arterial pressure and natriuresis through effects on adrenal gland, heart (negative

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inotropy), decreasing sympathetic activity and increasing systemic vasodilatation[115]. While activation of ETARs causes increased sympathetic activity with increased sodium retention, positive inotropy of the heart, increased catecholamine release, increased systemic vasoconstriction and arterial pressure[116,117].

3. Regulation of blood pressure after hemorrhagic shock:

A severe hemorrhage or bleeding causes an acute reduction in central blood volume (central hypovolemia), which may result inadequate tissue perfusion and lead to a clinical condition of hemorrhagic shock[118]. The hemorrhage has widely accepted four different stages based on the blood loss and body responses. Class 1 and class 2 stages represent mild to moderate blood loss conditions where blood loss is compensated by autonomic and neurohumoral compensatory responses to maintain the hemodynamic stability. In these stages, vital organ perfusion and oxygenation are preserved[119]. The class 3 stage is characterized by the failure of compensatory mechanisms and dysregulation of oxygenation in vital organs leading to decompensated shock. The class 4 stage of hemorrhage is the most severe level of hemorrhagic shock characterized with cardiovascular collapse, vital organ injury, which may cause death. Pathophysiological events after hemorrhage starts with an immediate decrease in blood volume and blood pressure[120], hence understanding of blood pressure regulation during compensatory and decompensatory phases of hemorrhagic shock is important. Decrease in blood pressure stimulates the compensatory mechanism in the body by the arterial baroreflex. Baroreflex activates autonomic system to promote sympathetic nervous activities and inhibit the parasympathetic nervous activities as well as cardioinhibitory center, resulting in increased peripheral vascular resistance and HR[121]. Moreover, sympathetic activation also causes constriction in major capacitance veins and improves increased venous blood return to the heart. It also stimulates the adrenal gland to secrete epinephrine and norepinephrine, which globally augment vasoconstriction and increase HR[122]. Baroreflexes in low blood pressure also stimulate the release of various neuroendocrine hormones. For example, release of renin from the kidney, which activates the renin-angiotensin system to mediate vasoconstriction, and vasopressin from the hypothalamus to increase intravascular volume[123]. Other neuroendocrine hormones include aldosterone and neuropeptide Y, which also help in the maintenance of vascular volume and organ perfusion[124,125]. Overall, these compensatory baroreflex responses and physiological autoregulation act synergistically to regulate blood pressure and maintain blood flow to vital organs despite blood volume loss after hemorrhage. With continued or more severe hemorrhage the compensatory physiological mechanisms eventually fail and result in sudden decrease in SVR, MAP, and HR[126]. The SV and CO also continue to decrease. Further prolongation of hemorrhage results in a mismatch between tissue oxygen delivery (DO2) and oxygen consumption (VO2), increased blood H^+ and CO2 level. Inadequate oxygen supply leads to anaerobic glycolysis, increases lactate production in the body, decreases blood pH and leads to metabolic acidosis[127]. The increased levels of H^+ and CO2 in the blood stimulate the chemoreceptor reflex, which activates central respiratory centers to compensate for the metabolic acidosis. However, continued tissue hypoxia and metabolic acidosis leads to the uncompensated phase of blood loss and produces cellular deterioration, cell death and multiorgan failure, which could be fatal[128].

Thus, the hemorrhagic patient has a variety of physiological deficits. The two most critical of them are 1) blood volume loss causing hemodynamic instability and 2) decreased oxygen delivery to vital organs[129]. Hence, the most effective treatment includes fluid resuscitation for increasing intravascular volume to restore blood pressure and promote oxygen delivery to tissues. Although, the whole blood is an optimal resuscitative fluid as it replaces both volume and oxygen-carrying capacity, its availability and logistics of blood delivery (e.g., the need for refrigeration, weight etc.) are difficult[130]. Therefore, development of low-volume pharmacological resuscitative agents (“antishock drugs”) with efficacy to delay or prevent the onset of hypoxic injury is required. Crystalloid (e.g.,

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lactated Ringer's, saline) and colloid (e.g., Hextend) solutions were initially tested and their prehospital infusion in hemorrhaging trauma patients became a standard procedure, followed by blood products administration in the hospital. However, prehospital infusion of these fluids was found to be associated with various detrimental side-effects such as hemodilution, endothelial dysfunction, and coagulopathy[131]. Development of artificial blood substitutes including hemoglobin-based oxygen carriers (HBOCs) was considered as one of the potential solutions[132]. HBOCs are purified hemoglobin based biological products, which can bind and release oxygen. They are generally made by hemoglobin cross-linking, polymerization, and conjugation to polymers, which help in enhancing intravascular half-life, stability, and safety of hemoglobin. However, direct infusion of HBOCs in the body is known to cause vasoconstriction, methemoglobin, and other side effects[133]. The factors responsible for HBOCs mediated vasoconstriction include nitric oxide (NO) scavenging, increased ET production, shear stress, and vessel wall hyperoxygenation. Safety and efficacy of HBOCs was explored using numerous preclinical and clinical studies and a HBOCs product, HBOC- 201 is approved for surgical patients with acute anemia and has been available in South Africa since 2001[134]. However, a meta-analysis of cell-free hemoglobin-based blood substitutes concluded that the use of HBOCs was associated with a significantly increased risk of death and myocardial infarction based on an analysis of the available data from 13 randomized controlled trials[135]. After that the USFDA suspended all HBOC trials in the United States. Nonetheless, it was argued that if the risk of death due to low hemoglobin outweighed the risk of HBOCs, suspension on all HBOC trials could be fatal for these patients[135]. Subsequently, clinical trials for HBOCs are made available only through expanded access to save patients' lives when other interventions are not available. At present, HBOCs are approved for veterinary use in the United States, Russia, and the European Union[136]; however, none are FDA approved for human use.

Another potential solution is to infuse plasma, which contains clotting factors and is protective of endothelial function[137]. Transfusion with plasma is used as a volume expander in shock and transfused in millions of patients annually; however, there is a limited understanding of its mechanisms of action. In traumatic blood loss, transfusion of plasma may improve survival by controlling the severe blood loss. Commonly, plasma is considered as a pro-coagulant blood product; nonetheless, it contains both coagulation factors as well as anticoagulant proteins. Therefore, the net effect of plasma on coagulation could be neutral[138]. Plasma transfusion has shown to increase the amount of coagulation factors as well as levels of anti-coagulant proteins resulting in unchanged thrombin generation in non-bleeding critically ill patients with coagulopathy. While on the other hand in patients with traumatic hemorrhagic shock, it is not clear whether plasma is directly involved in the correction of coagulopathy[139]. Other mechanisms including preservation of the endothelial glycocalix, decreasing inflammation and decreasing endothelial leak of could be the reason for the protective effect of plasma. Clinical trials in hemorrhaging patients with plasma resuscitation have shown somewhat conflicting results when thawed plasma in addition to standard of care was used during prehospital care. Nonetheless, post hoc analysis of the combined data set demonstrated improved survival when transport times were less than 20 min[140].

Another approach to maintain blood pressure after hemorrhage or blood volume loss is to pharmacologically produce vasoconstriction. Although norepinephrine and epinephrine are highly potent vasoconstrictors, they produce general vasoconstriction, which is mostly counterproductive. Recent studies from our group have suggested that selective constriction in venous blood vessels by centhaquine (CQ or Lyfaquin®) may be helpful in increasing venous blood return and improving CO. CQ acts on α2B- adrenoreceptors abundantly present in veins and induces venoconstriction, which helps in moving the pooled blood in the peripheral venous system to the heart and increases the preload as well as CO. It also activates central α2A- adrenoreceptors and reduces SVR by attenuating sympathetic outflow and helps in reducing the afterload. Thus, CQ modulates the peripheral and central circulatory system in hypovolemic shock in such a way that resultant

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effect causes increase of mean arterial pressure (**Figure 3**), which is a critical factor for the survival of patients in shock.

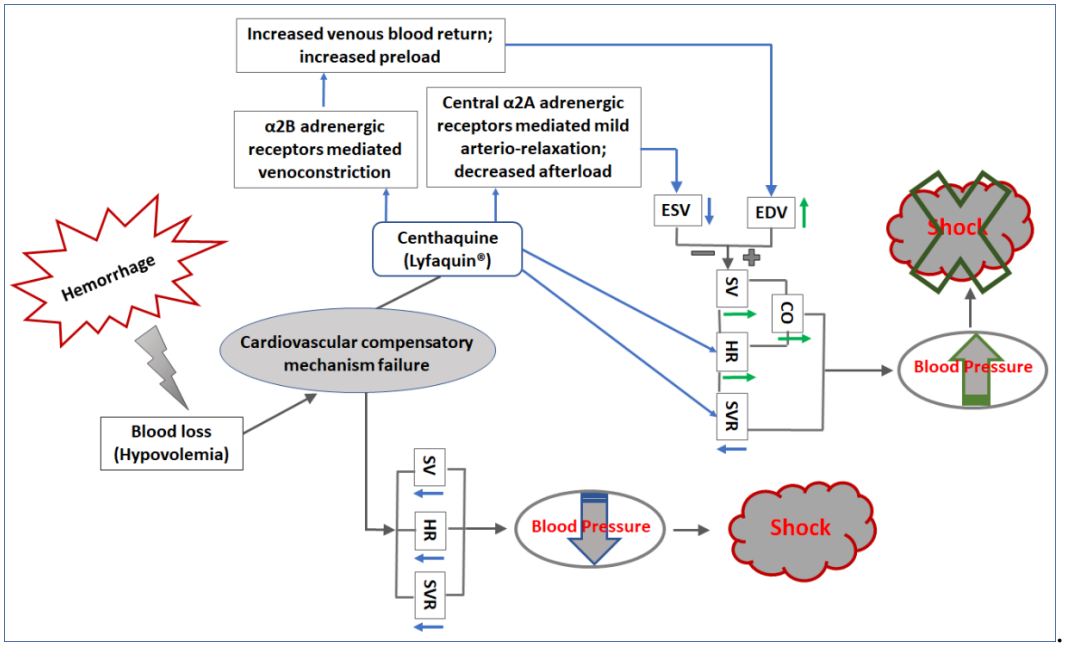

Figure 3. Diagrammatic representation of the effect of centhaquine treatment after hemorrhagic/hypovolemic shock. Onset of hypovolemia following various conditions such as hemorrhage affects cardiovascular system, which starts compensatory mechanism. However, failure of cardiovascular compensatory mechanism may lead to decreased SV, HR as well as SVR, which result in decreased blood pressure (hypotension) and shock (depicted in the lower panel of the figure). Centhaquine treatment after hypovolemia increases HR and induces α2B adrenergic receptors mediated venoconstriction and central α2A adrenergic receptors mediated arterial relaxation. The resultant effect of the simultaneous venoconstriction and arterial relaxation increases venous blood return to the heart; increases preload and decreases afterload with mild decrease in SVR. Overall effect of these signaling leads to increased CO and blood pressure, which may rescue from shock (depicted in the upper panel of the figure).

We have developed a low dose (~0.02 mg/kg body weight) of CQ (2-[2-(4-(3-methyphenyl)-1-piperazinyl)]ethyl-quinoline) citrate as a new resuscitative agent for hemorrhagic/hypovolemic shock (Pharmazz Inc., Willowbrook, IL, USA). Pre-clinical studies have demonstrated its superior effectiveness compared to commonly used resuscitative agents in reducing mortality following hypovolemic shock in animal models[141-143]. Clinical phase I study (NCT02408731) has shown it to be safe and tolerable in human subjects. Human phase II (NCT04056065) and phase III (NCT04045327) clinical trials carried out in India have demonstrated superior efficacy and effectiveness of CQ versus currently used resuscitative agents in treating hemorrhagic shock. The phase III trial was a prospective, multicentric, randomized study conducted in patients with hypovolemic shock having systolic blood pressure (SBP) of ≤90 mm Hg and blood lactate levels of ≥2 mmol/L. Randomization was in a 2:1 ratio with 71 patients to the CQ group and 34 patients to the control (saline) group. CQ (0.01 mg/kg) was administered in 100 mL of normal saline infusion over 1 hour in the CQ group, while only saline of the same volume was infused in the control group as drug besides standard of care (SOC). The demographics of patients and baseline vitals in both groups were comparable; however, trauma was the cause of hypovolemic shock in 29.41% of control and 47.06% of CQ, gastroenteritis in 44.12% of control, and 29.41% of CQ patients. Patients were followed for 28 days after resuscitation. The results of the trial showed that a lesser amount of vasopressors was required in the first 48 hours of resuscitation in the CQ group. Compared to control CQ patients had increased SBP and PP. A significant increase in PP in the CQ group suggests

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improved stroke volume due to CQ resuscitation. The shock index (SI) in the CQ group was significantly lower than control from 1 hour (p=0.0320) to 4 hours (p=0.0494) after resuscitation. A significantly greater number of patients had improved blood lactate and the base deficit in CQ than the control group. Acute Respiratory Distress Syndrome (ARDS), Multiple Organ Dysfunction Syndrome (MODS) scores were improved with CQ, and an 8.8% absolute reduction in 28-day all-cause mortality was observed in the CQ group[144-148]. Thus, CQ improves cardiovascular function and controls acidosis after shock. We have demonstrated that CQ acts on venous α2B adrenergic receptors and produce constriction in veins, which increases venous blood return to the heart. It also stimulates central α2A adrenergic receptors and decreases SVR[143]. However, CQ does not stimulate the β-adrenergic receptors and thus mitigates the effect of arrythmia. To our knowledge, CQ is the only late-stage clinical developmental drug that has demonstrated an 8.8% absolute reduction in mortality after hypovolemic shock. CQ was safe and well-tolerated and had no drug-related adverse events (AEs) in hypovolemic shock patients. A meta-analysis of the mortality data obtained from our phase II and III studies of CQ in hypovolemic shock found that mortality was 10.71% in the control group (N = 56) and 2.20% in the CQ group (N = 91) (OR 5.34; 95% CI 1.27–26.50; p = 0.03), which indicated statistically significant reduction in mortality in CQ group[147]. Our company (Pharmazz Inc., Willowbrook, IL, USA) has successfully received marketing authorization and launched CQ with the brand name, Lyfaquin® in India, for the treatment of patients with hypovolemic shock as a frontline adjuvant to standard of care[148]. Recently, Pharmazz Inc., has also received an approval from the US FDA for a multi-centric, double-blind, placebo-controlled phase III clinical study of CQ for the treatment of hypovolemic shock in the USA (NCT05251181; study start date June 2022 and estimated study end date September 2024). In the study, 430 patients will be randomly assigned equally to both arms with 28-day mortality as the primary endpoint.

The mortality in hemorrhagic shock patients is generally linked to multiple organ failure and among organs that fail, acute kidney failure is most frequent[149]. Presumably, because oxygen level starts to drop in the kidney at a much earlier stage than other organs after hemorrhage[150]. A damaged kidney in shock leads to further disturbance in the homeostasis and accelerates failures of other organs[151]. Hence, a resuscitative agent with inherent property of renal protection would significantly improve clinical outcomes of hemorrhagic shock patients. We explored the role of centhaquine on kidney perfusion and protection of renal tissues against hypoxic damage. We resuscitated rats after hemorrhagic shock and acute kidney injury with CQ and observed significant improvement in kidney blood flow and decrease in blood lactate level. Moreover, analysis of kidney tissues in these rats showed significant up-regulation (p=0.024) of hypoxia inducible factor 1α (HIF-1α). We also observed down-regulation of early acute kidney injury and apoptotic markers after resuscitation with CQ[152,153]. Overall, these results showed that CQ is as an effective resuscitative agent with potential to improve cardiovascular function as well as renal tissue perfusion and protection after hemorrhagic shock. Our future studies will further explore the therapeutic potential of CQ in treating other forms of shock associated with hemodynamic instability or refractory hypotension and resulting in multiorgan failure or fatality is of interest. Some of these conditions may include distributive shock such as septic shock, where a significant shift occurs within the vascular compartment and out of the vascular system, resulting in a state of hypovolemia. Our planned studies include determination of efficacy of CQ in patients with COVID-19 and septic shock.

Conclusion:

The CBP and PBP play a crucial role in driving the blood flow in vital organs according to their needs. Neural, hormonal, osmotic and cellular control systems work cooperatively and regulate sympathetic and parasympathetic nerve activities to modulate them to ascertain perfusion in the vital organs and survival of the organism during normal as

well as in the disease condition (e.g., shock). We have developed a novel resuscitative adjuvant, centhaquine (Lyfaquin®), which primarily increases venous blood return and cardiac output by inducing peripheral venous constriction through α2B- adrenoreceptors in hypovolemic shock patients. It also activates central α2A- adrenoreceptors and reduces SVR by attenuating sympathetic outflow. The overall effect of centhaquine (Lyfaquin®) on central and peripheral circulatory system results in the increase of mean arterial pressure as well as better organ-perfusion after hypovolemic shock. Thus, understanding the regulation of CBP and PBP in various pathological conditions would be helpful in better care of patients and drug development for diseases related to cardiovascular disorders.

Competing Interest: Dr. Anil Gulati (A.G.) is an employee of Pharmazz, Inc, and has issued and pending patents related to this study. Midwestern University is the patent assignee with Dr. Gulati as an inventor of this technology, while Pharmazz Inc. holds its exclusive worldwide license and is engaged in the clinical development and commercialization of centhaquine (CQ) for human use. Dr. Amaresh K Ranjan declares no competing interests.

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