



Clinical Group

Archives of Clinical Hypertension

DOI <http://dx.doi.org/10.17352/ach.000014>

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Dates: Received: 26 May, 2017; **Accepted:** 21 June, 2017; **Published:** 22 June, 2017

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Mini Review

Mechanisms involved in regulation of Systemic Blood Pressure

SUMMARY

Regulation of the circulatory system to maintain a constant arterial pressure is critical in ensuring adequate perfusion to meet metabolic requirements of tissues. Blood pressure (BP) can be considered in the context of Ohm's law, whereby BP (analogous to voltage) is directly proportional to the product of cardiac output (current) and total vascular resistance (TPR). Acute regulatory mechanisms are coordinated in the cardiovascular control centres in the brainstem, which are themselves influenced by impulses from other neural centres in addition to sensors both intrinsic and extrinsic to the circulation. However, certain organs such as the heart, kidneys and brain have the ability to coordinate blood flow locally, i.e. autoregulate. This enables alterations in regional perfusion without perturbations of BP. This mini-review provides an exploratory discussion of neural and humoral mechanisms that underpin regulation of systemic BP.

Neural Control

Cardiovascular control centres (CCC)

The cardiovascular control centres (CCC) of the central nervous system (CNS) are located in the lower pons and medulla oblongata (i.e. brainstem), in close proximity to the centres regulating respiration [1]. The CCC have two major subdivisions that innervate the heart and peripheral vasculature, with significant anatomical and functional overlap.

The cardiac control centre can be further subdivided. The cardioinhibitory centre has parasympathetic vagal efferents (PNS) to reduce heart rate (HR) and, to a lesser extent, atrial contractility. Activation of the cardiostimulatory centre increases myocardial contractility (inotropy) and HR (chronotropy) via activation of the sympathetic nervous system (SNS) [2]. The vasomotor centre has a vasoconstrictor area (C-1) containing a high concentration of neurons secreting noradrenaline (NA) [3]. This area has been proposed as one of the sites of clonidine, which binds to presynaptic α_2 receptors, inhibits release of NA and reduces TPR [4]. Neurons send vasoconstrictor fibres to the periphery via the sympathetic nervous system (SNS). A vasodilator region (A-1) inhibits activity of C-1 [3]. Finally, a sensory area A-2 receives input from cranial nerves IX and X, and efferent neurons project to vasoconstrictor and vasodilatory areas and hence modulate output.

The CCC receives modulatory neural input from various other regions within the brain, including the motor cortex, frontal cortex and limbic system (hypothalamus, hippocampus and amygdala), the latter being associated with emotional response [5]. The cardiostimulatory, cardioinhibitory and vasoconstrictor areas are tonically active.

Vasomotor tone

Vasomotor tone is the sum of the muscular forces intrinsic to the blood vessel opposing an increase in vessel diameter [6]. This is mediated by vascular smooth muscle cells (VSMCs) in the media layer of vessel walls. Parts of the endothelial cells project into this layer (myoendothelial junction) at various points along arterioles, suggesting a functional interaction between the two. VSMCs contain large numbers of thin actin filaments and lower numbers of thick myosin filaments [7]. Compared with skeletal muscle, they contract more slowly but generate higher forces with sustainable activity. Cell-to-cell conduction is via gap junctions as occurs in the myocardium.

The interaction between actin and myosin leading to contraction is regulated by intracellular calcium concentration as with other muscle, but the molecular mechanism differs [8]. VSMCs lack troponin and fast sodium channels. The increase in intracellular calcium concentration arises from voltage-gated channels and receptor-mediated channels in the sarcolemma, with additional release from the sarcoplasmic reticulum (SR). Agents that can mediate effects via agonism or antagonism of these pathways include nitric oxide (NO), acetylcholine (Ach),

catecholamines and angiotensin II [9]. The free calcium binds to calmodulin, which in turn binds to myosin light chain kinase. This activated complex phosphorylates myosin cross bridges and initiates contraction. Dephosphorylation of cross bridges in conjunction with reductions in intracellular calcium results in relaxation.

Vasomotor tone has various determinants, including the autonomic nervous system (ANS), humoral agents and autacoids (biological agents with paracrine effects) [10]. Basal vasomotor tone is mediated by low level, continuous impulses from the SNS (approximately 1 per second) in addition to partial arteriolar and venular constriction via VSMC contraction. Circulating adrenaline from the adrenal medulla may complement this. Basal tone is maintained at around 50% of maximum constriction. Hence, vasodilatation can arise from a reduction in tonic SNS activity without directly eliciting PNS activity. The existence of basal tone results in minimal resistance to flow in the venules compared to arterioles as they are highly distensible. Nonetheless, ANS effects mediate capacitance which has direct effects on venous return and preload [11].

The importance of vascular tone in regulation and maintenance of BP is reflected in clinical contexts associated with severe insults to the CNS such as brain injury and high level injuries to the spinal cord. The trauma results in a sudden interruption of sympathetic preganglionic vasoconstrictor fibres. This causes a drastic fall in BP and a state of neurogenic shock (or 'spinal shock') whereby only parasympathetic tone remains [12]. Clinically, patients may appear flushed, priapic and with an inability to generate a compensatory tachycardia. If the injury is above C3, a loss of neural control of the diaphragm can result in respiratory arrest.

Autonomic nervous system (ANS)

As indicated, the CCC modulates the ANS which directly innervates cardiac muscle and VSMCs. It has two complementary systems, sympathetic and parasympathetic, with each having two interconnected neurons [13]. The preganglionic neurons originate within the CNS but relay to the autonomic ganglion, with post-ganglionic neurons innervating the effector organs. In the ANS, all preganglionic neurons release the neurotransmitter Ach. The neurotransmitter between postganglionic neurons and effector organs is NA for the SNS and Ach for the PNS.

Heart: The ANS regulates chronotropy, inotropy and coronary perfusion. The SNS has similar supraventricular distribution to PNS but greater innervation of ventricular myocardium, mediated via the left stellate ganglion [14]. Stimulation of SNS results in increased HR via β_1 -adrenergic receptors, and increased SV via the stellate ganglion. Normal basal sympathetic activity maintains cardiac contractility around 20% greater than that of a denervated heart.

PNS fibres are distributed to the SAN, AVN and atria, but only minimally to ventricular myocardium. Stimulation results in a decreased rate of discharge and reduces SAN/AVN

excitability (via M2 receptors), hence decreasing HR [15]. The right vagus nerve innervates the SAN predominantly, and the left vagus nerve the AVN, which explains why left carotid sinus massage is more likely to be effective in terminating supraventricular tachycardias (SVTs) [16]. Because of the lack of efferent distribution to ventricles, the PNS has little effect on inotropicity.

Unlike with vasomotor tone, the heart is tonically stimulated by both SNS and PNS, though the latter predominates and is most apparent in younger individuals that demonstrate resting vagal tone. For this reason, total pharmacological ANS blockade or cardiac denervation in the context of heart transplantation results in higher resting HR [17]. There is a more gradual response in HR to sympathetic activity as opposed to parasympathetic, and this is mediated by two main factors. Firstly, the former is reliant on adenylyl cyclase producing cAMP as a secondary messenger in the pacemaker cells, as opposed to direct coupling. Secondly, release of the neurotransmitter NA at postganglionic nerve endings is slower than Ach.

Peripheral circulation: As alluded to, the SNS has the greater importance in regulation of vascular tone. The distribution of parasympathetic nerves is relatively limited and PNS effects mediate dilatation mainly via endothelial mechanisms. In contrast, the SNS causes vasoconstriction by stimulation of α_1 -adrenergic receptors. The vasculature of the skin, kidney, spleen and mesentery has extensive sympathetic innervation although vascular beds of the heart, brain and skeletal muscle have less [18].

Reflexes

Intrinsic: Arterial baroreceptors are specialised pressure-responsive nerve endings situated in the walls of the aortic arch and internal carotid artery just above the sinus (bifurcation) [19]. Afferent fibres relay with the CCC. There is basal discharge from baroreceptor afferents at physiological arterial pressures. When receptor endings are stretched, AP are generated and transmitted at a frequency roughly proportional to the pressure change. Afferent input results in negative chronotropic and inotropic effects, in addition to a reduction in vasoconstrictory tone of arterioles and venules. Hence, increased BP provides a reflex negative feedback loop to maintain homeostasis, with responses greatest to changes in blood pressure in the physiological range (80–150 mmHg). Clinically, this reflex is evident in the acute setting such as when standing from a sitting position with the kidneys playing a more prominent role in mediation of long-term pressure regulation [20]. A reduction in responsiveness can occur with age, hypertension and coronary disease. Baroreceptors are also present to a lesser extent in the atria, vena cavae and ventricles.

The aortic and carotid bodies also contain chemoreceptors, which respond to reductions in the arterial partial pressure of oxygen (PaO_2) and increases in arterial partial pressure of carbon dioxide (PaCO_2). Afferent pathways are located in the same nerves as adjacent baroreceptors. Their primary function

is to increase respiratory minute volume, but sympathetic vasoconstriction occurs as a secondary effect [21].

Extrinsic: Extrinsic influences play a smaller and less consistent role in circulatory regulation. Nonetheless, they become of increased relevance in states of stress, including pain, central nervous system (CNS) ischaemia and the Cushing reflex.

Pain can produce variable responses. Mild-moderate severity may generate a tachycardia and increases in arterial BP mediated by the somatosympathetic reflex [22]. Severe pain, however, may elicit bradycardia, hypotension and symptoms of shock. The CNS ischaemic response occurs when severe hypotension (mean BP <50mmHg) activates chemoreceptors in the vasomotor region of the CCC. A subsequent increase in SNS activity leads to profound, generalised vasoconstriction [23]. It is an emergency reflex for restoring cerebral blood flow in emergency states. Cushing reflex is a consequence of raised intracranial pressure (ICP) which results in direct compression of cerebral vasculature [24]. The resultant impairment of blood flow initiates the CNS ischaemic response and increased SNS activity as described. This reflex response to augment arterial BP is a mechanistic response to try and maintain adequate cerebral perfusion. However, simultaneous reductions in HR can occur and are mediated by the baroreceptor reflex.

Humoral Control

Catecholamines

The adrenal medulla is unique in that the gland is innervated by preganglionic SNS fibres which originate directly from the spinal cord [25]. The adrenal medulla secretes adrenaline and NA in response to stimulation and function as hormones by entering the bloodstream and exerting distant effects on target organs. In view of this, activity is prolonged in comparison to NA release as a neurotransmitter.

Renin-angiotensin-aldosterone (RAA) system

The RAA system does not play a major role in health, but is rather of increased relevance in BP maintenance during periods of hypovolaemia or impaired cardiac output when renal perfusion is compromised [26].

The enzyme renin initiates the cascade and is secreted by juxtaglomerular cells, which are modified VSMCs located in the media of the afferent arteriole immediately proximal to the glomerulus. Renin secretion is primarily secondary to renal hypoperfusion, but also occurs via SNS activation of β_1 -adrenergic receptors. Renin cleaves angiotensinogen, synthesised in the liver, to angiotensin I. This is physiologically inactive but rapidly hydrolysed by angiotensin-converting enzyme (ACE), found in high concentrations in pulmonary vascular endothelium, to form angiotensin II. Angiotensin II directly mediates arteriolar vasoconstriction in most vascular beds which increases TPR and BP. It also stimulates transmission in the SNS. Additionally, it stimulates the zona glomerulosa of the adrenal cortex to synthesise and secrete aldosterone which targets the sodium-potassium exchanger in

the distal collecting tubule and collecting duct of nephrons to cause sodium and water retention. This results in an increase in circulatory volume [27].

Angiotensin II also activates secretion of antidiuretic hormone (ADH), otherwise known as vasopressin. This peptide is synthesised in the brainstem and transported for storage in the posterior lobe of the pituitary gland [28]. In addition to angiotensin II, secretion is also triggered by increased plasma osmolality (detected by receptors in the hypothalamus) and decreased plasma volume (detected by receptors in the atria). ADH induces translocation of aquaporin-2 channels in collecting ducts to enhance free water permeability and resorption (anti-diuresis). ADH also has direct vasoconstrictory effects which are generalised and affect most regional circulations.

Angiotensin II is metabolised by aminopeptidases to angiotensin III. This is a less potent vasoconstrictor but has comparable activity in stimulating aldosterone secretion.

Nitric oxide (NO)

NO is deemed to be one of the most important mediators of vascular health. It can be synthesised by one of three isoforms of nitric oxide synthase (NOS): endothelial (eNOS), neuronal (nNOS) and macrophage/inducible (iNOS) [29]. For all three, NO synthesis depends upon binding of eNOS to the calcium-regulatory protein calmodulin. It is the constitutively active eNOS that is implicated in production of NO within the vascular endothelium. The amino acid L-arginine is the main substrate for synthesis, with the requirement of several co-factors to produce NO and L-citrulline as a by-product. Once synthesised, NO diffuses across the cell membrane of endothelial cells and enters VSMCs where activation of guanylate cyclase occurs. This catalyses conversion of GTP to cGMP, which is an important secondary messenger and mediates several biological targets implicated in vascular function [30].

eNOS expression can be regulated by multiple stimuli including insulin, shear stress and vascular endothelial growth factor (VEGF) [31]. There is continuous, basal synthesis of NO to relax VSMCs and maintain vasodilatory tone in vessels, with most of its effects exerted in the arterial rather than venous system. Pharmacological agents such as glyceryl trinitrate (GTN) and sodium nitroprusside (SNP) exert their effects via cGMP-dependent mechanisms after conversion into NO [32]. Indeed, the beneficial effects of ACE-I may be related, in part, to amplification of the actions of bradykinin, which potentiates NO release. Beyond vasomotor function, NO also has inhibitory effects on platelet adhesion and aggregation, local inflammatory responses and mitogenesis [33]. Hence, NO participates heavily in the provision of an overall anti-atherogenic and anti-thrombotic environment within the vasculature to preserve normal physiology.

Atrial natriuretic peptide (ANP)

Atrial natriuretic peptide (ANP) is synthesised directly by atrial myocytes in response to chamber distension and hormones such as adrenaline and ADH [34]. It directly relaxes

VSMCs and inhibits renin, therefore having an overall natriuretic effect to reduce BP. No direct inotropic or chronotropic effects have been documented.

Local autoregulation

Some vascular beds have the ability to locally regulate blood flow in a phenomenon termed autoregulation [35]. This occurs markedly in arterioles in the heart, kidneys and brain, and to lesser effect in the skin and lungs. This negative feedback mechanism maintains constant perfusion despite changes in arterial BP. In the absence of autoregulation, a linear relationship exists between pressure and flow. Vasodilatation and vasoconstriction allow a constant flow to be achieved despite alterations in BP. This response is greatest in organs with the smallest neurogenic tone and is largely intrinsic, with only marginal influence from neural and humoral mediators. In clinical contexts such as states of malignant hypertension, for instance, close assessment and regulation of BP is paramount to ensure that cerebral autoregulatory mechanisms are maintained to prevent linearity in pressure–flow dynamics.

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