Neurological and humoral control of blood pressure

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Abstract

There is a relationship between arterial blood pressure, cardiac output and vascular resistance which can be described mathematically, and helps us to understand the short-term control of blood pressure in the terms of a hydraulic system. The sensors in this system are the arterial baroreceptors which mediate changes in the hydraulic system though control of the autonomic nervous system, which in turn influences heart rate, inotropy and vascular tone. Altering the distribution of blood between the arterial and venous systems compensates for acute changes in total blood volume. The total blood volume is controlled predominantly by the kidney, with the renin–angiotensin–aldosterone system acting as both the 'sensor' of blood pressure/volume (via renin release in the juxtaglomerular apparatus) and the 'effector' of blood pressure/volume (via aldosterone secretion by the adrenal cortex). Overall control is shared; the baroreceptors being responsible for mediating short-term changes, and renal mechanisms determining the long-term control of blood pressure. These systems have to be adaptable in order to deal with physiological variation in the delivery of blood to tissues from rest to exercise, and with the large shifts in blood volume seen in acute haemorrhage. Pathophysiological changes in these systems lead to maladaptive responses, with systemic hypertension the most commonly seen.

Keywords Baroreceptor reflex; blood pressure; cardiac output; diuresis; haemorrhage; hypertension; natriuresis; renin–angiotensin–aldosterone system; vascular resistance

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Learning objectives

After reading this article you should understand:

- how arterial blood pressure is controlled by the baroreceptor reflex
- the sensory, transduction and effector systems in the baroreceptor reflex
- how vascular parameters (pressure, flow, radius, blood volume) are combined to create a hydraulic model of blood pressure
- how the kidney contributes to blood pressure control
- pressure natriuresis and diuresis as mechanisms that control blood volume

Introduction

Systemic blood pressure, the cardiac output and circulating blood volume determine the tissue blood flow and as such the function of organ system. Regional flow is governed by the pressure generated by the heart and the resistance to flow exerted by the blood vessels supplying that region. In order to maintain adequate blood supply to individual organs, a system of feedback loops regulate the blood pressure on a short-term (i.e. beat-to-beat) and long-term basis.

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Blood pressure

Grodins derived a number of equations to describe the flow through blood vessels.[1] These have become the standard by which acute blood pressure, circulating volume and vascular resistance are understood. Flow is proportional to the pressure gradient across a vessel, and indirectly proportional to its resistance. Expressed simply for the whole circulation:[2]

$$\text{Cardiac output} = (\mathbf{Pa} - \mathbf{Pv})/\mathbf{R}$$
$$V = Va + Vv$$
$$Pa = Va/Ca$$
$$Pv = Vv/Cv$$

Pa = arterial pressure, Pv = venous pressure, R = total peripheral resistance, V = total blood volume, Va = arterial blood volume, Vv = venous blood volume, Ca = arterial compliance, Cv = venous compliance. Where = heart rate × stroke volume, and R $\propto$ vessel radius^{-4}.

This model represents a hydraulic model of blood pressure control and versions are often used in reference to the treatment of hypertension.[3] It assumes a fixed total blood volume, and is thus a 'closed' system. This is useful in understand what happens to blood pressure acutely, for instance with pathological vasodilation. These equations contain only vascular factors, but over longer periods of time feedback systems allow total blood volume to be controlled independently of these. Total blood volume then becomes a balance between intake and excretion of fluid and is regulated by the kidney.

The mean systemic arterial pressure decreases from the aorta at 100 mmHg to 35 mmHg at the level of the arteriole, whereas mean systemic venous pressure is 3–8 mmHg (Figure 1). The arterial and venous pressures in the pulmonary circulation are about one-fifth of systemic values.

The arterial system comprises the resistance vessels. By varying the smooth muscle tone in their walls vasoconstriction and vasodilation can occur, with a direct and immediate effect on total peripheral resistance. Changes in their calibre results in alteration of perfusion pressure across tissue beds and the flow rate through these vessels. By varying the arteriolar radius in different tissue beds (and whole circulations), the pressure and flow to those organs can be managed independently, allowing a variety of operating flows at rest and exercise. In contrast, the

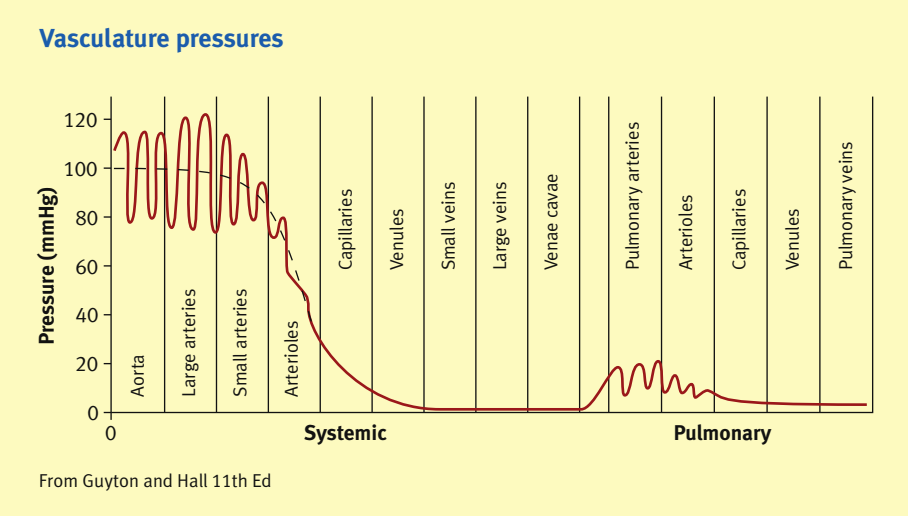

Figure 1

venous system comprises the capacitance vessels. They contain 70–80% of the blood volume, so venoconstriction or venodilation will influence this volume distribution (and will transiently alter venous return and stroke volume), but has little effect on total peripheral resistance.

Systemic arterial pressure is what is usually measured and treated in clinical practice. There is a large variation in mean arterial blood pressure with activity levels and wakefulness, with age, gender and ethnicity. As such, a population average is of little clinical use. A desirable blood pressure is said to be 115/75 mmHg,[4] a risk of cardiovascular disease is observed to progressively increase above these values. Hypertension is suspected based on a clinic-measured blood pressure of 140/90 mmHg or higher, though can only be confirmed with ambulatory or home blood pressure measuring 135/85 mmHg or higher.[5] Hypotension is only of clinical relevance when symptoms occur.

Neurological control of blood pressure

Arterial baroreceptor reflex

The baroreceptor reflex (Figure 2) is the predominant control mechanism of short-term blood pressure. It is a negative feedback loop, mediated by the specialized pressure sensors situated in the carotid sinuses, in the aortic arch and at the bifurcation of the internal and external carotid arteries. These mechanoreceptors are spray-type nerve endings, situated in blood vessel walls which respond to both circumferential and longitudinal stretch.

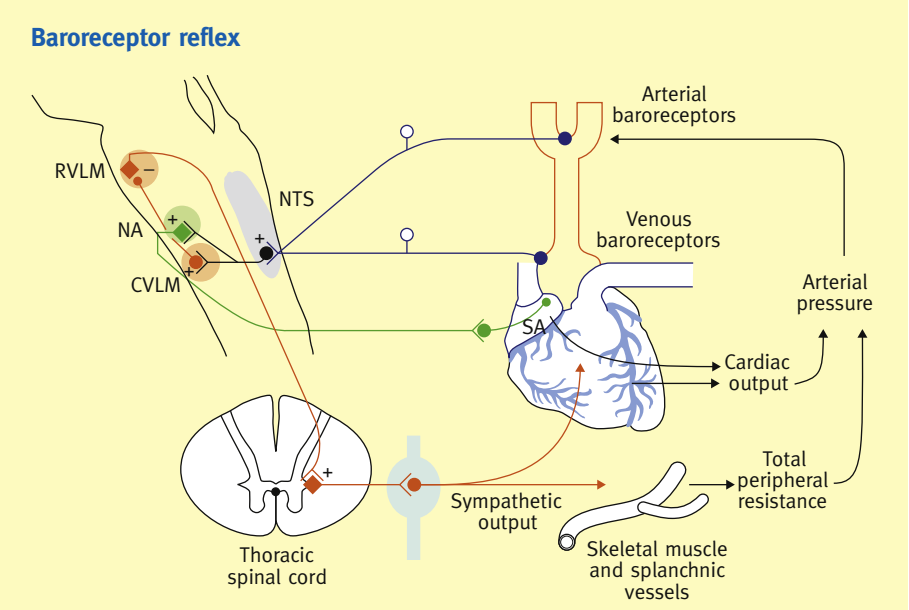

Figure 2

The baroreceptors fire impulses at a rate directly proportional to the blood pressure, and are quiescent at pressures below 50–60 mmHg. The discharge response rate is sigmoidal with respect to pressure. At the normal mean blood pressure of around 100 mmHg, small changes in pressure have relatively large effects on afferent nerve activity as a result of the gradient of this curve (Figure 3). This is the operating 'set point', where the maximal signal gain occurs. This may be altered in chronic hypertensive states. Above 180 mmHg, there is little gain in the system so changes in blood pressure hardly influence sympathetic outflow. The discharge is dynamic and has a response rate that varies with the cardiac cycle, with a greater rate of firing during systole than diastole (Figure 4).

The afferent signals are transmitted from the baroreceptors via the vagi and glossopharyngeal nerves to the nucleus tractus solitarius, part of the medulla oblongata, and onward to the vasomotor centres. The vasomotor centres are also under the influence of chemosensors and higher cortical inputs, which are excitatory, so that during exercise a higher pressure 'set point' is established. Without this extra somatosensory input, the baroreflex would offset the sympatho-excitatory response seen at the onset of exercise.

The autonomic innervation of the heart is both sympathetic and parasympathetic, with β_1-receptors the predominant adrenoreceptor. Stimulation of these receptors leads to the G-protein coupled activation of adenyl cyclase and rise in intracellular cyclic adenosine monophosphate with a resultant influx of Ca^{2+} as well as its release from the sarcoplasmic reticulum. Calcium binds to troponin C, causing allosteric modulation of the troponin complex and more efficient actin–myosin interaction thereby enhancing both the speed and force of sarcomere shortening. The effect on the whole muscle is an increased force of contraction independent of the degree to which the myocytes are stretched. The sino-artrial and atrioventricular nodes are under the same influence, with sympathetic stimulation increasing heart rate and the speed of atrioventricular conduction.

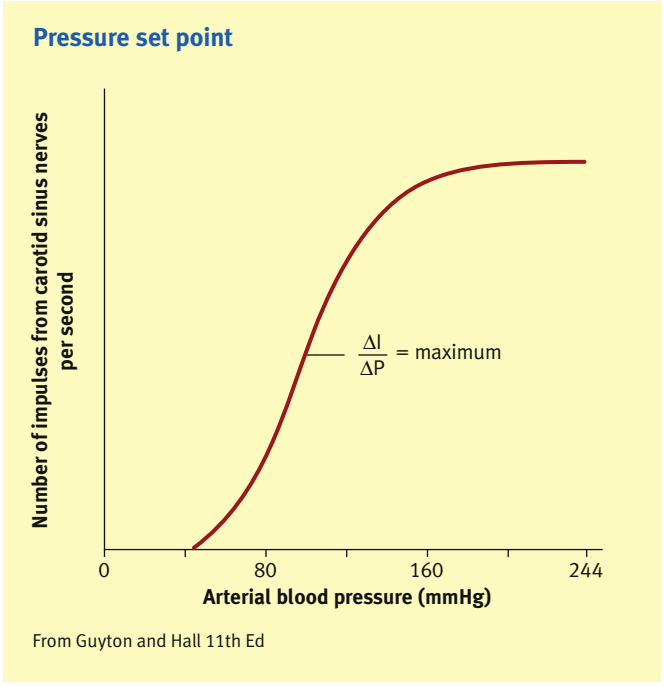

Figure 3

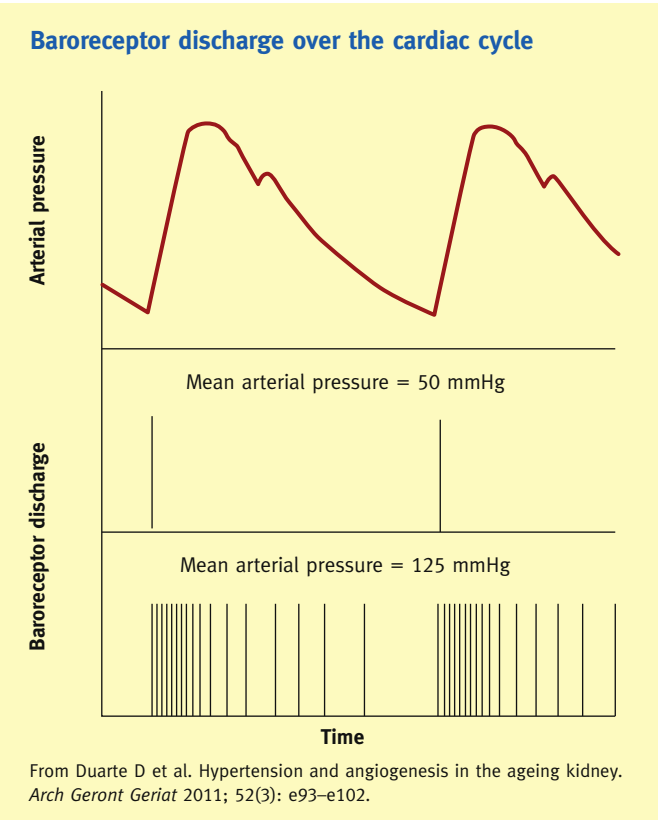

Figure 4

Constriction of the small arterial vessels and arterioles contributes more to the increase in total peripheral resistance than the larger vessels, as resistance to flow varies inversely with the fourth power of the radius of the vessel. This is mediated by sympathetic stimulation of α_1 adrenoreceptors in vascular smooth muscle cells which in turn results in G_q protein coupled increase in inositol triphosphate which triggers release of calcium from the sarcoplasmic reticulum. In this tissue, rather than binding to troponin as in cardiac muscle, calcium binds to and activates the soluble intracellular regulatory protein calmodulin which in turn activates myosin light chain kinase (MLCK). MLCK phosphorylates the myosin heads, increasing their adenosine triphosphatase activity resulting in cross-bridge cycling and the generation of vascular tone. It is through this mechanism that flow to different organ beds can be mediated independently. When blood pressure acutely decreases, vasoconstriction of the vessel bed in less critical organs (e.g. the skin and splanchnic beds) dominates, thereby maintaining flow to critical organs (e.g. the brain).

The only adrenoceptors that capacitance vessels express are α-receptors. With increased sympathetic outflow, adrenoceptor mediated venoconstriction is enhanced, transiently increasing venous return to the heart by decreasing the volume of blood in the capacitance vessels and displacing it into the central veins and right heart.

By contrast the net clinical effect of baroreceptor discharge (resulting in a reduction in sympathetic outflow) is vasodilatation, decreased heart rate and negative inotropy.

Cardiopulmonary baroreceptors

In addition to high-pressure receptors in the arterial system, low-pressure baroreceptors are found in the venae cavae, the atria and pulmonary veins. Often termed 'volume receptors', these stretch receptors transmit afferent signals, also via the vagi, to the hypothalamus. Decreasing venous volume unloads these receptors and results in increased sympathetic and decreased sympathetic tone to the heart and vasculature. It has been demonstrated that the cardiopulmonary baroreceptors enhance carotid baroreceptor gain. The 'Bainbridge reflex' is mediated through the atrial baroreceptors, so when blood volume increases, an increase in heart rate is initially seen.

Humoral control of blood pressure

Humoral mechanisms act to control blood pressure through vasodilation, vasoconstriction and alteration of blood volume.

Renin–angiotensin system

Decreased renal perfusion during periods of hypotension results in the secretion of renin from the juxtaglomerular apparatus. There are two transducers in this system. The afferent arteriolar baroreceptor reflex senses alteration in the rate of change of stretch in the afferent arteriole and results in renin secretion by juxtaglomerular cells. The other sensor is the macula densa which senses any change in sodium concentration in the distal tubular fluid. A reduction in glomerular filtration rate will cause a reduction in sodium concentration of the distal tubular fluid, since the tubules' capacity to reabsorb sodium will now exceed the rate of delivery of sodium via glomerular filtration. This decrease in sodium concentration is detected by the cells of the macula densa and results in renin release through paracrine mechanisms.

Once secreted, renin catalyses the conversion of angiotensinogen to angiotensin I. Through enzymatic conversion angiotensin II is produced which is a potent vasoconstrictor, acting both directly through widely expressed angiotensin receptors and also by interaction with β_2-adrenergic receptors. In addition to the direct effect angiotensin II has on the blood pressure, it increases tubular sodium reabsorption. It also acts to promote the synthesis and release of aldosterone and release of anti-diuretic hormone. The net effect of this mechanism is vasoconstriction, water and sodium retention by the kidneys and thus the expansion of the extracellular fluid volume.

The renin–angiotensin–aldosterone system runs as a negative feedback loop with two phases. Rapid vasoconstriction (within minutes of stimulus) mediated by angiotensin II and anti-diuretic hormone, and a more gradual increase in extracellular fluid through retention of sodium and water through the kidneys. Once juxtaglomerular perfusion returns the release of renin ceases.

Natriuresis and diuresis

Increases in extracellular fluid cause an increase in blood volume and pressure over time. Increasing renal perfusion pressure results in the increase in sodium excretion and decrease in reabsorption (pressure natriuresis) and increase in renal water output (pressure diuresis). This is a central component in the long-term control of arterial pressure. As these mechanisms make the cardiovascular an 'open' system in the long term, and any changes in pressure modelled in a hydraulic system will not be sustained. This is illustrated by the ability to maintain control of blood pressure with denervated baroreceptors. Here, although the acute compensatory mechanisms are lost, over a longer time-scale, a return to baseline is seen.[6]

The peptide hormones

Atrial natriuretic peptide (ANP) is secreted by atrial myocytes in response to stretch which occurs when venous return increases. It binds to a specific set of ANP receptors expressed in the distal convoluted tubule and collecting duct and in peripheral arterioles. The action of ANP is to constrict the efferent arteriole and dilate the afferent arteriole. It increases renal perfusion pressure thus increasing renal sodium and water clearance. In the vasculature it relaxes smooth muscles and antagonizes the effect of catecholamines.

In contrast, anti-diuretic hormone (ADH) acts to reduce renal water excretion by increasing water permeability of the distal tubule and collecting ducts through the insertion of aquaporins into the apical membrane. The main stimulation for its release is an increase in plasma osmolality, but secretion is also increased by angiotensin II and inhibited by ANP. In severe hypovolaemia, circulating levels of ADH increase fivefold, and at these levels it exerts a pressor effect via stimulation of vascular V2 receptors.

Response to acute haemorrhage

The response to acute haemorrhage illustrates the integrated physiological response which serves to maintain blood pressure and flow to critical organs, despite a decrease in circulating volume. Sudden severe haemorrhage results in a decrease in vessel wall tension in the aorta and carotid arteries. This offloads the baroreceptors, decreasing afferent discharge which results in increases efferent sympathetic output, increasing heart rate and cardiac contractility thereby moderating the fall in cardiac output. The increased sympathetic outflow also causes veno- and vasoconstriction, decreasing the arterial flow to non-essential organs and redistributing volume from the venous to arterial systems. This response is immediate, but over time the activation of the sympathetic system will alter capillary hydrostatic pressure to favour the mobilization of fluid into the intravascular space. The sympathetically mediated reduction in renal glomerular flow will decrease glomerular filtration of water and sodium, which will be synergized soon after by activation of the renin–angiotensin–aldosterone system.

Role of kidney in long-term control of hypertension

The final common pathway that determines long-term arterial pressure is the kidney.[7] By considering the effect that drugs have on the pressure–natriuresis relationship, anti-hypertensives can be categorized into three groups. The acute effects of these drugs on the heart and systemic vasculature are easily observed, but it is their renal specific effects that influence long-term efficacy.

The first group are the vasodilators (e.g. calcium-channel antagonists and α-blockers). By predominantly vasodilating the afferent arteriole, 'glomerular hypertension'[8] results in a greater urinary sodium excretion for any given systemic arterial pressure compared to untreated hypertensives.

The second group are the drugs acting to modulate the renal sympathetic system (β-blockers and angiotensin-converting enzyme inhibitors). These also increase the urinary sodium excretion rate for any given systemic arterial pressure, but act by inhibiting either the renal sympathetic response (i.e. inhibiting arteriolar

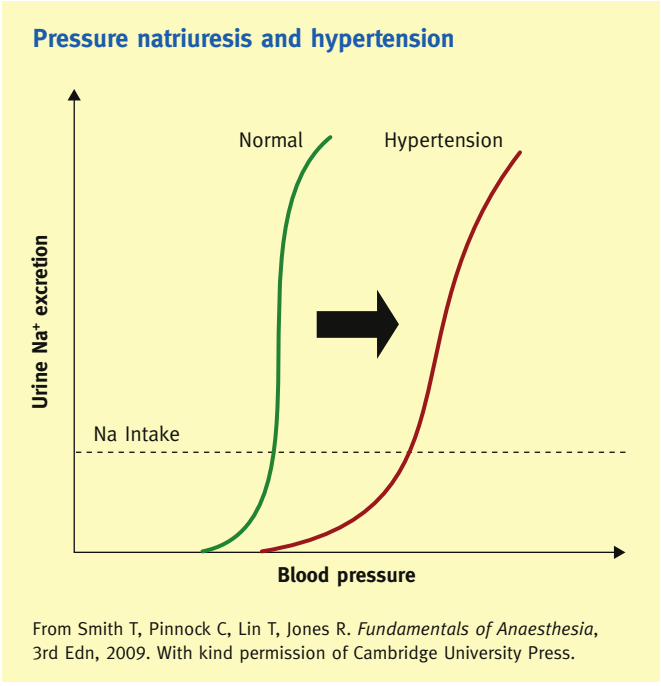

Figure 5

vasoconstriction thus increasing glomerular blood flow and filtration), or by decreasing the tubular absorption of sodium and water mediated by the renin–angiotensin system.

Thirdly are the diuretics (e.g. thiazides). Guyton postulated that increases in dietary sodium would result in a transient increase in blood pressure, leading to pressure natriuresis and restoration of the body's salt balance.[9] Hypertensives display impairment in the mechanisms to maintain this relationship such that higher pressures are required to maintain homoeostasis (Figure 5). Diuretics cause the pressure–natriuresis relationship of the kidney to become less pressure dependent (i.e. sodium is lost through the kidney at lower systemic pressures). This reverses the impaired natriuresis seen in chronic hypertensives.[10]

Summary

The neurological and humoral control of blood pressure are an integrated physiological response which maintains the essential homoeostasis of blood flow to tissues. While baroreceptors display the ability to respond to short-term changes in blood pressure, the renal mechanisms are responsible for long-term pressure setting. Both a hydraulic 'closed' model, with its fixed blood volume, and the 'open' renal model, with natriuresis and diuresis determining blood pressure are relevant, especially when considering the pathophysiology of short- and long-term control of systemic arterial pressure. ◆

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