Control of Vascular Resistance

Baroreceptors and Baroreceptor Reflexes

In order to maintain stable blood pressure, it is necessary to monitor whether blood pressure changes, and then to correct for these changes through negative feedback mechanisms. The principal negative feedback system that operates to maintain stable blood pressure is the baroreceptor reflex. As arterial pressure deviates from the set point, the baroreceptor reflex compensates for the change and thus maintains arterial pressure within a narrow normal range.

The afferent limb of the baroreceptor reflex is comprised of receptors associated with two major arteries: the aortic arch and the carotid sinus. These receptors are stretch receptors, and are activated when the vessels are distended by blood during increases in blood pressure. Thus, the receptors do not actually detect pressure, but a parameter that is correlated with pressure. The afferents from the aortic arch form the aortic depressor nerve, which runs with the vagus nerve (and is considered to be part of the vagus nerve). The cell bodies of aortic arch afferents, like other vagal afferents, are located in the nodose ganglion, which is in the neck. The afferents innervating the carotid sinus course in cranial nerve IX (the glossopharyngeal nerve). The cell bodies of these afferents are located in the petrosal ganglion. Both aortic arch and carotid sinus afferents terminate in nucleus of the solitary tract in the medulla.

When blood pressure increases, the baroreceptor terminals are stretched and the afferents fire more. As with other types of stretch receptors, the responses of these afferents adapt to prolonged stretch. In the case of baroreceptors, this adaptation (resetting) begins within a few minutes of a sustained change in blood pressure. Thus, baroreceptor afferents signal acute changes in pressure, rather than a specific pressure.
Activation of the baroreceptor reflex (increased firing of baroreceptor afferents) leads to increased parasympathetic outflow and decreased sympathetic outflow to the heart, and decreased sympathetic outflow to the blood vessels. These changes in activity in the autonomic nervous system will lead to decreased cardiac output and peripheral resistance, which will act to lower blood pressure. Decreased firing of baroreceptor afferents (signalling a drop in blood pressure) will have opposite effects: an increase in sympathetic outflow and a decrease in parasympathetic outflow to the heart and increased sympathetic outflow to blood vessels.

Note the shape of the curve reflecting changes in baroreceptor afferent activity during changes in blood pressure. The afferents are extremely sensitive to changes in blood pressure near the usual set point of ~92 mm Hg.

**Neuroanatomical Basis of the Baroreceptor Reflex**

The neuroanatomical substrate of the baroreceptor reflex arc has been well established through experiments in a variety of animals. Neurons in nucleus of the solitary tract that receive baroreceptor inputs have direct excitatory connections with parasympathetic preganglionic neurons located in the dorsal motor nucleus of the vagus and near nucleus ambiguus. The anatomical substrate of baroreceptor influences on sympathetic efferents is more complicated, as there must be an inhibitory interneuron in the pathway (an increase in baroreceptor activity leads to a decrease in firing of sympathetic efferents), and because the sympathetic preganglionic neurons are located in the spinal cord.

There is now considerable evidence to show that baroreceptor signals, like most inputs that influence sympathetic outflow to the heart and blood vessels, are relayed from the brainstem to the preganglionic neurons via spinally-projecting neurons located in the rostral ventrolateral medulla (RVLM). Physiological studies have shown that firing of neurons in the RVLM whose axons terminate in the sympathetic intermediolateral cell column is inhibited by baroreceptor stimulation. Furthermore, stimulation of the RVLM produces a big increase in blood pressure, and inhibition of this area (e.g., by injecting an agent such as Muscimol) leads to a drop in blood pressure equal to that produced by ganglionic blockade. These data cumulatively strongly suggest that the RVLM plays a major role in relaying baroreceptor signals to the spinal cord, and in controlling baseline blood pressure.

These data also suggest that inhibitory interneurons are located at a stage earlier than the RVLM in the baroreceptor reflex circuitry. Anatomical studies have shown that many neurons in the caudal ventrolateral medulla (CVLM) have ascending projections to the RVLM (see next page). Furthermore, inhibition of the CVLM leads to an increase in blood pressure, and stimulation of this area produces a drop in blood pressure. Cumulatively these data indicate that the CVLM is the site of many inhibitory interneurons in the baroreceptor reflex arc.
Locations of Brainstem Regions that Produce Baroreceptor Reflexes

ABBREVIATIONS:
CVLM—caudal ventrolateral medulla
DMV—dorsal motor nucleus of the vagus
N Ambiguus—nucleus ambiguus
NTS—nucleus tractus solitarius
RVLM—rostral ventrolateral medulla

This diagram summarizes the circuitry that mediates baroreceptor reflexes.
Some Real Data to Help Clarify the Baroreceptor Reflex

The example below shows the effects of mechanically stretching one carotid artery in an experimental animal on blood pressure (top trace) and the firing rate of an RVLM neuron (bottom trace). Note that the firing of the RVLM neuron ceases during carotid stretch, and that blood pressure subsequently drops.
Some recordings from small groups of muscle vasoconstrictor fibers showing how the efferents respond to various manipulations that affect baroreceptor activity:

A: Activity of both facial and hindlimb muscle vasoconstrictor (MVC) fibers was silenced by bilateral and intermittent stretch of the carotid arteries; note the subsequent depressor response and accompanying increase in MVC activity. The stimulation period is indicated by the bar at the bottom of the panel. 

B: Bilateral carotid occlusion led to unloading of carotid baroreceptors, an increase in MVC activity, and a subsequent pressor response. The occlusion period is indicated by bar at the bottom, and the times at which the two carotid arteries were clamped are indicated by arrows. Note the decreases in activity prior to occlusion of each artery and following release of occlusion: the former is presumably due to the carotid stretch prior to placement of the clamp, while the latter reflects re-exposure of the carotid sinuses to the (now raised) arterial pressure. 

C: Occlusion of expiratory outflow leads to a decrease in blood pressure, triggering an increase in MVC activity. 

D: Systemic administration of hexamethonium (14 mg/kg i.v.) silenced facial and hindlimb MVC activity.
What happens if the baroreceptor reflex is eliminated?

In a famous experiment first conducted by Arthur Guyton, baroreceptor afferents were destroyed surgically, and daily changes in blood pressure were compared before and after the surgery. In baroreceptor-intact animals, blood pressure remained quite stable over an extended period. Following baroreceptor denervation, however, blood pressure was much more labile, although mean blood pressure remained near 100 mm Hg. These data show that although baroreceptor inputs do not establish the “set point” in blood pressure, they are essential in maintaining blood pressure within a narrow range.

![Graph showing normal and denervated blood pressure](image)

Some other reflexes operate by modulating the activity of RVLM neurons that are part of the baroreceptor reflex arc

Feedback from arterial and atrial baroreceptors is not the only parameter involved in the short-term regulation of arterial pressure. Under some conditions, it is appropriate to sacrifice constant blood pressure to alter blood flow to particular body regions. In general, these additional reflexes that modulate blood pressure operate by altering the activity of RVLM neurons that influence sympathetic outflow and preganglionic parasympathetic neurons that influence the heart.

Decreased blood oxygen content activates arterial chemoreceptors, located predominantly in the carotid sinus, that trigger reflex vasoconstriction in most tissues so that perfusion of the brain will increase. We will discuss these afferents in detail in the Respiratory section.
**Blood Flow to Different Regions**

Under resting situations, all of the tissues of the body receive substantial perfusion. The perfusion rates to a number of organs are listed in the following table:

<table>
<thead>
<tr>
<th>Organ</th>
<th>Flow (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>0.75</td>
</tr>
<tr>
<td>Heart</td>
<td>0.3</td>
</tr>
<tr>
<td>Digestive T.</td>
<td>1.4</td>
</tr>
<tr>
<td>Kidneys</td>
<td>1.1</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.2</td>
</tr>
<tr>
<td>Skin</td>
<td>0.35</td>
</tr>
<tr>
<td>Other</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**Total Cardiac Output: 6.0 L/min**

Because all of the arterial beds in the body are arranged in parallel (i.e., they are fed by the same aorta), then total flow through all beds equals cardiac output.

**Myogenic Autoregulation**

During non-rest conditions, however, blood flow in particular arterial beds may change tremendously. For example, during vigorous exercise, blood flow to skeletal muscle may reach 14 L/min. Obviously, because cardiac output has limits, this level of flow to one bed is only permitted if flow to others diminishes. Control of peripheral resistance is accomplished through neural mechanisms and through **myogenic autoregulation**, the ability of vascular smooth muscle to regulate its own activity. Autoregulation is in part intrinsic and is also influenced by the release of **paracrines**, chemicals secreted by cells that affect the contraction of nearby vascular muscle. In addition, a number of hormones act to regulate blood flow throughout the body. Those hormones will be discussed during the next lecture.
Thus, when intraluminal pressure is increased, the initial distension of the arteriolar wall is a stimulus for the activation of smooth muscle cells. Consequently, vessel diameter will ultimately become smaller as the perfusion pressure rises. In effect, autoregulation provides for a constant rate of O2 delivery regardless of perfusion pressure.

Local control of vascular resistance is also controlled by the release of metabolites from tissues. For example, H+ from acids (e.g. lactic acid), K+, and CO2 release promotes vasodilation. Low oxygen levels can also induce vasodilation. This latter response is likely mediated by the release of adenosine from muscle cells during hypoxia. Each factor is additive, and the accumulation of all of these chemicals during exercise promotes the extensive increases in skeletal muscle perfusion that occur.

Adenosine and K+ appear to be the metabolites with the strongest effects on vasoconstriction. Adenosine appears to act by triggering an increase in cAMP, which activates protein kinase A (PKA). PKA phosphorylates and opens K-ATP channels, thereby resulting in a K+ efflux and hyperpolarization of the smooth muscle cell. Conductance through another K+ channel, the K-IR channel, subsequently increases when extracellular K+ rises, causing further hyperpolarization of the cell. Increases in extracellular K+ due to metabolism of surrounding tissues also opens and increases K+ conductance through K-IR channels, thereby hyperpolarizing the smooth muscle cells. Hyperpolarization of smooth muscle causes a closing of voltage-gated Ca2+ channels, thereby resulting in relaxation of the smooth muscle.

A large number of additional paracrine factors help to precisely regulate blood flow to particular vascular beds. One example is endothelin, which is released from damaged endothelial cells. Endothelin produces powerful vasoconstriction, which serves to reduce bleeding from damaged arteries. Similarly, release of serotonin from activated platelets can induce vasoconstriction and help prevent blood loss. In contrast, histamine release from healing tissues or mast cells promotes vasodilation.
**Endothelium-Derived Relaxing Factor**

Robert F. Furchgott (winner of the 1998 Nobel Prize in Medicine) discovered a substance in endothelial cells that relaxes blood vessels, which he called endothelium-derived relaxing factor (EDRF). By 1986, he had worked out EDRF’s nature and mechanism of action, and determined that EDRF was in fact nitric oxide (NO), an important compound in many aspects of cardiovascular physiology.

The production of NO is stimulated by a number of chemical agents (acetylcholine, bradykinin, ATP), and (most importantly) by the blood flow itself.

Sheer stress produced by the flowing of blood across the surface of endothelial cells opens mechanically-gated channels on the surface. Some of these channels are Ca2+ channels, and Ca2+ entering the endothelial cell through these channels combines with calmodulin (CM); the resulting Ca2+—CM complex activates NO synthase.

There is an additional mechanotransduction mechanism that initiates a kinase cascade, ultimately leading to phosphorylation of NO synthase. The phosphorylation causes activation of NO synthase and increased production of NO.

NO diffuses from endothelial cells to adjacent smooth muscle cells. NO produces smooth muscle relaxation by activating the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP). This intracellular messenger activates an ATPase that pumps calcium out of the smooth muscle cell, thereby inhibiting interactions between actin and myosin.

Nitric oxide release from endothelial cells also occurs when they exposed to bradykinin, an agent that is released during cellular damage. A number of products of metabolism also trigger vasodilation by causing the synthesis of NO.

As noted in previous lectures, the parasympathetic innervation of a limited number of vascular beds (i.e., genitalia) can also induce the production of NO. The vasodilation resulting from NO release in the male corpus cavernosum results in erection. Drugs such as Viagra (sildenafil) have no direct relaxant effect on the corpus cavernosum, but enhance the effect of nitric oxide (NO) by inhibiting phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum. When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil at recommended doses has no effect in the absence of sexual stimulation.
Atrial Stretch Receptors and their Role in Cardiovascular Control

Both the atria and the pulmonary arteries contain stretch receptors, which are called low-pressure receptors. These low-pressure receptors are much like arterial baroreceptors in structure, but because of their location do not sense pressure in the systemic circulation. Instead, they detect increases in pressure in the low-pressure parts of the circulation that are generated by increases in blood volume. Thus, atrial and pulmonary stretch receptors act functionally to sense blood volume, and their inputs serve to make regulation of blood pressure more precise than could be provided through arterial baroreceptors alone. For example, a simultaneous decrease in activity of atrial and arterial baroreceptors indicates that blood pressure has dropped because of a decrease in blood volume, perhaps due to hemorrhage.

The axons of atrial receptors reach the brainstem via the vagus nerve. Activation of atrial stretch receptors elicits a brainstem-mediated reflex that tends to increase heart rate and probably contractility. This response, called the Bainbridge reflex involves reflex activation of both the sympathetic and parasympathetic nervous system. This reflex helps prevent accumulation of blood in the veins, atria, and pulmonary circulation.

Signals from atrial stretch receptors are also transmitted to the hypothalamus, and affect the release of antidiuretic hormone (also called vasopressin). The main role of this hormone is to control water reabsorption in the kidney, as we will see later in this course. Signals from stretch receptors located in the atria and pulmonary arteries can elicit a decrease in vasopressin release, which will in turn act on the kidney to result in lowered volume in the cardiovascular system. This is a potent mechanism to maintain constant blood volume.

However, if levels of vasopressin increase high enough, potent vasoconstriction will occur. It is rare for such high levels of the hormone to appear in the blood, but this can happen during hemorrhage. In addition, vasopressin acts on circuitry in the brainstem to potentiate the baroreceptor reflex.

Mechanisms other than atrial stretch receptors can also affect vasopressin release. Vasopressin is released when the hypothalamus detects an increase in blood osmolarity, which occurs when blood volume decreases or the concentration of solutes increases. Signals from arterial baroreceptors also act to increase vasopressin release.

Effect of osmolarity on vasopressin release.

An increase in plasma osmolarity above about 280 mOsm also results in an increase in vasopressin release. Osmolarity is the measure of solute concentration, defined as the number of osmoles (Osm) of solute per litre (L) of solution. The change in blood osmolarity is detected by osmoreceptors located in the hypothalamus. A change in plasma osmolarity causes water to enter or leave the osmoreceptor, and the change in cell size affects sensory inputs relayed to vasopressin-producing neurons. We will learn more about this mechanism during the next lecture.
As discussed later in this lecture, release of the hormone renin from the kidney induces a cascade that results in increased blood levels of angiotensin II, which in turn induces vasopressin release.

In addition, atrial natriuretic factor is released from the atria when venous pressure (atrial stretch) is high. This hormone tends to produce vasodilation. This will diminish cardiac return, and will thus decrease the workload of the heart which is overloaded with blood. In addition, atrial natriuretic factor promotes secretion of water and salt by the kidney, to reduce blood volume. Also, atrial natriuretic hormone acts to inhibit the release of the hormone aldosterone from the adrenal cortex. Aldosterone promotes the reabsorption of salt and water, and thus inhibition of aldosterone release has the opposite effect (causes salt and water to be lost from the body).

B-type (brain) natriuretic peptide (BNP) was recently described. This peptide is released from ventricular myocytes in response to increased tension. The peptide’s name results from its first identification in pig brains. However, BNP was subsequently discovered to be present in high concentrations in cardiac tissues, particularly the ventricles.

The actions of BNP are very similar to those of ANP (diuretic, natriuretic, and antihypertensive effects).

Although ANP was identified first, concentrations of BNP in myocardial tissue are higher than those of ANP. Therefore, BNP is more useful than ANP as a marker of increased ventricular filling pressure.
Longer-Term Regulation of Blood Pressure

Hormonal Mechanisms

If blood pressure remains low for several minutes, the potent vasoconstrictor Angiotensin II appears in the bloodstream. This hormone is produced at the end of a long enzymatic cascade that begins in the kidney.

When blood pressure is low, special cells in the kidney called juxtaglomerular cells (JG cells), detect the condition and release a peptide called renin. The sympathetic nervous system can also act to induce renin release, as JG cells release this agent when NE binds to beta-receptors on these cells. Renin converts an inactive plasma protein made by the liver, angiotensinogen, into angiotensin I. Angiotensin I is converted by an enzyme located on the endothelium of blood vessels, called angiotensin converting enzyme, into the active form, angiotensin II. This enzyme is concentrated in blood vessels of the lung.

An elevated BNP level is a marker of increased left ventricular filling pressures and left ventricular dysfunction.

Synthetic BNP (Nesiritide; Natrecor) has been used to treat patients with decompenated congestive heart failure. However, subsequent studies have shown that the drug is not more effective than other therapies.
As mentioned earlier, Angiotensin II is a potent vasoconstrictive agent. It also has a number of indirect effects that stimulate an increase in blood pressure.

1) It stimulates the release of antidiuretic hormone (vasopressin) from the pituitary, which stimulates water retention and an increase in plasma volume.

2) It stimulates thirst, and the addition of water to the body

3) It affects the parts of the medulla that control sympathetic outflow, to increase heart rate and vasoconstriction.

4) It causes the adrenal cortex to release the hormone **aldosterone**, which causes the kidney to reabsorb salt and water into the blood. The net result is that blood volume is increased.

5) It potentiates the release of NE from sympathetic terminals.
Not all influences on the renin-angiotensin system are the same!

Increased sympathetic nervous activity induced through baroreceptor reflex mechanisms induces the largest augmentation in renin release. A drop in blood pressure is only effective if it is very large.
Clinical Notes: Value of ACE Inhibitors and Angiotensin Receptor Blockers in Treating Hypertension

Because of the large role that the renin-angiotensin system plays in regulating blood pressure, it is not surprising that inhibiting the formation of angiotensin II or blocking its effects on receptors are common mechanisms to treat hypertension.

Selective Angiotensin-2, Type 1 antagonists are available, that only block the receptor subtype in blood vessels and in the adrenal cortex (i.e., on cells that produce aldosterone). These drugs may have fewer side effects than ACE inhibitors.
Recent research has shown that the renin-angiotensin system is much more complicated than originally envisioned. A second angiotensin converting enzyme, angiotensin-converting enzyme 2, has been discovered that is involved in the production of Ang(1-9) and Ang(1-7). These peptides, like Angiotensin II, have strong effects on the cardiovascular system. These effects are currently being studied, and may be targets for future treatments for cardiovascular diseases.

Role of the Kidney and Behavioral Mechanisms

A major mechanism for long-term regulation of blood pressure is to alter blood volume. This is accomplished both through the actions of the kidney and behavioral mechanisms driving fluid consumption. We will discuss these mechanisms in the renal section of the course.