OBJECTIVES:

1. Describe the distribution of cardiac output among the various organs in the transition from rest to various states of exercise.
2. Describe the interplay between autonomic and metabolic factors in local regulation of coronary blood flow.
3. Describe the blood brain barrier and its function.
4. Describe the influence of the autonomic nerves on cerebral blood flow.
5. Compare and contrast the influence of changes in arterial PCO$_2$ and PO$_2$ on cerebral blood flow.

SUGGESTED READING ASSIGNMENT:


I. BLOOD FLOW REGULATION IN THE CIRCULATION (INTRODUCTION)

The distribution of the cardiac output to the various organ systems of the body is indicated in the table below.

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Light</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ml/min</td>
<td>% C.O.</td>
<td>ml/min</td>
</tr>
<tr>
<td>VO$_2$</td>
<td>240</td>
<td></td>
<td>720</td>
</tr>
<tr>
<td>C.O.</td>
<td>5800</td>
<td></td>
<td>9500</td>
</tr>
<tr>
<td>Splanchnic</td>
<td>1400</td>
<td>24</td>
<td>1100</td>
</tr>
<tr>
<td>Renal</td>
<td>1100</td>
<td>19</td>
<td>900</td>
</tr>
<tr>
<td>Cerebral</td>
<td>750</td>
<td>13</td>
<td>750</td>
</tr>
<tr>
<td>Coronary</td>
<td>250</td>
<td>4</td>
<td>350</td>
</tr>
<tr>
<td>Muscle</td>
<td>1200</td>
<td>21</td>
<td>4500</td>
</tr>
<tr>
<td>Skin</td>
<td>500</td>
<td>9</td>
<td>1500</td>
</tr>
<tr>
<td>Other</td>
<td>500</td>
<td>9</td>
<td>400</td>
</tr>
</tbody>
</table>

Figure 1.
As can be seen from the table, blood flow depends on the organ, as well as the level of activity of the body.

Note how blood flow through the various body regions changes as the human subject begins to exercise. In particular, note how cerebral blood flow is closely regulated, and how blood flow increases in the coronary, skeletal muscle and skin circulations, while it decreases in the splanchnic and renal circulations as exercise continues.

In the following sections we will discuss the circulations of several regions of the body and review the extrinsic and intrinsic factors which play a role in blood flow regulation in each particular region.

II. THE CORONARY CIRCULATION

A. Anatomy

The entire blood supply of the myocardium is provided by the right and left coronary arteries which arise at the root of the aorta behind the right and left cusp of the aortic valve. (See Figure 2.)

The right coronary artery supplies, for the most part, the right ventricle and atrium. The left coronary artery supplies principally the left ventricle and atrium. Most of the venous blood returns to the right atrium through the coronary sinus, however, a smaller amount returns via the anterior coronary veins. In addition, there exist some vascular channels between the vessels of the myocardium and the cardiac chambers.
B. Regulation of Coronary Flow

1. Neural (Extrinsic) Control

In the intact animal the autonomic nervous system appears to play a minor role in coronary blood flow regulation when compared with local, metabolic factors. When the sympathetic nerves are stimulated, a vasoconstriction of the coronary vessels does occur. However, the concomitant increase in myocardial metabolic rate results in the production of vasodilator substances which overshadow this
vasoconstrictor tendency.

The use of experimental preparations such as isolated coronary arteries and potassium-arrested hearts in which metabolism has been stopped has enabled investigators to look more closely at the effects of neural input on the coronary circulation. Histological studies have confirmed that adrenergic nerves innervate the coronary vessels, and, in addition, it has been demonstrated that two adrenergic receptors, alpha and beta, exist in coronary blood vessels.

2. Local (Intrinsic) Control

Blood flow autoregulation occurs in the coronary circulation over a wide range of perfusion pressure (see Figure 3.)

![Figure 3. Pressure-flow relationships in the coronary vascular bed. At a constant aortic pressure, cardiac output, and heart rate, coronary artery perfusion pressure was abruptly increased or decreased from the control level indicated by the point where the two lines cross. The closed circles represent the flows that were obtained immediately after the change in perfusion pressure, and the open circles represent the steady-state flows at the new pressures. There is a tendency for flow to return toward the control level (autoregulation of blood flow); this is most prominent over the intermediate pressure range (about 60 to 180 mm Hg).](image-url)
The dominant factor that controls coronary blood flow appears to be the metabolic rate of the myocardium. It has been shown by many investigators that any increase in the metabolic activity of the heart results in an increase in coronary blood flow. Whereas a myogenic mechanism cannot explain the changes in blood flow that accompany alteration in tissue metabolic rate, the metabolic mechanism appears to account for changes in blood flow quite well.

Any sudden increase in the metabolic rate of the heart initially produces tissue hypoxia, which refers to a state in which oxygen delivery by the blood is insufficient to meet the oxygen demand of the tissue. Hypoxia has been shown to be a potent stimulus for coronary vasodilation. It is still unknown whether the blood vessel wall is directly sensitive to oxygen (i.e., direct effect of oxygen) or whether hypoxia of the parenchymal tissue (i.e., indirect effect of oxygen) results in the increased production of a vasodilator metabolite that elicits arteriolar dilation. Recent evidence seems to indicate that the latter proposal is more likely. In fact, adenosine, a potent vasodilator metabolite, has been shown to rapidly increase in concentration when the oxygen delivery to the myocardium is inadequate.

Other vasodilator substances that have been considered are H\(^+\), K\(^+\) and prostaglandins, although none of these substances are as potent a vasodilator as adenosine when infused into the coronary circulation. At present it appears that coronary blood flow is closely linked to the metabolic needs of the myocardium with oxygen and adenosine playing key roles in the chain of events that bring about blood flow regulation.

### III. CEREBRAL CIRCULATION

#### A. Anatomy

Blood is supplied to the brain by the carotid artery (which feeds the circle of Willis) and by the basilar artery (which feeds the vertebral arteries). The circle of Willis supplies blood to the anterior, middle and posterior cerebral arteries. Blood from both the carotid arteries and the vertebral arteries can freely communicate through the circle of Willis. The beneficial aspect of this anatomy is that blood flow to the brain will not cease despite an occlusion of one of these vessels.

The capillaries of the brain have a unique feature that has been referred to as the blood-brain barrier. The walls of brain capillaries exhibit a low permeability that prevents the passage of most substances. However, gases (e.g., O\(_2\) and CO\(_2\)) and certain nutrients (e.g., glucose and certain amino acids needed for neurotransmitter synthesis with special carrier...
mechanisms) can pass with little difficulty between blood and cerebral tissue.

B. Regulation of Cerebral Blood Flow (CBF)

1. Neural (Extrinsic) Control

The arteries on the brain surface and the larger arterioles inside the brain are supplied with sympathetic and parasympathetic fibers. However, maximal stimulation of the sympathetic nerves reduces CBF by only 5-10%. The cerebral veins also receive a sympathetic nerve supply and constrict by 10-20% when the nerves are maximally stimulated. Similar stimulation of the parasympathetic fibers elicits only a modest response. It remains to be seen what role, if any, the constriction of cerebral veins by the sympathetic nerves may play in regulating intracranial pressure. Further research is required to determine the functional importance of the autonomic nervous system in regulation of CBF.

2. Local (Intrinsic) Control

The rate of CBF is regulated primarily by the concentration of carbon dioxide in the cerebral tissues. Acute increases in the level of CO$_2$ result in marked vasodilation and an increase in CBF (see Figure 4). If CO$_2$ tension (pressure) is reduced, vasoconstriction occurs, bringing about a decrease in CBF. Experimental results indicate that CO$_2$ does not act directly on vascular smooth muscle but, rather, changes in CO$_2$ lead to changes in pH in the fluid that bathes the vessels and it is this change in pH that elicits alterations in vascular caliber. It is unclear how pH changes cause variations in smooth muscle tone. However, it has been suggested that the pH inside smooth muscle cells is the important factor and that changes in the concentration of calcium ion may be involved.
Figure 4. Chemical control of CBF: cerebral blood flow variations induced by acute changes of arterial $P_{CO_2}$. The effect is mediated by pH changes in the brain extracellular fluid (CSF) surrounding the arterioles; probably it is pH inside the smooth muscle cells that (via $Ca^{++}$ changes?) causes the active changes in vascular tone (1).

When dealing with cases in which chronic changes of CO$_2$ are involved, one must consider the effect the blood-brain barrier may have on the pH of the cerebrospinal fluid (CSF). The blood brain barrier prevents the bicarbonate molecule from passing between the blood and the CSF. However, since CO$_2$ is freely permeable, it can pass across the blood brain barrier. In a case where CO$_2$ tension is chronically reduced, initially arterial hypocapnia and alkalosis occur. Next alkalosis of the CSF also occurs due to the reductions of CO$_2$ tension. However, with time (24-36 hours) the bicarbonate concentration of the CSF is adjusted so that the pH of the CSF returns to normal. In this case CBF is normal since the adaptation in CSF pH parallels (and probably causes) the CBF adaptation.

Minor alterations in the normal O$_2$ tension of the arterial blood do not cause significant changes in CBF. However, with more severe hypoxia ($PO_2 < 50$ mmHg), CBF increases dramatically. (See Figure 5)
Since severe hypoxia induces brain-tissue lactacidosis (due to lactic acid production), it has been suggested that chemical control of CBF by CO$_2$ and O$_2$ are virtually the same (i.e., via pH change). The answer, however, remains unsettled since some investigators feel that cerebral vasodilation in moderate hypoxia cannot be explained by tissue acidosis in the initial stages.

In the intact animal the effects of hypoxia are felt to be less pronounced than effects of CO$_2$ on the CBF. This is due to the hyperventilation following hypoxia that, in turn, results in hypocapnia. Hypocapnia would inhibit the vasodilatory actions of hypoxia.

Similar to the coronary circulation, autoregulation of the cerebral circulation occurs over a wide range (60-180 mmHg) of arterial blood pressure.
STUDY QUESTIONS

1. During light exercise (i.e., walking up the stairs from Dr. Costanzo’s office to the Sanger Hall 13th floor Health Club), blood flow to which of the following organs or tissues is likely to increase above resting levels?

   1. Coronary
   2. Skin
   3. Skeletal Muscle
   4. Cerebral

**ANSWER: A (1, 2, & 3)**

You need to recognize that any level of exercise will cause blood flow to the heart, skin, and active muscles to increase. Blood flow to the brain generally does not change during exercise.

2. Which of the following is/are thought to play a major role in control of the coronary circulation?

   2. Stimulation of beta-adrenergic receptors on myocytes.
   4. Production of adenosine by myocytes.

**ANSWER: C (2 & 4)**

The major determinant of coronary blood flow is the metabolic state of the myocardium. Stimulation of the beta-adrenergic receptors on the myocytes will lead to increased contractility of the heart and, hence, to an increased energy demand that is met by increased blood flow. Adenosine, a product of ATP degradation and a powerful vasodilator, appears to be the primary chemical mediator of imbalances between energy supply and demand. Although there are both alpha- and beta-adrenergic receptors on the coronary resistance vessels, they have minor influence on coronary blood flow and certainly play no major role in the control of the coronary circulation.

3. Which of the following statement(s) is/are true about the cerebral circulation?

   1. Cerebral arteries and veins receive sympathetic innervation.
   2. Cerebral blood flow is regulated primarily by carbon dioxide.
   3. Cerebral blood flow is relatively insensitive to changes in arterial PO₂ above 50 mmHg.
   4. A reduction in cerebral carbon dioxide levels leads to vasodilation.

**ANSWER: C (2 & 4)**
ANSWER: A (1, 2, & 3)

The vasculature of the cerebral circulation receives sympathetic innervation, but these nerves have very little influence on cerebral blood flow. The cerebral circulation is under the control of chemical influences, primarily carbon dioxide. Unless the arterial blood PO$_2$ drops below about 50 mmHg, CBF is insensitive to changes in blood oxygenation. A reduction in cerebral carbon dioxide levels leads to vasoconstriction, not dilation.

4. Which of the following statements is true about the cerebral circulation?

A. Cerebral arteries and veins do not receive sympathetic innervation.
B. Cerebral blood flow is regulated primarily by arterial [H$^+$].
C. Cerebral blood flow is very sensitive to changes in arterial norepinephrine concentration.
D. A reduction in cerebral carbon dioxide levels leads to vasoconstriction.
E. Cerebral blood flow falls during exercise.

ANSWER: D

Cerebral arteries and veins do receive sympathetic innervation, but the vasomotor response to sympathetic stimulation is minor. The blood brain barrier protects the chemical environment of the cerebral tissue and effectively insulates it from external influences, such as blood-borne [H$^+$] and norepinephrine. Carbon dioxide, through its conversion to H$^+$ on the brain tissue side of the blood brain barrier, is the agent to which the cerebral circulation is most responsive; decreasing CO$_2$ leads to vasoconstriction. Cerebral blood flow remains relatively constant during exercise, despite changes in arterial pressure (exquisite autoregulation), and the fact that arterial CO$_2$ is well controlled during exercise by the respiratory system.