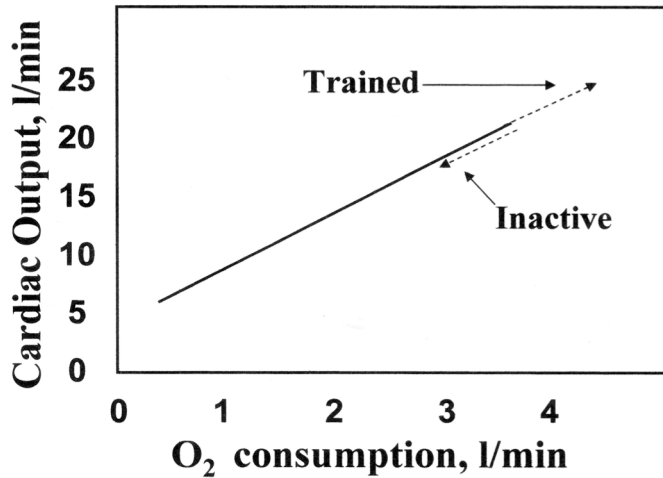


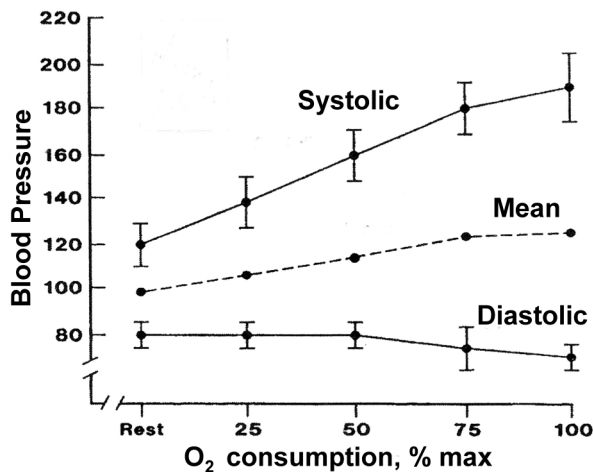
# NROSCI/BIOSC 1070 and MSNBIO 2070

## Cardiovascular 7

### October 2, 2017



Whole body O<sub>2</sub> consumption (Q<sub>O<sub>2</sub></sub>) at rest is approximately 250 ml O<sub>2</sub>/min. However, during exercise Q<sub>O<sub>2</sub></sub> can rise to 3-5 L/min. The increased Q<sub>O<sub>2</sub></sub> is permitted through a parallel increase in cardiac output, as shown in the graph to the left.



Since  $MAP = CO * TPR$ , you might think that the 4-fold increase in cardiac output during exercise would generate a huge increase in blood pressure. Although mean arterial pressure does rise, the peak values are only 10-20% higher than at rest.

One factor that accounts for this is that diastolic pressure does not increase in proportion to systolic pressure during exercise. In fact, diastolic pressure may even drop. Several factors help to explain the disproportional effect of exercise on systolic and diastolic pressure. First, vascular compliance is altered, which promotes the rapid drop in blood pressure during

diastole. In addition, the large reduction in total peripheral resistance (see below) provides for a rapid runoff of arterial blood into the capillaries, and a large drop in pressure during diastole.

<u>Organ</u>	<u>Resting Perfusion</u>		<u>Exercise Perfusion</u>	
Brain	0.75	L/min	0.75	L/min
Heart	0.3	L/min	0.8	L/min
Digestive T.	1.4	L/min	0.3	L/min
Kidneys	1.1	L/min	0.3	L/min
Muscle	1.2	L/min	20	L/min
Skin	0.35	L/min	0.7	L/min
Other	0.9	L/min	0.15	L/min
<b>Cardiac Output:</b>	<b>6.0</b>	<b>L/min</b>	<b>23</b>	<b>L/min</b>

The other factor that limits the increase in blood pressure during exercise is the decrease in peripheral resistance, as vessels in some organ systems dilate to permit increased perfusion and oxygen delivery. For example, the increase in perfusion of skeletal muscle is almost 20-fold during exercise. Since cardiac output has limits, the increase in blood flow to skeletal and cardiac muscle is paralleled by a decrease in flow

to the digestive system and kidneys. Skin blood flow also increases during exercise, to dissipate heat generated by working muscle. The relative increase in skin blood flow is partly dictated by environmental conditions, especially ambient temperature.

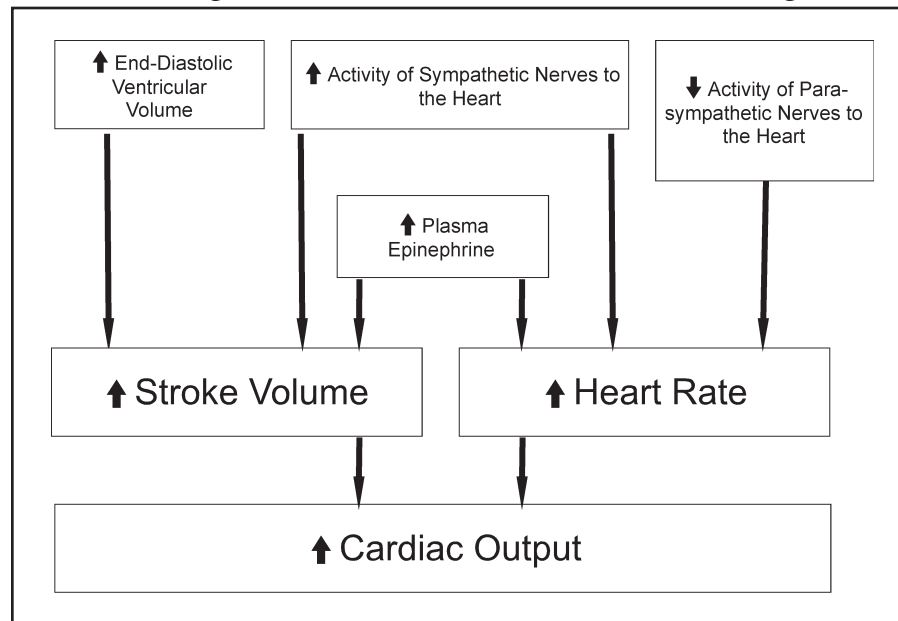
## Factors Contributing to Exercise-Related Cardiovascular Responses

### 1. Cardiac Output

Both heart rate and contractility increase during exercise to generate the large increase in cardiac output. Intrinsic heart rate generated by the SA node is 90-100 beats/min, but is tonically suppressed to about 70 beats/minute by the parasympathetic nervous system. Thus, one way of increasing heart rate is by “withdrawing” parasympathetic drive on the heart. Heart rate can be increased further by the actions of the sympathetic nervous system. Binding of NE or EPI to beta receptors on autorhythmic cells increases their firing rate, driving heart rate faster. Furthermore, the catecholamines enhance conduction through the AV node, bundle of His, and Purkinje fibers.

However, there is an upward limit on heart rate. If the heart beats too rapidly, there is insufficient time for filling. This begins to happen when heart rate exceeds ~140 beats/min. A limit on heart rate is imposed by the delay in conduction through the AV node as well as the long refractory period of myocardial cells. This limitation helps to insure that the heart will not beat too rapidly to effectively pump out blood. Accordingly, an increase in heart rate alone cannot explain the large increase in cardiac output during exercise.

You might think that any increase in heart rate would diminish stroke volume, as ventricular filling time decreases. This does not occur during moderate increases in heart rate for several reasons. First, most ventricular filling occurs early during diastole, just after the A-V valves open. This mitigates the effects of a shortened diastolic period on filling of the ventricle. In addition, increases in heart rate are normally coupled with an increased intensity of atrial contraction, which enhances ventricular filling. As such, the impact of atrial contraction on ventricular filling is much greater during exercise than at rest.



Previous ventricular contraction may also help draw blood into the relaxing chamber when residual volume is small. The Bowditch effect additionally increases contractility as heart rate increases.

Stroke volume must also increase in order to amplify cardiac output. Binding of catecholamines to beta-receptors on myocardial cells increases contractility. Another major factor facilitating the increase in stroke volume during exercise is the huge increase in venous return; Starling's Law of the Heart stipulates that the increase in venous return will be matched by an increase in cardiac output. The main factor contributing to increased venous return during exercise is skeletal muscle contractions, which compress intramuscular veins (reduce their compliance) and propel blood towards the heart.

However, there is a limit on the effects of preload on cardiac output. After the ventricle fills > 150 ml, there is a sharp increase in pressure in the ventricle as more blood enters (since the ventricle is full). Atrial pressure (venous pressure) must exceed the pressure in the ventricle for blood to enter.

Other direct factors also contribute to a lesser degree in enhancing venous return to the heart during exercise. First, increased respiratory muscle contractions help to “suck” blood into the thorax from the abdomen. In addition, contraction of the smooth muscle within veins facilitates the process.

Another factor that contributes to increased cardiac output during exercise is reduced total peripheral resistance. This results in a reduction in afterload, which reduces the workload to eject blood from the left ventricle. A reduction in afterload thus facilitates increasing cardiac output.

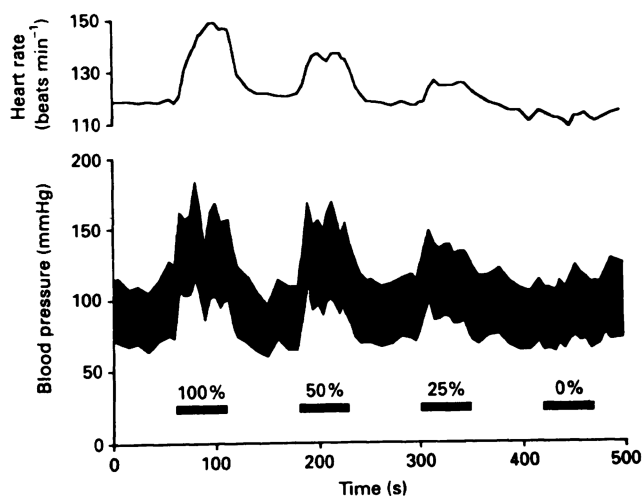
## 2. Changes in Blood Flow

Sympathetic nervous system outflow to blood vessels tends to increase during exercise, although the changes in activity are not the same in every vascular bed. The large increase in sympathetic outflow to the viscera explains the reduction in blood flow to the digestive organs. However, there is little increase in sympathetic outflow to the skin, as this would inhibit cooling of the body. There is also an increase in activity of sympathetic efferents innervating blood vessels in skeletal muscle. However, the effects of the muscle vasoconstrictor fibers is opposed by the release of epinephrine from the adrenal medulla. The moderate amounts of epinephrine released bind to beta-2 receptors in the walls of arterioles in skeletal muscle, promoting vasodilation.

However, the major factor contributing to muscle vasodilation during exercise is the release of paracrines from exercising muscle. For example  $H^+$  from acids (e.g. lactic acid),  $K^+$ , adenosine, and  $CO_2$  release from active muscle promotes vasodilation. The fact that muscle blood flow during exercise is largely regulated by local mechanisms makes good sense. This strategy assures that only the muscles that need a large blood flow to meet metabolic needs will have augmented perfusion.

### Triggers for Cardiovascular Responses During Exercise

In exercise, increased heart rate, contractile force, and vasoconstriction start even before physical activity is initiated. The central nervous system, through a mechanism called **central command**, induces these events.



The existence of central command was documented in experiments in completely paralyzed humans. These subjects exhibited similar changes in blood pressure and heart rate when they “imagined” performing exercise as when muscle contraction actually takes place, as illustrated in the figure to the left. This figure shows the changes in heart rate and blood pressure exhibited by a paralyzed subject imaging exercise at different intensities. The neural mechanisms that form the substrate of central command have not been worked out, but are the topic of active research.

From: Gandevia SC, Killian K, McKenzie DK, Crawford M, Allen GM, Gorman RB, and Hales JP. Respiratory sensations, cardiovascular control, kinaesthesia and transcranial stimulation during paralysis in humans. *J. Physiol.* 470: 85-107, 1993.

In addition, reflexes from skeletal muscle also elicit increases in cardiac output and vasoconstriction. The muscle afferents involved in this response appear to be unmyelinated fibers that are sensitive to chemicals produced by contracting muscle, as well as small myelinated fibers that respond to pressure changes during muscle contraction. One might think that the increase in blood pressure produced by these events would trigger the baroreceptor reflex to abolish the responses. This would happen, except for the fact that the baroreceptor reflex gain is markedly reduced during exercise. This down-regulation of the baroreceptor reflex is triggered by both inputs from muscle receptors and central command. These signals reach nucleus tractus solitarius through multi-synaptic relays, and inhibit the neurons that receive baroreceptor signals.

### What Happens in a Trained Athlete to Potentiate the Ability to Exercise?

The amount of heart muscle increases during training, as does chamber size. Thus, stroke volume increases. As a result, heart rate declines so that MAP will remain normal. Thus, the “reserve capacity” to increase cardiac output is higher in a trained athlete.

	Stroke Volume (ml)	Heart Rate (beats/min)
<b>Resting</b>		
NonAthlete	75	75
Marathoner	105	50
<b>Maximum</b>		
NonAthlete	110	195
Marathoner	162	185

This tendency is illustrated in the table to the left. Note that the marathoner has a much lower resting heart rate than a nonathlete, which is accompanied by a much higher stroke volume.

During maximal exercise, the heart rate in the marathoner can rise as much as in an untrained individual, while stroke volume is much larger. Vascularity of muscle also increases in trained athletes, allowing for more efficient oxygen delivery to the tissues.

### Enhanced Oxygen Delivery to Muscle During Exercise

A variety of factors facilitate the delivery of oxygen to working muscle during exercise. Most oxygen in the bloodstream is bound to hemoglobin. Local changes in pH and temperature in working muscle facilitate the shedding of oxygen from hemoglobin. The number of open capillaries increases in skeletal muscle, as precapillary sphincters relax in response to the levels of vasodilating paracrine factors. This increases the surface area available for exchange of oxygen between the blood and tissues. As such,  $CaO_2 - CvO_2$  is much larger for working muscles than for resting muscles.

## A Contrasting Integrated Cardiovascular Response: Moderate Hemorrhage

Loss of 30% or more of blood volume will cause blood pressure to drop significantly. This will result in a cascade of physiological responses, some of which are similar to those during exercise. Others are completely different, however. The following table compares the physiological triggers and responses during moderate hemorrhage and exercise.

Condition	Exercise	Moderate Hemorrhage
<i>Baroreceptor Activity</i>	Baroreceptors are activated by elevated blood pressure, but the baroreceptor reflex is blunted by CNS	Baroreceptors are unloaded by reduced blood pressure, and the baroreceptor reflex is potentiated by hormones such as ANG-2
<i>Muscle Paracrine Factors</i>	Very high, particularly in working muscle	High, due to hypoxia resulting from inadequate blood supply
<i>Angiotensin II Levels</i>	Moderately high, due to reduced renal blood flow and increased sympathetic activity	Extremely high, due to hypotension
<i>Vasopressin Levels</i>	Variable, depending on volume and salt loss associated with sweating	High due to decrease in blood volume
<i>Epinephrine Levels</i>	High, resulting in muscle vasodilation	Extremely high, resulting in muscle vasoconstriction (high EPI levels affect alpha receptors)
<i>Vasoconstrictor Activity</i>	High, to prevent TPR from dropping too low	High, to raise blood pressure
<i>Diameter of Gut Arterioles</i>	Constricted	Constricted
<i>Diameter of Brain Arterioles</i>	No appreciable difference from normal	No appreciable difference from normal
<i>Blood Pressure</i>	Mean pressure is slightly elevated; systolic pressure is high	Low to normal, depending on the success of corrective mechanisms
<i>Heart Rate</i>	High	High

The similarities in physiological responses between exercise and hemorrhage include elevated heart rate, vasoconstriction within visceral organ vasculature, and high circulating epinephrine levels. However, the levels of epinephrine tend to be much higher during hemorrhage, reaching a concentration where binding to alpha receptors occurs. As a consequence, epinephrine tends to promote muscle vasodilation during exercise but muscle vasoconstriction during hemorrhage. In addition, high levels of hormones such as angiotensin-2 during hemorrhage assure that muscle arterioles will constrict, despite the presence of muscle paracrines (produced in response to inadequate perfusion of the muscle) that might otherwise induce vasodilation. Angiotensin-2 levels also increase during exercise, but the increase is moderate.

The “bottom line” is that cardiovascular responses are very complicated, and some components may be similar despite very different circumstances. You must consider the entire integrated response to understand the challenges that are present in the system.

## Clinical Problems Affecting the Cardiovascular System

### **Shock**

About 10% of the total blood volume can be removed with almost no effect on arterial pressure or cardiac output. Larger amounts of blood loss can lead to **circulatory shock**. Shock is the general inadequacy of blood flow in the body such that body tissues are damaged. Hemorrhagic shock is only one form of shock. Shock can also be triggered by factors that lead to global vasodilation and thus loss of blood pressure. **Anaphylactic Shock** occurs when an antigen-antibody reaction takes place immediately after an antigen to which the person is sensitive enters the circulation. One of the principal effects is to cause a release of histamine from blood-borne immune cells (we will discuss the mechanism later in the course). Because histamine is a potent vasodilator, total peripheral resistance decreases. In addition, capillary permeability increases resulting in an increase in the filtration process and loss of fluid into the tissues. The net result is a major reduction in venous return and thus cardiac output. Unless treated rapidly, people with anaphylactic shock can die.

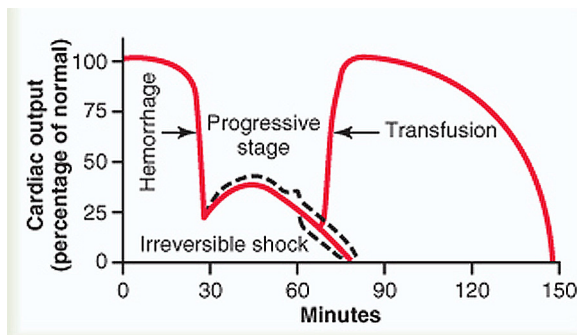
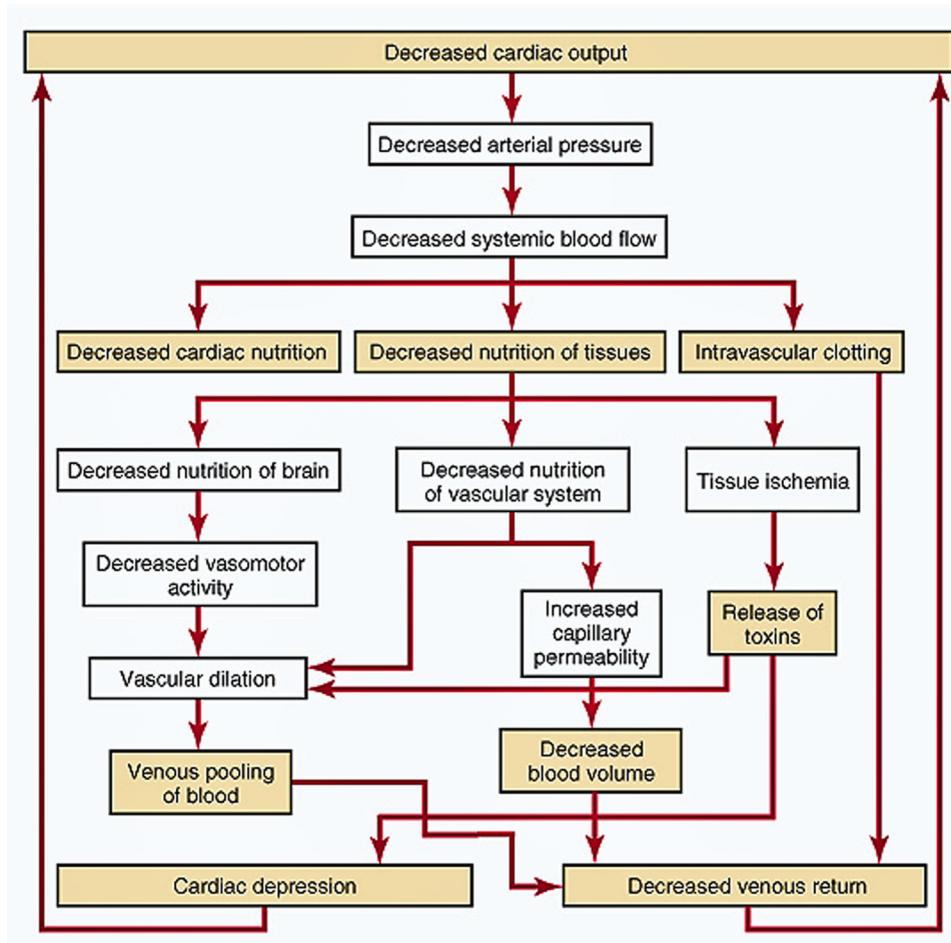
Another type of shock is **septic shock**. Septic shock is triggered by the release of bacterial toxins, which induce global vasodilation as in anaphylactic shock. Septic shock can occur rapidly during conditions such as peritonitis in which a high concentration of bacterial toxins can reach the blood.

A condition called **vasovagal syncope** is in some ways similar to shock. In this condition, the central nervous system paradoxically induces high parasympathetic activity and low sympathetic activity, resulting in a drop in cardiac output, peripheral resistance, and blood pressure. Vasovagal syncope is sometimes called “emotional fainting,” as it can occur when an individual is emotionally distressed.

During shock, the drop in blood pressure activates the baroreceptor reflex. Furthermore, the decrease in blood volume affects the “volume receptors” in the heart. At the same time, a decrease in blood flow to the kidney induces renin release, which triggers the enzymatic cascade that generates the potent vasoconstrictor agent angiotensin II. Decreased activation of volume receptors in the heart induces the release of vasopressin from the posterior pituitary, which both promotes fluid retention by the kidney (excretion of fluid diminishes) and causes vasoconstriction. Because hydrostatic pressure in the capillaries drops, fluid reabsorption from the tissue is enhanced. Of course, blood “stores” in the spleen and elsewhere in the venous side of the circulation are liberated during hemorrhage to help bolster blood pressure. Although epinephrine levels in the blood are high, vasodilation of muscle arterioles does **not** occur because most of the vasodilating paracrines are absent, and also because the circulating vasoconstrictor hormones (angiotensin II and vasopressin) counteract the vasodilatory actions of epinephrine on beta receptors in muscle arterioles.

If hemorrhage is only modest, then behavioral mechanisms (e.g., drinking) and replacement of red blood cells will eventually relieve the problem. Unfortunately, if hemorrhage continues and is severe, the process eventually becomes irreversible. After about 30% of the blood volume is lost, the brain begins to become ischemic. When this happens to neurons in the RVLM, they begin to fire maximally. As a result, sympathetic outflow to the heart and blood vessels is driven much higher than it ever could be by the baroreceptor reflex. This “ischemic response” can help to bolster blood pressure for a short period of time. However, the brainstem neurons will soon afterwards begin to die from ischemia, resulting in a total collapse in the circulatory system.

The following diagram shows what happens in the late stages of shock:



Once tissue damage during shock becomes severe, death is inevitable. Even a transfusion of blood at this point to replace all of the lost volume is not useful, as shown to the left.

## Cardiovascular Disease

A major cardiovascular problem is **atherosclerosis**, or hardening of the arteries. Atherosclerosis begins as an insult to the endothelial wall (produced by the effects of smoking, high blood pressure, high blood LDL-cholesterol [see below for more information], and some diseases). Subsequently, lipid-filled macrophages accumulate beneath the endothelium, and form **fatty streaks**. The macrophages are attracted by chemical factors released by the damaged endothelial cells. In turn, the macrophages can release chemical factors that attract smooth muscle cells from underlying levels of the vessel. The smooth muscle cells subsequently reproduce, and eventually form **plaques**, or bulges into the lumen of the vessel. As a result, both the diameter and elasticity of the vessel diminish.

The formation of atherosclerotic plaques in vessels can cause many cardiovascular problems. The rough surface of this structure can trigger the formation of blood clots that block vessels. Obviously, if a large blood clot forms and breaks free, it can lodge in a smaller vessel and completely block flow. If the plaque grows large enough, it can itself block blood flow.

Plaques can often serve as catalysts to induce turbulent flow, which increases the apparent viscosity of blood. Furthermore, by considering Ohm's law and Poiseuille's Law you can see that formation of plaques results in increased vascular resistance, often in large vessels near the heart.

## **Cholesterol and its Effects on the Cardiovascular System**

As mentioned above, the presence of large amounts of LDL-cholesterol in the blood can lead to the damage to arteries that induces atherosclerosis. Cholesterol and phospholipids are not water soluble, and when absorbed in the gastrointestinal tract are combined with a carrier, typically either **low-density lipoprotein (LDL)** or **high-density lipoprotein (HDL)**. LDL-cholesterol is removed from the blood by binding to receptors on cell membranes (mainly in the liver). However, these cell-surface receptors are down regulated when the intracellular pool of cholesterol is high. Thus, when the diet is rich in fats and cholesterol, the levels of circulating LDL-cholesterol will be high. Under these conditions, the LDL-cholesterol will move into the wall of arteries, where it is oxidized and becomes a toxic molecule that begins the cascade of events that produces atherosclerosis. For this reason, LDL-cholesterol is often referred to as "*bad cholesterol*".

In contrast, HDL-cholesterol is rapidly removed by the liver, and thus its half life in the blood is very short. High levels of HDL- in the bloodstream are associated with a short circulating time for cholesterol, diminishing the risk of damage to blood vessels. Thus, higher than normal levels of HDL-cholesterol are considered to be a *negative* risk factor for cardiovascular disease (i.e., people with high HDL- cholesterol levels are less likely to have atherosclerosis than people with low HDL-cholesterol levels). For this reason, HDL-cholesterol is often called "*good cholesterol*".

Note that the "cholesterol" carried by LDL- and HDL- is the same. The difference between the two complexes is the carrier. Individuals fortunate enough to produce large amounts of the HDL- carrier are unlikely to have atherosclerosis even if they eat a moderately fatty diet, as their capacity to rapidly transport cholesterol from the GI tract to the liver is high. In contrast, individuals who produce little HDL- carrier must rely on the LDL- carrier for transport, and as mentioned above LDL-cholesterol can damage blood vessels.

It is now standard practice during routine medical examinations to determine blood cholesterol levels. The following factors are considered in a typical blood lipid screening:

- 1) Total cholesterol (in mg/dl plasma)
- 2) HDL-cholesterol (in mg/dl plasma)
- 3) Ratio of total cholesterol/HDL-cholesterol
- 4) LDL-cholesterol (in mg/dl plasma)
- 5) Level of triglycerides (in mg/dl plasma)

### **What are acceptable levels of cholesterol in the blood?**

It is considered desirable to have a total blood cholesterol < 200 mg/dl, and LDL < 130 mg/dl. Furthermore, HDL- should be at least 35 mg/dl (but higher levels are better, and HDL- > 60 mg/dl is considered a negative risk factor).



Persons with total blood cholesterol between 200 and 239 mg/dl or LDL between 130 and 159 mg/dl are considered to have borderline high cholesterol. Persons with these levels are monitored carefully in the future to assure that levels of LDL- and total cholesterol do not rise, particularly if the cholesterol/HDL- ratio is higher than 6.5.

Persons whose total cholesterol level is higher than 240 mg/dl or whose LDL- is greater than 160 mg/dl are considered to be at risk for cardiovascular disease, particularly if the cholesterol/HDL- ratio is greater than 6.5.

## **Treating high blood cholesterol**

When a person without a history of heart disease is diagnosed with high blood cholesterol, often a program of diet, exercise, and weight loss is prescribed to bring levels down. The main goal of this treatment is to reduce LDL-, as levels of this carrier appear to have the best association with damage to blood vessels.

Often, however, due to lack of compliance or a genetic predisposition, diet and exercise are not sufficient to lower cholesterol to goal levels. Fortunately, a number of drugs are available to lower blood cholesterol levels without substantial side effects. The most common of these drugs are marketed under the following trade names: Mevacor, Lescol, Pravachol, Zocor, and Lipitor. These drugs are called *statins*.

All of the cholesterol-reducing drugs have a similar mechanism of action: they block the endogenous biosynthesis of cholesterol by the liver. Cholesterol is produced through a long biosynthetic pathway, and cholesterol-lowering drugs inhibit an enzyme that catalyzes an early and rate-limiting step in the process. In particular, the drugs inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. By reducing the liver's synthesis of cholesterol, total cholesterol levels in the blood drop, and there is also an up-regulation in the number of LDL-receptors. Thus, the modern anti-cholesterol drugs have a good track record in reducing the risk for cardiovascular disease.

However, some patients do not tolerate statins, and they do not adequately lower cholesterol levels in some cases. Thus, other treatments for high blood cholesterol have been developed. One strategy is to reduce absorption of dietary cholesterol in the intestine. A drug that does this is Ezetimibe. Cholesterol absorption inhibitors can be prescribed alone, or in combination with a statin (*e.g., Vytarin is a combination drug that contains both a statin and Ezetimibe*).

An important new therapy for high cholesterol is currently being approved by the FDA. Down-regulation and destruction of LDL-receptors is mediated by a regulatory protein: **proprotein convertase subtilisin/kexin type 9 (PCSK9)**. Individuals with mutations in the gene for PCSK9 can have extremely low blood cholesterol levels, as they have many LDL receptors in the liver (they can't target the receptors for destruction). New drugs such as *Alirocumab (trade name Praluent)* are monoclonal antibodies that inactivate PCSK9, preventing downregulation of LDL receptors.

## **Other Conditions that Produce Atherosclerosis**

**Familial Hypercholesterolemia** is a hereditary disease associated with a deficiency in LDL- receptors. As such, the concentration of LDL- in the blood is very high. People with this disease typically die from cardiovascular damage before the age of 20. Some patients with familial hypercholesterolemia have a mutation in PCSK9 that causes excessive down regulation of LDL receptors.

**Hypertension**, or high blood pressure (defined clinically as a systolic BP > 140 or a diastolic BP > 90), is another factor that may lead to atherosclerosis. In most cases, the cause of the hypertension is unknown (called **primary** or **essential hypertension**). Cardiac output in hypertensive patients appears to be normal, and the cause of the hypertension appears to be an increase in peripheral resistance. High blood pressure can lead to the damage of vessel walls, and can set-up the cascade of events that produces atherosclerosis.

## **A negative consequence of atherosclerosis—ischemic heart disease**

A severe consequence of atherosclerosis can be ischemic heart disease, the most common cause of death in Western culture. About 35% of people in the United States die of this cause. Some of these deaths are quite sudden, whereas others occur over a period of weeks to years as a result of progressive diminution of heart pumping.

Acute coronary artery occlusion often occurs at a location where a vessel's diameter has been decreased tremendously by the formation of atherosclerotic plaques. If the lumen diameter is compromised significantly, the heart will be chronically shortchanged of oxygen, and it will be impossible for the cardiac muscle to obtain sufficient oxygen to increase cardiac output during exertion. As noted above, plaques are good substrates for the formation of blood clots. These blood clots contribute to coronary artery occlusion. Sometimes, a clot will break free and will completely occlude a smaller artery downstream. Such a "traveling" clot is referred to as an **embolus**. When a coronary artery is blocked totally, the heart muscle that it perfuses will be completely deprived of oxygen and nutrients and will die. Many clinicians also believe that sudden spasms of partially-occluded coronary arteries can also produce occlusion.

Death occurs after coronary artery occlusion for a number of reasons. If a large amount of ventricular cardiac muscle dies, cardiac output may decrease so tremendously that the other tissues of the body also become ischemic and die. This death can be very rapid or slow, depending on how much cardiac output decreases. Damage confined to the left ventricle also generates a mismatch between left and right ventricular pumping. As a result, blood backs up in the pulmonary veins and hydrostatic pressure in the pulmonary capillaries increases. Filtration will then exceed absorption in the lung capillaries, and fluid will accumulate in the extracellular space. This fluid-build up compromises the process of gas exchange in the lungs, further compromising the oxygenation of tissues (as the blood is carrying less oxygen).

Another reason for death after coronary artery occlusion is fibrillation of the ventricles. This fibrillation can be induced by a number of factors. Loss of blood supply to an area results in an extracellular accumulation of  $K^+$ , which increases the probability of fibrillation. Furthermore, the ischemic muscle has difficulty in repolarizing its membranes, so the external surface of this muscle becomes more negative than normal coronary muscle. Electric current can then flow from the damaged cardiac muscle to undamaged muscle, thereby inducing fibrillation. Damaged cardiac muscle also loses its tone, and the ventricle dilates. This dilation can disrupt the conduction pathways in the heart

A few days after a "heart attack," the dead heart muscle can degenerate and become stretched very thin. As a result, a hole can form in the heart. Blood accumulation in the pericardial sac places pressure on the heart. Eventually, this pressure becomes large enough that the right atrium cannot fill with blood, and the patient dies of suddenly decreased cardiac output.

Persons with compromised blood flow through the coronary arteries often complain of chest pain, ***angina pectoris***. The reason for this pain is not well understood, but is probably related to the fact that pain-promoting substances such as lactic acid and histamine cannot be rapidly removed from cardiac muscle and build up. Patients with angina are at risk for developing acute coronary artery occlusion, and thus are provided medical treatment. Two pharmacological treatments are often used. Nitrate-based drugs such as nitroglycerin that induce vasodilation are given to insure that the coronary arteries remain maximally dilated. Beta-1 blockers are also given to prevent increases in heart rate and heart contractility during stressful situations, which prevents putting the heart into metabolic stress. The latter drugs also profoundly limit increases in cardiac output during exercise, and thus patients taking these drugs must avoid exertion.

Atherosclerosis may be limited to only a few places in the coronary artery, and in such cases surgical approaches are useful therapies. For example, it is possible to insert a vascular “bypass” around the occluded segment of the artery. Often, several blocked segments of artery are bypassed in the same surgery, and “double bypass” and “triple bypass” procedures are not uncommon.

In the past 25 years, less invasive procedures have also been developed to open partially-blocked coronary arteries before they become totally occluded. One procedure, called *coronary artery angioplasty*, involves placing a balloon-tipped catheter into the partially-blocked vessel, and then inflating the balloon until the artery is tremendously stretched. During this procedure, a hollow tube or *stent* is often placed in the coronary artery to maintain its patency. After this procedure, patients often have increased coronary artery blood flow that lasts for years. Angioplasty is much safer than bypass, as the patient does not have to undergo open heart surgery.

## **Formation of new blood vessels in an area—angiogenesis**

When blood vessels in an area are damaged or ruptured, or if an area of tissue increases in size, it is necessary to develop a new blood supply to the tissue. The process of ***angiogenesis***, by which new blood vessels develop, is of tremendous interest to investigators. For example, it would be of therapeutic value to induce the formation of a new blood supply to an area of cardiac muscle once the coronary arteries are partially occluded. A number of chemical factors, called **vascular endothelial growth factors**, have been identified that induce development of new blood vessels. Targeting these factors to areas where new blood vessel growth is needed is a next great challenge to clinical medicine. This general strategy is also being applied to cancer research. If one could block the effects of vascular endothelial growth factors, one might abolish formation of new blood vessels in tumors (thereby preventing tumor growth).