E. A. Rovenstine Memorial Lecture

Introduction

This lecture, established in honor of the late Dr. E. A. Rovenstine, is always one of the highlights of the meeting of the American Society of Anesthesiologists and I am privileged this year to introduce a renowned physiologist, Dr. Arthur C. Guyton, who will discuss "The Regulation of Cardiac Output."

Dr. Guyton has been Professor of Physiology and Biophysics and Chairman of the Department at the University of Mississippi School of Medicine since 1948. He is a master teacher; a respected investigator. His Textbook of Medical Physiology is used in medical schools around the world. He is a leader in basic medical research, and his investigations have won him international acclaim. His studies encompass comprehensive approaches to the circulatory system, the respiratory system, and the renal system, together with analyses of the controlling functions of the nervous and endocrine systems.

In 1951 the U. S. Junior Chamber of Commerce named Dr. Guyton one of the Ten Outstanding Young Men in America, and in 1965 he received a First Federal Foundation Award for outstanding service to Mississippi. Dr. Guyton was graduated from the University of Mississippi with special distinction in 1939 and from Harvard Medical School in 1943. He interned at Massachusetts General Hospital. While in a surgical residency there, he contracted paralytic poliomyelitis. During and immediately after his convalescence, he designed aids for the handicapped and, in 1956, received a Presidential Citation for his contributions.

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Regulation of Cardiac Output

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Cardiac output is perhaps the most important single weather-vane of functional effectiveness of the circulatory system. Yet, because of difficulties in making repeated cardiac output measurements, clinical assessment of circulatory function is based instead on less valuable criteria such as venous pressure, color of skin, and so forth. Even so, if one understands the basic factors that regulate cardiac output, he can often estimate it in the various normal and abnormal clinical states with a high degree of accuracy. Therefore, the goal of this article will be to express in terms as essential as possible the factors that play major roles in the regulation of cardiac output.

Basically, three factors are of primary importance in cardiac output regulation: (1) the function of the heart itself, (2) the re-
sistance to blood flow through the peripheral circulation, and (3) the degree of filling of the circulatory system with blood.

**Role of the Heart in the Regulation of Cardiac Output**

At the outset, we must dispel one of the great myths about the regulation of cardiac output: the myth that the heart itself regulates the normal day-by-day cardiac output. The heart indeed does play a major role in the regulation of cardiac output under some abnormal conditions, but its moment-to-moment, day-by-day role in the regulation of cardiac output is very small. True, the heart provides the cardiac output, but other factors, located primarily in the peripheral circulation, do the regulating. This is much the same as saying that the motor of an automobile provides the power to move the automobile, but the accelerator plays a far greater role in regulating its speed.

**Permissive Function of the Heart in Cardiac Output Regulation**

The normal resting heart of the young adult is capable of pumping about 12 to 15 liters of blood a minute, but the resting cardiac output is only 5 to 6 liters instead of 12 to 15 liters. What this means is that even in the normal resting state the human heart is capable of pumping much more blood than it actually does pump. The only requirement to make it pump an increased amount of blood is that an increased quantity of blood flow into the input side of the heart from the peripheral circulation. To pump up to 12 to 15 liters per minute, the heart does not even have to be stimulated by its nerves.

Therefore, we can state that the heart plays a permissive role in the regulation of cardiac output. That is, it permits the cardiac output to be regulated at any value between zero and the maximum level that it is capable of pumping. Figure 1 illustrates this basic principle. The top curve, labelled “normal,” is one type of Starling’s curve of cardiac function, relating cardiac output to right atrial pressure. This figure shows that when right atrial pressure rises to only a few mm Hg above atmospheric pressure cardiac output will increase to about 13 liters per minute. However, the dashed line illustrates that the normal resting tissue need for cardiac output is about 5 liters per minute; the amount of right atrial pressure required to cause the heart to pump this volume of blood is 0 mm Hg, almost exactly equal to atmospheric pressure. Thus, the pumping capability of the heart is 13 liters per minute, but the actual amount normally pumped is only 5 liters per minute. The heart permits the cardiac output to be regulated at 5 liters per minute because this is a value considerably below its pumping capability.

Note also the second curve, “slightly depressed heart.” This is a Starling’s function curve of a heart whose pumping capability has been depressed below normal as a result of a mild to moderate myocardial infarction. In this heart, increasing right atrial pressure to a few mm Hg above zero will cause cardiac output to increase to a maximum of about 9 liters per minute. Thus, even this depressed heart permits the cardiac output to be regulated at any value between zero and 9 liters per minute. For the normal resting human being this is a completely adequate permissive level of cardiac output, because the required cardiac output is still only 5 liters per minute, well below the permissive level.

On the other hand, observe the lowest curve, “severely failing heart.” In this heart, even the upper plateau of the curve never rises to the level of cardiac output that the
heart, which has been accomplished many times in animals and a few times in human beings, hardly affects the ability to regulate cardiac output. Even a greyhound can run around a racetrack almost as rapidly with his heart denervated as he can when it is completely innervated.

On the other hand, studies of isolated hearts and the heart-lung preparation have demonstrated that parasympathetic inhibition and sympathetic stimulation greatly increase heart rate and at the same time increase pumping capability. Thus, the permissive level of cardiac output regulation is increased.

If we translate this experience in animals to the human being, it means that even though the normal permissive level of cardiac output is only 12 to 15 liters per minute, when the heart is stimulated by the sympathetics (and the parasympathetics are inhibited simultaneously), the permissive level of cardiac output regulation increases to perhaps 25 to 35 liters per minute.

Yet, here again, the fact that autonomic stimulation can increase the permissive level of cardiac output to double normal does not mean that the actual cardiac output increases to values far above normal. Instead, the function of the autonomic nervous system in relation to cardiac output regulation is simply to keep the permissive level of cardiac output always above the actual required level. One of the most outstanding examples of this occurs during heavy exercise, for the required level of cardiac output then often increases to as high as 20 to 25 liters per minute, which is far above the 12 to 15 liters of cardiac output that the normal resting heart can pump. Yet, at the same time that the nervous system transmits nerve impulses to the skeletal muscles to cause muscle activity, it also transmits signals by way of the autonomic nervous system to the heart to increase both the heart rate and the strength of the heart muscle. As a result, the permissive level of cardiac output rises from the resting value of 12 to 15 liters per minute to 25 to 35 liters per minute (and perhaps even higher in the athlete). Thus, the permissive level of cardiac output is kept at a value somewhat above the actual required cardiac output.

**Effect of Nervous Stimulation of the Heart**

Many accounts, in both old and modern literature, have contended that cardiac output is controlled primarily by nervous stimulation of the heart itself. That is, nervous stimulation theoretically increases the heart's activity, and this in turn increases cardiac output. However, very simple experiments and many clinical evidences prove this not to be true. For instance, complete denervation of the tissues require for normal function. As a consequence, the tissues throughout the body suffer drastically, and the functions of some organs, especially the kidneys, become so deranged that a typical picture of circulatory congestion appears. In other words, once the heart has become so weak that it is incapable of pumping the required amount of cardiac output, the permissive level of cardiac output regulation has fallen below the required level. It is with these conditions that the cardiologist is most seriously concerned.

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**Fig. 2.** Family of cardiac function curves for hyper- and hypoeffective hearts. (Reprinted from Guyton: Cardiac Output and its Regulation, W. B. Saunders Co., Philadelphia, 1963.)
HYPO- AND HYPERRIEFFECTIVE HEARTS

Much of what has been stated above is summarized in figure 2. The curve labelled "normal" is a Starling’s function curve for the normal resting heart, relating cardiac output to right atrial pressure. Under some conditions the heart can become much stronger than normal. Autonomic stimulation can cause this, as was pointed out above. Another factor that can increase the pumping capability of the heart is cardiac hypertrophy, which occurs in conditions such as hypertension, athletic training, and patent ductus arteriosus. In figure 2 the curves above the normal curve are labelled "hyperrieffective," indicating that whatever the cause of increased pumping capability of the heart, whether it be hypertrrophy or autonomic stimulation, the permissive level of cardiac output is increased.

The lower curves of figure 2, labelled "hypoeffective," represent cardiac function curves of hearts depressed by any factor that makes the heart a poorer-than-normal pump. These factors include, among others, myocardial infarction, parasympathetic stimulation, valvular heart disease, myocarditis, and congenital heart disease.

Therefore, keeping in mind the curves of figure 2 and remembering that the normal resting human heart is capable of pumping several times as much blood as it is ordinarily called upon to do, one easily can understand the role of the heart in cardiac output regulation.

Role of the Peripheral Circulation in Cardiac Output Regulation

If the heart itself plays only a permissive role, then we must ask the question, what does

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**Fig. 3.** Relationship between cardiac output and work output (solid curve) and between oxygen consumption and work output (dashed curve) during exercise. Data is derived from studies by Douglas and Haldane (1922); Christensen (1931); Dexter, Whittenberger, Haynes, Codale, Corlin, and Sawyer (1951); and Donald, Bishop, Cummings, and Wade (1935). (Reprinted from Guyton: Cardiac Output and Its Regulation, W. B. Saunders Co., Philadelphia, 1963.)
regulate cardiac output? The answer is that under most normal physiologic conditions cardiac output is regulated primarily by the peripheral tissues and not by the heart.

Regulation of Cardiac Output by Resistance to Blood Flow in the Peripheral Tissues

Almost every tissue of the body is capable of regulating its own blood flow. Thus, during muscular exercise blood flow through each exercising muscle increases markedly. Likewise, blood flow through the kidney is regulated in proportion to the need for the kidney to excrete certain blood substances. For instance, an increase in blood sodium increases renal blood flow as much as 20 to 40 per cent, or an increase in nitrogenous waste products in the blood can increase renal blood flow 20 to 50 per cent. In the brain, blood flow is regulated primarily by the need for removal of carbon dioxide from brain tissues. The greater the concentration of carbon dioxide, the greater the cerebral blood flow. A high carbon dioxide concentration can double blood flow through the brain.

In general, therefore, one can state that blood flow through each local tissue of the body usually is controlled by some special control system related to the activity of that individual tissue. Obviously, the sum of the blood flows through all the different tissues equals the cardiac output. Consequently, we have, in effect, stated that the cardiac output is controlled by the sum of all the control systems in the individual tissues.

Role of Oxygen in the Regulation of Cardiac Output

For many years it has been recognized world-wide that cardiac output increases almost directly in proportion to the rate of oxygen usage by the body. This is true whether the increased oxygen usage is caused by increased muscular work load, by hyperthyroidism, by dinitrophenol poisoning, etc. Figure 3 illustrates this relationship for persons undergoing different degrees of exercise workload, showing a striking parallelism between increase in oxygen consumption and increase in cardiac output. It is very important to discuss why there is such a parallel relationship between oxygen usage and cardiac output regulation.

On study of blood flow regulation in local tissues, one is immediately impressed with the fact that blood flow through most tissues is highly responsive to changes in local availability of oxygen. This effect is illustrated dramatically in figure 4, a record of blood flow through an isolated hind limb of a dog under several different conditions. After a control blood flow measurement, the blood flow was completely blocked for ten minutes and then re instituted. When it was re instituted, the flow increased to approximately four times normal, illustrating that some effect had occurred in the tissues during the ten minutes of ischemia to cause very great dilatation of the blood vessels. This phenomenon is called reactive hyperemia. Ordinarily, the blood flow would have returned to normal in another minute or two, but this leg was perfused for the first ten minutes after the block was over with blood from which all oxygen had been removed. The blood still had all normal nutrients except oxygen; yet blood flow remained four times normal as long as the leg was perfused with this anoxic blood. Then, finally, oxygen was returned to the blood, and blood flow through the limb returned to normal within the next few minutes. This specific experiment demonstrates the high dependence of blood flow regulation in isolated body tissues on oxygen itself.

Critical studies have demonstrated that oxygen is perhaps the most important of all factors that regulate blood flow in skeletal muscles, smooth muscle, the heart, and many other tissues. These tissues represent well over half the body mass, which indicates that a majority of the local blood flow regulation in the body is highly dependent on the amount of oxygen available in the tissues.

The mechanism by which oxygen deficiency in the tissues causes increased blood flow is still cloudy. Many physiologists believe that oxygen deficiency causes release of metabolic end products that act directly on local blood vessels to cause vasodilation. One such product that has been mentioned very prominently is adenosine. However, other physiologists believe that the local vasculature requires oxygen to keep its own smooth muscle
contracted, and that in the absence of oxygen the strength of the vascular smooth muscle becomes diminished, which allows immediate vasodilatation.\textsuperscript{11}

**MECHANISM BY WHICH TISSUE VASODILATATION INCREASES CARDIAC OUTPUT—THE ARTERIOVENOUS FISTULA AS AN EXAMPLE**

One of the most instructive experiments for helping to understand the regulation of cardiac output is to study circulatory function at the very moment of opening or closing an arteriovenous fistula.\textsuperscript{12} Figure 5 shows such an experiment in which arterial pressure, cardiac output, and fistula flow were recorded. Within a few seconds after opening a very large fistula, fistula flow increased to a value almost equal to the original cardiac output. Within another few seconds, cardiac output had increased almost a similar amount; yet the arterial pressure dropped very slightly.

A few seconds later the fistula was closed, and a few more seconds cardiac output and arterial pressure were back to normal. This experiment demonstrates a basic principle of circulatory function: any time blood flow is allowed to course directly from arteries to veins, the rate of inflow of blood into the heart increases instantaneously, and the heart (if it has the pumping capacity) automatically responds to the extra flow and pumps the blood back into the arteries. As a result, the arterial supply of blood becomes replenished almost as rapidly as it is removed. The arterial pressure does not fall greatly, but what does happen is an increase in cardiac output almost equal to the extra flow through the fistula.

The same principles apply to the increase in cardiac output when the peripheral vessels in any tissue of the body dilate. Thus, in exercise, the blood vessels of the muscles dilate markedly, and blood flows rapidly from the arteries into the veins and thence into the heart which automatically puts it back into the arteries. Each time vasodilatation occurs in any single tissue, the local blood flow increases and correspondingly increases the cardiac output almost an equivalent amount.

The permissive role of the heart in this mechanism has been described. The normal resting heart has a pumping capacity several times as great as the normal cardiac output so that just as soon as the extra blood flows
into the input side of the heart, this reserve pumping capacity of the heart automatically moves the blood back into the arteries. This is what Starling’s law of the heart basically states, that the heart will pump whatever amount of blood flows into it (up to its physiological limit) without causing a significant back-pressure in the veins.

**Relative Importance of Venous Resistance and Arterial Resistance in Controlling Cardiac Output**

When an arteriovenous fistula is opened, the resistance all the way from arteries to veins is decreased. However, in other conditions venous resistance may become greatly increased while arterial resistance does not change, or, in still other instances, arterial resistance becomes greatly increased without any change in venous resistance. Experiments have shown that there is a marked difference between the effect of arterial resistance and that of venous resistance on cardiac output regulation, which can be explained in the following few paragraphs.13

Figure 6A illustrates a simplified schema of the circulation, in which a continuously-active pump pumps whatever amount of blood enters its input side. This blood is pumped into the systemic circulation, represented as a large, distensible bag. The flow of blood into this bag builds up pressure in the bag. It is this pressure in the bag that pushes the blood back through the veins and thence into the pump. If the pump tries to pump more blood than can flow from the bag to the pump, the collapsible veins entering the pump simply collapse like wet straws. Thus, the pump fails to pump any more blood than that amount which is made to flow through the veins by the pressure in the bag. In other words, the heart can pump with extreme activity, and yet the amount of blood that will go around and around the circuit is limited by the pressure in the bag and the resistance from the bag back to the pump. In the circulatory system the entire systemic circulation is the bag, so that all the vessels of the entire systemic system play a role in determining this pressure that will push the blood back toward the heart. This pressure, called the “mean systemic pressure,” will be discussed in more detail in following sections of this paper.

The second factor that plays a role is the resistance to blood flow from the bag to the heart. This resistance is an algebraic sum of

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**Figure 5.** Effect on arterial pressure and cardiac output caused by suddenly opening and closing an arteriovenous fistula, illustrating that opening of fistula increases cardiac output an amount almost equivalent to the fistula flow.
all the resistances in all the blood vessels of the systemic circulation. However, in sum-
miming these resistances, the venous resistance
must be weighted to a much greater degree
than the arterial resistance. The reason for
this can be understood by referring to figure
6B, in which the system has been changed to
contain two bags, an arterial bag and the ve-
uous bag. Arterial resistance is present from
the arterial bag to the venous bag, and ve-
uous resistance is present from the venous
bag back to the heart. Logically, one can see
that even a slight increase in venous resis-
tance can cause tremendous storage of
blood in the veins and thereby can prevent
flow of blood into the heart. On the other
hand, an increase in arterial resistance cannot
cause much blood storage in poorly-distensible
arteries and therefore cannot keep this blood
from getting back to the heart. Quantitative
experiments have shown that a change in ve-
uous resistance affects cardiac output about
eight times as much as does the same change
in arterial resistance. 13

This phenomenon has clinical importance
in several ways. For instance, venous obstruc-
tion of even the slightest magnitude, such as
that caused by tugging on the veins during
thoracic operations, can cause drastic reduc-
tion in cardiac output. On the other hand,
very marked changes in arteriolar resistance
generally have very little effect on cardiac
output. Indeed, in an experiment in which
microspheres were injected into the arteries
and then lodged in the arterioles, the arterial
pressure of the animal increased to two times
normal; yet cardiac output decreased only 10
per cent. 12 This explains why the very high
arteriolar resistance found in hypertension is
not associated with decreased cardiac output.
It also explains why drugs that cause relaxa-
tion of arteriolar tone do not necessarily in-
crease cardiac output, for again we can state
that changes in arterial resistance and arteti-
olar resistance play little role in the control
of cardiac output. It is either a change in
total resistance of the systemic circuit or a
change specifically in venous resistance that
is the important factor in cardiac output
regulation.

Fig. 6. A. Simplified schema of the circulatory
system, showing an elastic systemic circulatory
“bag,” the pressure in which causes blood to flow
through the vascular resistance back toward the
heart. B. Circulatory schema similar to the above
but with the peripheral circulatory system divided
into two elastic bags, the arteries and the veins,
ilustrating that venous resistance plays a far
greater role in determining venous return than
does arterial resistance. (See explanation in text.)

Effect of Blood Volume and Filling
of the Circulation on
Cardiac Output

Up to this point the discussion has centered
primarily around control of cardiac output
when various factors affect resistance to blood
flow through the peripheral vasculature. How-
ever, there is another major peripheral circula-
tory factor that can affect cardiac output mark-
edly, especially under abnormal conditions.
This is the degree of filling of the circulatory
system with blood. However, it is not blood
volume by itself that determines the degree
of filling of the circulation. Instead, it is the
ratio of blood volume to circulatory capacity.
Furthermore, this ratio can be expressed in
terms of the mean systemic pressure. 14

Mean Systemic Pressure and Its Role
in Regulation of Cardiac Output

The mean systemic pressure is the pressure
that would exist in the entire systemic circu-
lation if the veins and arteries at the heart
Fig. 7. Schematic illustration of the circulation, showing that the degree of filling of the systemic circulation with blood is one of the major factors that determines flow of the blood from the systemic system into the heart.

should be suddenly occluded and the blood then distributed in the systemic circulation until the pressures were equal everywhere. Obviously, the greater the blood volume or the smaller the capacity of the system, the higher will be the mean systemic pressure. This pressure is a measure of how tightly the systemic circulation is filled with blood, and one can show mathematically that the ability of blood to flow from the peripheral circulatory “bag” back to the heart is affected directly by the level of mean systemic pressure. Without going through the complex mathematics required to prove the importance of the mean systemic pressure in cardiac output regulation, we can explain the basic principle of this by referring to figure 7. To the right, in the figure, the systemic circulation is shown once again as a large bag. However, it is shown in three different states of filling. The normal state is represented by the bag bounded by a solid line, the over-filled state by long dashes, and the underfilled state by short dashes. Let us assume that the heart is pumping blood into the bag continually and that it is then the pressure in the bag that pushes the blood back through the resistance to the heart. If the bag is underfilled, the pressure is too little to push adequate quantities of blood back through all the vessels to the heart. On the other hand, if the bag is overfilled, the pressure will push excessive quantities of blood back through the resistance to the heart. Therefore, we can conclude that if the vascular resistances throughout the circulatory system remain constant, the rate of blood flow into the heart is related directly to the degree of filling of the bag.

Under many abnormal conditions, the degree of filling of the circulatory system is much

Fig. 8. A. Effect of transfusion on cardiac output. B. Effect of hemorrhage on cardiac output, illustrating that cardiac output recovery from the effects of hemorrhage is not as rapid as recovery from the effects of transfusion.
more important in the control of cardiac output than is the resistance to blood flow in the vessels. For instance, in shock, the resistance to blood flow may be entirely normal, or sometimes even less than normal, and yet cardiac output will still be low simply because the circulatory systemic “bag” is not filled with enough blood to build up adequate peripheral pressure to make the blood return to the heart.

**Effect of Transfusion and Hemorrhage on Cardiac Output**

Obviously, the easiest way to increase the mean systemic pressure above normal is simply to increase the blood volume, which occurs when a person is transfused with blood. And one would expect cardiac output to increase rapidly and markedly following transfusion. Figure 8A illustrates this effect, showing that a sudden transfusion of 300 mL of blood into a dog increased cardiac output 300 per cent. However, it will be noted that the cardiac output did not remain elevated for long, but instead fell back toward normal during the ensuing 25 minutes. There are many reasons for this rapid return of cardiac output to normal. First, immediately after the transfusion the circulatory system is literally stuffed with extra blood, and the mean systemic pressure rises drastically. In the example of figure 8A it rose from its normal value of about 7 mm. Hg to about 28 mm. Hg. Thus, cardiac output rose approximately the same percentage that mean systemic pressure rose. However, during the ensuing minutes the mean systemic pressure fell rapidly to a value only slightly above normal, for two reasons: (a) the circulatory system becomes stretched to accommodate the increased blood volume, and (b) a major share of the blood volume itself is lost. Thus, large quantities of blood are stored in the liver, spleen, and small veins throughout the body, and large quantities of the plasma portion of the blood leak rapidly out of the circulation into the interstitial spaces and into the abdomen in the form of ascites.

In summary, transfusion increases the cardiac output so long as the mean systemic pressure remains elevated. However, when the circulatory system is overfilled with blood, compensatory mechanisms reduce the mean systemic pressure back toward normal very rapidly, and the cardiac output returns to normal accordingly.

Following hemorrhage, almost exactly the opposite effects occur, except for one major difference. The mechanisms for returning the mean systemic pressure to normal following hemorrhage are much slower to become effective than is true when the circulatory system is overfilled with blood. Often several hours or even a day or more may be required to bring mean systemic pressure back up to normal. Figure 8B illustrates the effect on cardiac output of sudden removal of blood from the circulation, showing that cardiac output does not return to normal easily. Yet, replacement of enough blood to bring the mean systemic pressure back to the normal level will return the cardiac output immediately to normal also.

**Effect of the Nervous System on Peripheral Circulatory Regulation of Cardiac Output**

Massive stimulation of the sympathetic nervous system, such as occurs when the brain becomes ischemic, can increase the mean systemic pressure from its normal value of 7 mm. Hg to about 18 mm. Hg in 20 to 30 seconds. This occurs mainly because of contraction of the smooth muscle in the vascular walls throughout the body. As a result, the blood pumped by the heart into the circulatory “bag” builds up a much higher pressure in this bag than normally and, therefore, causes
greater mean systemic pressure to push the blood through the circulatory resistance to the heart. Therefore, one can see that the nervous system can affect cardiac output by acting on the peripheral circulatory system as much as it can affect cardiac output by acting on the heart.

On the other hand, there are times when the sympathetic nervous system becomes very inactive, rather than overactive, such as occurs in some types of vasomotor collapse. This effect is illustrated in figure 9. In this case, it is immediately evident what is wrong: the blood pouring into the systemic circulation is not enough to distend the system at all; instead, many of the vessels are collapsed, and the pressure generated in the peripheral vessels is too little to push the blood from the peripheral vessels back toward the heart. Under these conditions, hydrostatic factors play a major role in determining the level of cardiac output. Obviously, if the head is down the vessels toward the head will fill much better than those toward the feet, and since the heart is near the head, the veins entering the heart likewise will become filled reasonably well. Therefore, despite the vasomotor collapse, the cardiac output may still be completely adequate, but this same person in the foot-down position would fill his lower vessels because of hydrostatic factors, while leaving the veins entering the heart completely limp, the result of which obviously would be disaster.

In summary, it is not the blood volume alone that is important in determining the degree of filling of the circulation but, instead, it is the mean systemic pressure that is important, and this is determined by the ratio of blood volume to the momentary capacity of the circulatory system.

Role of Blood Volume and Mean Systemic Pressure in Maintenance of Cardiac Output When the Heart Becomes Drestically Weakened

A special feature of a slightly or moderately weakened heart is that it still can pump a normal cardiac output if the right atrial pressure simply rises a few mm. Hg above normal, which was illustrated by the cardiac function curves in figures 1 and 2. One means by which the right atrial pressure can be increased is to increase the mean systemic pressure, which causes increased tendency for blood to flow from peripheral vessels toward the heart. In cardiac failure, this very effect occurs by the following sequence of events: (a) The weakened heart causes the cardiac output to fall. (b) This has drastic mechanical and hormonal effects on the function of the kidneys, reducing urinary output of both salt and water. (c) Because of resulting fluid retention, the total body fluid volume increases, and a small share of this remains in the circulatory system itself, increasing the blood volume. (d) As a consequence, mean systemic pressure increases. (e) This increases the tendency for blood to flow into the right atrium, thus bringing right atrial pressure to a value a few mm. Hg above normal. Often, as a result of this sequence of events, the right atrial pressure finally rises high enough to make even the weakened heart pump a normal cardiac output. Thus, in the early stages of progressive cardiac disease, retention of fluid and expansion of blood volume seem to be an important feature of the compensatory mechanisms to keep the cardiac output normal. Indeed, this stage of compensation occurs so imperceptibly that the person himself usually does not know that it is occurring.

On the other hand, in the late stages of cardiac failure, the weakness of the heart becomes extreme. Precisely the same mechanisms are at play to increase the blood volume, but the maximum permissible level of cardiac output set by the weakened heart is now below that required by the body. As a consequence, cardiac output never rises high enough to return renal function entirely to normal. The kidneys continue to retain salt and water; blood volume continues to increase; mean systemic pressure continues to rise, sometimes reaching three to four times the normal value; capillary pressure continues to rise; and the person becomes progressively more edematous. This is the difficult picture of congestive heart failure, with the heart pumping absolutely as much blood as it can, but even this not enough to bring about reestablishment of fluid balance. Without treatment of the patient, the condition will proceed to death. On the other hand, a cardiotonic drug, a diuretic, or treat-
ment with bed rest to make the heart a little stronger often can reverse the lethal trend.

Cardiac Output Regulation in Abnormal States

Using the above principles of cardiac output regulation, it becomes very easy to understand most of the clinical abnormalities of cardiac output regulation, some of which are illustrated in figure 10.

In essentially all the states of high cardiac output, its basic cause is decreased resistance to blood flow in the peripheral circulation. Thus, an arteriovenous fistula greatly decreases peripheral resistance. Likewise, hyperthyroidism, anemia, Paget's disease, beriberi heart disease, and pregnancy all decrease peripheral resistance. In hyperthyroidism, this decrease is caused by excessive use of oxygen in the tissues and resultant hypoxic vasodilatation. In beriberi, it is caused by thiamine deficiency. In Paget's disease, it is caused by a multitude of small vascular shunts from arteries to veins in the bones. In anemia, the decreased resistance is caused by two factors: decreased viscosity of the blood itself, and some degree of vascular dilatation caused by relative hypoxia of the tissue.

Another condition that can cause increased cardiac output (as described above) is excessive blood volume caused by transfusion, although the increased cardiac output caused by this does not last long because of compensatory mechanisms.

On the other hand, most of the factors that decrease cardiac output to below normal are related to one of two conditions, either a weak heart that lowers the permissive level of cardiac output or a decrease in mean systemic pressure. Thus, in cardiac disease—whether it be caused by myocardial infarction, terminal stages of valvular heart disease, or any other condition—cardiac output can fall considerably below normal for days or weeks at a time, but once it falls below approximately
two-thirds normal, one can expect an early demise.

Likewise, one readily can understand that hemorrhage, which reduces the mean systemic pressure so much that blood will not flow from the peripheral circulation back to the heart, can cause all degrees of decreased cardiac output. Also, neurogenic shock, characterized by flaccidity of the peripheral circulation, can reduce the mean systemic pressure enough, despite normal blood volume, that cardiac output can fall to lethal levels, especially if the person is in a head-up position.

Summary

Under most normal conditions, cardiac output is regulated mainly by the tissues, each tissue regulating its own blood flow, cardiac output being the sum of the flows through all the peripheral tissues. This mechanism works very simply as follows: When the vasculature of the tissues dilates, blood flows rapidly from the arteries to the input side of the heart. The heart then automatically pumps the blood immediately back into the arteries, thereby keeping the arterial blood reservoir replenished with blood as rapidly as it runs off through the tissues.

The heart plays a permissive role in the regulation of cardiac output. The normal human heart under resting conditions can pump, perhaps 12 to 15 liters per minute, and when stimulated by the autonomic system, perhaps 25 to 35 liters per minute. Rarely does the cardiac output actually rise to the maximum levels. Thus, the heart permits the cardiac output to be regulated at any value between zero and its permissive level. Except for this effect, the heart plays a secondary role in cardiac output regulation unless it becomes too weak to meet the demands of the body.

The two principal factors that determine the rate at which blood will return to the heart from the peripheral circulation are (1) the degree of vasodilatation of the peripheral vasculature, especially of veins but to a lesser extent arteries as well, and (2) the degree of filling of the circulatory system, which is expressed as the mean systemic pressure. Either a decrease of resistance in the vasculature or an increase in the mean systemic pressure will increase cardiac output.

References