CURRENT TOPICS

The Relationship of Cardiac Output and Arterial Pressure Control

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SUMMARY Many basic concepts of cardiac output and arterial pressure control have changed considerably in the past few years. In general, each tissue controls its own local resistance and blood flow regardless of the level of arterial pressure; the sum of the local flows then determines the venous return and cardiac output. However, the arterial pressure is normally controlled by separate mechanisms that do not significantly alter the cardiac output. During acute circulatory stresses, such as exercise, the arterial pressure is controlled almost entirely by nervous reflex mechanisms; but over long periods, these reflex mechanisms fade away because they adapt. The arterial pressure is then controlled mainly by a renal-volume-endocrine pressure control system, in which the blood volume and total peripheral resistance are manipulated slowly to adjust the pressure.

RECENT EXPERIMENTS and analyses have led to several rather startling concepts on the relationships between cardiac output and arterial pressure control. For instance, a long-term increase in total peripheral resistance does not cause any increase in arterial pressure if there is not a concomitant increase in renal vascular resistance; instead, cardiac output decreases. Also, a chronic increase in blood volume causes hardly any increase in cardiac output, but rather, usually causes a marked increase in arterial pressure. These effects are almost exactly opposite to those observed during the first few minutes after acute increases in total peripheral resistance or blood volume.

Thus, there seems to be no logic in the way the body controls cardiac output and arterial pressure — almost as if these controls were a problem of metaphysics rather than of purpose.

The goal of this report is to show that there are logical systems for control of both cardiac output and arterial pressure, and especially that cardiac output and arterial pressure are mainly controlled for different purposes.

The Purposes of Cardiac Output and Arterial Pressure Control

Cardiac output and arterial pressure control are much easier to understand if we delineate the purposes of these controls.

Cardiac Output Control

The purpose of cardiac output control is to deliver to the body’s tissues the necessary blood flow to perform their functions. In most tissues, the need for flow is to transport nutrients to the tissues and excreta away from the tissues. In the kidneys, the need is for sufficient flow for proper excretory function; in the gastrointestinal tract, it is for adequate flow for glandular secretion and for absorption; and in the skin, it is for body temperature control. Thus, each tissue has a certain requirement for blood flow, and the cardiac output must keep in step with these needs.

However, the heart’s capability to pump blood is not unlimited. Even a cardiac output of two times normal, if it continues for days or weeks, seriously taxes the long-term abilities of the heart. Therefore, the cardiac output must be only great enough to deliver to the tissues that amount of blood flow that is required; no more, no less. Figure 1 is an illustration of this principle. In a series of dogs, we purposely increased the cardiac output to more than two times normal by acute infusion of blood, or we reduced the cardiac output below normal by hemorrhage. While the cardiac output was either too high or too low, we measured the total oxygen consumption of the animal. Increasing the cardiac output to two times normal increased the oxygen consumption by only a few percent. On the
other hand, decreasing the cardiac output below normal very rapidly caused a serious decrease in oxygen utilization by the tissues. Oxygen is the most important of all the flow-limited nutrients required by the tissues, and it is clear from this experiment alone that the normal cardiac output is very precisely optimized to the level that will supply essentially all the nutrient needs of the tissues and yet to a level that gives almost no excess flow, providing for both the needs of the tissues and yet protecting the heart from overload.

Arterial Pressure Control

One of the obvious purposes of pressure control is to keep the pressure high enough so that blood can flow to all of the tissues of the body even when some of the tissues are far above the level of the heart. For instance, in giraffes, the mean arterial pressure is regulated to a level between 200 and 300 mm Hg; this much pressure is required to assure blood flow to the top of the head. At the other extreme, the regulated level of the arterial pressure in primitive fishes may be as low as 30 mm Hg; because there are no hydrostatic pressure gradients in fishes, this is an adequate pressure to assure blood flow to all tissues.

However, pressure control involves more than simply assuring adequate pressure for flow to all of the tissues. When the pressure control system is operating normally, even massive changes in blood flow in one part of the body will hardly affect the arterial pressure. Therefore, this also will not affect the blood flow in other parts of the body. That is, proper arterial pressure control allows the blood flows in the separate parts of the body to be controlled independently.

The Basic Acute Hemodynamic Mechanisms of Cardiac Output and Arterial Pressure Control

Four basic factors control both cardiac output and arterial pressure: total peripheral resistance, heart pumping capacity, blood volume and vascular compliance. The chronic effect of each is often entirely different from the acute effect.

The Acute Effect of Total Peripheral Resistance Changes on Cardiac Output and Arterial Pressure

Figure 2 illustrates data from a basic experiment that demonstrate the hemodynamic effects of acute changes in total peripheral resistance. In this experiment, two groups of dogs were used; in one group the function of the nervous system was normal and in the other it was abrogated by removing the animal's head and injecting the spinal cord with alcohol. In each dog two large arteriovenous (A-V) fistulas were opened for 6 minutes by opening both femoral arteries directly into the adjacent femoral veins. In the dogs with nonfunctioning nervous systems, the acute hemodynamic effect of opening the A-V fistulas, which greatly decreased the total peripheral resistance, was a marked increase in cardiac output and a decrease in arterial pressure. On a percentage basis, the increase of cardiac output was almost exactly equal to the decrease in pressure.

Although the initial effects in dogs with intact nervous systems were almost identical to those in dogs without, within less than 30 seconds the arterial pressure returned about seven-eighths of the way back toward normal, while the cardiac output increased still a little more. Then, when the fistulas were closed, the arterial pressure rose somewhat above normal at first, but within another minute or so returned back to the normal level. This overshoot in pressure was the result of the compensatory mechanisms that had become activated during the period of the open A-V fistulas.

This A-V fistula experiment illustrates that the major circulatory control function of the nervous system is to control arterial pressure, not to control cardiac output. It also demonstrates that if the arterial pressure is maintained at a normal level by the nerv-
ous controls when a fistula is opened, the cardiac output will rise to a greater level than it will when the pressure is not maintained; that is, maintenance of a normal or nearly normal level of arterial pressure is important not only for pressure control itself, but also because it allows adequate blood flow through the tissues when an abnormal factor tends to drain this blood flow away from the tissues.

Effect on Cardiac Output and Arterial Pressure Caused by Changing the Heart Pumping Capacity

It is often stated that increasing the heart pumping capacity, either by increasing the heart strength or by increasing the heart rate, will increase the cardiac output and the arterial pressure. However, persons with less-than-normal heart pumping capacities do not necessarily have a low cardiac output or a low arterial pressure. Furthermore, some heart valve operations increase the heart pumping capacity tremendously, although this does not cause either excess cardiac output or hypertension. Therefore, let us examine the acute effect on circulatory dynamics of increasing the heart pumping capacity.

Figure 3 illustrates the results when the heart-pumping capacity of dogs was increased by electrically pacing the heart to increase the heart rate from 50 beats/min up to 200 beats/min. The upper curve shows the effect of the increasing heart pumping capacity when a very large fistula existed between the aorta and the inferior vena cava, so that there was always an excess preload on the heart (that is, a high right atrial pressure). Under these conditions, the increasing heart pumping capacity increased the cardiac output very markedly.

The lower curve of figure 3 shows the effect of the increasing pumping capacity when the circulation was normal. Cardiac output changed almost imperceptibly. How does one explain this failure of increased heart pumping capacity to increase the cardiac output? Figure 4 explains this; it shows an effect that has been learned from use of extracorporeal circulatory systems. Increasing the pumping capacity of the artificial heart in the extracorporeal system to two times normal has almost no effect to increase the cardiac output above normal. Likewise, an increase of heart pumping capacity to three times normal, five times normal or even greater will not increase the cardiac output. The veins entering the chest simply collapse when the right atrial pressure begins to fall below 0 mm Hg, which is what occurs when the heart tries to pump more blood than is made available by the normal venous return.

Therefore, there is no reason to believe that in the normal circulation, increasing the heart pumping capacity above normal will increase the cardiac output or the arterial pressure to higher than normal values. On the other hand, when increased amounts of blood return from the veins, an increase in pumping capacity of the heart often then becomes essential to keep up with the returning blood.

The Hemodynamic Effects of Increased Blood Volume or Decreased Vascular Compliance on Cardiac Output and Arterial Pressure

Though changes in blood volume and vascular compliance are known to play a very important role in acute hemodynamic control of the circulation, the quantitative effects of these factors are difficult to understand, partially because some of the experiments to clarify the effects have been performed in animals with normally functioning nervous systems and others have been in animals either without nervous systems or with greatly depressed nervous systems as a result of anesthesia.

Figure 5 illustrates composite effects recorded in three series of dogs in which transfusions of blood equal to 30–40% of the dog's original blood volume were given in only a few minutes. In some dogs, the function of the nervous system had been eliminated either by total spinal anesthesia or by decapitation and injection of the spinal cord with alcohol. In other dogs,
the nervous systems were normally functional. In both states, essentially the same effect was observed on cardiac output — a marked increase in output to about 100% above normal. However, cardiac output returned to normal in less than 1 hour, although the blood volume still remained about 20% greater than normal.

Although the presence or lack of a nervous system had very little effect on the cardiac output response, this did affect the arterial pressure response tremendously. Note that in the absence of the nervous system the arterial pressure rose about 130%, while it rose only about 15% when the nervous system was intact. Yet, whether the nervous system was intact or not intact, the pressure still returned essentially to normal within the first hour.

Several important lessons may be learned from the experiment illustrated in figure 5. First, the basic hemodynamic effect of increasing the blood volume is to increase the cardiac output markedly, and this in turn increases the arterial pressure markedly. However, if the nervous reflex pressure control mechanisms are fully functional, the arterial pressure will be reflexly prevented from rising very much despite the tremendous increase in the blood volume and despite the tremendous increase in cardiac output. Yet, the nervous reflexes have almost no effect on cardiac output, illustrating again that the nervous system is geared primarily to control arterial pressure, not cardiac output.

It is also significant that the blood volume had fallen from its peak of 40% above normal to only 20% above normal 1 hour after the transfusion; yet despite this excess 20% of volume, both the cardiac output and arterial pressure were at that time essentially normal. Simultaneous measurements of the so-called mean circulatory filling pressure were also made in these same experiments. To make these measurements, heart pumping is stopped completely for a short period until the pressure becomes the same all through the circulation. The pressure level at this point is the mean circulatory filling pressure, which is a measure of how tightly the circulatory system is filled with blood. In the first few minutes after the transfusion, this value had increased to about three times normal because of all the extra blood in the circulation. However, 1 hour later the mean circulatory filling pressure had returned entirely to normal even though the blood volume was still 20% above normal. This illustrates that the circulatory system itself had enlarged during this hour, with compliance increasing enough to accommodate the extra 20% blood volume. Thus, an increase in compliance can nullify the hemodynamic effects of an increase in blood volume. This is one of the reasons the relationships between blood volume and circulatory function are so difficult to understand, especially since it is almost impossible to measure circulatory compliance.

The most important principle illustrated by these experiments is that in the absence of the nervous reflexes the cardiac output and arterial pressure are both highly responsive to changes in blood volume. However, when the circulatory reflexes are fully functional, these reflexes can maintain almost exactly normal arterial pressure despite marked changes in blood volume.

Cardiac Output and Arterial Pressure During Exercise: An Example of Complex Short-term Control

The two upper curves in figure 6 illustrate the approximate changes in cardiac output and arterial pressure in normal dogs when they begin to exercise at a moderately heavy rate. Note the 2.5-fold increase in cardiac output and the 50% increase in arterial pressure. The next two curves illustrate the effect on cardiac output and arterial pressure in sympathectomized dogs caused by exercise at about the maximum level that these dogs could tolerate. The cardiac output increased only 32%, while the arterial pressure fell about 21%. Thus, the nervous system obviously plays a major role in the capability of an exercising animal or person to achieve both greatly increased cardiac output and moderately increased arterial pressure during exercise.

The lowerest curve in figure 6 shows the effect of exercise on total peripheral resistance in both the normal and the sympathectomized dogs. In both instances,
the change in total peripheral resistance was essentially the same.

At the onset of exercise, two major control events occur almost simultaneously: The resistance to blood flow through the contracting muscles decreases markedly because of local factors in the muscles directly dilating the blood vessels, and the sympathetic nervous system constricts the capacitance vessels of the circulation, especially the veins, and it also constricts the arterioles in those parts of the body besides the exercising muscles. This sympathetic drive to the circulation derives at least partly from signals generated in the central nervous system during the course of exercise and probably partly from reflexes that originate in the active muscles themselves. Dogs that had been sympathectomized experienced only one of the above control factors, the very large decrease in resistance in the muscles, while the normal dogs had the benefit of the sympathetic drive. The decreased muscle resistance decreased the total peripheral resistance by about 40%, which also decreased the arterial pressure and raised the cardiac output, but only by 32%. Obviously, if the arterial pressure had not fallen, far more blood would have flowed through the greatly dilated muscle blood vessels, and the cardiac output would have been much greater. Furthermore, if the arterial pressure had actually risen, as occurred in the normal dogs with normal sympathetic signals, then the cardiac output would have risen still much more. This is the effect that was observed in the normal dogs: an increase in cardiac output of 130% instead of the almost insignificant increase of 32% seen in the sympathectomized dogs.

Yet, the total peripheral resistance changes were almost equal, whether or not the dogs were sympathectomized. The basic difference between the sympathectomized and the normal animal depends in the ability of the normal animal to increase its arterial pressure despite the marked decrease in total peripheral resistance. This undoubtedly resulted from increased venous return and cardiac output caused by a sympathetically stimulated decrease in vascular compliance and an increase in cardiac pumping. But, by way of circular logic, the increase in arterial pressure in the normal animal also increased the flow through the peripheral circulation, allowing the very large increase in venous return in the normal compared with the slight increase in return in the sympathectomized dog.

Thus, arterial pressure control is exceedingly important to allow adequate blood flow to those parts of the body where vasodilatation occurs. The vasodilatation usually results not from direct effects of nervous signals, but from local changes in the tissues, such as increased metabolism, that relax the blood vessels. However, if the arterial pressure is not kept at a normal level, or even raised above normal as occurs during exercise, then the local vasodilatation of the blood vessels may not be enough in itself to provide the needed local blood flow.

Long-Term Control of Cardiac Output and Arterial Pressure: The Importance of Very Slight Blood Volume Changes

Long-term control of cardiac output and arterial pressure is quite different from short-term control for three reasons: (1) The nervous reflexes adapt (that is, they become inoperative as controllers) within a few hours to a few days after an acute circulatory change. (2) Blood flow autoregulation occurs in almost all tissues of the body, which returns the blood flows in these tissues essentially to normal regardless of what happens to the arterial pressure. (3) The kidneys respond very markedly to changes in arterial pressure, increasing their output of salt and water at higher pressures and decreasing their output at lower pressures. These three factors altogether make blood volume extremely important in long-term circulatory control.

Effect of Adaptation of the Circulatory Reflexes

The baroreceptor reflex is a typical arterial pressure-controlling reflex that every physician knows, but other reflexes also originate in the heart, the lungs, and in the basal regions of the brain that also play very important roles in pressure control. However, a consideration of the baroreceptor reflex will illustrate the effect of pressure receptor adaptation on long-term control of the circulation.

When a factor such as an increase in blood volume increases the arterial pressure, the rising pressure immediately stimulates the baroreceptors. This in turn causes reflex dilatation of the peripheral circulation and at the same time decreased strength of heartbeat, and these factors together prevent much of the rise in arterial pressure that otherwise would occur.
However, during the next 24–72 hours, the baroreceptors themselves gradually stop sending excess signals to the brain even though the pressure is still high. Therefore, the reflex effects that had been preventing the rise in pressure disappear. As a result, the full effect of the increased blood volume to increase arterial pressure then becomes manifest.

This effect of adaptation of the nervous reflexes to sensitize the arterial pressure response to changes in volume is illustrated in figure 5. When the nervous reflexes were operative, the increase in blood volume had little effect on arterial pressure. However, in the absence of the reflexes, which is the state that exists after the reflexes have adapted, the same change in volume increased the arterial pressure eight times as much.2

Control of Local Blood Flow by the Autoregulation Mechanism

The local ability of each tissue to control its own blood flow is called autoregulation. Autoregulation is not instantaneous. In some tissues, such as the kidneys, most of the autoregulation response takes place within less than 30 seconds. In most other tissues, the autoregulatory response during the first minute is relatively weak and becomes progressively more intense with time. The initial autoregulation is caused by constriction of the smooth muscle walls of the blood vessels when the blood flow is too great or relaxation when the blood flow is too low. However, over a period of weeks and months, actual structural narrowing or enlargement of blood vessels occurs to return the blood flow toward normal. Thus, by both these means, the local blood flows seem to be progressively adjusted to the needs of the tissues.

Why does this autoregulatory mechanism make volume control of the circulation more sensitive? When the blood volume increases and this in turn increases arterial pressure and cardiac output, the initial autoregulation in the entire circulation is very slight because some blood vessels are dilated as a result of the rising pressure at the same time that other vessels begin to constrict as a result of autoregulation. Therefore, the total peripheral resistance hardly changes at first. Consequently, the high cardiac output can persist at least temporarily. Yet, over time, the autoregulatory response becomes progressively enhanced, and the total peripheral resistance increases steadily in an attempt to decrease the local blood flows and the cardiac output back toward normal. However, as first observed by Markwalder and Starling in 1914, excess volume keeps the heart pumping an excess cardiac output despite progressively increasing total peripheral resistance. The increasing total peripheral resistance has only a small effect to decrease the cardiac output back toward normal. Instead, it simply raises the arterial pressure to a higher level. Thus, over a period of days and weeks only a few percent increase in volume may increase the cardiac output only a few percent, but nevertheless increase the arterial pressure as much as 50%.

The Kidney Mechanism for Control of Blood Volume and Arterial Pressure: “Pressure Diuresis and Pressure Natriuresis”

The arterial pressure itself is one of the major factors that affect the rate at which the kidneys excrete water and salt. Experiments in hundreds of laboratories have demonstrated that a decrease in arterial pressure to about 60% of normal decreases the urinary output almost to zero. On the other hand, an increase in arterial pressure to about 20% above normal approximately doubles urinary output, and a doubling of arterial pressure increases urinary output an average of about sevenfold, both the water output and salt output participating in these changes. The very great effect of pressure on water output is called pressure diuresis and the effect on salt output is called pressure natriuresis.

Therefore, when the arterial pressure rises above normal in the person with normal kidneys, the body fluid volumes will continue to decrease until the arterial pressure returns exactly back to normal. Conversely, when the pressure falls below normal the kidneys retain water and salt, and this retention occurs until the pressure rises again exactly back to normal.

Thus, the kidneys play a central role in a volume feedback mechanism for controlling arterial pressure. Figure 7 shows changes in cardiac output, arterial pressure, and urinary output after transfusion of blood.

**Figure 7.** Function of the kidney–blood volume feedback mechanism to return the arterial pressure back to normal after transfusion of blood into dogs without nervous reflexes. The transfusion increased the blood volume approximately 30% and was administered in a period of 4 minutes. The dogs were made areflexic by removing their heads and injecting their spinal cords with alcohol. (Modified from Dobbs WA Jr.)
into dogs equal to 30% of their blood volume.22 The nervous reflexes had been blocked so that the full effect of the volume could be observed. Note the marked increases in arterial pressure and cardiac output, similar to those in figure 5, but note also the 12-fold increase in urinary output. This excessive urinary output continued as long as the arterial pressure remained above normal. However, as the arterial pressure returned toward normal, so also did the urinary output. Thus, this mechanism is an extremely powerful one to return the arterial pressure all the way back toward its normal level. This phenomenon is an especially important characteristic of this mechanism that is not manifest by any other arterial pressure control system. It is called the principle of "infinite gain" for control of blood pressure by the kidney-volume-pressure control mechanism.3

Thus, even small changes in blood volume are extremely important in long-term control of the arterial pressure; but far greater changes in volume are required in short-term control to achieve the same results.

Role of Total Peripheral Resistance in the Long-term Control of Cardiac Output and Arterial Pressure

Although an acute change in total peripheral resistance affects cardiac output and arterial pressure about equally (fig. 2), this is not the case when the total peripheral resistance remains chronically increased or decreased. Figure 8 shows the effects of long-term total peripheral resistance changes on cardiac output and arterial pressure. This figure was constructed from measurements of arterial pressure and cardiac output in many different clinical conditions in which the total peripheral resistance was chronically decreased or chronically increased.23 For instance, such factors as beriberi, A-V shunts, anemia and thyrotoxicosis cause a chronic decrease in total peripheral resistance. At the other extreme, hypothyroidism or removal of all four limbs of a person can cause a chronic increase in total peripheral resistance. Yet, the measurements show that in none of these conditions is the arterial pressure abnormal. Instead, the cardiac output changes exactly inversely to the changes in total peripheral resistance because when the arterial pressure rises above or falls below the normal level, the normally functioning kidneys will either eliminate fluid from the body or retain fluid until the pressure returns back to the original level. This again is a manifestation of the infinite-gain principle of pressure control by the kidney-volume-pressure system.

A Complex Example of Long-term Cardiac Output and Arterial Pressure Control: Development of Volume-loading Hypertension

Many experiments have shown that long continuation of excess blood volume in a circulatory system will almost invariably lead to severe hypertension.24-28 Ordinarily, though, an excess volume is difficult to maintain in the circulation for more than a few hours because the kidneys are extremely effective in removing the excess volume. Indeed, the salt and water intake of a person can be increased to as much as 10-15 times normal with no more than a 5-10 mm Hg pressure rise simply because of this vast capacity of the kidneys to eliminate the excess water and salt. Nevertheless, under special experimental conditions it is possible to cause long-term volume loading, and this seems always to cause hypertension if all other aspects of the circulation are normal. Though not all investigators agree on the successive events in the development of this volume-loading hypertension, the following analysis fits with the available data.

Figure 9 presents a composite set of curves illustrating the hemodynamic changes during the onset of typical volume-loading hypertension. These curves were normalized from several dog experiments in which the kidney mass was first reduced to approximately 30% of normal so that the kidneys could not excrete sodium and water rapidly.24-28 Then, several weeks later, at "zero" time, the dogs were placed on a salt intake approximately five to seven times normal. Immediately, the extracellular fluid volume, blood volume, mean circulatory filling pressure, pressure gradient for venous return, and cardiac output all increased 20-50%. At the same time, the arterial pressure began to rise, but much more slowly than the other variables. The reason for this slowness was that the nervous reflexes decreased the total peripheral resistance below normal, which nullified much of the pressure rise. Yet, over a period of days the nervous reflexes adapted and thereby became inoperative. At the same time, the excess cardiac output caused progressive autoregulatory increase in the vascular resistance throughout the body. These effects — the diminution of the reflex effects and the autoregulation — then increased the total peripheral resistance. This
Figure 9. A composite figure of the results from many experiments in which volume-loading hypertension was caused by decreasing the renal mass to 30% of normal and several weeks later increasing the salt and water intake to five to seven times normal. Note that the final result was hypertension in which the cardiac output was essentially normal but the total peripheral resistance was greatly increased. (Reprinted with permission from Guyton AC.1)

in turn caused all of the volume factors and cardiac output factors to return toward normal even though the arterial pressure remained greatly elevated.

Thus, the initial cause of the volume-loading hypertension is excess volume and excess cardiac output. However, secondary changes in total peripheral resistance return the cardiac output and fluid volumes back to or very near to normal while substituting instead a high total peripheral resistance.

One of the most important features of this analysis is that, in the long run, cardiac output is controlled relatively independently of the arterial pressure. That is, the cardiac output returns so nearly to normal that one actually can not tell from experiments that it is abnormal. On the other hand, if the heart is strong enough to withstand the extra pressure load, the arterial pressure will eventually rise high enough so that the impaired kidneys can then excrete the greatly increased daily load of water and salt.

Conditions in Which the Long-Term Control Mechanisms Fail

So far, this report has presented the long-term control of cardiac output and arterial pressure in a person who has a normal circulatory system. However, under abnormal conditions, these mechanisms frequently fail and may lead to persistent tissue ischemia when blood vessels have become so contracted that they cannot possibly vasodilate, heart failure when the heart cannot sustain an increased pressure or increased cardiac output load, or edema when the capillary system cannot retain fluid in the circulating blood.

The long-term volume-renal mechanism of pressure control has two functional requirements. First, the heart be strong enough to increase the cardiac output at least slightly and the arterial pressure considerably when the blood volume increases. This is well-known from animal experiments but even more so from clinical practice, for infusion of fluid or blood into a patient with a failing heart, or even eating large amounts of salt, all of which tend to increase blood volume in the normal person, will lead to loss of fluid from the capillaries into the tissue spaces, causing edema rather than increased arterial pressure. This is a well-known characteristic of congestive heart failure, representing failure of the system to regulate either cardiac output or arterial pressure normally.

Second, the systemic capillaries must be able to hold fluid in the circulation, preventing excessive filtration into the interstitial spaces. It is not only in heart failure that the capillaries cannot retain fluid in the circulation. The clinical conditions of anaphylaxis and nephrosis also often make it difficult or impossible to maintain even a normal blood volume, much less excess volume, despite massive fluid therapy; instead, the fluid rapidly transudes into the tissues — in the first instance because of increased capillary porosity and in the second because of decreased plasma colloid osmotic pressure. In both conditions, excess infusion or intake of fluid and salt lead only to increased edema, not to increased arterial pressure.

Another condition that makes it difficult for the capillary system to maintain an adequate blood volume is paralysis of the arterioles throughout the body. For instance, animals whose arteriolar tone has been acutely paralyzed as a result of total spinal anesthesia are incapable of maintaining the arterial pressure above 60 mm Hg despite transfusion of blood equal to more than 50% of the animal’s normal control volume. Instead, fluid leaks so rapidly out of the circulation into the interstitium that within 20 minutes extreme hemoconcentration occurs while the blood volume returns essentially to normal and the arterial pressure equilibrates below 60 mm Hg.

Therefore, the volume-kidney-pressure control mechanism can fail in many ways. In some of these instances the hemodynamics of the failure are known; in others, proper explanations are not available. Onesti et al. performed an especially interesting study and showed that increasing the extracellular fluid volumes
of totally nephrectomized patients caused hypertension in some patients but not in others. Those in whom hypertension failed to occur developed peripheral edema instead. Unfortunately, not enough information was available from these patients to tell whether one of the known causes of failure of the system might have been operative. There might have been something about the humoral or hormonal makeup of these patients that affected either the arterioles or the capillaries to prevent retention of fluid in the circulation. This type of problem represents one of the foremost areas of research still in process for defining the long-term mechanisms of circulatory control.

Role of Nervous, Hormonal, and Electrolyte Systems in Long-term Regulation of the Circulation

Although the emphasis of this paper has been that cardiac output and arterial pressure control, over the long-term, are mainly controlled by separate hemodynamic mechanisms, there are special conditions under which nervous, hormonal and electrolyte systems play powerful roles in long-term regulation of both of these.

Recent experiments have shown that the human being can tolerate changes in sodium intake from 10–1500 mEq per day, a 150-fold change, with only a 10–20-mm Hg arterial pressure change. Yet, animal experiments in our laboratory have shown that blockade of the renin-angiotensin system makes this wide range of tolerance no longer possible; instead, the pressure then changes about 10 times as much and almost in direct proportion to the changes in sodium intake. Therefore, the renin-angiotensin system, along with its associated aldosterone system, plays an exceedingly important long-term role in fine-tuning the basic hemodynamic pressure control system.

Although circulatory reflexes were emphasized as extremely important short-term controllers of arterial pressure, they seem to adapt within a few days and therefore probably do not play a significant role in long-term pressure control. Nevertheless, there are other aspects of nervous control of the circulation besides the reflexes. For instance, minute-by-minute or hour-by-hour bursts of sympathetic activity often result from stress situations. Recent experiments have illustrated that the hormones released by the sympathetic nervous system, norepinephrine and epinephrine, can have not only short-term effects on the kidneys, but long-term effects as well, and these could easily lead to a long-term increase in the arterial pressure.

Thus, in addition to the basic circulatory hemodynamic and renal hydraulic mechanisms for long-term control of the circulation, the body has also developed still other special mechanisms for fine-tuning the system. When these special mechanisms fail to function properly, they too can cause clinical abnormalities of cardiac output or arterial pressure control.

Conclusions

The basic theory of long-term circulatory control is that the tissues control their own blood flows and also the cardiac output by changing the resistances throughout the body. A separate system controls the arterial pressure independent of cardiac output control. This system is based mainly on long-term control of blood volume by the kidneys. Though an acute increase in volume increases the cardiac output markedly, over a period of days to weeks the resultant excess flow through each tissue leads to autoregulation; this increases the local resistances and returns the local flows, as well as the cardiac output, back to normal; but this elevation of the peripheral resistance now maintains a high arterial pressure. Thus, in a round-about way, a small change in blood volume may cause a large change in arterial pressure.

Superimposed onto this intrinsic long-term, hemodynamic control system of the circulation are important hormonal and nervous mechanisms that normally fine-tune the system; but they themselves can cause abnormal cardiac outputs or arterial pressures when they malfunction.

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