Blood Pressure Control—Special Role of the Kidneys and Body Fluids

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The arterial pressure of the adult human rarely deviates from normal by more than 10 to 15 percent during each day. To achieve such constancy, the body has a network of pressure control systems. Several are based on neural receptors that respond within seconds to help correct any abnormal pressure. The activities of these systems are followed within minutes by activation of hormonal controllers. Within hours or days, a kidney pressure control system is induced that increases body fluid volume when the pressure falls (or decreases the volume when the pressure rises). This kidney-fluid system is the dominant method of establishing long-term pressure control.

IN THE NORMAL ADULT, ARTERIAL BLOOD PRESSURE IS ABOUT 120/80, which means a peak of 120 mmHg each time the heart beats and a minimum of 80 mmHg between heartbeats. However, when discussing blood pressure control, we usually are concerned not with these rises and falls in pressure but instead with the mean pressure over the whole heart cycle. This pressure normally is maintained at approximately 100 mmHg. However, it can rise to more than 160 mmHg in individuals with hypertension or fall, even to 0 mmHg, in persons who have bled severely or otherwise have a compromised circulation.

The body has many systems for controlling the pressure. Figure 1 illustrates the approximate time of activation of eight separate control systems after the arterial pressure suddenly becomes abnormal (*1*). Several systems based on neural receptors [baroreceptors, chemoreceptors, and central nervous system (CNS) ischemic response] react within seconds. Then, several hormonal and some minor systems react within minutes. Finally, a kidney-fluid volume system reacts within hours or days; in the end its contribution is by far the greatest.

The degree of activation of each pressure control system can be expressed quantitatively in terms of feedback gain, which is the ratio of the correction of the pressure abnormality to the remaining uncorrected pressure abnormality. If the control system has corrected the pressure to its exact normal level, the feedback gain is infinity.

Controllers Based on the Nervous System as the First Line of Defense

The baroreceptor system. The simplest and most rapidly acting of the neural pressure controllers is the arterial baroreceptor system (*2*). It is induced by nerve receptors called "baroreceptors" located mainly (i) in the walls of the aorta in the chest and (ii) in the walls of the internal carotid arteries in the neck. These receptors are stimulated when increased pressure stretches the vessel walls. The receptors send signals through the nervous system into the brain, which then relays other signals back to the circulatory system to dilate the peripheral blood vessels and reduce the force and rate of heartbeat. The result is a reduction in the arterial pressure.

The baroreceptor control system is a valuable first line of defense against abnormal pressure. Researchers have demonstrated this utility by examining the changes in arterial pressure after rapid transfusion of blood into dogs whose baroreceptor systems they have made nonfunctional by blocking the neural signals (Fig. 2) (*3*). The increase in pressure in the dogs that lacked this powerful feedback control system was eight times the increase in normal dogs. Yet, even when the baroreceptor system was nonfunctional, the pressure still returned to normal in about an hour (Fig. 2A). Thus, over longer periods of time, other pressure controllers take over.

An abnormal arterial pressure can never be corrected entirely by the baroreceptor mechanism because this would eliminate the stretch of the arteries that initiates the neural feedback (*4*). The total baroreceptor system, as measured in dogs, has a feedback gain of about 7 (*3*); thus, this system can independently correct about seven-eighths of a pressure abnormality.

The CNS ischemic and chemoreceptor pressure controllers. Some pressure control systems, such as the CNS ischemic (*5, 6*) and chemoreceptor pressure controllers, have highly specialized functions (*1, 7*). The CNS ischemic controller is only activated when the CNS becomes "ischemic," that is, when the blood flow to the brain becomes too low to maintain normal activation of the brain neurons. A neural center in the medulla responds by transmitting strong signals through the sympathetic nerves to the heart and blood vessels to increase the pressure, sometimes to the maximum that the heart can achieve.

The chemoreceptor pressure controller, on the other hand, is excited by chemically sensitive cells located in minute (a few millimeters in diameter) bodies that lie adjacent to the baroreceptor regions of the aorta and carotid arteries. The chemoreceptors are stimulated when either the amount of O_2 in the blood is too small or the amount of CO_2 is too great. They send signals to the blood pressure–controlling centers of the brain. This controller is especially important during exercise because the muscles frequently use as much as 20 times or more the resting amount of O_2 (and excrete equally increased amounts of CO_2).

Intermediate Pressure Controllers

Still other pressure controllers begin to function a few minutes after activation of the neural pressure controllers. The renin-angiotensin-vasoconstrictor pressure controller (*8*) is activated when low blood pressure causes the blood flow through the kidneys to fall

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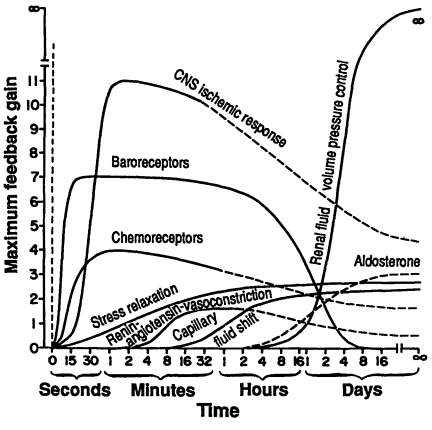

Fig. 1. Degree of activation, expressed in terms of feedback gain at optimal pressure, of different pressure control mechanisms after a sudden change in arterial pressure (indicated by the vertical dashed line). [Adapted from (*1*) with permission, copyright 1980, W. B. Saunders and Co.]

below normal. The low flow makes the kidneys secrete renin into the blood, and the renin enzymatically splits angiotensin from a blood protein called renin substrate. Angiotensin then constricts the small arteries throughout the body, which returns the arterial pressure toward normal. This renin-angiotensin-vasoconstrictor mechanism is normally only a moderately powerful pressure controller, with a feedback gain of 1 to 2. Yet, in special circumstances, such as after foods containing very high or very low amounts of salt are eaten, it functions in association with the kidney-fluid pressure control system to become one of the most important of all controllers.

The other three intermediate pressure controllers in Fig. 1 also act rapidly to help correct abnormal pressure. For example, high pressure, in addition to causing short-term elastic stretch of the small resistance arteries, also induces much slower blood vessel stretch during the following minutes or hours, called stress relaxation. This further reduces the vascular resistance and allows the pressure to return toward normal. If the high arterial pressure results in high pressure inside the blood capillaries, capillary fluid shift occurs; that is, excess capillary pressure causes fluid to filter outward through the capillary pores into the tissue spaces, thus reducing the blood volume and returning the arterial pressure toward normal. Moreover, decreased arterial pressure indirectly stimulates the adrenal glands to secrete aldosterone; this causes the kidneys to retain salt and water, thus helping the kidney-fluid system to return the arterial pressure to normal.

The Kidney-Fluid System for Long-Term Arterial Pressure Control

The pressure control systems discussed thus far all have one limitation: none can restore normalcy entirely. Therefore, they are mainly a stopgap to keep the pressure near normal until a different pressure controller can correct the pressure entirely, namely, a system with infinite feedback gain. This is achieved under most conditions by the kidney-fluid system for pressure control (*1, 9, 10*).

The kidney-fluid system operates as follows. When the arterial pressure rises above normal, the excess pressure causes the kidneys to excrete more water and salt than are entering the body. Therefore, the blood volume decreases. This causes the heart to pump less blood, and the arterial pressure falls. Conversely, when the pressure falls below normal, the incoming fluid overbalances the excreted fluid, and the pressure rises.

The importance of the kidney-fluid system in pressure control, and especially its ability to dominate long-term control, first became clear when a mathematical model of pressure control was developed to quantitate the relative contributions of the different pressure control systems (*11*). In programming the model, we used well-established information about the ability of rising pressure to increase renal excretion of fluid in the urine (*12*) and about the effect of different levels of extracellular fluid volume and blood volume on arterial pressure (*13*).

The computer results indicated that the kidney-fluid system constitutes a pressure feedback control mechanism with the feature of infinite feedback gain (Fig. 3). The "renal function curve" shows the normal effect of different arterial pressure levels on the rate of fluid excretion by the kidneys (*1, 12, 14, 15*). Below a mean pressure of 40 to 60 mmHg normal kidneys excrete no urine at all, but above this basal level kidney excretion increases rapidly with pressure. If the rate of fluid intake ("net intake" line) is greater than the excretion, then fluid will accumulate in the body until the relative rates of intake and excretion change. Conversely, if intake is less than excretion, the opposite will occur. Therefore, over time, the intake and excretion rates must exactly equal each other, not merely be close to each other. This occurs only at the exact pressure level where the net intake line crosses the renal function curve, at the point labeled "equilibrium pressure."

The kidney-fluid system for pressure control is an "integrating" type of control system; the pressure returns toward normal in incremental integrating steps that approach zero as the target pressure is approached (*9*). However, the kidney-fluid system does not act rapidly. Even under optimal conditions, the first effects on pressure may not be visible for an hour, and usually 2 to 4 days pass before the pressure is within a millimeter of Hg of the equilibrium level. Furthermore, in special types of circulatory instability, such as during incipient heart failure, the time required may be weeks.

The derived principles of the kidney-fluid system have become the basis for many experiments in both animals and humans. Kimura and associates (*16–19*) are now systematically measuring the renal function curves in humans whose hypertension is caused by widely differing types of renal and nonrenal pathology. Their studies have fully supported the central role of the kidney-fluid system in determining the long-term arterial pressure level.

Effect of Low and High Salt Intakes on Arterial Pressure

Salt plays a special role in blood pressure regulation. Increased salt intake results in increased thirst; therefore, a proportionate amount of water is consumed to match the salt. This increases the body fluid

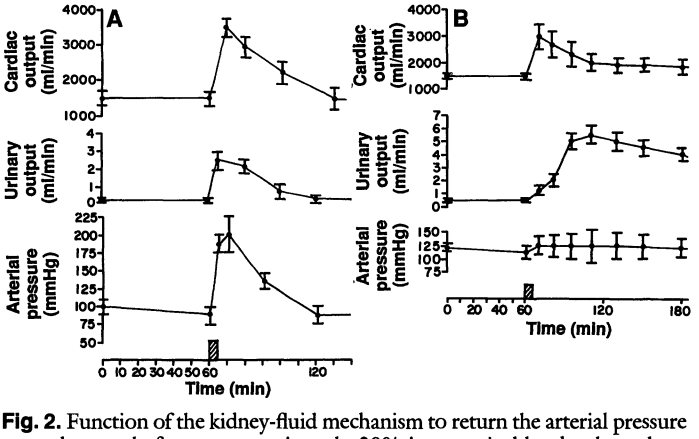

Fig. 2. Function of the kidney-fluid mechanism to return the arterial pressure toward normal after an approximately 30% increase in blood volume by a 4-min transfusion of blood (at time = 60 min; shaded box shows infusion period). (**A**) Dogs whose nervous systems had been rendered nonfunctional, and (**B**) dogs whose nervous systems were still functioning. [Adapted from (*1*) with permission, copyright 1980, W. B. Saunders and Co.]

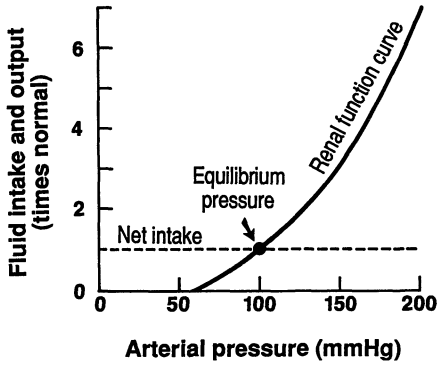

Fig. 3. Graphical analysis of the "equilibrium pressure," which is the long-term arterial pressure level that is achieved by the kidney-fluid system for pressure control after full equilibrium. [Adapted from (*1*) with permission, copyright 1980, W. B. Saunders and Co.]

volume and leads to the subsequent effects of volume on pressure. Yet, as long as both the kidney-fluid system for pressure control and the renin-angiotensin system function normally, we can eat either extremely small amounts of salt or as much as 50 times as much without a major alteration in arterial pressure. The maintenance of homeostasis is based on the intertwining actions of the kidneys, angiotensin, and salt in pressure control (*1, 20, 21*) (Fig. 4). Three groups of dogs, with different blood levels of angiotensin, were fed amounts of salt that were changed over a period of 12 days. A renal function curve was recorded for each group of dogs, expressed in terms of Na^+ output in the urine at each arterial pressure level. The high salt state caused normally functioning kidneys to stop forming angiotensin; therefore, the top of this "normal" curve shifted to the left and nearly coincided with the top of the "zero angiotensin" curve. On the other hand, the low salt state greatly increased angiotensin formation; therefore, the bottom of the "normal" curve shifted to the right and almost coincided with the bottom of the "angiotensin" curve. Thus, the leftward shift at the top and the rightward shift at the bottom caused the normal curve to become very steep, with the arterial pressure changing only 4 mmHg despite a 50-fold increase in salt output. However, when this system falters, as it does in people with kidney disease, salt intake almost always must be limited to prevent serious hypertension.

Small Increases in Body Fluid Volume Causing Large Long-Term Pressure Increases

Until recently, most scientists who are doing research on high blood pressure believed that increased fluid volume was rarely an important cause of hypertension. The reasons for this belief were twofold. First, infusion of very large amounts of extra fluid into the blood will usually increase the arterial pressure by only a few millimeters of Hg during the first few minutes to several hours. Second, the measured increases in fluid volume in most patients with high blood pressure are small, if measurable at all—most often a maximum increase of less than 3 to 5%. How is it possible to reconcile these findings with the research that has implicated fluid volume as a primary factor in determining the long-term arterial pressure level?

One reason for the very slight increase in pressure during the first minutes after an infusion of large amounts of fluid is the almost instantaneous action of the nervous system pressure controllers to prevent significant short-term pressure increase. Figure 2 shows that a given blood volume transfusion caused only one eighth the short-term increase in pressure when the nervous system controls were functioning as when they were not operating. Yet, numerous studies have also shown that almost all of the nervous system feedback signals that block the short-term pressure increase stop working in 1 to 2 days (*22–24*); that is, they "adapt." This adaptation alone could allow an eightfold increase in long-term arterial pressure after increasing the body fluid.

A second physiological effect also increases the pressure rise caused by a small volume increase—a mechanism called "autoregulation of blood flow." In autoregulation, the small blood vessels in most parts of the body automatically constrict when too much O_2 and other nutrients are carried to the tissues or too much CO_2 and other metabolic products are carried away (*1, 25–27*). Therefore, when the blood volume rises and drives the heart to pump excess blood, this autoregulation mechanism constricts most of the small arterioles throughout the body. The constriction in turn causes the pressure to rise as much as an additional five times because of increased resistance to blood flow. Therefore, this fivefold increase combined with the eightfold initial effect after adaptation to nervous system controls mean that one fortieth of the volume needed to cause a short-term increase in pressure will cause a comparable long-term pressure increase.

Graphical Analysis of Abnormal Pressure States

The quantitative values for renal function curves are markedly different in different disease states, which can cause abnormal arterial pressures (and often hypertension). Figure 5 illustrates six renal function curves for physiological and pathological states of the kidneys (*1*). The mean pressure level to which a normal person's blood pressure will be regulated is 100 mmHg (point A). By contrast, when the renal mass is decreased (which often occurs after disease or injury has destroyed much of the two kidneys), the regulated pressure during normal fluid intake might be only slightly above normal (point G). Yet, at high intake, the pressure is very hypertensive (point H) (*28, 29*).

An excess of either aldosterone or angiotensin, as a result of secretion by tumors (*30, 31*) or excess hormone administration, shifts the curve rightward; increased blood pressure is then required to excrete normal amounts of urine, and hypertension results. Abnormalities of the kidneys' blood vessels can do the same; these occur in (i) patients with Goldblatt's disease, in which the major renal arteries are constricted, (ii) spontaneously hypertensive rats (SHR), in which the kidney microvessels are constricted because of defective genes, and (iii) individuals with reduced glomerular filtration coefficients, which means that filtration of fluid from the blood

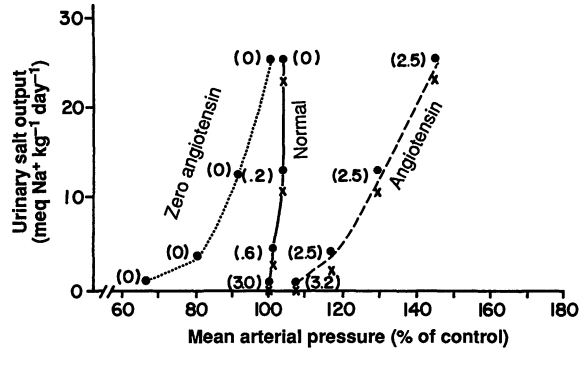

Fig. 4. Renal function curves for dogs under three different conditions. "Zero angiotensin" curve data were taken from a dog to which the drug captopril (SQ 14,225) was given to block angiotensin formation; "normal" curve data from normal dog; "angiotensin" curve data from dog to which angiotensin was infused. The values in parentheses are the calculated relative blood concentrations of angiotensin, with the value 1 considered normal. [Adapted from (*1*) with permission, copyright 1980, W. B. Saunders and Co.]

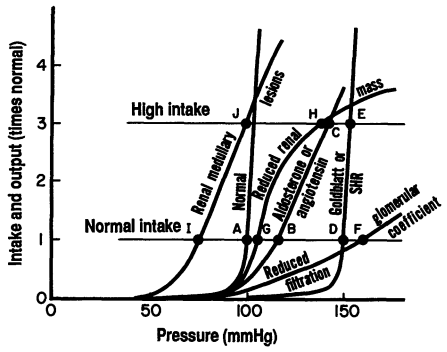

Fig. 5. A pressure-analysis diagram predicting the long-term arterial pressure levels in different types of renal abnormalities; four of these cause hypertension and one causes hypotension. [Adapted from (*1*) with permission, copyright 1980, W. B. Saunders and Co.]

into the urine-forming kidney tubules is partly blocked. At point I in Fig. 5, on the curve that represents patients with lesions in the midkidney medullary area, the analysis predicts hypotension (low blood pressure) instead of hypertension. These lesions reduce the ability of the renal tubules to reabsorb water and salt into the blood, thus causing excess loss into the urine of both salt and water.

Unsolved Problems in Pressure Control

Although quantitative analyses of arterial pressure control have helped explain the basic relationships among the rapid, intermediate, and long-term control systems, so many different factors affect arterial pressure that the quantitative interrelations must still be clarified. Two areas of research are currently especially important. One of these is the development of new drugs for treating hypertension, a disease that affects 20% of the population at some time during life. Attention should be focused on drugs that change kidney-fluid system function. A recent example is the development of converting enzyme inhibitors (*32*), drugs that block the activation of angiotensin. These drugs allow the kidneys to excrete greatly increased amounts of salt and water, which shifts the renal function curve in the hypotensive direction.

An area for future research is the attempt to understand the importance of the neural control of pressure. Many prominent researchers believe that much, if not most, hypertension in human beings is initiated by nervous stress. But how can stress cause hypertension? One way would be for the nervous system to alter kidney function (*33*). When the brain's blood flow becomes too low because of too little blood pressure or because of blocked blood vessels, the CNS ischemic response is activated and causes powerful sympathetic nerve signals to be sent to the kidneys. This sometimes shifts the renal function curve within seconds to pressure levels as high as 100 mmHg above normal. If the brain could maintain such stimulation indefinitely, the neurogenically stimulated kidney-fluid system would also establish a new long-term pressure 100 mmHg above normal. Ordinarily, however, the nervous stimulation wanes in the ensuing minutes and hours, and the target level for pressure regulation diminishes as well. Therefore, the question of how high the pressure can be maintained during indefinite periods of nervous stress is still a subject of intensive research (*34*).

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