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Personal and Historical Perspectives

The Surprising Kidney-Fluid Mechanism for Pressure Control—Its Infinite Gain!

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In this short paper, I have tried to explain the elation that we felt when we first realized that the kidney-fluid mechanism for controlling the arterial pressure has an infinite feedback gain property. Because of this, all the other pressure control mechanisms, none of which has ever been shown to have a similar infinite gain property, must themselves alter the kidney-fluid mechanism if they are to succeed in causing long-term changes in the arterial pressure. We have not been able to refute this principle despite many experiments over the last 2 decades. For this reason, our first understanding of the infinite gain property of the kidney-fluid mechanism was like a light at the end of the tunnel. I hope that I can explain to the reader the excitement of those few seconds when we first recognized the principle in 1966. (*Hypertension* 1990;16:725–730)

I, like virtually everyone else in the field of hypertension, fully accept Page's mosaic theory of multiple causes of hypertension.[1] Nevertheless, an event occurred in 1966 that like a flash of lightening, caused my colleagues and myself to focus our attention on the extreme importance of a single characteristic of one of the pressure control mechanisms. This was the infinite feedback gain property of the kidney-fluid mechanism for pressure control.

I hope to explain several points: First, what do we mean by the kidney-fluid mechanism for pressure control? Second, what is the infinite gain property of this mechanism? Third, why is this infinite gain so important—why does it cause the kidney-fluid mechanism to become a common focal point through which most of the other pressure controlling mechanisms operate? Fourth, why has this influenced so much of the focus of our own hypertension research since that day in 1966?

A Simple Computer Model of Pressure Control—An Unexpected Revelation

Before 1966, computer models of arterial pressure control, including our own, had been more for the purpose of displaying what we already knew than for discovering new principles. However, in 1966, while exploring the relation between body fluid control and arterial pressure control, we had a surprise that changed the whole direction of our experiments on hypertension.

Dr. Thomas Coleman, who had recently come to work with me in hypertension studies, had exceptional capability in the use of computers in science; this matched beautifully my own interest in computer models of physiological systems. I had designed a model emphasizing those mathematical equations that I personally believed to be most important in arterial pressure control, and Dr. Coleman programmed this on the computer.[2] We agreed that he would exercise the model in multiple different ways to see how various factors might affect the long-term level of arterial pressure. One exercise was to demonstrate the effect of increased total peripheral resistance to cause chronic hypertension. This was meant to be nothing more than a simple exercise of what we already knew because without doubt everyone already understood that increased total peripheral resistance did indeed cause chronic hypertension.

However, when Dr. Coleman brought me the results of the computer simulation he simply stated, "The patient developed hypertension all right, but the pressure came back to normal after a few days." This quickly proved to be a sudden "light at the end of a tunnel," which is actually the topic of this paper.

Very often it is far more rewarding when a computer model fails to support preconceived notions than when it does. Why had we not understood in advance that hypertension caused by an increase in total peripheral resistance might not be sustained? Why did it require the computer to tell this to us? Or was this just another instance in which some crazy fools had made a mathematical simulation that was nowhere near reality?

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Yet, this simple computer experiment explained like a flash of light why investigators had found that total peripheral resistance varied as much as fourfold between different cardiovascular abnormalities but still with normal long-term arterial pressures. For instance, the total peripheral resistance is often decreased to as little as one half normal in beriberi patients and in patients with arteriovenous fistulas and almost as much so in patients with hyperthyroidism, anemia, pulmonary disease, or Paget's disease.[3] Yet, in all of these, the arterial pressure is usually normal or near to normal. At the other extreme, the total peripheral resistance is often doubled in hypothyroidism with no increase at all in the arterial pressure.[3] Also, in persons who have lost all four limbs, the total peripheral resistance calculates to be increased 30% or more but with no increase in pressure. These facts are exactly what the computer model told us—that long-term changes in total peripheral resistance do not have an invariable effect in changing long-term arterial pressure. Therefore, why was it a known "fact" by virtually all researchers in hypertension that the "cause" of hypertension was increased total peripheral resistance? Was it possible that the increased resistance was an associated phenomenon but not necessarily the cause?

Explanation of Infinite Feedback Gain Property of Kidney-Fluid Mechanism

One of the important components of any computer model of the circulation is the very strong effect that high arterial pressure has on an increase in kidney output of fluid and electrolytes: As a result, when the pressure rises above a critical level, loss of extracellular fluid from the body becomes greater than fluid intake, and this decreases both blood volume and cardiac output, returning the pressure back toward normal. Conversely, when the arterial pressure falls below this same critical level, the kidneys excrete less fluid, and the blood volume and cardiac output increase because of continued intake of fluid and electrolytes; therefore, the pressure increases back toward normal again.

Without going into the actual computer equations, the logical explanation for the infinite gain of this kidney-fluid mechanism in pressure control is illustrated in Figure 1. The solid curve in this figure shows the approximate average effect of different levels of arterial pressure on urinary output of salt and water by the normal kidney.[4–6] In addition, the dashed line denotes the normal intake of salt and water that must be eliminated through the kidneys (not counting the small amounts of salt and water that are eliminated by other means). Obviously, over any extended period of time the intake and output must exactly equal each other, for an intake that remains forever greater than output will swell the person indefinitely until he or she dies of dropsy. Conversely, an indefinite output greater than intake will cause fluid loss until dehydration causes death. In Figure 1, the "equilibrium point" between intake and output occurs exactly where the renal function curve crosses the intake line.

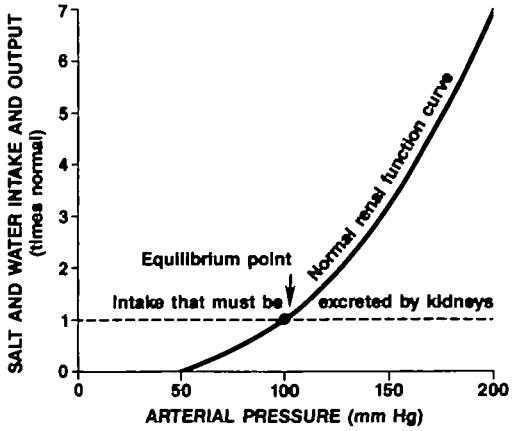

FIGURE 1. *Equilibration of the normal renal function curve with the salt and water intake. Point labeled "equilibrium point," where the curve crosses the line, gives pressure level at which kidney-fluid mechanism will control arterial pressure. Modified from Reference 3.*

This same mechanism that balances intake and output of fluid also provides a very exact method for arterial pressure control.[7] That is, if the arterial pressure rises to even a single millimeter of mercury greater than the pressure level of the equilibrium point, Figure 1 shows that the urinary output will become greater than the intake. This means that the person will lose fluid from his or her body until the pressure falls back to the exact pressure level of the equilibrium point. Conversely, if the arterial pressure falls slightly below that of the equilibrium point, the output of fluid becomes less than the intake. This will increase the body fluid volumes, including the blood volume, and will eventually raise the pressure back to the equilibrium point. Thus, it is only at the equilibrium point, and exactly at this point, that the pressure will stabilize.

It is this fact, that the pressure must always return exactly and precisely to the equilibrium point, that makes us realize that this feedback mechanism for arterial pressure control has infinite feedback gain. To state this still another way, this mechanism has infinite capability always to return the pressure precisely to the exact level where the renal function curve crosses the intake line. Furthermore, because of this infinite capability, none of the other pressure-controlling mechanisms has any possibility of controlling the arterial pressure level for long periods of time without at the same time altering the kidney-fluid mechanism. This can be done in only two ways: 1) by causing the renal function curve in Figure 1 to shift to the right or left along the arterial pressure axis, or 2) by causing an increase or decrease in the intake level of salt and water.

Which Changes in Circulatory Function Can Increase the Long-term Arterial Pressure Level, and Which Cannot?

Using the above principles, we can separate those changes in circulatory function that can cause long-

term elevated pressure from those that cannot. Those that cause long-term elevated pressure must affect one of the above two factors: either the renal function curve or the level of salt and water intake. On the other hand, those factors that fail to change one of the above two factors will not change the long-term arterial pressure level.

Let us analyze several specific circulatory changes:

First, why does a change in total peripheral resistance not necessarily change the long-term arterial pressure level? To answer this question, let us ask, does increased total peripheral resistance change the renal function curve of Figure 1? Or does it change the intake of salt and water? The answer is: a change in the total peripheral resistance by itself, if it is not associated with altered internal resistance in the kidneys, does not have any effect in changing the renal function curve. Also, a change in total peripheral resistance has no direct effect in altering the intake of salt and water. Therefore, even though an increase in total peripheral resistance does indeed elevate the arterial pressure acutely, the increased pressure in turn causes renal loss of fluid from the body until the pressure decreases back to the equilibrium point. This explains the results that Dr. Coleman and I saw when we first ran our simulation on the computer (i.e., that increased total peripheral resistance by itself was not able to increase the long-term arterial pressure level).

Second, an increase in the pumping capability by the heart will also cause an acute increase in arterial pressure; but again, this does not change either the renal function curve or the intake of salt and water. Therefore, over several hours to several days, the pressure returns to normal. Thus, the long-term effect on arterial pressure of increased pumping capability by the heart is a decrease in blood volume that reduces the cardiac output exactly as much as it had been increased by the increased cardiac pumping—therefore, no effect on the long-term pressure level. This also explains why operations on the heart to correct depressed heart pumping capability usually have no long-term effect on the arterial pressure.

Third, a change in the capacitance of the circulatory system, which alters the immediate return of blood to the heart and therefore alters the arterial pressure acutely, nevertheless has no effect on the renal function curve or the intake of salt and water. Therefore, this also has no long-term effect on arterial pressure. This is demonstrated especially in patients with extreme varicose veins, which cause very abnormal circulatory capacitance but no long-term abnormality of arterial pressure.[3]

Thus, three separate changes in the circulatory system that have very acute pronounced effects on the arterial pressure—changes in total peripheral resistance, pumping capability of the heart, or vascular capacitance—all become completely compensated by the infinite feedback gain mechanism of the kidney-fluid system for controlling the pressure.

Yet, many other factors can change the renal function curve, or can change the intake level of salt and water, the two primary control elements of the kidney-fluid mechanism of pressure control. Some of these include angiotensin, vasopressin, aldosterone, changed afferent and efferent arteriolar resistance in the kidneys, altered degree of constriction of the major arteries to the kidneys, abnormal reabsorption of fluid by the kidney tubules, multiple effects of nervous stimulation on renal excretion or fluid and electrolyte intake, and many others.[3] All of these can affect the long-term level of arterial pressure; but note that they do so by changing the equilibrium point of the kidney-fluid mechanism of pressure control. In fact, in over 20 years of studying this problem, we have not found any factor to affect the long-term pressure level without altering either the renal function curve or the level of salt and water intake.

In other words, the infinite gain property of the kidney-fluid mechanism for pressure control is so dominating that it will not allow a factor from outside this mechanism to alter the blood pressure permanently unless the kidney-fluid mechanism is itself altered at the same time. The value of this concept is that it focuses attention on analyzing the different ways in which the kidney-fluid mechanism itself functions in the different types of hypertension and even in daily control of pressure. As examples, let us discuss briefly two of these analyses: the normal day-to-day role that angiotensin plays in pressure control and a possible explanation for the high total peripheral resistance that occurs in 95% or more of all patients with hypertension.

Function of the Renin-Angiotensin System in Daily Pressure Control

One of the most powerful depressants of renal secretion of renin and subsequent formation of angiotensin in the blood is a high intake of salt. In turn, the decreasing blood level of angiotensin has its own powerful effect to shift the renal function curve to the left, as illustrated by the shift in Figure 2 from the right-hand curve to the left-hand curve, that is, toward lower arterial pressure levels.[8,9] By putting these two bits of information together, we can see a very valuable everyday function for the renin-angiotensin system in pressure control.

In Figure 2, the curve labeled "normal angiotensin" is a normal renal function curve, similar to the normal curve in Figure 1, and the lower dashed line labeled "low salt intake" represents the normal low level of salt intake. Note that the curve crosses the line at equilibrium point A, showing the normal mean arterial pressure stabilizes at 100 mm Hg. Now, let us see what happens if the salt intake is increased to the "high salt intake" level illustrated by the upper dashed line in Figure 2. If the renal function curve should not change, the new equilibrium point would be at point B where the normal renal function curve crosses the high salt intake level; therefore, the

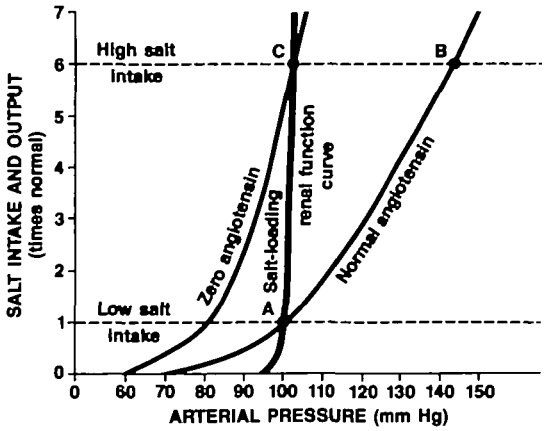

FIGURE 2. *Analysis of normal role of renin-angiotensin system in controlling arterial pressure. Normal renal-function curve is labeled "normal angiotensin," and normal arterial pressure is a point A where this curve crosses normal low salt intake level. At a high salt intake level, renal function curve shifts to curve labeled "zero angiotensin," and this equilibrates with high salt intake at point C, depicting a pressure increase above normal of only 2 mm Hg. Therefore, increasing the salt intake has very little effect on arterial pressure level in the normal person because high salt intake decreases or even turns off angiotensin formation; this in turn shifts the renal function curve to a lower pressure. Modified from Reference 3.*

pressure would stabilize at 145 mm Hg. However, this is not what actually happens because the high salt intake turns off the formation of angiotensin. In turn, the decrease of angiotensin to zero shifts the renal function curve from the normal curve of Figure 2 in the leftward direction to the curve labeled "zero angiotensin." This new renal function curve crosses the high intake level at equilibrium point C. Thus, point C represents the actual level to which the arterial pressure becomes stabilized, at a level of 102 mm Hg, not 145 mm Hg. Note that this is an increase of only 2 mm Hg above the normal pressure of 100 mm Hg at point A.

Thus, it can be seen that the renin-angiotensin system keeps the arterial pressure almost exactly normal even at times of tremendous changes in salt intake; it does so because of the very important changes in renal excretion of salt and water when the angiotensin level changes. In fact, in a study performed by Murray and his colleagues[10] in normotensive humans, a 150-fold increase in salt intake, from 10 to 1,500 meq/day, was shown to increase the arterial pressure only 10–20 mm Hg.

Finally, let us draw a new curve through points A and C, the very dark curve in Figure 2. This curve is called the "salt-loading renal function curve" because it depicts the normal changes in arterial pressure and renal output at different levels of salt loading. The extreme steepness of this salt-loading curve is mainly a function of the renin-angiotensin mechanism; furthermore, the steepness is very important to human life because it prevents the vast changes in daily salt intake experienced by individual humans from causing severe daily changes in arterial pressure as well.

Why Is Total Peripheral Resistance Increased in Almost All Persons Who Have Hypertension?

Now we come to the question that immediately pops into the mind of every hypertension researcher whenever anyone mentions fluid retention as the principal cause of hypertension. That is, if fluid is so important, why is it that what is actually found in most persons with hypertension is greatly increased total peripheral resistance but little increase in body fluid? In former times, the answer to this question was very simple: high total peripheral resistance itself was the cause of the hypertension. With the new mathematical modeling, and multiple animal experiments that have supported this modeling, the answer is no longer so simple. In fact, there are probably two major answers: One is that when the total peripheral resistance increases, whatever its cause, in many if not most instances there is a simultaneous increase in resistance in the blood vessels of the kidneys. The increased total peripheral resistance causes an instantaneous rise in pressure, and at the same time the increase in renal resistance shifts the renal function curve to a hypertensive level. Were it not for this shift, the kidney-fluid mechanism would rapidly return the pressure back to normal despite the increased total peripheral resistance. Actually, in fully established essential hypertension, the renal vascular resistance is usually increased several times as much as the vascular resistances elsewhere in the body.[11] Therefore, it is virtually certain that it is the shift of the kidney-fluid mechanism to the hypertensive level, not the increase in total peripheral resistance, that causes the hypertension to persist longer than a few days.

A second way in which high total peripheral resistance could occur in hypertension would be for the resistance to increase secondarily to the hypertension, occurring after the hypertension has already developed. To give an experimental example of this, Figure 3 presents the approximate combined results of multiple experiments on "volume-loading" hypertension in dogs.[3,12–15] In these experiments, about 70% of the kidney mass was removed several weeks earlier. Then, at day zero in the figure, the intake of salt and water was increased fivefold to sixfold. This resulted in pronounced hypertension within a few days. Note also that both the extracellular fluid volume and blood volume increased markedly during the first day or two. In turn, the increased blood volume caused the cardiac output and arterial pressure to increase as well, but without an initial increase in the total peripheral resistance, which occurred several days later. Thus, the hypertension occurred because of increased cardiac output, and it occurred before the increase in total peripheral resistance. Then, after 3–4 days, the total peripheral resistance began to rise above normal while the fluid

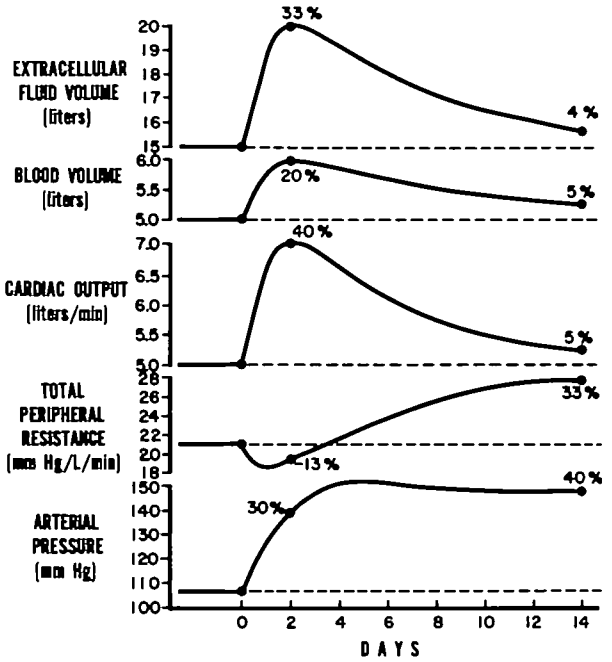

FIGURE 3. *Approximate changes in several circulatory variables during onset of volume-loading hypertension. Note large increases in extracellular fluid volume, blood volume, and cardiac output at onset of hypertension but a delayed rise in total peripheral resistance; this illustrates a secondary increase in total peripheral resistance during development of volume-loading hypertension. Modified from Reference 3.*

volumes and cardiac output returned near to normal—in fact, so near to normal that their final elevations a week or so later were not statistically significant. Therefore, the increase in total peripheral resistance occurred in these animals after the hypertension had developed, not as a primary nor even concurrent event.

There has been much discussion about the cause of this secondary elevation of the total peripheral resistance in volume-loading hypertension. The only explanation that fits all the observations seems to be the phenomenon of "whole body blood flow autoregulation." This is supported by a multitude of studies on blood flow autoregulation in different tissues of the body and even in the whole body. That is, blood flow in excess of the metabolic needs through virtually any tissue causes a secondary local arteriolar vasoconstriction that returns the blood flow back toward normal. In long-term experiments, the vasoconstriction is followed later by actual structural decrease in the arteriolar internal diameters, as demonstrated in individual limbs by Folkow and his colleagues.[16,17] Thus, the necessary event in causing the high total peripheral resistance in volume-loading hypertension seems to be the initial increase in cardiac output that also causes the hypertension. The increased cardiac output at first increases the blood flow through all or most of the tissues, but this sets off the autoregulation phenomenon, thus decreasing the local blood flows throughout the body (and also cardiac output) back to or near to normal, while substituting high total peripheral resistance instead.

Reactions to These Concepts

Now let me speak for a few moments about the reactions of others—and also of myself—to these ideas, especially to the dominating importance of the kidney-fluid mechanism for long-term control of arterial pressure.

First, what was my own personal reaction in 1966 when the infinite gain feature of the kidney-fluid mechanism initially flashed into my mind? The answer is very simple: Although I was well aware of the importance of fluids in the control of arterial pressure, I like most others, had equated fluids with multiple other factors I considered equally important. Then, out of the blue, the computer model told me that the kidney-fluid mechanism would, with time, totally and completely and unequivocally override many other pressure-controlling factors that most of us had considered to be already well proved. For a few seconds there was total disbelief. But after looking quickly at the mathematics of the computer program and recognizing the integrating nature of pressure control by the fluid balance system, it became clear that an infinite gain principle was involved. It was this that dispelled further disbelief. Then there was almost ecstatic euphoria, for with a little more thought, many other cloudy aspects of circulatory control began to clear as well. My next reaction was to think how stupid I had been not to have seen this same principle without the use of a computer. For how simple can a principle be? It is elemental that if the arterial pressure is too low for the kidneys to eliminate all the fluid entering the body, then fluid will accumulate until the pressure does rise high enough; but the pressure will not rise any higher because at higher pressures more output than intake would then occur, and the pressure would fall again to that same exact level required for fluid balance. How much simpler could a principle be?

The most common reaction of others has been one of amusement—amusement because all of us already know that fluids play at least some role in pressure regulation; so, what are we getting excited about? But amusement occurs too because it is almost axiomatic in biology that nothing is absolute. There could not possibly be a biological regulatory system that has infinite feedback gain. This is not the nature of biology. In fact, one of my most valued friends in physiology told me almost exactly this while speaking before an international symposium of hypertension scholars. Yet, strangely enough, I did not then and do not now take offense, for this has been the usual first reaction. Only later does it begin to sink in that the kidney-fluid mechanism does not compromise; it will not be satisfied until the pressure reaches the exact level required for exact balance between fluid intake and fluid output. I think that I can safely say that my friend not too long afterward did begin to understand the extraordinary importance of this principle—at

least, the emphasis of recent experiments from his laboratory suggest this!

Sometimes, others have told me of their own sudden feeling of elation, much the same as I had felt, when they first and instantly understood the infinite gain principle and its importance. Perhaps this is best expressed in a letter that I received only last month from a professor of molecular physiology and biophysics in one of our leading medical schools: "The moment I understood the relation was a high point in my life as a scholar. I remember the time and place the way many remember when and where they first heard of Kennedy's assassination. That principle is foundational to the understanding of circulatory physiology," and he went on to describe other important concepts of circulatory function, especially relating to myocardial decompensation, that had followed in his own mind.

Therefore, please choose your own reaction—amusement or elation—but, hopefully, do understand thoroughly the widespread implications of the principle before making a choice.

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