Renal Function Curve — A Key to Understanding the Pathogenesis of Hypertension

In this issue of Hypertension is an article by Kimura and his colleagues1 entitled “Renal Function Curve in Patients with Secondary Forms of Hypertension.” When I was asked to write a comment on this article, I first thought that it might not be useful because the article itself is quite clear. Yet, for very subtle reasons, considerable confusion does remain about the importance and utility of renal function curves in understanding the pathophysiology of hypertension. This is true partly because there are several different types of renal function curves, and each has a slightly different significance, as I shall explain.

Historically, my own interest in renal function curves as a tool for understanding hypertensive mechanisms dates back to the mid-1960s, when Dr. Thomas Coleman and I were first developing computer models of arterial pressure regulation and hypertensive mechanisms. At one step in a model we used a renal function curve that depicted the effect of arterial pressure on urinary output. In running the model, we were quite surprised to see that so long as the renal function curve remained immutable and the rate of salt and water intake also remained constant changing any other variable in the model did not change the predicted level to which the arterial pressure was regulated.2 Among the changes that did not alter the predicted pressure level were 1) changes in heart strength, 2) changes in total peripheral resistance, and 3) changes in vascular compliance. The reader will recognize these hemodynamic variables as the ones most often invoked in various explanations of hypertension. Therefore, at first, we were greatly surprised to see the predictions. Yet, within seconds, we were able to trace through the model and understand exactly why the final predicted level of arterial pressure was always the same so long as the renal function curve and the rate of intake remained constant. Let me first discuss this result of the computer model; then I will attempt to explain its applicability both to the article by Kimura et al.1 and to the general principles of arterial pressure regulation and hypertension.

The essence of the computer model that Dr. Coleman and I used for understanding arterial pressure regulation as well as many types of hypertension is summarized in the simple diagram shown in Figure 1. This figure illustrates one type of renal function curve, the type that plots the urinary sodium output at progressively increasing mean arterial pressure levels. The plotted curve intersects a line that represents the rate of net sodium intake (intake minus nonrenal losses), and the point of intersection, called the “equilibrium point,” represents the point at which the sodium intake and output are in balance. In this example, the balance point occurs at a mean arterial pressure of 96 mm Hg. If the renal function curve and the intake line both remain immutable, then it is intuitively clear that there is only one arterial pressure level at which sodium intake and sodium output can remain in balance. This is at the unique mean arterial pressure of 96
mm Hg. If the pressure rises above this level, the output becomes greater than the intake, and the person (or animal) will have a negative sodium balance indefinitely until, after sufficient depletion of sodium (and of water that goes with the sodium), the pressure falls back to and stabilizes at 96 mm Hg. Conversely, if the arterial pressure falls below 96 mm Hg, then the intake of sodium is greater than the output. This gives a positive sodium balance, with increasing body fluid volumes, until either the pressure rises to 96 mm Hg or the person swells so greatly that he or she dies of edema. Thus, very simply, if the renal function curve and the line depicting sodium intake do not change, the arterial pressure will always eventually return to exactly the same level.

Yet, we all know that the renal function curve and sodium intake do change; either or both of them can change markedly. Correspondingly, the level at which the arterial pressure will eventually be regulated will also change as either the curve or the line depicting sodium intake changes. For instance, in the article by Kimura et al., the patients with renovascular disease had function curves that were shifted to the right almost parallel to the normal curve. In the patients with primary aldosteronism, the renal function curves were also shifted to the right, but the slope of the curves was decreased as well. In both instances, the renal function curves crossed the line representing normal sodium intake at pressure levels far above normal, thus representing the hypertensive states of renovascular hypertension and primary aldosteronism.

**Alteration of the Renal Function Curve**

The different factors that are known to alter the renal function curve (and thereby to alter the long-term level at which the arterial pressure is regulated) can be divided into 1) intrinsic changes that occur within the kidneys themselves and 2) extrinsic changes that occur outside the kidneys but that either directly or indirectly affect the kidneys' ability to excrete sodium. Some of the intrinsic renal changes that can lead to altered renal function curves are

1. Constriction of the renal arteries
2. Constriction of the afferent arterioles
3. Constriction of the efferent arterioles
4. Changes in the glomerular membrane filtration coefficient
5. Changes in tubular reabsorption
6. Reduced kidney mass

Extrinsic factors that can alter the renal function curve (and also alter the long-term level to which the arterial pressure is regulated) include

1. Changing levels of renin-angiotensin activation
2. Changing levels of aldosterone
3. Changing levels of vasopressin
4. Changing levels of nervous stimulation of the kidneys
5. Perhaps changing levels of atrial natriuretic factor
6. Changing levels of electrolytes and perhaps other constituents in the body fluids.

Most of these factors shift the renal function curve in Figure 1 to the right and thereby increase the arterial pressure, but this is not invariably true. The roles of most of these factors in shifting the curve and in arterial pressure regulation have been reviewed previously.

Contrary to the beliefs of many in the field of hypertension research, the fact that the renal function curve plays a major role in arterial pressure regulation is not in conflict with the known high degree of correlation between total peripheral resistance and arterial pressure in persons with hypertension. For instance, a generalized increase in total peripheral resistance not only has the direct and immediate effect of increasing arterial pressure, which is a well-known hemodynamic fact, but almost always the arteries and arterioles of the kidneys are constricted as well, shifting the renal function curve to the right. This rightward shift is essential if the hypertension is to be sustained, for without this shift the high arterial pressure would cause a tremendous natriuresis, resulting in the return of the pressure to normal after a few hours or days.

One must also remember that in a large variety of clinical conditions the total peripheral resistance is far from normal, either abnormally high or abnormally low, while arterial pressure is absolutely normal. For instance, the marked increase in total peripheral resistance that occurs in hypothyroidism is not normally associated with hypertension; at the other extreme, the great decreases in total peripheral resistance
caused by arteriovenous fistulas or by hyperthyroidism are virtually never associated with hypotension. If one examines each of these conditions carefully, one finds that the excretory function of the kidney is not affected significantly and the renal function curve is not altered. Therefore, the concept that the renal function curve is very important in determining the long-term level of arterial pressure, irrespective of changes in the total peripheral resistance, can readily explain the normal arterial pressures in these different conditions, even though the total peripheral resistance may change as much as 100 to 300% between one condition and the other.

Three other types of evidence have also emerged in the past few years that strongly support the importance of the kidneys (and the renal function curve) in determining the arterial pressure both in normotension and in hypertension. First, when kidneys were transplanted from hypertensive animals to normotensive animals, the hypertension “followed” the kidneys. Similarly, when kidneys were transplanted from normotensive animals to hypertensive animals, the normotension again “followed” the kidneys. Also important are studies by Curtis et al. in which normal kidneys were transplanted into six essential hypertensive patients in whom end-stage hypertensive renal disease had occurred; in each instance the arterial pressure reverted to normal. Evidence of this type has given increasing credence to the concept that the function of the kidney (as expressed by the renal function curve) is a key factor in all or virtually all types of long-term arterial pressure regulation.

Second, multiple studies have been conducted in which the renal arterial pressure was maintained at an exactly normal level regardless of what happened to the systemic arterial pressure. An early study of this phenomenon used a computer model of the circulatory system in which the renal arterial pressure was fixed at 100 mm Hg regardless of any change in systemic arterial pressure. The model predicted that any extraneous factor that normally might increase or decrease the systemic arterial pressure only a slight amount, such as a high or low salt intake, would now make the arterial pressure drift incessantly either far above or far below normal, without any long-term stabilizing control. More recently, this principle has been tested very rigorously in animal experiments by Dr. John Hall et al. They used a servocontrol system that automatically impeded arterial blood flow to the kidneys whenever the renal arterial pressure tried to rise above normal. While maintaining the renal pressure at its normal control value, Hall et al. continuously infused various hormones: aldosterone, angiotensin, or vasopressin. Each of these caused salt and water retention. However, because the renal arterial pressure did not rise when the systemic arterial pressure rose, the kidneys did not respond with increased salt and water output. Therefore, the animals remained indefinitely in positive salt and water balance until very severe hypertension developed along with edema and signs of congestive heart failure. Then, Hall et al. removed the servocontroller and allowed the renal arterial pressure to rise to equal the systemic arterial pressure; the kidneys immediately began to natriurese and diurese, bringing the arterial pressure back down to a stabilized level, a level that was determined by the degree of shift that the respective hormone had caused in the renal function curve (i.e., to a level about 25–30 mm Hg above normal in the case of aldosterone, about 35–40 mm Hg for angiotensin, and about 15–20 mm Hg for vasopressin).

A third type of evidence that has made the renal function curve concept of long-term pressure regulation more believable is that multiple studies in animals have shown the renal function curve to be shifted to the right in every type of hypertension studied thus far—hypertension in spontaneously hypertensive rats, Goldblatt hypertension, hypertension caused by aldosterone infusion, hypertension caused by angiotensin II infusion, and hypertension caused by volume loading.

In the past, only anecdotal studies have suggested a rightward shift of the renal function curve in humans with different types of hypertension. However, Kimura et al., in their article in this issue of Hypertension, have performed a prospective, intentional study to demonstrate this rightward shift in two important clinical types of hypertension, which makes this a landmark study.

The Salt-Loading Renal Function Curve
I alluded earlier to the fact that there are several different types of renal function curves. The renal function curves measured in the study by Kimura et al. are not of the same type as the function curve depicted in Figure 1. The curve of Figure 1 was
FIGURE 1. Typical renal function curve showing the effect of arterial pressure on urinary sodium output as recorded from an isolated kidney. The equilibrium point defines a unique pressure level at which the arterial pressure will be regulated regardless of other circulatory changes if the function curve and the sodium intake remain constant.

constructed from measurements in isolated, perfused dog kidneys. To record this type of curve, the renal perfusion pressure was raised through a range of pressures and the effect of the changing pressure on renal sodium output was measured. Obviously, recording a renal function curve in this way would not be possible in humans.

The type of renal function curve depicted in the study by Kimura et al. has been called the "chronic renal function curve" or the "salt-loading renal function curve." It is measured not by changing the mean arterial pressure directly but by changing it indirectly in the following way: A human (or an animal) is subjected for several days at a time to successively different levels of salt intake. After salt balance has been achieved at each salt intake level and the various circulatory functional variables have come to steady state, the arterial pressure is recorded. Because salt balance has been achieved, the sodium output is quantitatively equal to the intake. Therefore, a resulting curve can be plotted with mean arterial pressure on the abscissa and the sodium output (even though only intake is measured) on the ordinate, in the same manner that the isolated perfused kidney renal function curve of Figure 1 is plotted. Figure 2 illustrates (by the long-dashed curve) the approximate salt-loading renal function curve in both the normal dog and the normal human.

What are the differences between the isolated kidney renal function curve and the salt-loading renal function curve? Figure 2 illustrates these differences, with the isolated kidney curve illustrated as the solid curve and the salt-loading curve as the long-dashed curve. Note especially the extreme steepness of the salt-loading curve in contrast to the much gentler slope of the curve for the isolated kidney. Note also that the salt-loading renal function curve and the isolated kidney renal function curve still cross the normal sodium intake level at exactly the same point. The fact that both curves cross the intake level at exactly the same point allows one to use either the isolated kidney function curve or the salt-loading curve to predict the level at which the arterial pressure will stabilize.

Why is the salt-loading renal function curve different from the isolated kidney curve? In recording the isolated kidney curve, only arterial pressure alone is changed during the measurement process. In contrast, in measuring the salt-loading renal function curve, increasing the salt intake not only causes the arterial pressure to rise but simultaneously changes several other factors that also affect renal function. Especially important, the levels of circulating angiotensin II and aldosterone in the blood change. Thus, the salt-loading renal function curve depicts the relationship of mean arterial pressure to sodium output, while taking into consideration not only the direct effect of arterial pressure but also the simultaneous effects of several other renal control variables.
Referring again to Figure 2, note the dotted and the dashed renal function curves. The dotted curve is labeled “low sodium,” and the dashed curve is labeled “high sodium.” These curves have been constructed from data recorded in several different laboratories. At low sodium intake, the level of angiotensin II is greatly increased, and experiments have shown that angiotensin II has a direct effect on the kidneys to shift the renal function curve to the right. Conversely, increasing the salt intake diminishes the level of angiotensin II in the circulating blood, which shifts the curve to the left.

Thus, in Figure 2, the low sodium, high angiotensin renal function curve equates with the low sodium intake (dotted line) at the lowermost cross at an arterial pressure of about 94 mm Hg. At the other extreme, the high sodium, low angiotensin renal function curve equates with the high sodium intake (dashed line) at the uppermost cross at an arterial pressure of about 99 mm Hg. When these three equilibrium points in Figure 2 are joined together — beginning at the low salt level, then at the normal salt level, and, finally, at the high salt level — the curve drawn through these points depicts the salt-loading renal function curve.

The importance of the salt-loading renal function curve is threefold. First, the salt-loading renal function curve is very easy to measure in animals and humans. Second, the salt-loading renal function curve at any given intake level of salt passes through exactly the same salt intake-output equilibrium point as does the isolated kidney renal function curve when the kidney is adapted to that same level of salt intake. Finally, based on the two preceding points, the salt-loading renal function curve can be used to predict the long-term level at which the mean arterial pressure will be regulated for any given salt intake level. In fact, since the salt-loading renal function curve takes into consideration hormonal feedback mechanisms as well as the direct hemodynamic effect of the arterial pressure on renal salt output, the salt-loading renal function curve is in many ways more valuable than the isolated kidney curve for understanding arterial pressure regulation and the pathophysiology of hypertension.

The article by Kimura et al. is especially important because it is the first instance of which I am aware in which the renal function curves have been used prospectively in human experiments to study the pathogenesis of clinical hypertension and the ways in which therapy can return hypertensive patients to normotension.

ARTHUR C. GUYTON
Department of Physiology and Biophysics
University of Mississippi Medical Center
Jackson, Mississippi
References

Address for reprints: Arthur C. Guyton, M.D., Department of Physiology and Biophysics, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216-4505.
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A C Guyton

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