Brief Review

Abnormal Pressure Natriuresis
A Cause or a Consequence of Hypertension?

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In all forms of chronic hypertension, the renal-pressure natriuresis mechanism is abnormal because sodium excretion is the same as in normotension despite the increased blood pressure. However, the importance of this resetting of pressure natriuresis as a cause of hypertension is controversial. Theoretically, a resetting of pressure natriuresis could necessitate increased blood pressure to maintain sodium balance or it could occur secondarily to hypertension. Recent studies indicate that, in several models of experimental hypertension (including angiotensin II, aldosterone, adrenocorticotropic hormone, and norepinephrine hypertension), a primary shift of renal-pressure natriuresis necessitates increased arterial pressure to maintain sodium and water balance. In genetic animal models of hypertension, there also appears to be a resetting of pressure natriuresis before the development of hypertension. Likewise, essential hypertensive patients exhibit abnormal pressure natriuresis, although the precise cause of this defect is not clear. It is likely that multiple renal defects contribute to resetting of pressure natriuresis in essential hypertensive patients. With long-standing hypertension, pathological changes that occur secondary to hypertension must also be considered. By analyzing the characteristics of pressure natriuresis in hypertensive patients and by comparing these curves to those observed in various forms of experimental hypertension of known origin, it is possible to gain insight into the etiology of this disease. (Hypertension 1990;15:547-559)

In many patients with hypertension, there are no obvious renal defects. Most of the common indexes used to evaluate renal function, such as glomerular filtration rate (GFR) or renal plasma flow, are often within the normal range, which leads many investigators to believe that hypertension can develop in the absence of kidney abnormalities. Yet, there is one aspect of kidney function, the relation between renal sodium and water excretion and arterial pressure, that is abnormal in all types of experimental and clinical hypertension. Normally, an increase in arterial pressure would elevate sodium excretion, a phenomenon often referred to as pressure natriuresis.1-3 The fact that hypertensive patients are in sodium balance and have normal sodium excretion (equal to intake) despite increased blood pressure indicates that pressure natriuresis is reset. The mechanisms responsible for this resetting and its role in hypertension have been the subject of considerable controversy. The goal of this paper is to briefly review the function of pressure natriuresis in normal regulation of arterial pressure and body fluid volumes, the evidence that abnormalities of pressure natriuresis play a causal role in hypertension, and some potential mechanisms by which pressure natriuresis may be reset in hypertension.

Renal-Body Fluid Feedback Control of Arterial Pressure

The renal-pressure natriuresis mechanism has been postulated to be a primary component of a feedback system for long-term regulation of arterial pressure and body fluid volumes.1,4 Under most conditions, this mechanism acts to stabilize arterial pressure as well as body fluid volumes. For example, disturbances that elevate arterial pressure without impairing renal excretory capability also tend to increase sodium and water excretion through pressure natriuresis and diuresis, thereby reducing extracellular fluid volume and returning blood pressure toward normal (Figure 1). Hypertension caused by increases in cardiac output or total peripheral resistance cannot be sustained if pressure natriuresis is unaltered because sodium excretion would remain above sodium intake until arterial pressure returned completely to the original set point. Similarly, reductions in blood pressure tend to lower sodium excretion and increase extracellular fluid volume until blood pressure returns to normal. An important aspect of this

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Peripheral Vasoconstriction
No Renal Action

**FIGURE 1.** Graphs showing predicted effects of a hypertensive stimulus, caused either by increased cardiac output or increased total peripheral resistance, without a shift of the renal-pressure natriuresis curve. Blood pressure is initially elevated but cannot be sustained at that level because sodium excretion exceeds intake, thereby reducing extracellular fluid volume until blood pressure eventually returns to normal where intake and output of sodium are balanced.

Feedback system is that there are many neurohumoral systems that act to amplify its effectiveness. For example, increases in blood pressure not only tend to raise renal excretion directly through hydraulic effects on the kidney but also inhibit formation of angiotensin II (Ang II) and aldosterone, which further elevates renal excretion and decreases extracellular fluid volume, promoting a more rapid recovery of blood pressure.

Although pressure natriuresis normally acts to stabilize blood pressure, abnormalities of renal hemodynamics or tubular reabsorption can alter the set point at which arterial pressure and sodium excretion are controlled. For example, excessive formation of antinatriuretic hormones or diseases that reduce renal excretory capability could shift the pressure natriuresis curve to higher pressures and tend to cause sodium retention and increased extracellular fluid volume if intake remained constant. Accumulation of fluid would continue until blood pressure increased sufficiently to restore renal excretion to normal through pressure natriuresis. In the steady state, renal excretion would be maintained equal to intake but at the expense of hypertension.

Neurohumoral Modulation of Pressure Natriuresis

Any neurohumoral system capable of causing long-term changes in renal excretory function could influence blood pressure regulation by altering pressure natriuresis. A reduction in renal excretory capability would tend to shift the curve to high pressures, whereas a chronic increase in renal excretory capability would be associated with a shift of pressure natriuresis toward lower blood pressures. Under steady-state conditions, no change in sodium excretion would be observed because changes in blood pressure would compensate for primary changes in renal excretory function. In most instances, the various neurohumoral systems act in concert with the basic pressure natriuresis mechanism to prevent chronic changes in blood pressure, but there are certain pathophysiological conditions associated with abnormal activity of these neurohumoral systems that may alter the set point at which blood pressure is regulated.

Renin-Angiotensin System

One of the most powerful modulators of pressure natriuresis, and consequently of long-term blood pressure control, is the renin-angiotensin system (RAS). Figure 2 shows an analysis of the steady-state interrelations between Ang II, arterial pressure, and sodium excretion during chronic changes in sodium intake in three groups of dogs with different levels of activity of the RAS. In these experiments, sodium intake was raised progressively in steps from 5 to approximately 500 meq/day and maintained at each level until balance between intake and output of sodium was achieved. In normal dogs with an intact RAS, sodium balance was maintained with only
minor changes in blood pressure (5–10 mm Hg) over the entire range of sodium intake, indicating a very effective pressure natriuresis mechanism. In fact, the steepness of the chronic curve relating arterial pressure to sodium excretion is due in large part to changes in Ang II formation in response to changes in sodium intake or arterial pressure. When Ang II was infused at a low rate (5 ng/kg/min) throughout the experiment so that circulating levels could not decrease, very large increases in blood pressure (40–50 mm Hg) were needed to maintain sodium balance when intake was raised. This observation indicates that the inability to suppress Ang II formation greatly reduces the effectiveness of pressure natriuresis. In a third group of dogs, Ang II formation was blocked throughout the experiment with the converting enzyme inhibitor captopril (SQ-14,225). After blockade of Ang II formation, renal excretory capability was markedly increased because sodium balance was maintained at lower than normal blood pressures.

Thus, appropriate changes in activity of the RAS play a key role in allowing the normal individual to adapt to a wide range of sodium intakes with minimal changes in blood pressure. However, abnormalities of the RAS, such as the inability to decrease Ang II formation appropriately in response to high sodium intake, can also cause pronounced effects on pressure natriuresis and therefore long-term blood pressure regulation.

### Atrial Natriuretic Factor

Another hormone that may play a role in modulating pressure natriuresis is atrial natriuretic factor (ANF). Numerous studies have demonstrated that ANF has powerful acute effects on sodium excretion (See References 7 and 8 for reviews) and that this hormone shifts the acute pressure natriuresis curve to lower blood pressures. Recently, ANF has been demonstrated to have powerful chronic effects on renal excretory function. To assess the long-term direct actions of ANF on the kidney while controlling for various neurohumoral changes that might override its natriuretic effects, Mizelle et al. used a split bladder technique and infused ANF into one renal artery for several days while infusing vehicle into the contralateral kidney; thus, measurements of separate renal function could be made in ANF- and vehicle-infused kidneys. This is a powerful method for studying the long-term direct effects of ANF on renal function because both the infused and contralateral kidneys are exposed to the same blood pressure and neural influences and the same circulating hormones and other constituents of the blood except for ANF. Therefore, any differences in renal function can be attributed to differences in ANF concentrations. In these experiments, ANF infusion at low physiological rates caused pronounced increases in renal excretion that persisted as long as ANF was infused. Sodium excretion in the contralateral kidney decreased by almost an identical amount so that the total sodium balance was maintained relatively constant. These findings indicate that ANF, at physiological concentrations, is capable of increasing renal excretory function chronically and provides the basis for a possible role of ANF in long-term regulation of body fluid volumes and blood pressure.

To further examine the importance of intrarenal versus systemic actions of ANF in long-term regulation of blood pressure, Hildebrandt et al. recently compared the chronic blood pressure effects of ANF infused at very low rates directly into the kidney with the effects produced by intravenous infusions at the same rates. The results from these studies demonstrated that intrarenal infusions of ANF at rates too low to have any major systemic actions caused pronounced decreases in blood pressure over a period of several days. These findings demonstrate that physiological increases in intrarenal levels of ANF can reduce blood pressure chronically while increasing renal excretory capability, indicating a shift of renal-pressure natriuresis. However, the importance of this effect in different physiological and pathophysiological conditions has not been fully elucidated.

The precise mechanisms by which ANF alters long-term pressure natriuresis are not well understood. Part of the natriuretic effect of ANF may be mediated through interactions with the RAS. For example, ANF reduces renin secretion and may antagonize the renal tubular and vascular actions of Ang II. Further studies are needed, however, to quantify the importance of interactions between ANF and the RAS and the exact mechanisms by which ANF influences chronic pressure natriuresis and blood pressure regulation.

In addition to the RAS and ANF, other neurohumoral systems may also influence blood pressure by altering renal-pressure natriuresis. For example, DiBona recently reviewed evidence that the renal nerves may influence renal excretory capability and blood pressure regulation in several models of experimental hypertension. Other hormone systems, such as the kallikrein-kinin system, the renal prostaglandins, and other natriuretic factors besides ANF, have also been postulated to be important in regulating renal excretory function and arterial pressure. Unfortunately, there are few data concerning the quantitative importance of these systems in long-term regulation of pressure natriuresis, and it is not always prudent to extrapolate from the results of acute experiments.

### Abnormal Renal-Pressure Natriuresis in Hypertension

As discussed above, renal-pressure natriuresis is abnormal in all forms of chronic hypertension because average sodium excretion is approximately the same as in normotension, assuming that sodium intake is normal. Figure 3 illustrates the approximate steady-state relations between blood pressure and sodium excretion in several types of hypertension. In each example, the pressure natriuresis curve is
SODIUM INTAKE AND OUTPUT (X Normal)

FIGURE 3. Schematic drawing showing steady-state relations between arterial pressure and sodium excretion and sodium intake in various forms of hypertension. K̄, glomerular capillary filtration coefficient; SHR, spontaneously hypertensive rats; Goldblatt, one-kidney, one clip Goldblatt hypertensive rats.

shifted so that sodium balance occurs at elevated blood pressures. Obviously, a shift of this curve to higher pressures must occur in all forms of chronic hypertension, otherwise sodium excretion would remain above intake until it caused severe volume depletion and circulatory collapse. However, note that the characteristics of pressure natriuresis differ in various forms of hypertension. As discussed below, the differing slopes and intercepts of the pressure natriuresis curves in various forms of hypertension may provide clues about the etiology of hypertension.

Although it is clear that there are abnormalities of pressure natriuresis in hypertension, the importance of these abnormalities as a cause of hypertension has been debated. According to the renal–body fluid feedback concept, a primary reduction of renal excretory capability, caused by decreased GFR or increased tubular reabsorption, initiates a compensatory increase in blood pressure that serves to maintain fluid balance. Reductions in renal excretory capability can be due to various intrinsic functional or pathological changes in the kidney or to neurohumoral factors that influence renal excretion. In the steady state, normal sodium excretion would be maintained and the initial change in GFR or tubular reabsorption would be masked by the elevated blood pressure.

An opposing view of abnormal pressure natriuresis in hypertension is that it occurs secondarily to increased arterial pressure. This concept predicts that hypertension is initiated by abnormalities of the heart or peripheral vasculature that tend to elevate cardiac output or total peripheral vascular resistance and that the kidneys secondarily adapt to increased blood pressure to maintain sodium balance. Obviously, if the kidneys could completely reset their pressure natriuresis mechanism and maintain normal sodium excretion independently of changes in blood pressure initiated by nonrenal abnormalities, renal-pressure natriuresis would not play a significant role in long-term blood pressure regulation. Therefore, one of the most important and controversial issues concerning the role of the kidneys in the pathogenesis of hypertension is whether arterial pressure has a long-term effect on sodium and water excretion, or alternatively, whether the kidneys can regulate sodium excretion independently of blood pressure. Unfortunately, this has been a difficult question to answer experimentally because attempts to produce long-term changes in renal perfusion pressure (e.g., renal artery stenosis) are usually accompanied by compensatory changes in systemic arterial pressure or neurohumoral changes that also influence renal excretion. However, recent studies have addressed this problem by examining the role of pressure natriuresis in various models of experimental hypertension in which the direct effects of increased blood pressure were separated from other factors that influence renal excretion.

**Hypertension Caused by Antinatriuretic Hormones**

Excessive secretion of mineralocorticoids or other antinatriuretic hormones such as Ang II typically causes transient sodium retention and gradual elevation of blood pressure. Sodium retention lasts for only a few days and is followed by an "escape" in which sodium excretion returns to normal. The mechanisms responsible for this escape have been the subject of considerable research, and various concepts have been proposed to explain this phenomenon. According to the renal–body fluid feedback concept, mineralocorticoids or Ang II reduce renal excretory
capability and initiate a sequence of events that elevate arterial pressure. Increased blood pressure then restores sodium excretion to normal through pressure natriuresis. However, because mineralocorticoids and Ang II almost invariably raise total peripheral vascular resistance, the high blood pressure has also been postulated to be caused by direct or indirect effects of these agents to constrict the peripheral vasculature. For example, mineralocorticoids have been postulated to activate the sympathetic nervous system or to stimulate the release of an ouabain-like circulating inhibitor of sodium-potassium adenosine triphosphatase secondary to volume expansion, changes that are believed to cause peripheral vasoconstriction and hypertension. The escape from sodium retention has also been postulated to be independent of increased arterial pressure and to be mediated by increased formation of various natriuretic factors, such as an ouabain-like natriuretic hormone, ANF, kinins, prostanoids, or reduced renal sympathetic nerve activity.

To resolve these issues and to directly test the importance of pressure natriuresis in regulating sodium balance in hypertension, we compared the chronic blood pressure and renal effects of aldosterone or Ang II infusion in dogs in which renal perfusion pressure was either permitted to increase or servo-controlled at the normal level. In normal dogs, aldosterone or Ang II infusion caused relatively mild hypertension, with sodium excretion decreasing transiently and then returning toward control on the second day of infusion, and after 7 days cumulative sodium balance was only slightly elevated. In contrast, when renal perfusion pressure was servo-controlled during aldosterone (Figure 4) or Ang II infusion (Figure 5), sodium excretion remained considerably below intake throughout the experiment. Therefore, cumulative sodium balance continued to increase, which caused pronounced edema in several dogs. The systemic arterial hypertension was also much more severe when renal artery pressure was prevented from increasing, and some dogs developed severe ascites or pulmonary edema within a few days. When the servo-controller was stopped and renal perfusion pressure was allowed to increase to hypertensive levels while Ang II or aldosterone infusions were continued, there was a prompt escape from sodium retention and cumulative sodium balance, and arterial pressure returned to about the same levels measured in normal dogs during aldosterone or Ang II infusion.

The results from these studies indicate that pressure natriuresis plays an essential role in maintaining sodium balance in mineralocorticoid and Ang II hypertension. When this mechanism was prevented from operating, severe fluid retention occurred, which would eventually lead to complete circulatory collapse. Although these observations emphasize the importance of pressure natriuresis, they do not rule out the possibility that other factors may also be important in maintaining sodium balance in response to Ang II or mineralocorticoid excess. It is possible that various natriuretic hormones, especially ANF, could play a role in minimizing the rise in blood pressure needed to maintain sodium balance.

The intrarenal mechanisms by which increased arterial pressure allows escape from the antinatriuretic effects of aldosterone or Ang II appear to be related to small increases in GFR and renal plasma flow and decreases in fractional sodium reabsorption (see References 18 and 19 for further review). With prolonged hypertension, lasting for months or years, pathological changes in the glomerular capillaries may cause reductions in GFR that necessitate further elevations in arterial pressure and inhibition of tubular reabsorption to maintain sodium balance. However, the observation that GFR and renal plasma flow are elevated as mineralocorticoid hypertension develops, even though renal excretory capability is reduced, illustrates an important point: evaluation of renal excretory capability cannot be based on steady-state measurements of renal hemodynamics, tubular reabsorption, or even sodium excretion as each of these variables is influenced by various compensatory mechanisms that are set into motion as hypertension develops. In the case of mineralocorticoid hypertension, increased GFR and renal plasma flow, along with a reduction in proximal fractional reabsorption, appear...
to be important compensations for a primary increase in distal tubular sodium reabsorption. In the steady state, distal tubular delivery of sodium is increased to offset increased distal reabsorption, and a decrease in renal excretory capability is apparent only when the arterial pressure that is needed to maintain sodium excretion equal to intake is considered.

**Hypertension Caused by "Vasoconstrictors"

An abnormality of renal-pressure natriuresis has also been found in several forms of hypertension that are usually considered to be caused by peripheral vasoconstriction. For example, both norepinephrine and vasopressin are among the most potent peripheral vasoconstrictors of the body. In fact, vasopressin is more powerful as a vasoconstrictor than Ang II. Yet, with chronic infusions of vasopressin or norepinephrine, only small increases in blood pressure are observed as long as kidney function is not impaired. The fact that these powerful vasoconstrictors do not usually cause pronounced chronic hypertension, even though they elicit large acute increases in vascular resistance and blood pressure, is difficult to explain if one considers changes in peripheral vascular resistance to be a primary cause of hypertension. However, the failure of vasopressin or norepinephrine to cause severe sustained hypertension is explainable if one considers their modest antinatriuretic actions.

Although vasopressin is a potent antidiuretic hormone, it does not have a major antinatriuretic action. Therefore, increases in arterial pressure that result from peripheral vasoconstriction tend to cause natriuresis, which offsets the fluid retention initiated by vasopressin. When vasopressin was infused chronically in normal dogs at a rate that produced maximal antidiuresis, there was initially a modest increase in blood pressure associated with transient increases in urine osmolality and decreased urine volume. However, after 3–4 days urine volume and osmolality returned toward normal and arterial pressure began to decrease, averaging only a few millimeters of mercury above control after 1–2 weeks of infusion. This decline of blood pressure was associated with increased sodium excretion and a negative sodium balance. In contrast, when pressure natriuresis was prevented by servo-controlling renal arterial pressure, vasopressin infusion caused pronounced and sustained decreases in urine volume, increased urine osmolality, a slight retention of sodium, and severe hypertension.

Thus, the pressure natriuresis and diuresis mechanisms play an essential role in offsetting the antinatriuretic effect of vasopressin, thereby minimizing volume expansion and hypertension even though vasopressin is one of the most powerful vasoconstrictors known. The modest transient hypertension that occurs when renal function is normal depends primarily on increased volume rather than the peripheral vasoconstriction. Cowley et al found that, when total body weight was held constant by decreasing fluid intake during vasopressin infusion in dogs, there was no significant increase in blood pressure. However, when fluid retention is severe because of impaired pressure natriuresis, vasopressin may cause large increases in blood pressure. In our experiments, when renal artery pressure was servo-controlled during chronic vasopressin infusion, continuous retention of fluid occurred and blood pressure increased markedly. Thus, the chronic hypertensive effects of vasopressin, although modest in animals with normal renal function, may be more severe when renal function is impaired. Similar results have also been observed with other vasoconstrictors, such as norepinephrine, and with adrenocorticotropic hormone, which potentiates the hypertension produced by vasoconstrictors such as norepinephrine. Each of these forms of hypertension begins with an increase, rather than a decrease, in sodium excretion. The finding that sodium excretion increases transiently could be interpreted as evidence that the hypertensive action of these hormones is unrelated to any impairment of renal excretory capability. However, it appears that the transient natriuresis occurs secondarily to increased blood pressure caused by peripheral vasoconstriction or increased cardiac output and that norepinephrine and adrenocorticotropic hormone both have a slight antinatriuretic effect on the kidney.
PERIPHERAL VASOCONSTRICTION  
WEAK RENAL ACTION

![Graph showing probable long-term relation between arterial pressure and sodium excretion and sodium intake before and during infusion of a powerful peripheral vasoconstrictor](image)

**Figure 6.** Graphs showing probable long-term relation between arterial pressure and sodium excretion and sodium intake before and during infusion of a powerful peripheral vasoconstrictor that has a relatively weak effect on renal-pressure natriuresis. The normal curve (solid line) is compared with the vasoconstrictor curve (dashed line). Initially, the vasoconstrictor would cause natriuresis, because arterial pressure is elevated (to point B) above the set point for balance between intake and output of sodium (point C).

that is responsible for the mild hypertension that these hormones produce chronically. If pressure natriuresis is prevented by servo-controlling renal artery pressure, both of these hormones can cause severe hypertension that parallels sodium retention.

Figure 6 shows the probable relation between blood pressure and sodium excretion after infusion of a powerful peripheral vasoconstrictor that has a relatively weak antinatriuretic effect on the kidney (e.g., norepinephrine). The antinatriuretic effect of the vasoconstrictor would shift the renal-pressure natriuresis mechanism to higher blood pressures, thereby necessitating a small increase in blood pressure to maintain sodium balance. However, if the antinatriuretic action of the vasoconstrictor is weak, compared with its peripheral vascular actions, blood pressure would be elevated above the renal set point for regulation of sodium balance (to point B rather than point C where intake and output are balanced) and would cause a transient natriuresis. Only a transient natriuresis would be expected because extracellular fluid volume would decrease and arterial pressure would eventually stabilize at a level (point C) at which sodium intake and output are balanced. This explanation fits with our finding that the natriuretic effects of vasoconstrictors such as norepinephrine and vasopressin are abolished when renal perfusion pressure is prevented from increasing. In fact, there is a slight sodium retention when renal perfusion pressure is servo-controlled in these models of hypertension.

Thus, there is strong experimental support for the basic premise of the renal-body fluid feedback concept, that increases in blood pressure have a major long-term effect on sodium excretion. In all forms of experimental hypertension studied thus far, there is a shift of the pressure natriuresis mechanism to a higher blood pressure, which initiates and sustains the hypertension. In some cases, the renal actions of these hypertensive stimuli may be obscured by other effects, such as peripheral vasoconstriction or changes in vascular capacity, that increase blood pressure above the renal set point at which sodium balance is maintained. In these circumstances, sodium excretion may actually increase as hypertension develops. However, the maintenance of elevated blood pressure chronically depends on the changes in renal function that contribute to the shift of renal-pressure natriuresis.

**Can Abnormal Pressure Natriuresis Mechanism Occur Secondarily to Chronic Increases in Blood Pressure?**

In the experimental models of hypertension discussed above, primary changes in renal-pressure natriuresis resulted in adaptations of blood pressure (i.e., hypertension occurred as a compensatory response to maintain sodium and water balance). These experiments also illustrate another important point: if pressure natriuresis is impaired and imbalances between fluid intake and output are maintained, severe edema and complete circulatory collapse occur within a few days. Rapid adaptations of blood pressure to primary alterations in renal function are essential for survival in these forms of hypertension.

Although high blood pressure may satisfy the immediate need to maintain sodium balance, it may also lead to additional changes in renal excretory function that can exacerbate the hypertensive process over long periods of time. A good example is the hypertension that develops after placing a Goldblatt clip on one renal artery while leaving the contralateral kidney intact (two-kidney, one clip Goldblatt hypertension). Initially, the hypertension is caused by impaired function of the clipped kidney, while the contralateral intact kidney undergoes natriuresis, which partly ameliorates the hypertension. Full compensation for impaired function of the clipped kidney is not achieved by the contralateral kidney because its excretory function is also partly attenu-
ated by various functional changes, such as increased circulating Ang II.\textsuperscript{1,42} Therefore, increased blood pressure is necessary to maintain sodium excretion and intake in balance.

In the early stages of hypertension, removal of the clipped kidney restores blood pressure to normal, whereas removal of the contralateral kidney exacerbates the hypertension.\textsuperscript{43} However, with prolonged hypertension pathological changes in the vasculature of the contralateral kidney begin to appear and add to the impairment of renal function.\textsuperscript{44} At this stage, removal of the clipped kidney or unclipping only partially restores blood pressure.\textsuperscript{44,45} However, removal of the contralateral "normal" kidney and unclipping together usually normalizes blood pressure.\textsuperscript{46} This observation indicates that chronic exposure to high blood pressure in the untouched kidney may cause structural changes that alter its pressure natriuresis mechanism and contribute to progression of hypertension. Thus, the two-kidney, one clip Goldblatt model of hypertension, although initiated by increased preglomerular resistance in part of the renal tissue, is characterized by functional or pathological changes in the remaining normal renal tissue that contribute to the maintenance of hypertension. A similar situation could occur when there are patchy areas of renal ischemia due to a variety of causes, including renal infarcts, nonhomogeneous constriction of the renal vasculature, or nonhomogeneous nephrosclerosis.\textsuperscript{1,47} In fact, any abnormality of renal function that causes underperfusion in one area of the kidney is likely to cause impairment of the remaining nephrons via the renin released from underperfused nephrons.\textsuperscript{1,47}

Conceivably, any initial disturbance of renal function that leads to compensatory increases in intrarenal pressures due to increased systemic arterial pressure or preglomerular vasodilation could cause pathological changes that would eventually result in glomerular membrane or arteriolar damage,\textsuperscript{48} thereby gradually shifting pressure natriuresis to higher and higher blood pressures. In this way, renal-pressure natriuresis could gradually adapt to chronic increases in blood pressure. This adaptation, however, would not act as a physiological mechanism to maintain sodium balance; instead, these changes could be a pathological cause of further increases in blood pressure that would in turn be important in maintaining sodium balance.

**Abnormal Pressure Natriuresis in Essential Hypertension**

In most patients with hypertension, no specific renal dysfunction can be identified in the early stages of the disease, and there is little evidence for increased levels of antinatriuretic hormones such as Ang II or aldosterone. Thus, the hypertension of these patients is usually referred to as "idiopathic" or "essential." However, it is clear that renal excretory function is not normal in these patients because the renal-pressure natriuresis mechanism is reset so that normal sodium excretion is maintained only at elevated blood pressures. Omvik et al\textsuperscript{42} demonstrated that when arterial pressure was acutely reduced by nitroprusside infusion in patients with essential hypertension, sodium excretion decreased below normal indicating that pressure natriuresis was reset in these patients. Similar abnormalities of renal-pressure natriuresis have been found in all animal models of genetic hypertension studied thus far.\textsuperscript{2,41,49–53}

The observation of abnormal pressure natriuresis in essential hypertension is not direct evidence that such an abnormality plays a causal role in elevating blood pressure. However, in genetic models of spontaneous hypertension that have many similarities to human essential hypertension, there is evidence that abnormalities of pressure natriuresis occur before the development of hypertension and are not merely secondary to increased blood pressure. For example, in prehypertensive Dahl salt-sensitive (DS) rats the slope of the relation between urine flow and renal perfusion pressure measured in acute experiments is considerably less than that seen in Dahl salt-resistant (DR) rats\textsuperscript{53} (Figure 7). The fact that this occurs before the rats develop hypertension suggests that abnormal pressure natriuresis in the DS rat is not caused by renal damage secondary to hypertension but represents an intrinsic difference between the kidneys of DS and DR rats. The mechanisms that underlie the shift of pressure natriuresis in DS rats are not entirely clear but may be related in part to abnormalities of renal hemodynamics. Roman\textsuperscript{53} demonstrated that a shift of GFR autoregulation to higher pressures occurred in prehypertensive DS rats fed a low sodium diet. Recently, Tobian et al\textsuperscript{54} also demonstrated that there is a glomerular defect in prehypertensive DS rats that limits their capacity to increase GFR in response to amino acid infusion. Cross transplantation studies between DS and DR rats indicate that the hypertension of these rats follows abnormal kidney function.\textsuperscript{55,56}

In Okamoto spontaneously hypertensive rats (SHR), abnormalities of renal function also appear to play a role in causing hypertension. Transplantation of kidneys from SHR to Wistar-Kyoto (WKY) rats produces hypertension in the previously normotensive recipient.\textsuperscript{57–59} Moreover, this alteration in renal function is not merely the result of damage secondary to hypertension because transplantation of kidneys from SHR even before they develop hypertension eventually causes hypertension in the WKY rat recipient.\textsuperscript{57} Acute studies in SHR suggest that multiple abnormalities of renal function may occur at different stages of hypertension. Renal blood flow autoregulation has been reported to be shifted to higher blood pressures in young 10-week-old SHR compared with WKY control rats.\textsuperscript{60} When differences in neural and endocrine influences in the kidneys are minimized by renal denervation and by maintaining plasma levels of vasopressin, aldosterone, cortisol, and norepinephrine constant by intravenous infusion, the slope of the renal-pressure
natriuresis curve of SHR is reduced compared with that of WKY rats. This finding suggests that there may be intrinsic changes in renal function that contribute to resetting of pressure natriuresis in SHR. However, chronic studies in intact SHR suggest that increased renal nerve activity and immunological abnormalities may also contribute in part to a parallel shift of pressure natriuresis.

In the Milan strain of SHR, cross transplantation studies between normotensive and hypertensive rats also indicate that the hypertension follows the kidney. Several lines of evidence recently reviewed by Bianchi et al suggest that hypertension in Milan rats may be initiated by a primary increase in renal tubular reabsorption. However, the exact intrarenal mechanisms responsible for abnormal pressure natriuresis in each of these models of genetic hypertension have not been fully elucidated.

The possibility that these observations in animals may be relevant to the pathogenesis of human essential hypertension is supported by the findings of Curtis et al. who reported that transplantation of kidneys from normotensive donors to patients with essential hypertension and renal failure led to complete normalization of blood pressure. If the high blood pressure in these patients was caused by some factor extrinsic to the kidneys, hypertension should have eventually reappeared after transplantation. However, blood pressure remained normal in all patients for an average follow-up period of 4.5 years. Parfrey also reported that, in children born to parents who were both hypertensive, the pressure natriuresis curve was shifted when compared with that of children with normotensive parents, even before the onset of hypertension. These observations provide further support for the view that abnormal pressure natriuresis in essential hypertensive patients may be a cause and not merely a consequence of increased blood pressure. However, as discussed above, once the hypertensive process begins pathological changes can occur in the kidneys that can add to the shift of the pressure natriuresis curve and further elevate blood pressure.

Possible Mechanisms of Shift in Pressure Natriuresis in Essential Hypertension

A single renal defect responsible for shifting pressure natriuresis and elevating blood pressure in human essential hypertension has not been found. It seems likely that essential hypertension is a heterogeneous disease beginning with different abnormalities of renal hemodynamics or tubular reabsorption in different patients. Unfortunately, measurements of various indexes of kidney function after hypertension is established or even during the slow insidious development of hypertension may not provide a great deal of insight into the pathophysiological processes that initiate hypertension because these measurements represent a summation of compensatory mechanisms and abnormalities involved in causing hypertension. For example, renal vascular resistance is almost invariably increased in patients with essential hypertension. Yet, high renal vascular resistance could be an autoregulatory response to increased blood pressure in some cases or it could play a causal role in others if it is increased sufficiently to lower renal blood flow and GFR.

In some instances, reduced renal excretory capability may be associated with a compensatory increase in renal blood flow and GFR, as occurs when there is a primary increase in tubular reabsorption (i.e., early stages of mineralocorticoid hypertension). In an attempt to document abnormalities of renal hemodynamics in essential hypertension, various workers have reported increased, decreased, or no change in renal blood flow at various stages of hypertension.

Such variability is expected with different insults to the kidney and when factors known to influence renal blood flow and GFR, such as sodium and protein intake, are uncontrolled. Also, episodic measurements made during resting conditions may not accu-
Effects of Increased Preglomerular Resistance

The observation that many patients with essential hypertension demonstrate a parallel shift of the renal-pressure natriuresis curve, similar to that found in experimental models of hypertension caused by increased preglo-\textm{c}\text{m}erular resistance (e.g., Goldblatt hypertension), is consistent with the possibility that hypertension in these patients may be caused by increased preglomerular resistance. Widespread constriction of preglomerular vessels, due to extrinsic neurohumoral influences or intrinsic abnormalities such as resetting of the macula densa feedback mechanism, would be predicted to cause essentially the same renal and circulatory changes as observed in the one-kidney, one clip Goldblatt model of hypertension. After compensatory increases in blood pressure, one might expect to find nearly normal renal blood flow, GFR, and plasma renin activity that are in fact observed in many essential hypertensive patients.

Effects of Reduced Glomerular Capillary Filtration Coefficient

Another abnormality of renal function that could lead to hypertension by altering pressure natriuresis is a reduction in the glomerular capillary filtration coefficient \(K_f\). The chronic hypertensive effect of a decrease in \(K_f\) would, of course, depend on the sensitivity of GFR to changes in \(K_f\). In some rat strains in which filtration pressure equilibrium exists, GFR is relatively insensitive to changes in \(K_f\) and is highly dependent on renal plasma flow. However, in many rat strains and in other species, such as the dog, as well as humans, filtration pressure equilibrium probably does not occur in most circumstances. Therefore, reducing \(K_f\) would be expected to initially lower GFR and sodium excretion while increasing renin secretion via the macula densa mechanism. However, as arterial pressure increased, GFR and renin release could be restored toward normal so that the only persistent abnormality of renal function would be reduced filtration fraction, increased glomerular hydrostatic pressure, and perhaps small increases in renal blood flow. Increases in renal blood flow and restoration of GFR could occur in part through a macula densa feedback as well as through increases in blood pressure. Unfortunately, a compensatory increase in glomerular hydrostatic pressure, needed to offset a decrease in \(K_f\), could lead to additional renal dysfunction over a period of years by causing glomerulosclerosis, thereby reducing \(K_f\) even further and requiring additional increases in arterial pressure and glomerular hydrostatic pressure to maintain GFR constant. Obviously, such a sequence could initiate a vicious cycle leading to progressive renal damage and eventually kidney failure. The clinical counterpart to this sequence may be found in hypertension caused by glomerulonephritis or possibly essential hypertension with more subtle dysfunction of the glomerular capillary membrane. In contrast to hypertension caused by increased preglomerular resistance, hypertension due to reduced \(K_f\) is associated with a decreased slope of the pressure natriuresis curve (Figure 2). The significance of this reduced slope is that it causes arterial pressure to be very salt sensitive; increases in sodium intake exacerbate the hypertension, whereas low sodium intake ameliorates the high blood pressure.

Effects of Increased Tubular Reabsorption

Some essential hypertensive patients show pressure natriuresis characteristics that cannot be explained entirely by preglomerular constriction or decreased \(K_f\). For example, renal-pressure natriuresis may have a decreased slope in some individuals indicating that they are salt-sensitive, whereas hypertension caused primarily by preglomerular constriction is usually not salt-sensitive. Also, many patients with essential hypertension have decreased plasma renin activity. Both abnormalities, the low plasma renin activity and the salt-sensitivity of blood pressure, could be explained by increased tubular reabsorption or by a combination of changes leading to increased fractional reabsorption and renal vasoconstriction.

In general, those forms of experimental hypertension that are initiated by increased tubular reabsorption (e.g., mineralocorticoid hypertension) are salt-sensitive. In these types of hypertension, the pressure natriuresis curve has a reduced slope rather than a parallel shift as occurs with increased preglomerular resistance. Another feature of hypertension caused by primary increases in tubular reabsorption in distal parts of the nephron beyond the macula densa is that it is often associated with secondary suppression of plasma renin activity and a tendency toward extracellular volume expansion (e.g., mineralocorticoid hypertension). However, when increased tubular reabsorption is coupled with peripheral vasoconstriction (e.g., Ang II hypertension), the degree of volume expansion depends on the relative severity of renal...
and peripheral vasoconstriction. With severe peripheral vasoconstriction and decreased vascular capacitance, much less volume is needed to raise blood pressure sufficiently to offset the increase in tubular reabsorption and to maintain fluid balance. If vascular capacitance is markedly reduced, a much smaller volume is needed to raise blood pressure, and extracellular fluid volume may actually be reduced despite an increase in tubular reabsorption.

Effects of Reduced Nephron Number

Another factor that could increase salt-sensitivity of blood pressure and decrease plasma renin activity in essential hypertensive patients is a gradual loss of nephrons due to aging or to periodic mild insults to the kidney occurring over a long period of time. Reduction in kidney mass, in the absence of other abnormalities, usually does not cause hypertension. Experimental studies have demonstrated that surgical removal of large portions of the kidney, to the point that uremia occurs, rarely causes severe hypertension as long as sodium intake is normal. When entire nephrons are lost without ischemia occurring in the remaining nephrons, overall glomerular filtration and tubular reabsorption capability are simultaneously reduced so that balance between filtration and reabsorption can be maintained without major adaptive changes in arterial pressure. However, kidneys with reduced numbers of nephrons are very susceptible to additional insults that impair renal excretory function. Thus, hypertension associated with mineralocorticoid excess is much more severe after renal mass is reduced. Also, the ability to increase sodium excretion in response to the additional challenge of high sodium intake requires a greater arterial pressure after decreasing kidney mass (i.e., blood pressure becomes very salt-sensitive).

Loss of nephrons could also lead to decreased plasma renin activity. Although total renal blood flow and GFR would tend to be reduced with nephron loss, functional and morphological compensations in the remaining nephrons would tend to cause vasoconstriction and increased single nephron GFR as well as increased distal delivery of sodium chloride. An increase in single nephron GFR and distal tubular sodium chloride delivery in the surviving nephrons would be expected to inhibit renin synthesis and secretion via a macula densa mechanism. In support of this possibility, there is usually a gradual decline in the number of functioning glomeruli after the fourth decade of life. Also, the observation that urine concentrating ability decreases with age, even though levels of antidiuretic hormone are normal or elevated, supports the possibility of a gradual decrease in medullary tonicity with age that in turn could be the result of high solute delivery or increased medullary blood flow in the remaining nephrons.

Although it is clear that essential hypertensive patients have abnormal pressure natriuresis, the precise causes of this defect are unclear. It is probably unwise to ascribe a single cause for all essential hypertensive patients. It may be more useful to analyze the renal and circulatory abnormalities of these individuals and then compare them to various known causes of experimental hypertension. In this way, it may be possible to determine whether the hypertension is initiated by increased preglomerular resistance, increased tubular reabsorption, decreased numbers of functioning nephrons, reduced glomerular capillary filtration coefficient, or some combination of these abnormalities. With long-standing hypertension, pathological changes that occur secondary to hypertension must also be considered. By analyzing the characteristics of pressure natriuresis in hypertensive patients and by comparing these curves to those observed in various forms of experimental hypertension of known origin, it is often possible to gain insight into the etiology of this disease.

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References


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