Renal

THE ROLE OF THE KIDNEY IN CONGESTIVE HEART FAILURE

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Medical Grand Rounds

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THE ROLE OF THE KIDNEY IN CHF

The major clinical symptoms of heart failure are caused by increased retention of salt and water. The resultant edema, increased volume of salt and water in the interstitial space, is a manifestation of heart failure. The heart failure may be due to "backward failure" "forward failure" or the result of a combination of forward and backward failure. However, the common denominator in the pathogenesis of fluid retention in all forms of heart failure is low blood flow to the kidneys. In the case of "backward failure" this is due to poor cardiac output while in "forward failure" a large fraction of the cardiac output is shunted away from the kidney due to the presence of low resistance circulatory pathways.

Why does the kidney continue to absorb salt and water when the total body salt and water compartment are already in an expanded state in cardiac failure? Obviously the kidney is an obedient organ and will respond appropriately to the signals it receives. The primary signal for salt and water excretion is the rate of blood which it receives. Thus, if a component of total body salt and water does not circulate to the kidneys or to areas which generate signals to the kidneys, this part of the total body salt and water is not relevant in total body salt and water regulation. Or, as stated by Peters (1), "accumulation of fluid in the extracellular compartment is a matter of indifference to the kidneys." The kidney responds mainly to the circulation of blood that flows to it. This concept ultimately was the basis for the formulation of the "effective arterial blood volume" hypothesis.

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"EFFECTIVE" CIRCULATING BLOOD VOLUME (EABV)

The concept of EABV was formalized in the late 1940's and early 1950's with the realization that the blood volume was regulated by the kidney in response to the signals that it receives from the cardiopulmonary system. Thus, the EABV is a functional concept and not an absolute quantity that can be measured. In 1948, John Peters (1) wrote one of the clearest statements on the subject when he stated that "Reductions of the volume of the circulating blood or plasma appear to cause the kidneys to reabsorb salt in efforts to conserve water, even if there is an excessive amount of water in the body as a whole." He further stated that "It may, of course, be not the actual volume of circulating plasma but some function usually related to the volume of circulating plasma--such as renal blood flow--that apprises the kidney of the need to conserve water" (1). He then felt so strongly of the EABV hypothesis that he gave injections of salt-poor human serum albumin to patients with heart failure, since Warren and Stead (2) in 1944 and Merrill (3) in 1946 had earlier formulated their theories on "forward failure" as a cause of edema in cardiac failure. By injections of salt-poor albumin, Peters argued that he might increase diuresis by increasing renal blood flow.

The concept of EABV also was supported by the number of studies which had pointed out that quiet standing, in contrast to a supine position, was associated with antinatriureses (4-6). These observations are of importance since it has been estimated that central blood volume decreases by approximately 500 ml as a result of pooling of blood in the

lower extremities. Indeed, in one such study in 1951, Epstein and co-workers (6) came to the conclusion that the decrease in sodium excretion in response to standing was due to alterations in "the 'effective' distribution of the circulating plasma....in initiating acute renal adjustments in sodium excretion." Thus, while the concept of EABV was clearly talked about by many laboratories in the late 1940's and early 1950's, it was the paper of Epstein et al (6) which first used the term "effective distribution of circulating volume."

Further support of the concept of EABV soon came from Epstein, Post and McDowell's (7) studies in 17 young male casualties of the Korean war who had compressible arteriovenous fistulas. These investigators demonstrated that occlusion of an established A-V fistula results in an increased renal excretion of sodium, while the opposite was true with allowing the A-V fistula to return to potency. This clearly was consistent with the view that A-V shunting was associated with altered distribution of blood flow which caused changes in renal sodium excretion. These concepts have been subsequently advanced by Seldin (8) and now there is general agreement that it is the EABV and not the absolute blood volume which, through various volume receptors, regulates renal sodium excretion. Indeed, Eisenberg (9) has shown that the total blood volume is significantly increased in CHF while the EABV is often decreased. This decrease in EABV is the primary stimulus for increased renal salt reabsorption.

Since the EABV is a dynamic function, there are no specific equations or laboratory measures of EABV. However, since EABV is a functional concept, and since the kidney is the target organ of the functional definition, it therefore is not surprising that some

parameter of renal function is used to determine the status of the EABV. Indeed, the fractional excretion of Na or Cl is the parameter.

The utility of fractional excretion of Na was not appreciated until the late 1960's. Up to that time it had been generally recognized that urinary Na was over 30 mEq/L in established renal failure. In 1967 Handa and Marrin (10) noted that renal failure could be due to either poor renal blood flow to otherwise normal kidneys (pre-renal failure--or what they termed "functional renal failure") or acute tubular necrosis (ATN). They tried to use urinary Na excretion as an index to differentiate between patients with pre-renal involvement and those with ATN. While they found pre-renal patients had a U_{Na} of 14±4.2 mEq/L and ATN patients had a U_{Na} of 42±12 mEq/L, there was significant overlap between these two groups. When they factored the U_{Na} by urine-to-plasma creatinine concentration, the resultant ratio was significantly different (<0.001) between the two groups (0.56±0.23 vs 5.64±1.55, Figure 1).

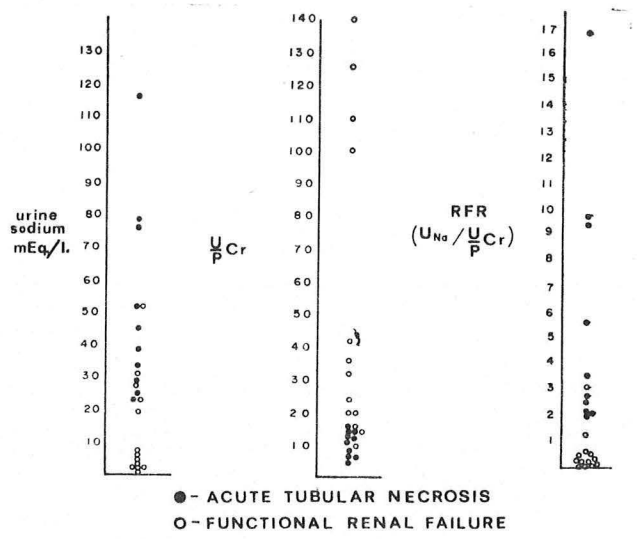

Fig. 1 Comparison of the urine sodium concentration, urine/plasma, creatine ratio and renal failure ratio. Reproduced from Handa et al (10).

Currently, the $U_{Na} \div (U_{Cr}/P_{Cr})$ is known as the renal failure index (RFI) and essentially gives the same information as the fractional excretion of Na (FE_{Na}):

$$FE_{Na} = \frac{U_{Na}/P_{Na}}{U_{Cr}/P_{Cr}} \times 100$$

This test requires only a spot urine sample so the uncertainties of volume collections are obviated. Obviously, the test has to be conducted in the absence of drugs, mainly diuretics, that influence urinary Na excretion.

The clinical data has shown that patients with pre-renal failure have a FE_{Na} of less than 1% while patients with oliguric ATN have a FE_{Na} of greater than 3%. However, is this conclusion warranted? In a prospective analysis of a large number of patients, Miller et al reported that RFI and FE_{Na} was less than 1% in 88 to 94% of patients with pre-renal azotemia and less than 1% in only 0 to 4% or patients with acute oliguric renal failure (11). Thus, if the FE_{Na} is low, there is a high degree of certainty that the patient has contraction of the EABV.

Similarly, patients with oliguric ATN had a high RFI of 10±2 and FE_{Na} 7±1.4% (11). This has been the experience of others also. However, there are patients who fall into the overlap category, mainly patients with acute nonoliguric renal failure. They had a RFI of 4±0.6 and a FE_{Na} of 3±0.5% in their initial study and a FE_{Na} of 2.9±0.6% in a larger follow-up study (12). There is a wider scatter of data in the nonoliguric patients' FE_{Na} and therefore they are more difficult to evaluate.

Also, there is a group of patients who can have a low FE_{Na} in spite of ATN (13-15). These are the rare patients with severe contraction of EABV (i.e., in a highly Na-avid state) such as occurs with severe liver disease, burns or ocassionally sepsis. It is difficult to be certain of the frequency of low FE_{Na} in a combination of ATN and severe EABV but it appears to be a distinct exception. By far the overwhelming majority of patients with oliguric ATN have a high FE_{Na} (10-12).

There are other indices of low EABV that are listed in Table I.

TABLE I

URINE PROFILE IN OLIGURIC ACUTE RENAL FAILURE

Profile	Functional Renal Underperfusion (Salt Depletion, Blood Loss, etc.)	Acute Tubular Necrosis
Urinary osmolality (mOsm/kg H_2O)	>350	<350
Urinary sodium (mEq/L)	<20	>40
U/P urea nitrogen	>8	<3
U/P creatinine	>40	<20
Renal failure index (RFI)	<1	>1
Fractional excretion of sodium (FE_{Na})	<1	>1
Urine sediment	Normal	Dirty with cellular casts

While none of these have the same clinical utility as FE_{Na}, they nevertheless can be used as corroborating evidence for or against contraction of EABV. In addition, there are a number of hormonal consequences of changes in EABV. For example, decreased EABV is associated with increased levels of ADH (16-18), increased plasma renin activity (18-23), and increased rate of aldosterone secretion (19-25). Thus, a

rise in these substances in an appropriate clinical setting is consistent with the diagnosis of decreased EABV. In spite of all these measures, the clinician will still be faced rarely with a patient when it is difficult to evaluate the effectiveness of renal perfusion. Fortunately this is a rare case and then it is prudent to consider a volume challenge if the cardiopulmonary status will so permit.

RENAL RESPONSE TO LOW EABV

The antinatriuretic response to low EABV is an appropriate renal response since one of the main functions of the kidney is to maintain normal EABV. Thus, the kidney absorbs salt and water in an attempt to restore the previously contracted EABV to normal.

Filtration Fraction in CHF

One of the primary mechanisms of how the kidney increases its conservation of salt is by increasing the filtration fraction. Filtration fraction (FF) is the ratio of glomerular filtration rate (GFR) to renal plasma flow (RPF).

$$FF = \frac{GFR}{RPF}$$

The early papers on congestive heart failure noted that these patients had GFRs which, while reduced, were not reduced to the same extent as the RPF (2, 3). Thus the FF in CHF was increased and this finding has been confirmed repeatedly. Indeed, Merrill (3) in 1945 suggested that the "specific diversion of blood away from the kidney" might be of importance in the development of salt and water retention and he wondered what the role of increased filtration fraction might be in development of edema.

This issue can be appreciated by considering events depicted in Figures 2 and 3. Figure 2 is a simple schematic to demonstrate that

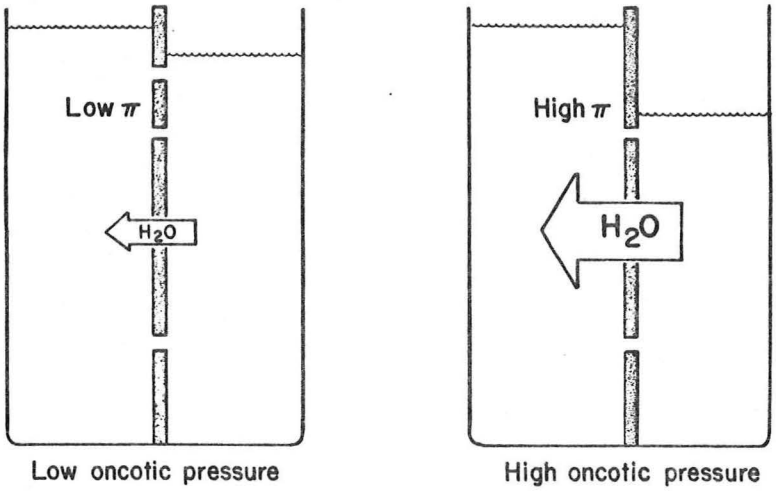

Fig. 2 Schematics to demonstrate water equilibration according to oncotic pressure gradients

oncotic pressure gradients induce net water movement across any semipermeable membrane. Figure 3, on the other hand, demonstrates that an increased oncotic pressure gradient exists across the proximal tubule in CHF as a result of increased filtration fraction. As pointed out earlier, in CHF a greater proportion of the renal blood flow is filtered, and therefore, the postglomerular capillary will have an increased oncotic pressure (since glomerular filtrate has no protein, therefore, the remaining postglomerular capillary protein concentration will rise in direct proportion to the filtration fraction). Figure 4 shows that the post glomerular capillary is in close juxtaposition to the proximal tubule. Part of the proximal tubule reabsorption is the result of passive forces induced by the peritubular oncotic pressure. Thus, with increased peritubular oncotic pressure there is an increased driving force for salt and water reabsorption. However, increased proximal reabsorption of salt and water is not the sole factor leading to salt poor urine and expanded total body salt and water content. A

number of hormonal factors, to be discussed later, also contribute to the increased salt and water absorption.

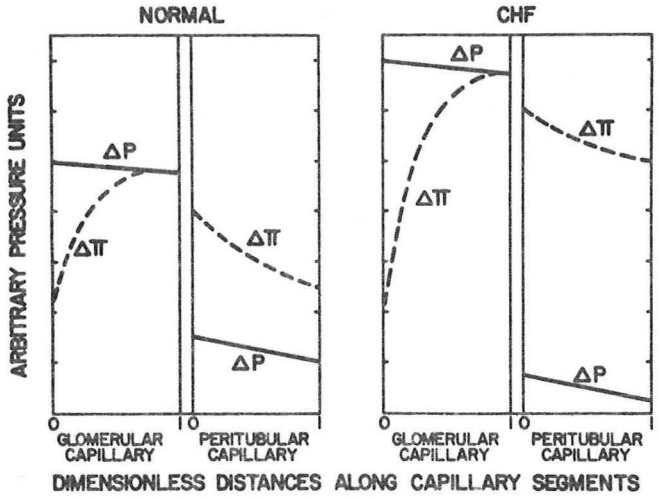

Fig. 3 Approximate intrarenal transcapillary pressure profiles in the normal state and in CHF. The left-hand portion of the figure depicts approximate transcapillary pressure profiles for the glomerular and peritubular capillaries in normal man. Vessel lengths are given in normalized, nondimensional terms, with 0 being the proximal-most portion of the capillary bed and 1 the distal-most portion. Thus, 0 for the glomerulus corresponds to the afferent arteriolar end of the capillary bed and 1 the efferent arteriolar portion. For the peritubular capillary, 0 represents the efferent arteriolar end of the vessel, and 1 the renal venous end. The transcapillary hydraulic pressure difference, ΔP, is relatively constant with distance along the glomerular capillary, while the net driving force for ultrafiltration, $\Delta P - \Delta \pi$, diminishes primarily as a consequence of the increase in $\Delta \pi$, the latter resulting from the formation of an essentially protein-free ultrafiltrate. As a result of the hydraulic pressure drop along the efferent arteriole, the net driving pressure in the peritubular capillaries, $\Delta P - \Delta \pi$, becomes negative, thus favoring reabsorption.

The hemodynamic alterations thought to occur in the renal microcirculation in CHF are depicted in the right-hand portion of the figure. The fall in RPF in CHF is associated with a compensatory increase in ΔP for the glomerular capillary, thus favoring a greater rise than normal in the plasma protein concentration, and hence $\Delta \pi$, along the glomerular capillary. This increase in the value of $\Delta \pi$ by the distal end of the glomerular capillary also translates to an increase in $\Delta \pi$ in the peritubular capillaries, resulting in the increase in the net driving pressure responsible for enhanced proximal tubule fluid absorption thought to take place in CHF. The increased peritubular capillary absorptive force in CHF also very likely results from the small decline in ΔP, a presumed consequence of the rise in renal vascular resistance. Figure and associated legend reprinted from Humes et al (55).

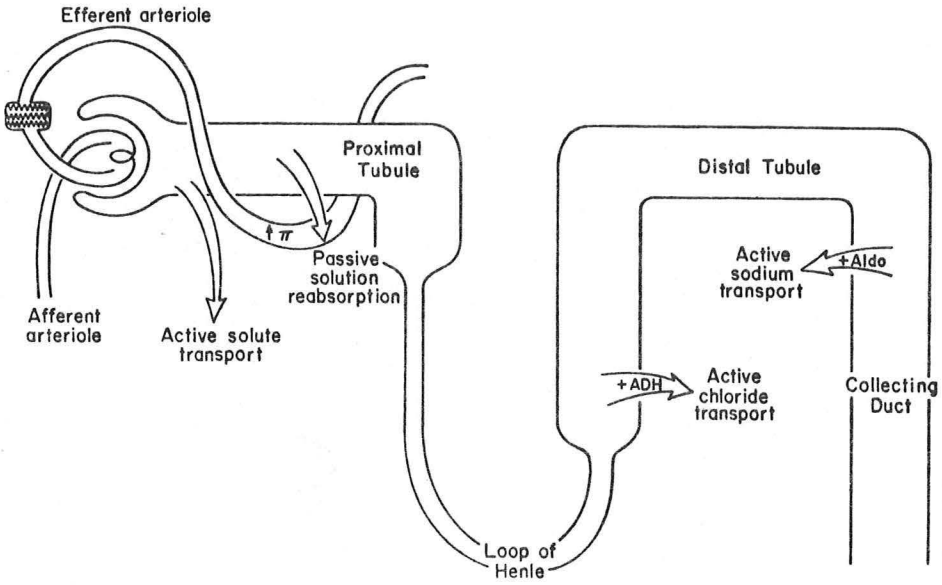

Fig. 4 Transport of solute and water in various nephron and capillary segments.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS) IN CHF

Renin is a proteolytic enzyme which is primarily produced by the juxtaglomerular apparatus cells of the kidney. Its principal function is to split off a decapeptide angiotensin I (AI) from a circulating alpha globulin (renin substrate) that is synthesized in the liver. The inactive AI in turn is broken down to the active angiotensin II (AII) by converting enzyme that splits off two amino acids from AI. The intra-renal conversion of AI to AII thus is responsible for local generation of AII which, in turn, is one of the primary regulators of renal plasma flow. Thus, to appreciate factors that regulate renal blood flow it is important to understand factors that control renin release.

Figure 5 summarizes the three main stimuli that cause renin release. Of these, the most important determinant is decreased plasma flow to the afferent arteriole. Thus, decreased EABV is a potent promoter of renin release that causes intrarenal synthesis of AII.

The other two stimuli for renin release depicted in Figure 5 are increased sympathetic activity via beta receptors in the juxtamedullary apparatus and decreased delivery of Na and Cl to the macula densa cells located within the cortical thick ascending limb of Henle. Thus, beta blockers such as propanolol and increased delivery of salt to the macula densa, as associated with volume expansion, can both decrease renal renin synthesis and release.

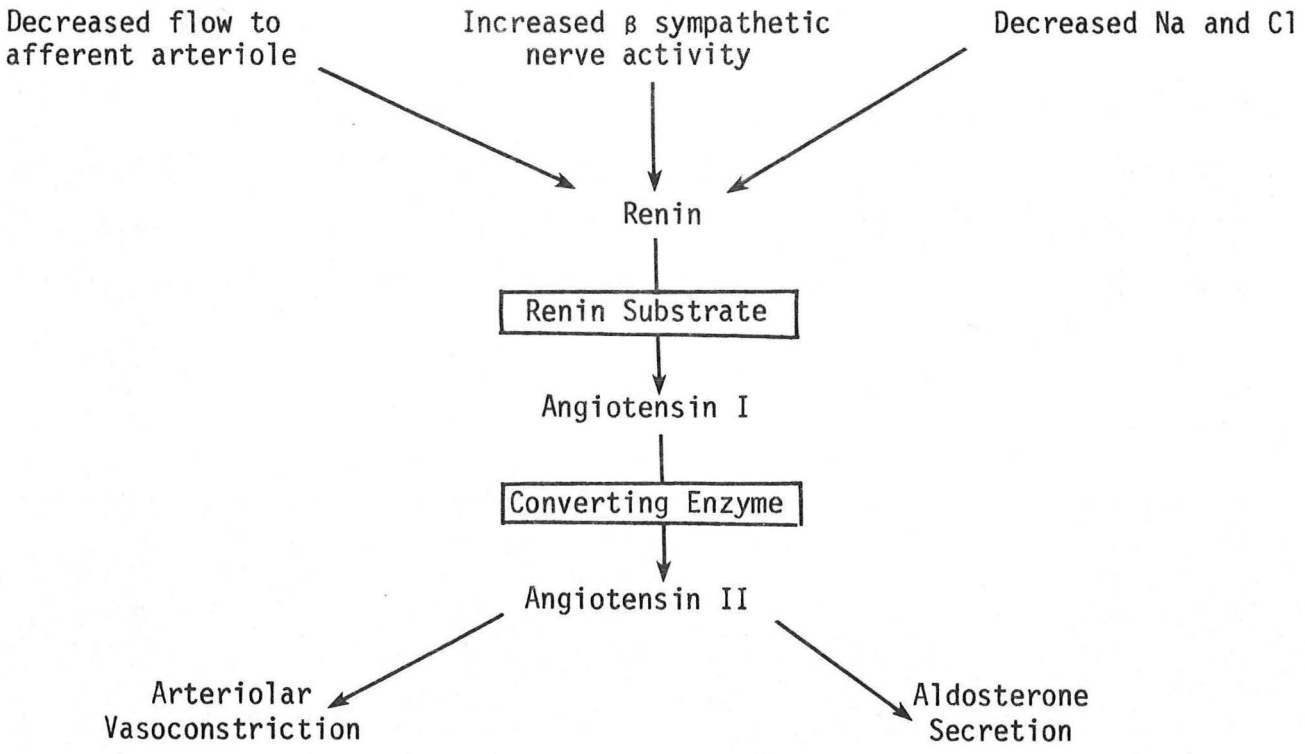

Fig. 5 Schematics of renin-angiotensin--aldosterone system

How does increased angiotensin II contribute to increased sodium and water reabsorption? It can do so by increasing the previously described filtration fraction and by increasing secretion of aldosterone. This issue has recently been examined by Ichikawa et al (26) who developed a rat model of myocardial infarction which they used to define the role of AII in renal Na retention in CHF. Their rats, like the earlier studies in humans, were characterized by reduced glomerular plasma flow rate and a decline in GFR. However, the decline in GFR was proportionately less than the decline in RPF so there was a rise in single nephron filtration fraction. In these studies they also measured the fractional Na reabsorption from the proximal tubule and found it to be elevated. The increase in FF was the result of a specific increase in glomerular efferent arteriolar resistance as was originally suggested by Merrill in 1945 (3). Since the rise in efferent arteriolar resistance was most likely the result of increased AII, Ichikawa and coworkers (26) used an angiotensin I converting enzyme inhibitor in their myocardial infarcted rats and demonstrated that this led to the return of glomerular plasma flow rate, single nephron filtration rate, efferent arteriolar resistance, and fractional reabsorption of proximal fluid toward normal values. Thus, they concluded that elevation and concentration of angiotensin II have a major role in the pathogenesis of salt and water retention in a model of CHF in a rat.

Angiotensin II also causes an increased secretion of aldosterone from the adrenal gland. Aldosterone is the primary hormone that stimulates active Na reabsorption from the cortical collecting duct (27-33). While elevated aldosterone concentrations do cause increased renal Na reabsorption, elevated aldosterone levels do not cause edema in normal

patients or in patients with primary aldosteronism. However, in a setting with decreased EABV with decreased delivery of salt to the collecting duct as a result of more enhanced fractional proximal tubule reabsorption of Na, aldosterone will contribute to further removal of sodium from the urine and thus a low fractional excretion of sodium. Thus, states with contracted EABV are associated with increased total body sodium.

It should be recognized, however, that increases in total body sodium are usually associated with hyponatremia and not hypernatremia. This is due to increased release of ADH associated with contracted EABV. ADH, in turn, causes increased water absorption from the collecting duct contributing to hyponatremia. It is interesting that a number of investigators have noted an inverse relationship between serum Na concentration and renin-angiotensin system in CHF (23, 24, 34, 35; Figure 6). Indeed, some investigators have used a low serum Na concentration as an index of high renin concentration but one must be cautious of this extrapolation because of the multifactorial control mechanisms for renin release and total balance of salt and water.

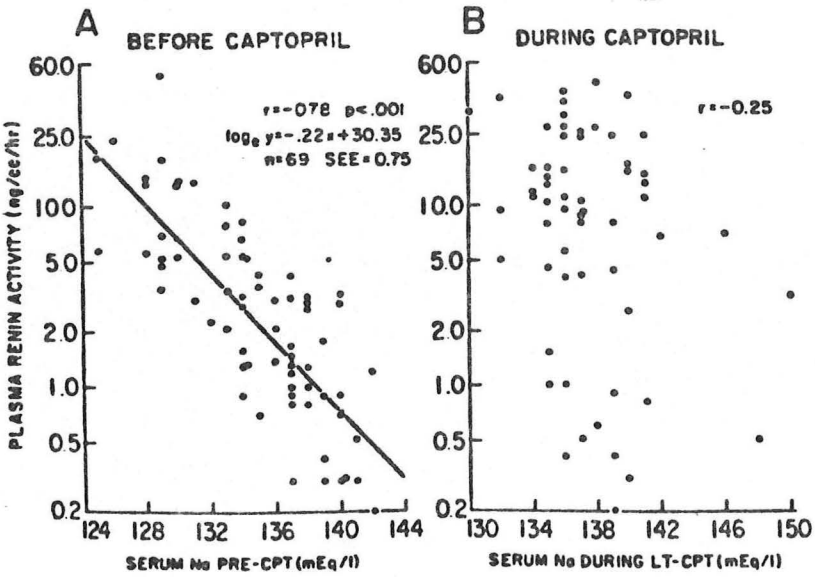

Fig. 6 Relation between serum sodium concentration and plasma renin activity before (A) and during (B) long-term treatment with captopril. LT-CPT = long-term treatment with captopril; Na = sodium; PRE-CPT = before captopril. Figure and legend reproduced from Packer et al (24).

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THE ROLE OF RENIN-ANGIOTENSION-ALDOSTERONE SYSTEM IN CLINICAL CONGESTIVE HEART FAILURE

Because of the great variability in patients with CHF, the role of the RAAS in the pathogenesis of CHF can best be evaluated using animal models. The initial studies in this area were by Watkins et al (36) where they determined the role of the RAAS in a conscious dog with CHF. The CHF was induced by inflation of a previously implanted cuff around the thoracic inferior vena cava or the pulmonary artery. One might argue about the adequacy of the model but their vena cava dogs developed the hemodynamic consequences of impaired cardiac function, while the dogs developed right-sided CHF over the course of several days with ascites and edema. The response of the RAAS was monitored from the time of constriction to the development of CHF. The renin activity rose within 15 minutes of the constriction and peaked within three days and gradually fell to control levels. Aldosterone values followed this same pattern, while urinary Na excretion was reduced in a recipocal fashion. Other investigators have also shown that the RAAS is activated early in CHF and returns toward normal with expansion of the extracellular fluid volume (37).

However, the role of RAAS in patients has been more controversial because of the variability in reported renin and aldosterone levels (19, 20, 38-44). It is for these reasons that Dzau et al (23) recently studied patients in early (less than a week) decompensated CHF and in patients with chronic but stable heart failure. In early decompensated CHF the plasma renin, aldosterone, and serum creatinine were all elevated, while in the chronic CHF group all of these variables were normal. Four patients were followed from acute decompensated state

until their CHF stabilized. Their plasma renin values were markedly elevated during acute CHF and returned toward normal with compensation of the CHF. They came to the reasonable conclusion that the activation of the RAAS in CHF depends largely on the acuteness of the patients studied (23). Dzau et al feel that the variability of the RAAS values reported in lituerature is due to the clinical status of the patient (23).

TREATMENT

The purpose of the treatment section of this Grand Rounds is to consider an approach to patients with acute myocardial decompensation in contrast to patients with chronic heart failure. By far the majority of patients with acute heart failure are characterized by low cardiac output (backward failure) though some patients have high output states and signs and symptoms of CHF. In each case, retention of salt and water is the hallmark of the heart failure.

In patients with low cardiac output, the basic approach is to increase the heart output. This can be accomplished by multiple drugs designed to: 1) increase myocardial contractility (inotropic agents); 2) decrease right- and left-sided filling pressures (preload reducing agents); and 3) decrease the pressure that the heart has to work against (afterload reducing agents). On the other hand, patients with high output failure[1] (at PMH mainly patients with sepsis), the salt and water excretion can be increased by agents that disproportionately decrease renal resistance to perfusion. In each of these cases a specific use of diuretics can be of benefit.

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[1]It is self evident that the primary therapeutic approach in these patients is to treat the cause of the high output failure.

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The clinical utility of inotropic agents and preload reducing agents has been reviewed well in a recent SWMS Grand Rounds which were subsequently published by Brian Firth (45). Thus, these agents will not be discussed. However, the main approach of these Grand Rounds is to give a renal view to the treatment of congestive heart failure by the use of inhibitors of renin-angiotensin-aldosterone system and the use of diurectics.

Captopril

The first reported use of arterial dilators to decrease the cardiac after load was from Stanley Taylor's group in 1971 when they used phentolamine, an alpha-receptor-blocking drug, in twelve patients with severe progressive heart failure due to ischemic heart disease (46). This resulted in a rapid improvement of symptoms that were associated with a reduction in left ventricular end diastolic and pulmonary artery mean pressures and an increase in stroke volume and cardiac output. Thus started one of the most important approaches to treatment of severe CHF. The list of commonly used vasodilators to reduce afterload in CHF now includes sodium nitroprusside, phentolamine, hydralazine, prazosin, trimethaphan, calcium-channel antagonists and captopril.

Captopril probably is the most effective of the afterload reducers listed. It is an orally effective angiotensin-converting enzyme (ACE) inhibitor. It is thought to work by competing competitively to the same active site on ACE as angiotensin I. Thus, it blocks the conversion of AI to AII, Figure 5. Captopril reduces total peripheral vascular resistances while having either no effect upon or increasing cardiac output. In heart failure it reduces both the preload and after load (47). Table 2 lists the potential mechanisms of captopril in patients with CHF (48).

TABLE II

POTENTIAL MECHANISMS OF CONVERTING ENZYME INHIBITORS IN PATIENTS WITH HEART FAILURE

Inhibition of AII formation resulting in arteriolar dilation
Inhibition of AII formation resulting in reduced aldosterone production
Inhibition of AII formation resulting in reduced NE release
Inhibition of AII formation resulting in "desensitization" of vascular tissue to constrictor substances
Inhibition of AII formation resulting in Ne biosynthesis
Inhibition of brain AII formation resulting in CNS sympathetic activity
Inhibition of AII resulting in improved right ventricular-pulmonary vasculature compliance
Direct α_1 adrenergic vascular receptor blockade (reqdires large doses in vitro)
Increase in local prostaglandin production with venodilation

AII = angiotensin II; NE = norepinephrine; CNS = central nervous system. Reproduced from Francis (48)

Inhibition of ACE in animal model of CHF gave the first promising results in the mid to late 1970's (35, 49, 51). In 1978 it was first reported to be effective in patients with CHF (52, 53). In patients with acute CHF, captopril causes a fall in renin and angiotensin as well as stabilization of CHF (23).

The most common cardiological problem for a nephrologist is a CHF patient who is being treated by conventional approaches for peripheral edema and develops progressive azotemia. Any further attempt at diuresing these patients will lead to worsening of pre-renal azotemia while administration of salt to correct contracted EABV will worsen

peripheral and pulmonary edema. Often these patients are on maximum inotropic agents and often various unloading agents have been of failure. Figure 7 from Dzau et al addresses just this type of patient (22).

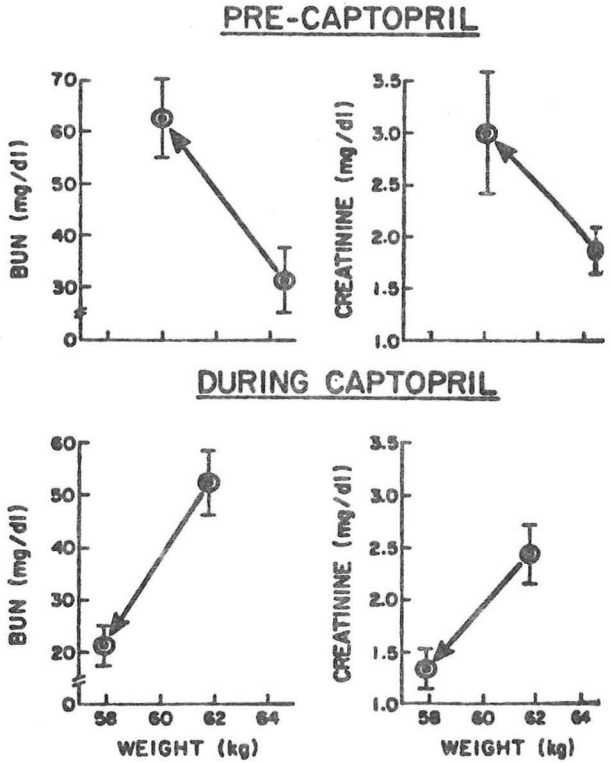

Fig. 7 Top panel shows events before captopril therapy, attempts at diuresis resulted in weight loss with progressive azotemia, reflected by a parallel increase in blood urea nitrogen (BUN) and serum creatinine concentrations. After institution of captopril therapy there was a parallel fall in blood urea nitrogen and serum creatinine concentration despite the initiation of a diuresis and clearing of edema reflected in the sharp drop in weight. Figure and legend reproduced from Dzau, et al (22).

In this study, weight loss pre-captopril was associated with a rise in BUN and Cr to unacceptable levels but after initiation of captopril in a dose to induce a fall in diastolic pressure of 10 mmHg there was a fall in BUN and Cr toward normal despite diuresis and weight loss. Admittedly, this study was not controlled or randomized, but it does portray impressive results in a group of patients with CHF and progressive azotemia. Many of us have seen similar anecdotal results.

The real issue is the ability to predict which patient will have a favorable response to captopril. From the laboratory and clinical studies available, it appears that most patients with contracted EABV and acutely elevated systemic vascular resistance with symptoms of CHF will benefit from a trial with an initial low dose of captopril (6.25 mg po)[2] with later titration to higher doses depending on blood pressure response. Using this approach, the physician will often note acute improvement of cardiac function associated with a decrease in vascular resistance. Indeed, double-blind randomized studies have noted prolonged improvement in cardiac and renal function with continuous captopril therapy (47, 54).

The real problem is the patient with hypotension and progressive azotemia. This combination is often seen acutely with sepsis and chronically in patients with liver disease with AV shunting and low EABV. Often these patients have normal or significantly increased cardiac outputs. Thus, further increases in cardiac output are not expected to be associated with parallel improvement in symptomatology. Also, these patients have low fractional excretion of sodium and chloride and behave as if the kidney is not being perfused in spite of high cardiac output. In an acute setting with sepsis, a Swan-Ganz catheter should be placed for monitoring pulmonary capillary wedge pressure. Providing that the Swan-Ganz catheter is giving accurate readings the wedge pressure should be raised to 15-20 mmHg with isotonic saline. If this causes a rise in systemic blood pressure, but without

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[2]This recommendation can be made only if the patient's diastolic blood pressure will tolerate an additional 10 mmHg drop.

significant increase in urine output, then captopril can be considered. It should be cautioned, however, that captopril has not been approved for use in patients with low mean blood pressures, and therefore, its use in this setting awaits appropriate clinical trials.

Similarly, the chronic patient with high-to-normal cardiac output but with rising BUN presents a problem. Often these patients are ambulatory. If their blood pressure will tolerate it, a trial with captopril can be considered. The initial try should be done in an MICU setting with careful monitoring of the hemodynamic status. If these patients tolerate captopril, then the loop diuretics become more effective in freeing the patient of edema without inducing azotemia (22). If, on the other hand, they do not tolerate captopril, one should not be too vigorous with diuretics. Rather, many of these patients will have better long-term improvements if they are allowed to remain on the "wet" side.

Diuretics

Diuretics increase the renal excretion of salt and water. Thus, they have an important role in the management of patients with retention of salt and water. However, diuretics are not without their dangers, especially in patients with contracted EABV. This is best illustrated by considering the Frank-Starling relationship depicted in Figure 9 (55).

When are diuretics indicated? They should be given to those patients who have compromised respiratory function due to retention of salt and water. Often these symptoms are subtle and only evident in a recumbent position. Also, diuretics often will allow a patient to eat a more palatable diet and thus will provide for a more compliant situation.

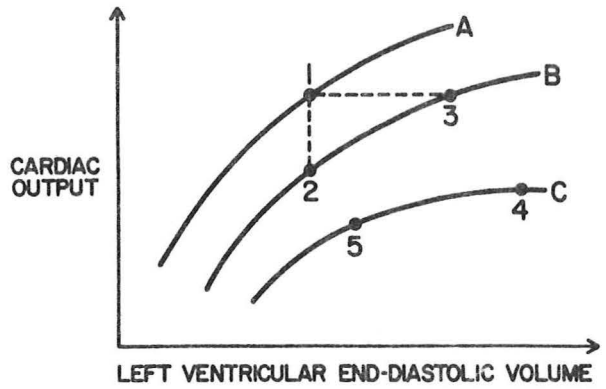

Fig. 8 The Frank-Starling relationship in CHF. Curve A: Normal myocardial contractility; Curve B: Mild myocardial failure; Curve C: Severe myocardial failure. With the onset of myocardial failure the patient moves from the normal reference point (1) on Curve A to point (2) on Curve B. Despite altered myocardial mechanics, the patient may increase cardiac output to the normal reference level by the retention of salt and water, leading him to point (3). With severe myocardial failure, the patient may move to point (4) on Curve C. With the use of cardiac glycosides and/or reduction in afterload, the patient may move to a more favorable curve, as from C to B. Diuretics are employed to control excessive fluid retention, but overdiuresis with resultant intravascular volume depletion may result in a lower cardiac output and move the patient from point (4) to point (5) on Curve C or point (3) to point (2) on Curve B. Figure and legend reproduced from Humes et al (55).

The least important reason to give a diuretic is to rid patient of cosmetically unattractive edema. However, some patients will pressure the physician enough that this will become an indication. Finally, diuretics are indicated in some non-edematous conditions. The most common of these if the antihypertensive effect of diuretics. While some of the diuretics have direct vascular effects clinically, the most important antihypertensive effect is the result of reduction of the extracellular fluid volume.

The clinical use of diuretics has been discussed in detail in several recent Grand Rounds. Figure 9 is a reproduction from one of these Grand Rounds which was recently published (56). It depicts the

site of action of the various categories of diuretics. It is evident that the diuretic categories should have different effects since they have different sites of action. Various diuretics should be considered for use in acute or semiacute decompensated heart failure.

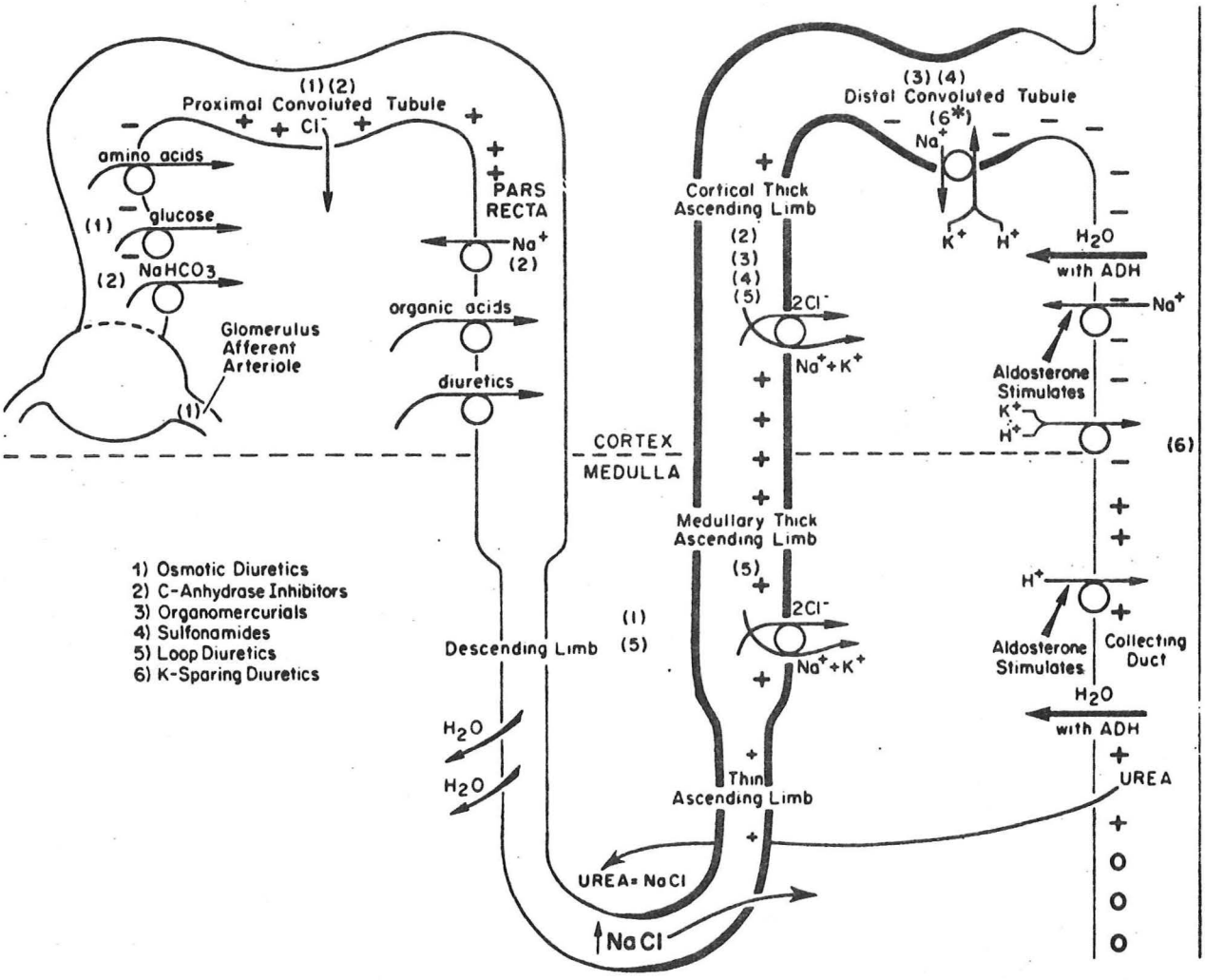

Fig. 9 Schematic of major transport processes along the mammalian nephron and the principal sites of action of the various groups of diuretics. The diuretic groups are referenced in the inset. The luminal "+" and "-" refer to the polarity of the transepithelial potential difference while the bold line along some nephron segments refers to osmotic water impermeability. Reproduced from Kokko (56).

Loop diuretics include ethacrynic acid, bumetanide and furosemide. Each of these diuretics must be secreted into the luminal side before they exert their pharmacological diuresis. Therapeutic doses should be individualized. However, without contraction of EABV and azotemia, satisfactory diuresis can be obtained by IV furosemide (40 mg IV bid), ethacrynic acid (50 mg IV bid), or bumetanide (1 mg IV bid). These diuretics have the same site of action, Figure 9, and have no known advantages over each other. During azotemia, the blood concentration of the diuretics has to be increased to obtain the same effective urinary concentrations due to competitive inhibition for secretory sites with organic acids which rise during uremia. Indeed, Brater et al (57) have examined patients with creatinine clearance of less than 20 cc/min and have noted that fractional excretion of Na was actually increased in these patients when compared to fractional excretion of furosemide. However, in contrast to normal patients, a much lower percentage of administered furosemide reached the urine in chronic renal failure patients. Under these circumstances, furosemide (or other loop diuretics) doses should be increased until the desired diuretic effect is achieved by obtaining appropriate urinary concentrations of furosemide. Furosemide doses can be raised to 400 mg IV bid. However, diuresis should not be forced in patients with severely contracted EABV and progressive azotemia.

If adequate diuresis is not obtained with loop diuretics, then a trial of metalozone is warranted. Metalozone partly inhibits net salt and water absorption from the proximal convoluted tubule in addition to having an effect across the thick ascending limb of Henle. Thus, it

will increase delivery of salt and water to the sites where the loop diuretics have their main effect. Metalazone dose should be individualized according to desired response and can be given up to 10 mg po qam. Life-threatening hypokalemia has been reported when metolazone has been used in combination with the loop diuretics. Therefore, it is mandatory to measure serum potassium concentrations on frequent intervals when metalazone is used in combination with loop diuretics.

None of the other categories of diuretics have a significant role in the treatment of acute congestive heart failure. Thiazides, as a group, are relatively "weak" diuretics in this situation and do not offer an advantage over the loop diuretics. Carbonic anhydrase inhibitors are even weaker diuretics. There is no indication to give osmotic diuretics and indeed these may worsen pulmonary edema if they are not excreted. The potassium-sparing diuretics also are weak diuretics in circumstances where acute diuresis is desired. Their main role is as adjunct diuretic to prevent hypokalemia in a more chronic setting.

SUMMARY

These grand rounds have called attention to the central role that the kidney has in salt and water homeostasis during acute congestive heart failure. Clearly the therapeutic approach needs to be individualized according to patients' symptoms and responses. However, clinical improvements in an increasing number of patients have been quite gratifying by judicious use of captopril and diuretics in addition to inotropic agents.

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