The American Journal of Medicine

VOL. XXV OCTOBER, 1958 No. 4

Editorial

Re-examination of Salt and Water Retention in Congestive Heart Failure*

Significance of Renal Filtration Fraction

SINCE the work of Starr [*1*] who concluded that the increase in venous pressure observed in congestive heart failure is due to an increased plasma volume, the "forward" theory of heart failure has been the subject of much research attempting to describe the precise mechanisms by which the extracellular volume is expanded during cardiac decompensation. Warren and Stead [*2*] emphasized the diminished renal excretion of sodium and water as the cause of fluid retention in patients in whom edema forms. The cause of this renal salt and water retention was investigated by Merrill [*3*], who found that in patients in severe cardiac failure, filtration rates were reduced to one-third or one-half of normal, and renal blood flow was reduced to an even greater degree. Similar decreases in glomerular filtration rate had been observed by Seymour et al. [*4*], and Merrill theorized that renal ischemia leads to a decreased glomerular filtrate which is almost completely reabsorbed by normally functioning transport systems. Decreases in glomerular filtration rate (GFR) and renal blood flow (RBF) have been confirmed by numerous investigators [*5–9*].

However, much evidence has been reported which does not substantiate this theory: (1) Cases of cardiac failure in man have been reported in which GFR is within normal limits [*10–12*]. (2) Diuresis (spontaneous or induced by bedrest or therapeutics other than diuretics) occurring in cardiac compensation is often not accompanied by an increase in glomerular filtration rate [*4,10,12,13*]. (3) Renal retention of salt in experimental heart failure in the dog takes place before any decrease in filtration rate is observed and may continue for long periods of time without any reduction in filtration rate [*14–16*].

These experiments demonstrated that the decreased renal sodium and water excretion in heart failure showed no constant relationship to filtered load. Moreover, since the clinical symptoms of heart failure (edema, venous distention, basilar pulmonary rales, etc.) are quite gross, the work on experimental animals indicates that the earliest stages of salt retention in most patients may occur before any decrease in filtration rate. It seemed evident, therefore, that the primary cause of salt retention was an increased tubular reabsorption of electrolytes and water. It has been shown that in patients with congestive heart failure and edema, the production as well as excretion of aldosterone are much greater than normal [*17–20*]. On the basis of these observations it is concluded that

* This work was supported by the American Heart Association, TJ56-198; the Life Insurance Medical Research Fund, G-57-46; the National Institute of Arthritis and Metabolic Diseases, U.S. Public Health Service, A-1740; and a teaching grant from the U.S. Atomic Energy Commission, BM-2-58A.

increased tubular reabsorption as a result of increased aldosterone production is the mechanism of salt retention in congestive failure before there is any change in GFR. The stimulus for this increased aldosterone production is believed to occur by way of an arterial receptor mechanism which is triggered by a decreased *effective* blood volume [*21*].

It should be noted, however, that these increased aldosterone levels have been demonstrated in patients or dogs with fully developed congestive failure, rather than in those with the early, clinically undetectable stages of the disease during which the onset of salt retention is occurring. It has also been shown that in compensated patients urinary levels of aldosterone still remain pathologically elevated, although somewhat diminished from former levels [*22,23*], i.e., diuresis and sodium balance can be affected by "standard therapeutic measures" (Gordon gives no other details) in the presence of large quantities of aldosterone. Moreover, in patients suffering from primary aldosteronism [*24*] polyuria is present, as contrasted with the water retention in patients with congestive heart failure. The following explanation has been offered by Johnson and Conn [*21*]: The pitressin resistant polyuria of primary aldosteronism is due to effects of chronic potassium deficiency produced by the aldosterone. "The rarity of kaliopenia in congestive heart failure with secondary aldosteronism may be due to the inability to increase the GFR. A load of sodium sufficiently large to bring about potassium depletion never reaches the distal tubule for exchange with potassium." This explanation meets with the same difficulties described in the first section, i.e., it cannot account for the cases in which a normal GFR is present, since in these patients and dogs, ample amounts of sodium would reach the distal tubule. The most damaging evidence against aldosterone being primarily responsible for salt retention is the work of Davis, Howell and Hyatt [*15*], who performed adrenalectomy in eight dogs, allowed a control period during recovery, and then induced a progressive cardiac failure by partial ligation of the pulmonary artery. During the control period, the dogs were maintained in sodium balance by administration of 3 mg./day DCA (25 mg./day cortisone was given throughout the experiments). After partial pulmonary artery ligation and the development of clinical signs of cardiac failure it was found that GFR had decreased in only four of the eight dogs. Yet all eight dogs exhibited salt retention on a dosage of only 1 mg./day DCA, whereas, as already mentioned, 3 mg./day DCA was required for salt balance before cardiac failure was induced. This retention ranged from 50 to 80 per cent of the salt intake. If administration of DCA was discontinued, diuresis occurred, indicating that a small amount of hormone was necessary for retention to occur. If the dose of DCA given was increased from 1 to 25 mg./day the retention grew progressively greater, becoming almost complete at very high dosage levels, indicating that the increased aldosterone found in congestive failure certainly increases salt retention. However, these experiments demonstrate clearly that salt retention would still occur even in the presence of reduced amounts of hormone, and that aldosterone is not the primary or initiating factor. Since GFR was normal in half the animals, the conclusion must be drawn that the primary cause of salt retention in congestive heart failure is an increased tubular reabsorption of electrolyte and water which is not dependent on adrenal hormones. We believe this factor to be the presence of an increased renal filtration fraction.

FILTRATION FRACTION IN CONGESTIVE HEART FAILURE

It is generally accepted that approximately 85 per cent of filtered sodium is reabsorbed actively in the proximal tubule, followed by the passive reabsorption of an equivalent amount of water necessary to maintain isotonicity within the tubule. Almost all the remaining sodium is then actively reabsorbed in the distal tubule possibly under the influence of aldosterone, water most likely following passively in the presence of ADH. On the basis of these physiologic mechanisms, a decreased excretion of sodium chloride could be explained only by a decreased filtered load or by increased enzyme activity, usually presumed to be caused by aldosterone. Within the past year a new method called "stop flow" analysis [*25–27*], developed in our laboratory, has made possible a practical and easily applied procedure for the direct localization and quantification of function of the various nephron segments. Using this procedure, it was found that during the infusion of a strong osmotic diuretic (mannitol), the sodium concentration of the fluid reabsorbed from the proximal tubule remained identical with that of plasma, i.e., the proximal tubule was unable to lower sodium concentration even in

the presence of large amounts of an osmotic diuretic. These and other experiments, and the conclusions drawn from them are described in detail elsewhere [*28*]. We have been led to believe that both water and sodium reabsorption by the proximal tubule is a passive process, mediated through the colloid osmotic pressure within the peritubular capillaries. Since the hydrostatic pressures within the peritubular capillaries and the proximal tubular lumens are equal, as shown by Wirz [*29*] and by Gottschalk and Mylle [*30*], the plasma protein within the capillaries exerts an osmotic force favoring water reabsorption, which is not offset by any opposite force within the tubule (essentially no protein is filtered through the glomerulus). Sodium, concentrated by the reabsorption of water, then moves passively to maintain isotonicity. In such a system filtration fraction would become of major importance in determining this colloid osmotic pressure (COP). Under normal conditions one-fifth of the renal plasma flow is filtered at the glomerulus (filtration fraction = 0.2), increasing the protein concentration of the plasma which then flows into the efferent arteriole. For example, the normal plasma COP of 25 mm. Hg would be elevated to 31 mm. Hg after filtration had occurred. This would then be the effective pressure causing proximal reabsorption of water and sodium. Consider now a situation in which the glomerular filtrate was 40 per cent of the renal plasma flow, i.e., the filtration fraction rose to 0.4. The COP would now be changed from 25 to 42 mm. Hg after filtration, thus promoting increased proximal reabsorption. This view is substantiated by the work of Vogel [*31,32*] who showed that infusion of colloid into the renal portal system of the frog greatly decreased the excretion of water and electrolytes without affecting GFR. This also explains the results of Elkinton and co-workers [*33*], and Selkurt [*34*] who reported that acute reductions in renal blood flow (accomplished by administration of neosynephrine and aortic narrowing, respectively), not sufficient to cause reduction in GFR, resulted in reductions of sodium excretion, from 0.336 to 0.200 mEq./minute in the latter paper. Conversely, the former workers reported that increasing RBF without changing GFR resulted in increased sodium excretion. Similar results have been obtained by Shipley and Study [*35*], who increased RBF by increasing renal arterial blood pressure and found an increase in urine flow but no change in GFR. A more detailed study of the literature has been described previously [*28*].

The ability of the kidney to stabilize GFR in the presence of a wide range of RBF is one of the major features of renal hemodynamics. Even when GFR is changed by large increases or decreases in RBF, the GFR changes are much less than the changes in RBF [*36*], i.e., the poorly understood phenomenon of "auto-regulation" maintains GFR by changing filtration fraction.

The existence of this mechanism in congestive heart failure is readily apparent. Even in those patients with reduced GFR [*3–9*] the RBF, when measured, was always found to be reduced to a much greater extent, resulting in an increased filtration fraction. The important question, however, was whether or not such a mechanism could explain the cases reported earlier in which compensation or decompensation occurred without any change in filtration rate.

Cardiac Failure in Man in Whom GFR is within Normal Limits. Heller and Jacobson [*10*] studied patients in the edematous state and found filtration rates as high as 105 ml./minute, but the lowest filtration fraction was 0.323, the average being 0.405 ± 0.083, as compared to a normal average of 0.174 ± 0.023. Davis and Shock [*11*] found normal filtration rates in four patients in congestive failure. All had very reduced RBF, with filtration fractions from 0.60 to 0.38. Sinclair-Smith et al. [*12*] followed a cardiac patient as decompensation occurred. There was no change in GFR but RBF was greatly reduced, raising filtration fraction to 0.49 from the value of 0.23 during the previous period of compensation.

The Occurrence of Compensation Not Accompanied by an Increase in GFR. Seymour and his colleagues [*4*] actually found slight decreases in GFR during compensation in two patients. In both cases, RBF showed approximately 50 per cent increases, resulting in a lowering of filtration fraction to 0.38 and 0.30 from previous values of 0.74 and 0.48. It is of interest to note that the patient with the filtration fraction of 0.74 had a normal GFR while in severe congestive failure. Heller and Jacobson [*10*] effected compensation in patients by digitalis, bedrest and salt restriction. Filtration rate increased in only two of four patients, but RBF increased in all, resulting in a reduction of the average filtration rate from 0.48 to 0.32. Sinclair-Smith et al. [*12*] effected recovery in a patient by the use of digitalis. GFR did not change but RBF

greatly increased, lessening filtration fraction from 0.54 to 0.23 at the end of compensation. Brod and Fejfar [*13*] studied nineteen patients, in various states of heart failure, at night during spontaneous diuresis. They reported variable changes in GFR, often showing only very slight rises, which in their opinion could not explain the magnitude of the diuresis. However, in every case, diuresis was accompanied by a large increase in RBF and a fall in filtration fraction.

Renal Retention of Salt in Experimental Heart Failure with No Change in GFR. Barger, Rudolph and Yates [*14*] observed that in dogs with surgically created valvular lesions of the heart, the salt retention which occurred during the early stages of failure was not accompanied by any decrease in GFR. However, all dogs showed markedly decreased RBF with filtration fractions up to 0.4. As discussed earlier, only one-half of the adrenalectomized dogs of Davis, Howell and Hyatt [*15*] showed a decrease in GFR during the onset of failure resulting from partial pulmonary artery ligation. RBF decreased and filtration fraction rose in seven of eight dogs (no specific excretory data are given for dog number 8). It is also significant that only one dog responded to the administration of digoxin. Only in this dog did administration of the drug cause improvement in "renal circulation" (no figures given), resulting in a natriuresis which occurred in spite of the administration of 3 mg./day DCA, whereas 1 mg./day DCA had caused retention before the circulatory improvement. These authors also report findings [*16*] on non-adrenalectomized dogs with similarly induced heart failure. Only five of seven showed any reduction in GFR, but RBF fell in every case, the average reduction being 31 per cent, resulting in an equivalent rise in filtration fraction.

It is evident from this discussion that the salt retention of congestive heart failure is almost invariably associated with changes in renal filtration fraction. This intimate relationship has been noted and speculated upon by several investigators, including Barger [*37*] who stated that "a rise in filtration fraction implies an abnormally high colloid osmotic pressure in the first portion of the peritubular capillaries. Whether such a force may tend to accelerate the tubular transport of the filtrate is not known." However, if the reabsorption of sodium and water in the proximal tubule is passive and dependent upon the COP in the peritubular capillaries, then the role of filtration fraction as the primary and essential factor in the renal salt retention of cardiac failure becomes clear.

SEQUENCE OF PHYSIOLOGICAL MECHANISMS LEADING TO FLUID RETENTION AND CONGESTIVE FAILURE

Whenever the cardiac output becomes inadequate to meet the total metabolic requirements of the patient with cardiac disease, RBF is decreased (the mechanisms responsible for this are not understood at the present time). This decrease in RBF, with no or very slight change in GFR, results in an increased filtration fraction, which causes an abnormally large rise in the COP within the peritubular capillaries. This increased COP promotes tubular reabsorption, resulting in the retention of salt and water. This series of events must occur quite frequently and in exaggerated form in patients with a weakened myocardium and reduced cardiac reserve, resulting in a progressive retention of salt and water which the individual is not capable of completely excreting during periods of relative inactivity. There is a gradual expansion of the extracellular volume and a rise in venous pressure. The heart becomes unable to pump the increased venous return, RBF is chronically reduced, resulting in a constantly increased filtration fraction and marked fluid retention. Venous pressure rises higher, resulting in transudation of fluid. It is probably this event [*20,21*], or the decreased effective blood volume [*21*], that stimulates the production of increased amounts of aldosterone. This combination of increased filtration fraction and increased production of aldosterone, as well as the later development of decreased GFR, combine to produce almost complete salt and water retention with the development of the full-blown clinical picture of severe congestive heart failure. The possibility that the mechanisms described in this paper may play an important role in the nephrotic syndrome and cirrhosis also deserves serious consideration.

ARTHUR J. VANDER, A.B.,
RICHARD L. MALVIN, PH.D.,
WALTER S. WILDE, PH.D.,
and LAWRENCE P. SULLIVAN, M.S.
Department of Physiology,
School of Medicine,
University of Michigan,
Ann Arbor, Michigan

REFERENCES

1. STARR, I. Role of the "static blood pressure" in abnormal increments of venous pressure, especially in heart failure. II. Clinical and experimental studies. *Am. J. M. Sc.*, 199: 40, 1940.
2. WARREN, J. V. and STEAD, E. A., JR. Fluid dynamics in chronic congestive heart failure. An interpretation of the mechanisms producing edema, increased plasma volume, and elevated venous pressure in certain patients with prolonged congestive failure. *Arch. Int. Med.*, 73: 138, 1944.
3. MERRILL, A. J. Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as the primary cause of edema. *J. Clin. Invest.*, 25: 389, 1946.
4. SEYMOUR, W. B., PRITCHARD, W. H., LONGLEY, L. P. and HAYMAN, T. M., JR. Cardiac output, blood and interstitial fluid volumes, total circulating serum protein and kidney function during cardiac failure and after improvement. *J. Clin. Invest.*, 21: 229, 1947.
5. MOKOTOFF, R., ROSS, G. and LEITER, L. Renal plasma flow and sodium reabsorption and excretion in congestive heart failure. *J. Clin. Invest.*, 27: 1, 1948.
6. AAS, K. and BLEGEN, E. The renal blood flow and the glomerular filtration rate in congestive heart failure and some other clinical conditions. *Scandinav. J. Lab. & Clin. Invest.*, 1: 22, 1949.
7. BLEGEN, E. Kidney function in heart failure. *Scandinav. J. Clin. & Lab. Invest.*, 1: 298, 1949.
8. MILLER, B. F., LEAF, A., MAMBY, A. R. and MILLER, Z. Validity of the endogenous creatinine clearance as a measure of glomerular filtration rate in the diseased human kidney. *J. Clin. Invest.*, 31: 309, 1952.
9. WESTON, R. E., ESCHER, D. J. W., GROSSMAN, J. and LEITER, L. Mechanisms contributing to unresponsiveness to mercurial diuretics in congestive failure. *J. Clin. Invest.*, 31: 901, 1952.
10. HELLER, B. I. and JACOBSON, W. E. Renal hemodynamics in heart disease. *Am. Heart J.*, 39: 188, 1950.
11. DAVIS, J. O. and SHOCK, N. W. The effect of theophylline ethylene diamine on renal function in control subjects and in patients with congestive heart failure. *J. Clin. Invest.*, 28: 1459, 1949.
12. SINCLAIR-SMITH, B., KATTUS, A. A., GENEST, J. and NEWMAN, E. V. The renal mechanism of electrolyte excretion and the metabolic balance of electrolytes and nitrogen in congestive cardiac failure; the effects of excerise, rest and aminophyllin. *Bull. Johns Hopkins Hosp.*, 84: 369, 1949.
13. BROD, J. and FEJFAR, Z. The origin of edema in heart failure. *Quart. J. Med.*, 19: 187, 1950.
14. BARGER, A. C., RUDOLPH, A. M. and YATES, E. F. Sodium excretion and renal hemodynamics in normal dogs, dogs with mild valvular lesions of the heart and dogs in frank congestive heart failure. *Am. J. Physiol.*, 183: 595, 1955.
15. DAVIS, J. O., HOWELL, D. S. and HYATT, R. E. Sodium excretion in adrenalectomized dogs with chronic cardiac failure produced by pulmonary artery constriction. *Am. J. Physiol.*, 183: 263, 1955.
16. DAVIS, J. O., HYATT, R. E. and HOWELL, D. S. Right-sided congestive heart failure in dogs produced by controlled progressive constriction of the pulmonary artery. *Circulation Res.*, 3: 252, 1955.
17. DEMING, Q. B. and LUETSCHER, J. A., JR. Bioassay of desoxycorticosterone-like material in urine. *Proc. Soc. Exper. Biol. & Med.*, 73: 171, 1950.
18. SINGER, B. and WENER, J. Excretion of sodium retaining substances in patients with congestive heart failure. *Am. Heart J.*, 45: 795, 1953.
19. AXELROD, B. J., CATES, J. E., JOHNSON, B. B. and LUETSCHER, J. A., JR. Aldosterone in urine of normal man and of patients with edema; its increased recovery after hydrolysis with acid and with beta-glucuronidase. *Brit. M. J.*, 1: 196, 1955.
20. DAVIS, J. O., PECHET, M. M., BALL, W. C., JR. and GOODKIND, M. J. Increased aldosterone secretion in dogs with right-sided congestive heart failure, and in dogs with thoracic inferior vena cava constriction. *J. Clin. Invest.*, 36: 689, 1957.
21. JOHNSON, R. D. and CONN, J. W. Aldosterone, antidiuretic hormone, and congestive heart failure. *Mod. Concepts Cardiovas. Dis.*, 27: 431, 1958.
22. GORDON, E. S. Role of aldosterone in congestive heart failure. *J. Lab. & Clin. Med.*, 46: 820, 1955.
23. DUNCAN, L. E., JR., LIDDLE, G. W. and BARTTER, F. C. Effect of changes in body sodium on extracellular fluid volume and aldosterone and sodium excretion by normal and edematous men. *J. Clin. Invest.*, 35: 1299, 1956.
24. CONN, J. W. Presidential address. Central Society for Clinical Research. II. Primary aldosteronism, a new clinical syndrome. *J. Lab. & Clin. Med.*, 45: 3, 1955.
25. MALVIN, R. L., SULLIVAN, L. P. and WILDE, W. S. Stop flow analysis of renal tubule localization *Physiologist*, 1: 1, 1957.
26. MALVIN, R. L., WILDE, W. S. and SULLIVAN, L. P. Localization of nephron transport by stop flow analysis. *Am. J. Physiol.*, 194: 135, 1958.
27. WILDE, W. S. and MALVIN, R. L. Graphical placement of transport segments along the nephron from urine concentration pattern developed with stop flow technique. *Am. J. Physiol.* (In press.)
28. MALVIN, R. L., WILDE, W. S., VANDER, A. J. and SULLIVAN, L. P. Localization and characterization of sodium transport along the renal nephron. *Am. J. Physiol.* (In press.)
29. WIRZ, H. Drukmessung in Kapillaren und Tubuli der Niere durch Mikropunktion. *Helvet. physiol. et pharmacol. acta*, 13: 42, 1955.
30. GOTTSCHALK, C. W. and MYLLE, M. Micropuncture study of pressures in proximal tubules and peritubular capillaries of the rat kidney and their relation to ureteral and renal venous pressures. *Am. J. Physiol.*, 185: 430, 1956.
31. VOGEL, G., HEYM, E. and ANDERSSOHN, K. Versuche zur Bedeutung kolloidosmotischer Druckdifferenzen für einen passiven Transportmechanismus in den Nierenkanalchen. *Ztschr. ges. Exper. Med.*, 126: 485, 1955.
32. VOGEL, G. and HEYM, E. Untersuchungen zur Bedeutung kolloidosmotischer Druckdifferenzen für den Mechanismus der isosmotischen Flüssigkeits-resorption in der Niere. *Pflüger's Arch. ges. Physiol.*, 262: 226, 1956.

33. ELKINTON, T. R., CROSLEY, A. P., JR., BARKER, H. G. and CLARK, J. K. Alterations in renal hemodynamics and excretion of electrolytes. *Federation Proc.*, 9: 37, 1950.
34. SELKURT, E. E. Physical factors in relation to electrolyte and water excretion. In: Renal Function, p. 103. New York, 1952. Josiah Macey, Jr. Foundation.
35. SHIPLEY, R. E. and STUDY, R. S. Changes in renal blood flow, extraction of inulin, glomerular filtration rate, tissue pressure and urine flow with acute alterations of renal artery blood pressure. *Am. J. Physiol.*, 167: 676, 1951.
36. SMITH, H. W. The Kidney, Structure and Function in Health and Disease. New York, 1951. Oxford University Press.
37. BARGER, A. C. Na retention in congestive heart failure. *Metabolism*, 5: 480, 1956.