Studies on Water Excretion Following Intravenous Hydration and the Administration of Pitressin or Nicotine in Congestive Heart Failure

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The diuretic response to intravenous infusions of 5 per cent glucose in water and the antidiuretic response to intravenous injections of nicotine salicylate and aqueous Pitressin, during maximal water diuresis, were studied in normal subjects and patients in congestive failure of varying severity. Patients in moderately severe congestive failure exhibited normal diuretic responses during the periods of intravenous hydration and normal antidiuretic responses following nicotine or Pitressin injections. Patients in more severe congestive failure failed to achieve comparable diuretic responses, following intravenous hydration; in the course of this, signs of increasing congestive failure developed, which were associated with further decrease in urine flows, at times, without any further decrease in renal hemodynamics. These studies confirm the impression that patients in moderate congestive failure have neither increased sensitivity to, nor reduced ability to, inactive endogenous or exogenous antidiuretic hormone. In addition, the observation, that patients in more severe failure do not achieve adequate water diuresis during intravenous hydration, suggests that sustained production of antidiuretic production, independent of normal osmoreceptor control, may be contributing to their fluid retention.

Evidence has accumulated that under certain circumstances in congestive failure mechanisms leading to the retention of water in excess of sodium may be activated. Metabolic studies from several laboratories have established that in cardiac patients the weight changes during the accumulation or removal of edema fluid are often greater than anticipated on the basis of the observed sodium balances. In addition, there have been reports that urine of edematous cardiac patients may contain increased amounts of antidiuretic material. More recently, it has been demonstrated that, in patients on low salt diets, retention of water without sodium, leading to increasing edema, hyponatremia and hypochloremia, may occur when chronic congestive failure is acutely intensified by the development of severe respiratory infection, digitalis toxicity or escape from adequate digitalization. However, patients in congestive failure ordinarily can achieve water diuresis in response to intravenous hydration and exhibit no increased sensitivity to aqueous Pitressin. Therefore, it was suggested that this water retention, occurring despite extracellular hypotonicity, may reflect sustained posterior pituitary antidiuretic hormone production, presumably independent of osmoreceptor control and induced by the inadequacy of the cardiac output relative to the body's metabolic requirements.

The present study is a comparison of the diuretic and antidiuretic responses of subjects without heart disease and patients in congestive failure of varying severity, who were given intravenous water loads and, whenever feasible, intravenous injections of aqueous Pitressin and of nicotine salicylate, which is known to induce discharge of posterior pi-

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tuitary antidiuretic hormone. The data permit evaluation of the response to exogenous and endogenous antidiuretic material, and of the influence of the severity of congestive failure on water diuresis during intravenous hydration.

**Methods and Materials**

The 19 subjects of this study included 14 patients with chronic rheumatic heart disease and five without heart disease. Seven of the patients (A. E., A. McD., V. B., A. G., G. S., M. F., and K. S.) were clinically classified as being in moderately severe failure. They could be maintained relatively comfortable and free of edema by bed rest, a sodium intake of 0.5 to 1.0 Gm., digitalis, and the periodic administration of mercurial diuretics. In contrast, six others (B. K., M. H., A. S., M. G., C. L. and E. R.), who responded only transiently to vigorous therapy and followed a progressively downhill course, were considered to be in severe congestive failure. One cardiac patient (G. G.), who had undergone mitral valve commissurotomy several months earlier for peripheral embolization, was maintained on digitalis, but exhibited no hemodynamic or clinical evidence of congestive failure. It should be noted that the cardiac patients were maintained on a low sodium diet, whereas the noncardiac subjects were on a regular diet.

Studies were performed with the patients semi-recumbent and in the postabsorptive state. About one hour after administering approximately 600 ml. of water orally, a soft rubber, multi-holed, urethral catheter was inserted and an indwelling needle placed in the femoral artery. After control blood samples were withdrawn, induction of diuresis was attempted by giving a constant intravenous infusion* of 5 per cent glucose in water, generally containing sufficient potassium acetate or phosphate to maintain a slightly positive potassium balance. Except when urine flows exceeded 10 ml. per minute, urine collection periods, which varied in duration inversely with urine flow, were terminated by injections of sterile water and air into the bladder.

When urine flow reached fairly constant maximal values, a 0.3 milliunit per kilogram dose of aqueous Pitressin was given intravenously, and urine collections were continued until the flow returned to control levels. Then, nicotine salicylate was given intravenously in a dose of 2 to 6 mg. and the antidiuretic response followed as before. The higher doses of the alkaloid were given to smokers and to larger patients. In three patients (V. B., A. McD. and B. K.), the sequence was reversed, the nicotine being given first.

After completion of the water loading-Pitressin study, the clinical condition of several of the patients (G. S., A. G. and A. E.) interdicted the administration of nicotine. In five of the patients in severe congestive heart failure, neither drug was administered because adequate diuresis could not be achieved by intravenous hydration.

In some patients, inulin and para-aminohippurate clearances were measured throughout the studies. In others, the endogenous creatinine clearance was determined as an index of glomerular filtration rate.

Analyses of blood and urine samples were performed by methods described in previous publications from this laboratory.** Urine and serum total solute concentrations were measured by determining freezing point depression with a thermistor osmometer.*

**Results**

**Response of Normal Subjects to Intravenous Water Loads and Pitressin**

All five normal subjects, during hydration, reached maximal urine flows equal to or slightly greater than the infusion rate of 10 to 20 ml. per minute. Following Pitressin, the antidiuresis persisted for 40 to 60 minutes, reaching maximal flows of 1.2 to 5.7 ml. per minute (fig. 1). No consistent changes in electrolyte excretion or renal hemodynamics were observed, other than transient falls, attributed to “urinary tract dead space”. Serum electrolyte concentrations varied in accord with the body fluid changes during hydration and antidiuresis (fig. 2).

**Response of Patients in Moderately Severe Congestive Heart Failure to Intravenous Water Loads and Pitressin**

In order to obviate untoward changes in circulatory dynamics, the patients in moderately severe congestive failure were given 5 per cent glucose infusions at rates which did not exceed 10 ml. per minute.

Five of the seven achieved maximal urine flows approximating the rate of infusion, whereas two (M. F. and A. E.) achieved maximal urine flows of only 6.8 and 8 ml. per minute, respectively (fig. 3). Following Pitressin, the flows fell to 0.7 to 2 ml. per minute, the antidiuresis persisting 50 to 70 minutes. One

* Constancy of infusion rate was maintained by use of a Bowman infusion pump.

** Manufactured by Fiske Associates, Boston, Mass.
subject (A. G.), after attaining a maximal flow of 10.4 ml. per minute, demonstrated a spontaneous fall to 5.7 ml. per minute, but subsequently responded like the others to Pitressin. The changes in renal hemodynamics

![Graph showing urine flow over time](image1)

**Fig. 1.** The antidiuretic response of control subjects to the intravenous injection of 0.3 mU of aqueous Pitressin per kilogram of body weight, at the point of maximal diuresis during constant infusion of 5 per cent glucose in water solution. Note that zero time indicates the time of injection of aqueous Pitressin.

![Graph showing antidiuretic response](image2)

**Fig. 2.** The effects on urinary electrolyte and water excretion and renal hemodynamics, following intravenous injections of aqueous Pitressin and nicotine salicylate, in a typical control subject (R. S.), receiving a continuous infusion of 5 per cent glucose in water at the rate of 10 ml. per minute.

and electrolyte excretion again reflected the influence of urinary tract "dead space" during periods of acute antidiuresis and diuresis (figs. 4 and 5).

One patient (B. K.) in severe failure, with intractable anasarca, achieved a maximal urine flow of only 4.7 ml. per minute after receiving a 5 per cent glucose in water infusion for 72 minutes at a rate of 5.7 ml. per minute (fig. 6). Although her serum osmolarity continued to fall, subsequently her urine flow gradually declined to 2.8 to 3.3 ml. per minute without sig-
significant change in her inulin clearance. When given Pitressin following a partial recovery from a prolonged nicotine antidiuresis (167 minutes), her urine flow fell from 2.8 ml. per minute to 0.58 ml. per minute and within 67 minutes rose to 3.8 ml. per minute, at which time the infusion was discontinued.

Response of Normal Subjects and Patients in Moderate Congestive Heart Failure to Nicotine Administration during Intravenous Hydration

All five normal patients were given intravenous injections of nicotine salicylate. The resulting antidiuresis persisted for 50 to 100 minutes with minimal urine flows ranging from 0.7 to 2.9 ml. per minute (fig. 7) and bore no apparent relationship to the dose, even when this was corrected for body weight. However, it seemed to be increased in those patients who had severe and protracted reactions such as nausea, vomiting, dizziness, headache, paresthesia or local venous spasm.

In four of the six patients in moderately severe congestive failure (fig. 8), the nicotine antidiuresis was of equivalent intensity, but tended to be of somewhat longer duration than in the normal subjects. In one cardiac patient...
1 ml per minute. In one patient (M. F.), the antidiuresis persisted for three and one half hours, at which time the study was discontinued. During this part of the study, none of the normal subjects or patients had any significant changes in renal hemodynamics or electrolyte excretion (figs. 2, 4, 5, and 6), with the exception of C. C., a normal subject who had a transient rise in endogenous creatinine clearance with natriuresis and chloruresis following the nicotine antidiuresis.

Response of Patients in Severe Congestive Failure to Intravenous Water Loading

The diuretic response to intravenous infusions of 5 per cent glucose in water was also investigated in five patients who clinically were considered to be in more advanced congestive failure.

Patient M. H. was studied on three occasions, during the first two of which the infusion was administered at 10 ml per minute. During the first procedure, her urine flow reached a peak of 1.4 ml per minute, then gradually fell to 0.5 ml per minute 80 minutes later as she developed increasing dyspnea, cough, neck vein congestion, tachycardia and other signs of congestive failure. Three weeks later, despite some clinical improvement, which was reflected by the rise in her serum sodium to 136 mEq per liter and by her higher creatinine clearance, her urine flow achieved a maximum of only 2.1 ml per minute, and declined as before with signs of increasing failure (fig. 9). This time, however, after discontinuing the infusion, she improved clinically and, subsequently, there was a gradual rise in urine flow to 5.2 ml per minute, associated with an increase in creatinine clearance and urinary electrolyte excretion. In the third study, eight weeks later, the infusion rate was reduced to 5.7 ml per minute because of the patient's low filtration rate. Again, the urine flow reached a maximal value of 1.5 ml per minute, and then fell. Clearances of inulin and para-aminohippurate (C$_{IN}$ and C$_{PAM}$) (fig. 10) averaged 36.3 and 64.5 ml per minute, respectively. No significant changes in electrolyte excretion occurred.

In patient C. L., who was given a 5 per cent
concentrations, urinary water excretion, and creatinine clearance during the second study on a patient in severe congestive failure (M. H.). Note the decrease in urine volume during the infusion, after achieving a maximal urine flow of only 2.1 ml. per minute, and the subsequent water diuresis following discontinuation of the infusion.

FIG. 9. The effect of infusing a 5 per cent glucose in water solution at a rate of 10 ml. per minute on serum electrolyte concentrations, urinary electrolyte and water excretion, and renal hemodynamics produced by infusing a 5 per cent glucose in water solution at a rate of 10 ml. per minute in a patient in severe congestive failure (M. G.).

Concurrently, his inulin clearance fell from 0.36 to 0.8 ml. per minute, and fell to a level of about 0.07 ml. per minute. Conclusively, his inulin clearance first fell from about 1.5 ml. per minute, and later rose, and his para-aminobipurpurate clearance fell from 234 to 149 ml. per minute and then rose slightly, filtration fraction increasing from 0.36 to 0.53. The very low urinary electrolyte excretions were not notably changed.

Patient A. S. had intractable anasarea and serum sodium and chloride concentrations of 108 and 82 mEq. per liter, respectively. While receiving an infusion of 5.6 ml. per minute, his urine flow increased to 2.65 ml. per minute after 43 minutes, but, during the next 140 minutes, gradually declined to 0.65 ml. per minute, as signs of increasing failure developed. His inulin and para-aminobipurpurate clearances fell from 41.9 to 37.2 ml. per minute and 144 to 115 ml. per minute, respectively. No changes in urinary electrolyte excretion occurred.

Patient M. G. was given the usual infusion at a rate of 9.2 ml. per minute (fig. 11). As the infusion was continued, her congestive failure increased and her urine flow diminished from a preinfusion maximum of 2.1 ml. per minute to 0.54 ml. per minute. Subsequently, although her serum sodium had fallen from 132 to 122 mEq. per liter, her urine flow increased to only 1.2 ml. per minute.

The final patient in this group (E. R.) had rapidly reaccumulating ascites and repeated episodes of hyponatremia due to water retention. After ingesting 600 ml. of water, her serum sodium and chloride concentrations were 113 and 81.9 mEq. per liter, respectively, her serum total solute concentration was 242 milliosmols per liter, and urine flow only 0.67 ml. per minute (fig. 12). During the 5 per cent glucose in water infusion at a rate of 5.7 ml. per minute for 186 minutes, her urine flow rose to a maximum of only 1.07 ml. per minute and

FIG. 10. The effect of infusing a 5 per cent glucose in water solution at the rate of 5.7 ml. per minute on serum electrolyte concentrations, urinary electrolyte and water excretion, and renal hemodynamics produced by infusing a 5 per cent glucose in water solution at a rate of 5.7 ml. per minute in a patient in severe congestive failure (M. G.).

FIG. 11. The effect on serum electrolyte concentrations, urinary electrolyte and water excretion, and renal hemodynamics produced by infusing a 5 per cent glucose in water solution at a rate of 10 ml. per minute in a patient in severe congestive failure (M. G.).
gradually fell to 0.8 ml. per minute, as she developed symptoms of precordial constriction and signs of increasing congestive failure. Despite the fall in her serum sodium to 108 mEq. per liter, her inulin clearance remained between 126 and 132 ml. per minute and her para-aminohippurate clearance 270 and 303 ml. per minute with a filtration fraction of 0.44 to 0.46. Eighty minutes after the infusion was stopped her urine flow remained below 0.9 ml. per minute.

Discussion

The present studies confirm the reported, essentially normal, response of patients in moderate congestive heart failure to intravenously administered Pitressin. This suggests that such cardiac patients have neither increased sensitivity to, nor impaired ability to metabolize, presumably physiologic doses of an exogenous antidiuretic material. That both the osmoreceptor control of posterior pituitary antidiuretic hormone production and the metabolism of circulating antidiuretic hormone are also normal in these patients is suggested by the normal time required to achieve maximal urine volumes during infusion of isotonic glucose in water.

The attempt to compare the response of cardiac and noncardiac subjects to endogenous antidiuretic hormone released following nicotine salicylate was less successful. Although nicotine stimulates posterior pituitary release of antidiuretic hormone, the usual dose-response relationship has not been established. Identical doses, calculated on the basis of body weight or surface area, produce variable responses in different subjects, particularly in nonsmokers. All patients noted generalized tingling sensations, dizziness and some transient pain along the course of the veins of the injected arm, none of which appeared to influence the degree or duration of antidiuresis. Whenever the injections produced nausea and vomiting, antidiuresis was prolonged, as previously reported. However, when the degree of antidiuresis following nicotine was comparable to that produced by Pitressin, as in patients A. McD., V. B. and K. S., the duration of antidiuresis was approximately the same. The analogous antidiuretic responses and patterns of recovery in these patients point to physiologic similarity or identity of endogenous antidiuretic hormone and Pitressin.

Evidence from several laboratories suggests that abnormal production of antidiuretic hormone, despite hypo-osmolarity of the body fluids, may contribute to the primary water retention in cardiac edema. That there may be some derangement in the metabolism of antidiuretic hormone in edematous patients with hepatic cirrhosis or nephrosis also has been suggested repeatedly. The viewpoint that the underlying defect in hepatic disease was impaired ability of the damaged liver to inactivate the antidiuretic hormone was apparently supported by the observations that extracts of normal rat liver inactivate Pitressin in vitro. However, as in cardiac patients in moderate congestive failure, both the maximal water diuresis during intravenous hydration and the antidiuretic response to physiological doses of aqueous Pitressin or nicotine were later found to be normal in cirrhotic patients.

In an earlier report, it was suggested that continuing water retention need not require the large amounts of antidiuretic hormone in the serum sought by the proponents of the increased production theory. Such water retention may rather result from sustained or only slightly increased production of antidiuretic...
hormone, in amounts not detectable by present methods and induced by mechanisms independent of control by the osmoreceptor system. Thus, in two of the five severely ill patients (M. H. and C. L.), infusing a 5 per cent glucose in water solution at a rate of 10 cc. per minute produced hypotonicity of the body fluids but resulted in only slight rise in urine flow, followed by spontaneous antidiuresis. In both patients, the increased antidiuresis was associated with evidence of increasing severity of congestive failure and slight, but continued, fall in filtration rate. The change in filtration rate was probably not the primary cause of the antidiuresis because similar patterns of decreasing urine flow have been observed without any significant change in inulin clearance (cf. patient E. R.).

Unless some unknown mechanism is causing water retention, such persistent or increasing oliguria, with increased urine/plasma ratios for total solute concentration, creatinine and inulin, but without significant change in filtration rate, suggests that there may be continued release of antidiuretic hormone despite the hypotonicity of the extracellular fluid. Spontaneous development of similar persistent antidiuresis has been observed in patients with acute intensification of chronic congestive failure. Only those therapeutic procedures which presumably either improved the cardiac output or diminished the abnormally high metabolic needs were found to result in water diuresis and re-establishment of more normal body fluid tonicity.8

Several investigators have advanced the concept that a common mechanism may be responsible for primary water retention in edematous patients with cardiac, hepatic or renal disease. Although some have suggested that the common denominator is a decrease in effective circulating volume,29 others5, 9 have felt that the change is not in blood volume per se but rather in the dynamics of the circulation. Although the receptors and effectors for this circulatory "homeostat" have not been delineated, evidence has been presented that the receptors may be situated in the cephalad portion of the systemic circulation,21 the pulmonary circulation22 or the arterial vascular tree.23 This mechanism appears to affect excretion of both water and electrolytes in conditions as diverse as hemorrhage,24 adrenal insufficiency, postural changes25 or experimental expansion or contraction of total body fluid volume.26

In the present series of more severely ill cardiac patients, the intravenous water load not only failed to elicit normal water diuresis but, apparently, overburdened the already diminished cardiac reserve, leading to increasing severity of congestive failure. The decrease in renal plasma flow during the infusions may well be a reflection of the failure to maintain cardiac output, with consequent activation of the mechanisms described above, including augmented antidiuresis, although blood volume per se was probably increasing at the time.

It is not yet established what role the marked impairment of renal hemodynamics, and particularly the greater reduction in renal plasma flow than in glomerular filtration rate, may play in the impaired water excretion of patients in severe congestive failure. The increase in filtration fraction results in increased plasma protein concentration in the blood leaving the glomerulus to perfuse the peritubular capillaries. However, if the consequent rise in plasma oncotic pressure does influence tubular reabsorption, it should promote movement of not only peritubular fluid but also solute across the capillary membrane into the blood. This purely physical process may be augmented also by the marked slowing of renal blood flow, which prolongs the time available for osmotic equilibration.

In addition, the reduction in filtration rate, which decreases the load of both electrolyte and fluid delivered to the distal renal segments, might be expected to increase the final concentration gradient produced by a given level of circulating antidiuretic hormone. However, it has been recently reported that acute unilateral reduction in glomerular filtration rate in dogs does not result in an increased urine/plasma total solute ratio.28 Unfortunately, the filtration fraction in these experiments decreased.

Although the hypothesis of sustained antidiuretic hormone production is attractive, it
must be emphasized that these studies could not determine definitively whether impaired inactivation of circulating antidiuretic hormone and/or other mechanisms may not also be involved in the unsatisfactory diuresis of patients in very severe congestive failure. However, following oral water administration or after discontinuance of the intravenous hydration, all five were able, finally, to increase their urinary water excretion, presumably by inhibiting antidiuretic hormone production and inactivating circulating antidiuretic hormone. Moreover, cardiac patients in equally severe congestive failure exhibited neither increased sensitivity to, nor impaired ability to inactivate Pitressin tannate in oil given intramuscularly. Therefore, their primary water retention may represent sustained or increased antidiuretic hormone production secondary to intensification of congestive failure.

**Summary**

Seven cardiac patients in moderately severe congestive failure achieved urine flows of 6.8 to 14 ml. per minute during constant intravenous infusions of 5 per cent glucose in water at rates of 10 ml. per minute. One cardiac subject with intractable anasarca achieved a maximum urine flow of 4.7 ml. per minute during a similar infusion at a rate of 5.7 ml. per minute. All eight patients gave an antidiuretic response to intravenous injections of 0.3 mU of aqueous Pitressin solution per kilogram of body weight, which was equivalent in degree and duration to that given by five normal subjects.

The antidiuretic response of four of five cardiac patients in moderately severe congestive failure to intravenous injections of 1 to 3 mg. of nicotine salicylate was also equivalent in degree and duration to that of five normal subjects. The antidiuretic response of the fifth cardiac persisted throughout the 205 minutes of observation following the nicotine injection. After rapidly smoking two cigarettes, a sixth cardiac patient gave an antidiuretic response which was equivalent to that of normal subjects given nicotine injections.

Five patients in more severe congestive failure, when given intravenous infusions of 5 per cent glucose in water solutions at rates of 5.7 or 10 ml. per minute, achieved maximal urine flows of only 1.1 to 2.7 ml. per minute. As the infusions were continued, signs of increasing congestive failure developed and, despite the continued fall in serum sodium and total solute concentrations, their urinary flows decreased to 0.4 to 1.2 ml. per minute, at times, without any further change in renal hemodynamics.

These studies support the view that patients in congestive failure of moderate severity have neither increased renal tubular sensitivity to, nor decreased capacity to inactivate antidiuretic hormone of endogenous or exogenous origin. The inability of the patients in more severe congestive failure to achieve satisfactory water diuresis during intravenous hydration suggests that one of the mechanisms contributing to their salt and water retention may be sustained production of antidiuretic hormone, which is independent of osmoreceptor control.

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**Summario in Interlingua**

Iste studios supporta le concepione que patientes in disfallimento congestive de grado moderate ha ni un augmentate sensibilitate reno-tubular a hormones antidiuretic de origine endogene o exogene, ni un reduce capacitate a inactivar tal hormones. Le incapacitate del patientes con plus sever disfallimento congestive a attinger un forma satisfacente del diurese de aqua pare indicar que un del mechanismos contribuiunte a lor retention de sal e aqua es possibilemente le production sustenie de hormon antidiuretic, lo que es independente del regulation osmoreceptoris.

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