Edema of Cardiac Origin

Studies of Body Water and Sodium, Renal Function, Hemodynamic Indexes, and Plasma Hormones in Untreated Congestive Cardiac Failure

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This study provides data on plasma hormone levels in patients with severe clinical congestive cardiac failure who had never received therapy and in whom the presence of an accumulation of excess water and sodium had been established. Eight patients were studied; two had ischemic cardiac disease, and six had dilated cardiomyopathy. Mean hemodynamic measurements at rest were as follows: cardiac index, 1.8 l/min/m^2; pulmonary wedge pressure, 30 mm Hg; right atrial pressure, 15 mm Hg. Total body water content was 16% above control, extracellular liquid was 33% above control, plasma volume was 34% above control, total exchangeable sodium was 37% above control, renal plasma flow was 29% of control, and glomerular filtration rate was 65% of control. Plasma norepinephrine was consistently increased (on average 6.3 times control), whereas adrenaline was unaffected. Although plasma renin activity and aldosterone varied widely, they were on average above normal (renin 9.5 times control, aldosterone 6.4 times control). Plasma atrial natriuretic peptide (14.3 times control) and growth hormone (11.5 times control) were consistently increased. Cortisol was also increased on average (1.7 times control). Vasopressin was increased only in one patient. (*Circulation* 1989;80:299–305)

At a certain moment in the natural history of chronic cardiac disease in many patients, the body accumulates water. The syndrome of edema and engorged veins that accompanies the accumulation of water is referred to as "congestive cardiac failure." The clinical study of the mechanisms by which the accumulation occurs has proved elusive because patients are rarely found with this syndrome who have not already received treatment that may itself affect the mechanisms being studied.

Patients with severe cardiac disease who have not yet developed peripheral edema may be used to study what is presumed to be the early stages of the syndrome of water accumulation. However, identifying the earlier stages of the syndrome is difficult. The accumulation of water may precede any perceptible increase in venous pressure or edema.[1] The symptom of dyspnea, often used for identification purposes through the New York Heart Association classification, is not sufficiently specific and may precede edema for a long period of time. Also, measurements of cardiac hemodynamics or mechanics assess "failure" differently.

Other studies examining the mechanisms of the syndrome have used patients in whom cardiac therapy has been withdrawn for a short period of time. Such studies also may not be free from error because to what extent the results are the effects of recovery from chronic diuretic therapy rather than the evolution of the pure cardiac syndrome cannot be ascertained.

A need therefore exists for primary data on the established edematous syndrome, unaffected by any previous medication. To this end, we present data on a group of eight patients who had obvious peripheral edema of cardiac origin and who had never received cardiac therapy.

We have made the following groups of measurements: 1) total body water content, to ensure that the patients were suffering from the syndrome of water excess, 2) extracellular liquid volume, plasma volume, and total body exchangeable sodium, 3) renal plasma flow and glomerular filtration rate,

4) cardiac hemodynamics, and 5) a variety of plasma hormone concentrations or activity.

Methods

Hemodynamics

Hemodynamics were measured in the postabsorptive state with a Swan-Ganz catheter. Cardiac output was determined by thermodilution with a Gould Model SP 1445 cardiac output computer (Cleveland, Ohio).

Water and Sodium Spaces

Body water and sodium spaces and renal function were estimated with standard isotope dilution techniques.[2] Plasma volume was calculated from the volume of distribution of 5 μCi ^{125}I-labeled human serum albumin at 10 minutes.[3] Extracellular volume and glomerular filtration rate were measured simultaneously with 100 μCi ^{51}Cr-labeled ethylenediaminetetraacetic acid (EDTA) and calculated by numerical analysis.[4-6] Effective renal plasma flow was estimated with 100 μCi ^{125}I-labeled sodium iodohippurate (Hippuran) and calculated by numerical analysis.[4-6] Total body water was determined with 100 μCi tritiated water.[7] Total body exchangeable sodium was measured as described by Haxhe[2] with 20 μCi ^{22}Na administered orally. All radioactive substances were obtained from Amersham International (UK). The total dose of radiation for each subject was 2.6 mSv.

A protocol was designed that allowed all measurements to be made during a single 24-hour period, the essential feature being the sequence and timing of the radiopharmaceuticals administered to minimize errors due to cross interference between the different radionuclides. It also avoided reliance on the use of accurately timed urine samples. All subjects were studied at 9 AM, 2 hours after a light breakfast. Nothing was given orally for the next 4 hours. An intravenous cannula for sampling was inserted into a forearm vein. Hippuran was injected at time zero into the antecubital vein of the other arm. Exactly 1 minute later, ^{51}Cr-labeled EDTA was injected, and the subjects were then asked to drink the tritiated water. Heparinized blood samples were collected at 4, 20, 44, 90, 150, 240, 360, and 420 minutes. These samples were used for estimating extracellular volume, glomerular filtration rate, and effective renal plasma flow. The 240-minute sample was also used for measuring total body water. Immediately after collection of the 420-minute blood sample, ^{125}I-labeled human serum albumin was injected, and a blood sample was collected 10 minutes later for estimating plasma volume. Plasma was separated from all samples and stored for counting in a specially designed three-channel gamma counter.[8] Subjects were then given a drink of ^{22}Na to measure 24-hour total body exchangeable sodium.

Hormone Assays

Hormone assays were carried out on 30-ml samples of blood drawn from the forearm vein. For the assays of catecholamine and renin activity, the samples were collected into chilled tubes containing 1 mg/ml EDTA, whereas the samples for the determination of atrial natriuretic peptide (ANP) were collected into chilled tubes containing 1 mg/ml EDTA and 400 U/ml aprotinin. The assays of aldosterone, vasopressin, cortisol, growth hormone, and prolactin were carried out on serum. All the samples were centrifuged immediately. Those for catecholamine determination were stored at -70° C; all the other samples were lyophylized.

Plasma noradrenaline and adrenaline were measured by high-performance liquid chromatography with electrochemical detection. Plasma renin activity, aldosterone, vasopressin, cortisol, growth hormone, and prolactin were measured by radioimmunoassay. Standard commercial kits were used for the following assays: renin activity,[9] aldosterone,[10] vasopressin,[11] cortisol,[12,13] growth hormone,[14] and prolactin.[14]

The radioimmunoassay for ANP followed extraction with a Sep-Pak C$_{-18}$ column. ^{125}I-Synthetic α-hANP (Eiken, Immunochemical, Tokyo, Japan) and rabbit anti-α-hANP antibody (Eiken) were used. Standard curves were constructed with serial dilutions of standard α-hANP in radioimmunoassay buffer throughout a range from 10 to 1,280 pg/ml. The percent extraction of standard quantities of exogenous α-hANP added to plasma samples averaged 92 ± 4.3 (mean$\pm$SEM; $n=12$). The intra-assay variation and the interassay variation were 6% ($n=8$) and 8% ($n=8$), respectively. The lower limit of sensitivity of the assay was 7 pg/ml α-hANP, and the normal range was 9.5–50 pg/ml.

Patients

The studies were carried out at the Postgraduate Medical Institute, Chandigarh, India, on eight patients (Table 1) and 24 normal control subjects. The average age of the patients was 45.5 years. Two (C2 and C4) had ischemic cardiac disease; the other patients had cardiomyopathy. Symptoms had been present for 3–12 months (average, 8 months). All patients were short of breath, most of them severely so (Table 1). Pitting edema of the ankles, a raised jugular venous pressure, and enlargement of the liver were present in every patient. Five patients had signs of ascites (C1, C2, C6, C17, and C19). Patients C1 and C6 had pleural effusions. The average transverse diameter of the cardiac shadow was 68% of the thorax. The mean left ventricular ejection fraction calculated from the two-dimensional echocardiogram was 31% (±4 SD).

Except where indicated in the tables, hemodynamic, metabolic, renal, and hormonal measurements were recorded for all patients. No hemodynamic measurements were recorded for control subjects. Hormone assays were carried out in 16

TABLE 1. Hemodynamic Measurements in Eight Patients With Cardiac Edema Due to Left Ventricular Disease

Patients	Age (yr)	Gender	BSA (m²)	Dyspnea (NYHA)	HR (beats/min)	RAP (mm Hg)	MPAP (mm Hg)	MWP (mm Hg)	MAoP (mm Hg)	Cardiac index (l/min/m²)	Resistance (mm Hg · min · m²/l) Pulmonary	Resistance (mm Hg · min · m²/l) Systemic
C1	62	M	1.88	III b	100				116			
C2	45	F	1.66	IV	178	22	39	28	85	1.4	7.9	41.0
C4	45	F	1.42	IV	122	16	39	29	99	1.6	6.2	43.3
C6	54	F	1.43	IV	84	16	50	32	119	2.1	8.6	41.4
C13	15	M	1.17	II b	107	10	41	28	90	2.1	6.1	29.0
C14	45	F	1.45	IV	116	7	34	24	84	1.5	6.6	39.6
C17	68	M	1.76	II b	91	11	51	33	101	1.8	9.7	36.8
C19	30	M	1.65	IV	120	23	52	35	103	1.7	10.2	40.9
Mean	46		1.55		114.8	15.0	43.7	29.9	99.6	1.75	7.9	38.9
SEM	6		0.08		10.9	2.3	2.7	1.4	5.0	0.11	0.6	1.8
n	8		8		8	7	7	7	8	7	7	7

NYHA, New York Heart Association; BSA, body surface area; HR, heart rate; RAP, right atrial pressure; MPAP, mean pulmonary arterial pressure; MWP, mean wedge pressure; MAoP, mean aortic pressure; M, male; F, female.

control subjects, and body sodium and water compartments and renal function were measured in 11 control subjects, the appropriate numbers being indicated in the tables.

The studies were performed after obtaining written, informed consent from the patients and the volunteers. Permission was obtained from the Administration of Radioactive Substances Advisory Committee and from the Ethics Committees of the National Heart and Chest Hospitals, London, and the Postgraduate Institute for Medical Research, Chandigarh.

Results

Hemodynamics

The hemodynamic data provide evidence of severe cardiac dysfunction (Table 1). The mean value for the cardiac index was as low as one half of normal while the heart rate averaged 116 beats/min. Right atrial and pulmonary wedge pressures were greatly increased. The pulmonary arterial pressure was also increased, whereas the aortic pressure was normal. The pulmonary and the systemic arterial resistances were raised, the pulmonary to an average value of 7.9 mm Hg·min·m²/l body surface area and the systemic to an average of 47.3. The total hemodynamic condition is one of extreme impairment of contraction of the left ventricle on which the circulatory effects of an expanded blood volume have been imposed.

Body Water and Salt

The total body water content of the patients was substantially increased (Table 2). Expressed per body weight, it was found to have risen by 16% in the patients. The increase in total body water was accommodated almost entirely in the extracellular space; the former expanded by 87 ml/kg and the latter by 74 ml/kg. The increase in extracellular water was divided between the extravascular and intravascular compartments in proportion to their normal volumes; the total extracellular water rose

TABLE 2. Measurements of Water Volumes, Electrolytes, and Renal Function in Eight Patients With Cardiac Edema Compared With Measurements in Normal Subjects

	Extra-cellular volume (ml/kg)	Plasma volume (ml/kg)	Packed cell volume (%)	Blood volume (ml/kg)	Body water (ml/kg)	Exchange-able Na (mmol/kg)	Serum Na (mM)	Serum K (mM)	Glomerular filtration (ml/min/ 1.73 m²)	Renal plasma flow (ml/min/ 1.73 m²)	Serum urea (mg/dl)	Serum creatine (mg/dl)
Patients												
C1						62	127	4.3			36	2.0
C2	330	56.9	45	93.1	727	70	132	4.3	55	58	24	2.0
C4	274	49.0	42	77.0	531	45	130	4.0	100	235	48	1.0
C6	386	56.9	36	82.6	619	69	134	4.8	43	155	56	1.4
C13	331	70.3	36	102.1	620	57	142	4.3	76	173	28	1.4
C14	220	60.0	41	92.3	570	52	130	4.4	63	120	56	2.0
C17					623	72						
C19	268	54.3	36	78.8	670	63	139	3.1	54	97	54	1.5
Mean	301	57.9	39.3	75.1	623	61.3	133	4.2	65.0	139.6	43	1.6
SEM	24	2.9	1.6	13.0	24	3.3	2	0.2	8.3	25.3	5	0.1
n	6	6	6	6	7	8	7	7	6	6	7	7
Control subjects												
Mean	227	43.2	45.6	61.7	536	44.7	139	4.4	99.3	479.4		
SEM	13	3.0	1.3	7.0	20	1.9	1	0.1	2.5	19.1		
n	11	11	7	11	9	10	11	11	9	11		
p (Wilcoxon)	0.035	0.012	0.015	0.016	0.017	0.030	0.030	NS	0.010	0.009		

TABLE 3.   Measurements of Plasma Hormones in Eight Patients With Cardiac Edema Compared With Measurements in Normal Subjects

	Epinephrine (pg/ml)	Nor-epinephrine (pg/ml)	Renin (ng/ml/hr)	Aldosterone (pg/ml)	ANP (pg/ml)	Vasopressin (pg/ml)	Growth hormone (ng/ml)	Prolactin (ng/ml)	Cortisol (ng/ml)
Patients									
C1			3.7	311		2.2	13.5	13.0	135
C2	163	6,968	16.0	1,000		1.7	19.6	77.0	160
C4	123	1,287	0.8	280	109		6.3	6.6	175
C6	65	698	0.3	25	269	3.9	2.1	3.2	99
C13	157	506	3.9	199	628	4.3	13.4	1.9	121
C14	52	713	4.1	94	111	4.3	3.6	11.2	87
C17	43	430	0.5		289	2.7	5.3		86
C19	54	1,428	11.9	398	477	19.3	3.3	2.9	168
Mean	94	1,719	5.2	330	314	5.5	8.4	16.5	129
SEM	18	821	1.9	113	77	2.2	2.1	9.4	12
n	7	7	8	7	6	7	8	7	8
Control subjects									
Mean	84	275	0.55	51.8	22	7.6	0.73	7.28	74.0
SEM	16	34	0.06	7.3	5	1.2	0.16	0.88	32.0
n	15	16	16	16	16	15	16	16	16
p (Wilcoxon)	NS	0.0004	0.0234	0.0232	0.0004	NS	0.0001	NS	0.0036

ANP, atrial natriuretic peptide.

by 33%, and the plasma volume rose by 34%. The total exchangeable body sodium increased by a similar extent (37%). The serum concentration of sodium was slightly lower in the cardiac patients ($p<0.05$). Serum potassium was unaffected.

The total blood volume increased to a lesser extent than did the plasma volume (22% in comparison with 34%). This is explained by a decrease in the hematocrit level. No precise measurement was made of the total red cell volume, but simple calculations from the venous hematocrit level and the total plasma volume suggest that the total red cell volume increased by only 5%.

Renal Function

Renal plasma flow was severely diminished, averaging only about 30% of normal, the proportional decrease being more severe than that in the cardiac output. Glomerular filtration rate was diminished to a lesser extent, averaging 65% of normal. Thus, the filtration fraction increased on the average from 0.21 to 0.47.

Plasma Hormones

The plasma concentration of norepinephrine was consistently increased, the average being over six times that of the control subjects ($p<0.001$) (Table 3). In contrast, epinephrine was unaffected. Plasma renin activity varied greatly. In three patients, it was within normal limits, whereas in the remaining five, it was increased, exceptionally so in two. The mean value for renin activity was nine times that of the control subjects ($p<0.05$). Aldosterone levels also varied widely, the average being six times that of control subjects ($p<0.05$). The plasma concentration of ANP was greatly raised in every patient, the average being 14 times normal ($p<0.001$).

The plasma concentration of vasopressin was abnormally high in only one patient (C19), and no significant difference was found between the control subjects and the patients. Growth hormone was consistently raised, with an average value 11 times normal ($p<0.001$). The prolactin concentration was greatly increased in one female patient (C2) who also showed the highest values for norepinephrine, renin activity, aldosterone, and growth hormone. In general, the level of prolactin was about twice as high in the patients as it was in the control subjects, but the difference was not significant. Plasma concentrations of cortisol were increased ($p<0.01$).

Discussion

Body Water and Salt

A prerequisite to any study of the syndrome of water accumulation is the demonstration of an abnormally increased total body water. The present measurements confirm that such was the case, for the excess water averaged approximately 4 l. The values for body water per kilogram are very similar to those found by Birkenfeld et al[15] in control subjects and patients. The separate measurements of the extracellular water volume showed that the excess water was retained almost entirely within the extracellular space. The extravascular and intravascular divisions of the extracellular space increased in the same proportion. The proportionate increase in the plasma volume was greater than that of the red cell volume, a finding similar to that of Samet et al.[16]

The concentration of sodium in the plasma and, by presumption, in the extracellular liquid was a little lower in the patients ($p<0.05$). A tendency to hyponatremia in congestive cardiac failure is well known[17] but may often be the result of diuretic therapy. In our present study, we are sure that hyponatremia was attributable only to the disease and not to therapy. Although the plasma sodium concentration was

reduced, the total body exchangeable sodium was increased by approximately 37%, the figures being, again, close to those of Birkenfeld et al.[15]

Renal Function

A reduction in renal blood flow has been repeatedly noted since the original observation by Merrill.[18] In our patients, the reduction was substantial and proportionately more than the reduction in cardiac output, implying a particularly severe degree of renal vasoconstriction. From early studies onward,[19] the glomerular filtration rate has been shown to be reduced to a lesser extent than the renal blood flow and, as in our patients, the filtration fraction was shown to be increased.

Hemodynamics

The extreme decrease in cardiac index and increase in right atrial and pulmonary wedge pressures confirm the severity of the underlying cardiac disease. The constancy of the arterial pressure in the presence of dramatic changes in all other hemodynamic measurements supports the theory[20,21] that the response of the body during congestive cardiac failure is directed to the maintenance of arterial pressure.

Hormones

Catecholamines. Many subsequent studies have confirmed the original observation by Chidsey et al[22] of an increased plasma concentration of norepinephrine in patients with congestive cardiac failure. In our patients, the increase was unusually great, reaching values more than five times the normal. The average norepinephrine level in patients with congestive failure in the literature reviewed by Goldstein[23] was 740 pg/ml, which is less than half the mean value of our patients. In striking contrast, the plasma concentration of epinephrine was not affected. We are unaware of any observation of the concentration of epinephrine in untreated congestive failure. However, in treated patients, it has been found to be increased.[24]

Renin. In their early study, Brown et al[25] found plasma renin to be increased in only one third of patients with untreated clinical congestive cardiac failure from a variety of causes. Recently, Bayliss et al[26] reported normal values for plasma renin activity in patients with mild untreated clinical congestive cardiac failure and increased plasma norepinephrine, whereas Kubo et al[27] reported normal values in patients with mild clinical congestive cardiac failure and normal plasma norepinephrine from whom cardiac therapy had been withdrawn for 1 week. In the present series, every patient was suffering from an excess accumulation of water, and plasma renin activity was still not universally increased, although the mean was significantly higher than normal. The experiments by Watkins et al,[28] on dogs with inferior vena caval or pulmonary arterial constriction, provide an explanation for such a lack of consistency. In their experiments,

plasma renin activity increased immediately after the constriction but returned to normal as the plasma volume expanded and the arterial blood pressure was restored. Plasma renin activity can be greatly influenced by diuretic therapy,[26,29] but such interference can be ruled out in the present series.

Aldosterone. Diuretic therapy also has important effects on the plasma concentration of aldosterone[26,29] and thus makes difficult the interpretation of a number of previous studies. In the mild cases of clinical congestive cardiac failure studied by Bayliss et al,[26] plasma concentrations of aldosterone were normal. In the present series, in which the extracellular volume was known to be expanded, the plasma concentration was not universally increased, although the mean level was significantly higher than that of the control subjects. The explanation of such variability is probably the same as that offered for renin activity because the excretion of aldosterone is mainly regulated by angiotensin II.

Atrial natriuretic peptide. By far, the most striking hormonal response in our study is the increase in the plasma concentration of ANP. Increased concentrations of ANP have been found in patients with treated congestive cardiac failure.[30–40] The peptide has been shown to be released by stretching of atrial tissue[41] and by volume loading of the circulation,[32] and doubtlessly, the increased concentration in the blood of patients with congestive failure is due to excessive release from overstretched atria. The intravenous infusion of ANP has been shown to decrease plasma renin activity and aldosterone concentration,[42] and the high circulating concentrations of ANP in patients with congestive failure may contribute to the great variability of plasma levels of those two hormones. On the other hand, ANP infusions have not affected plasma cortisol levels.[42]

Vasopressin. In general, the plasma concentration of vasopressin was not increased in our patients, although it was increased in one. Previous investigations have been limited to treated patients and have given diverse results. Perry and Fyles[43] found no difference between patients with congestive failure and normal subjects. Stein et al[44] found that the concentration of vasopressin was increased in a minority of patients, and Yamane et al[45] found vasopressin increased in about half. Szatalowicz et al[46] found the absolute level of vasopressin to be low, but they considered it abnormally high in relation to the hypo-osmolar plasma. Riegger et al[47] also found vasopressin levels that were inappropriately high with respect to the osmolarity of the plasma in half of their patients. Hyponatremia and consequent hypo-osmolarity of the plasma is usual in congestive heart failure[45–47]; therefore, there is no osmotic stimulus to the release of vasopressin. Nonosmotic stimuli may, however, be operating through baroreceptors and may account, for instance, for the increase in plasma vasopressin that follows the injection of frusemide.[45] Distension of

the atria would be expected to decrease vasopressin release, but in patients with inappropriately high levels of vasopressin, this mechanism appears to be blunted.[47] An impairment of free water excretion may also be due to a reduced delivery of filtrate to the distal tubule.[48] In congestive cardiac failure, the glomerular filtration rate is not reduced as much as the renal plasma flow, and this was also the case in our patients. However, the filtration of almost half of the glomerular plasma flow would result in a high osmotic pressure in the capillaries surrounding the proximal tubule and thus favor reabsorption at that site.[49] In studies on dogs with inferior vena caval constriction, Anderson et al[50] found evidence that free water clearance was reduced both by such intrarenal factors and by vasopressin release. Therefore, in considering all the evidence, intrarenal factors are probably responsible for a degree of water retention and hypo-osmolality of the plasma, but the inhibition of release of vasopressin that would normally accompany such hypo-osmolality is countermanded by nonosmotic stimuli arising, probably, from arterial baroreceptors.

Anterior pituitary. The response of the anterior pituitary in congestive cardiac failure has been little studied. The present results show a consistent and large increase in circulating growth hormone. The physiologic significance of the response is not clear. It is unlikely to have any hemodynamic implications and probably is involved in part of the general restorative response of the body to trauma from which the neuroendocrine response in congestive failure may have evolved.[51] Within this restorative response, growth hormone will favor compensatory cardiac hypertrophy. On the average, plasma prolactin was also increased but not significantly so. However, it was greatly increased in one female patient (C2) in whom other aspects of the endocrine response were particularly severe. Plasma cortisol was significantly increased. This may be presumed to be due to an increased release of adrenocorticotropic hormone from the anterior pituitary, which has been shown to accompany congestive failure.[29]

General Conclusion

The results permit a reconstruction of the events that lead to cardiac edema. The purely mechanical results of a weakened myocardium would be expected to be an increase in venous and a decrease in arterial pressure. In our patients, the arterial pressure was maintained. An important factor in the maintenance of arterial pressure was an increase in systemic resistance, which may be attributed in part to a greatly increased activity of the sympathetic nervous system. Renal vascular resistance was particularly affected; therefore, the renal blood flow decreased disproportionately. Although glomerular filtration rate fell less, it seems probable that the intrinsic intrarenal effects of a reduced renal blood flow led to a degree of sodium and water retention, water being more affected than sodium. Superim-

posed on these mechanisms was the influence of the renin-angiotensin-aldosterone system, tending to increase systemic arterial resistance and retain sodium. This system is also evoked by a threat to the arterial pressure and acts to maintain it at the expense of an expanded plasma volume. The negative feedback control of the system through the blood pressure may explain the great variability in plasma concentration of aldosterone and in plasma renin activity. Vasopressin secretion, subjected to opposing osmotic and nonosmotic influences, led to plasma concentrations that were within normal values but high with respect to plasma sodium levels. Atrial distension, due to the mechanical effects of cardiac disease and to the expansion of the plasma volume, gave rise to an increased secretion of ANP. The natriuretic and vasodilatory influences of the peptide, however, were clearly overwhelmed by those influences leading to sodium and water retention. The results are, therefore, consistent with the theory[20,21] that the neuroendocrine response to a severely impaired heart is an expression of evolutionary forces that maintain the arterial pressure.

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