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Research Article

THE RELATIONSHIP OF CARDIOVASCULAR AND RENAL HEMODYNAMIC FUNCTION TO SODIUM EXCRETION IN PATIENTS WITH SEVERE HEART DISEASE BUT WITHOUT EDEMA [1, 2]

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Patients in congestive heart failure with peripheral edema are known to have an impairment of sodium excretion (1), which may persist for some time after they recover from clinical "heart failure" (2). However, little information is available concerning the sodium excretion of patients with severe heart disease and dyspnea but without a history of peripheral edema. Therefore, the present study was undertaken to investigate sodium excretion in such non-edematous cardiac patients during a moderately high sodium intake. When it was found that this group had no obvious disturbance in the renal excretion of sodium, measurements were made of their cardiovascular and renal hemodynamic functions both at rest and during exercise. These measurements were compared with similar determinations in a group of patients with severe heart disease but with peripheral edema in order to determine whether circulatory differences existed which might account for the observed differences in renal excretion of sodium.

PATIENTS, METHODS AND COLLECTION OF DATA

The first group of cardiac patients had dyspnea on exertion but no history or finding of peripheral edema although some had previously received an occasional diuretic. Most of the subjects had severe valvular heart disease and evidences of pulmonary congestion in spite of the fact that they were on maintenance doses of digitalis. None had received a diuretic for at least three weeks prior to the study. Simultaneous cardiovascular and renal hemodynamic measurements were made at rest and during exercise by methods identical to those previously described (3). Exercise was performed in the supine position by alternate straight leg-raising for six to nine minutes.

Within one week after these measurements were made, each patient was placed on a diet unrestricted in salt for three to five days. Following this, he was placed on a diet containing 1 gram of sodium chloride, and, in addition, was given oral tablets containing 13 grams of sodium chloride a day. This regimen was continued for 7 to 14 days during which time the patient was ambulatory but was observed for changes in symptoms or weight. Twenty-four-hour collections of urine were analyzed for sodium and chloride content at intervals of two to three days. Within a week after the completion of this study, ten of the twelve patients were studied during and after an infusion of 300 ml. of 5 per cent sodium chloride given at a rate of 10 to 12 ml. per minute. Sodium and chloride excretions were measured over the ensuing 24-hour period by taking urine collections at the end of the infusion, one hour later, and then at intervals of about six hours. Control observations were obtained by making similar studies on nine normal individuals. Urinary sodium was determined by the internal standard (lithium) flame photometer. Urinary chlorides were analyzed by the method of Wilson and Ball (4).

The second group of 10 cardiac patients were in congestive heart failure with peripheral edema. They had considerable "right sided failure" as indicated by the degree of venous distention and hepatomegaly. Most of these patients received 1 gram of salt daily in the diet, a maintenance dose of digitalis, and frequent injections of a mercurial diuretic. Cardiovascular and renal hemodynamic functions in this group were studied in the same way as the first group.

RESULTS

Sodium excretion

The data for sodium chloride balance in patients without edema of group I are shown in Table I.

The "non-edematous" patients (who had never had a history of edema) failed to gain weight or develop any change in their signs or symptoms during the entire seven to fourteen days during which they were maintained on a diet containing 14

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TABLE I

Sodium chloride excretion in a group of cardiac patients without peripheral edema *

Patient Age	Sex	Clinical classification	Days on 14 gram (approx.) NaCl diet	Change† in weight (*pounds*)	Urinary Na conc. (*mEq./L.*) Average	Urinary NaCl excretion in 24 hours (*gm.*) Average	Changes in signs and symptoms
C. S. 37	M	R.H.D. M.S. N.S.R. III D	13	+ .50	136	13.2	None
A. F. 32	F	R.H.D. M.I. A.F. IV E	14	− .75	145	12.8	None
V. C. 32	F	R.H.D. M.I. A.F. III D	10	+1.00	94	12.6	None
S. A. 41	F	R.H.D. M.S. N.S.R. III D	12	+ .25	126	12.9	None
J. D. 39	M	R.H.D. M.I. A.F. IV E	14	0	155	12.7	None
C. J. 49	M	A.S.H.D. R.H.D. M.S. A.F. III D	7	−1.25	137	13.4	None
E. M. 48	F	R.H.D. N.S.R. III D	10	+1.00	157	13.5	None
A. H. 47	M	Chron. Pulm. Emphysema Cor pulmonale N.S.R. IV E	7	− .5	95	12.5	None
D. C. 48	M	H.C.V.D. A.F. III C	10	+1.25	105	14.0	None
A. C. 40	M	R.H.D. M.S. N.S.R. II C	7	−1.5	132	12.0	None
E. T. 22	F	R.H.D. M.S. A.I. N.S.R. III C	10	+ .5	140	12.5	None
M. M. 22	M	Sarcoid Pulm. Emph. & Fibrosis Cor pulmonale II C	10	−2.00	117	14.4	None

* Approx.—Approximately.
R.H.D.—Rheumatic Heart Disease.
A.S.H.D.—Arteriosclerotic Heart Disease.
H.C.V.D.—Hypertensive Cardiovascular Disease.
A.F.—Auricular Fibrillation.
N.S.R.—Normal Sinus Rhythm.
M.S.—Mitral Stenosis.
M.I.—Mitral Insufficiency.
A.I.—Aortic Insufficiency.
Chronic Pulm. Emph.—Chronic Pulmonary Emphysema.
Sarcoid Pulm. Emph. and Fibrosis—Sarcoid Pulmonary Emphysema and Fibrosis.

† The difference between the weight obtained on the day preceding the 14-gram NaCl diet and that on the last day of the diet.

TABLE II

Individual cardiovascular and renal data

Patient Age	Sex	Clinical classification	Cardiac index *L./min./m²* R	E	Oxygen consumption *ml./min./m²* R	E	A-V oxygen difference *Vol. %* R	E	Arterial oxygen saturation % R	E
							Group A. Patients with Cardiac			
C. S. 37	M	R.H.D. M.S. N.S.R. III D	2.67	3.19	179	427	6.73	13.36	93	90
A. F. 32	F	R.H.D. M.I. A.F. IV E	1.46	1.82	139	222	9.51	12.18	96	100
V. C. 32	F	R.H.D. M.I. A.F. III D	2.19	3.65	145	371	6.59	10.20	95	94
S. A. 41	F	R.H.D. M.S. N.S.R. III D	3.12	3.58	140	355	4.51	9.94	94	96
J. Di. 39	M	R.H.D. M.I. A.F. IV E	1.60	3.21	139	389	8.70	12.12	95	98
C. J. 49	M	A.S.H.D. R.H.D. M.S. A.F. III D	1.99	3.09	143	358	7.16	11.60	96	100
E. M.* 48	F	R.H.D. N.S.R. III D	2.24		127		5.66	9.71	89	86
A. H. 47	M	Chron. Pulm. Emphysema Cor pulmonale N.S.R. IV E	2.82	4.45	116	196	4.10	4.40	44	32
D. C. 48	M	H.C.V.D. A.F. III C	4.30	6.73	211	606	4.90	9.00	93	93
A. C. 40	M	R.H.D. M.S. N.S.R. II C	3.27	4.79	150	470	4.57	9.83	99	94
E. T.* 22	F	R.H.D. M.S. A.I. N.S.R. III C	3.28	4.58	146	377	4.42	8.24	94	92

* Developed pulmonary edema during exercise.

R.H.D.—Rheumatic Heart Disease.
A.S.H.D.—Arteriosclerotic Heart Disease.
H.C.V.D.—Hypertensive Cardiovascular Disease.
A.F.—Auricular Fibrillation.
N.S.R.—Normal Sinus Rhythm.
M.S.—Mitral Stenosis.
M.I.—Mitral Insufficiency.
Thyroid H.D.—Thyroid Heart Disease.

TABLE II—*Continued*

Pressures (*mm. Hg*)													
Pulmonary artery		Mean pulmonary capillary		Right ventricular end diastolic		Systemic arterial		Pulse rate *Beats/min.*		C_{PAH} *ml./min./1.73 m²*		C_{IN} *ml./min./1.73 m²*	
S D M R	S D M E	R	E	R	E	S D M R	S D M E	R	E	R	E	R	E
Insufficiency without Peripheral Edema													
102/47/65	138/61/99	30	41	10	18	130/80/100	170/100/135	85	136	256	220	95	82
43/25/30	62/38/48	26	35	7	10	110/62/80	135/75/90	90	129	357	268		
40/	65/			12	30	110/65/85	140/80/100	82	160	477	207		
72/46/57	130/75/100	32	45	5	10	95/60/80	118/75/95	84	128	448		97	
50/32/36	80/38/50			14	18	110/80/90	125/80/100	88	136	206	106	94	44
50/20/30	60/25/38			12	15	160/90/105	160/90/105	87	126	279	332	104	123
76/38/55	110/52/75	34	55	5	10	170/90/120	265/150/207	77	104	267	94	98	42
94/60/72	105/65/78	18	22	14	24	160/80/105	165/90/110	105	108	313	200	138	117
59/31/40	80/42/55	27		13	19	204/84/135	260/114/180	84	120	250	184	76	59
45/35/40	90/60/68	30	48	5	20	138/80/100	140/80/100	78	138	268	140	76	54
45/20/33	82/46/65	20	40	2	5	105/60/80	125/72/88	62	110	486	324	127	36

A.I.—Aortic Insufficiency.
C.P.—Cor pulmonale.
A.S.—Aortic Stenosis.
P.E.—Pulmonary Emphysema.

Chron. Pulm. Emphysema—Chronic Pulmonary Emphysema.
Sarcoid Pulm. Emphysema and Fibrosis—Sarcoid Pulmonary Emphysema and Fibrosis.

TABLE II—*Continued*

Patient		Clinical classification	Cardiac index *L./min./m²*		Oxygen consumption *ml./min./m²*		A-V oxygen difference *Vol. %*		Arterial oxygen saturation *%*	
Age	Sex		R	E	R	E	R	E	R	E
							Group A. Patients with Cardiac Insufficiency			
M. M.		Sarcoid Pulm. Emph.								
22	M	and fibrosis C.P. II C	3.05	5.33	154	368	5.06	6.90	87	87
							Group B. Patients with Cardiac			
F. A.		A.S.H.D. A.F.								
61	F	III D	2.10	2.46	122	266	5.78	10.79	97	98
M. R.		H.C.V.D. N.S.R.	1.46		167		11.40		95	
39	M	IV E								
R. A.		H.C.V.D. N.S.R.	2.40	3.50	176	395	7.32	11.13	94	92
54	M	IV D								
L. G.		R.H.D. A.S. N.S.R.								
36	F	III C	1.97	2.97	163	312	8.30	10.51	96	
C. M.		Thyroid H.D. A.F.	4.62		205		4.44		93	
42	F	III C								
C. J.		R.H.D. M.S. A.F.								
42	F	IV E	2.10	2.27	216	315	10.13	13.89	88	90
J. C.		R.H.D. M.S. A.F.								
45	M	III C	2.74	4.06	158	391	5.76	9.65	93	88
W .T.		R.H.D. A.S., M.I.,								
40	M	and M.S. A.F. III D	2.38		161		6.76		95	
W. H.		P.E. C.P.								
56	M	N.S.R. IV E	3.49	3.84	154	283	4.42	7.37	75	67
W. D.		Silicosis C.P.								
66	M	N.S.R. III D	3.65	3.50	137	215	3.75	6.12	52	51

TABLE II—*Continued*

Pressures (*mm. Hg*)													
Pulmonary artery				Mean pulmonary capillary		Right ventricular end diastolic		Systemic arterial				Pulse rate *Beats/min.*		CPAH *ml./min./1.73 m²*		CIN *ml./min./1.73 m²*	
S D M		S D M						S D M		S D M							
R		E		R	E	R	E	R		E		R	E	R	E	R	E
without Peripheral Edema—*Continued*																	
53/30/38		70/40/48				8	12	120/90/102		148/100/120		92	116	266	180	84	77
Insufficiency and Peripheral Edema																	
60/40/45		85/57/62		27		18	22	118/66/84		128/78/90		92	116	143	130	56	46
72/53/60						30		220/160/180				106		171		113	
85/47/60		125/75/95		40	55	22	45	195/90/120		280/140/180		88	104	240	162	92	62
98/48/65						27		95/65/75				86		180		82	
65/34/45						20		180/70/115				110		462		103	
140/80/100		145/90/120		30	40	23	28	180/120/145		200/120/160		90	112	221	177	98	80
70/38/49		95/50/70		33	45	20	25	140/70/100		180/80/110		74	108	394	299	117	89
68/36/50		120/62/78				19	38	140/80/100		150/90/110		52	60	316		104	
60/44/50		75/50/60		18	25	22	25	130/80/90		120/60/85		94	110	212	187	91	87
81/42/53		110/58/68		18	18	23	30	150/75/100		210/90/130		92	112	212	106	91	58

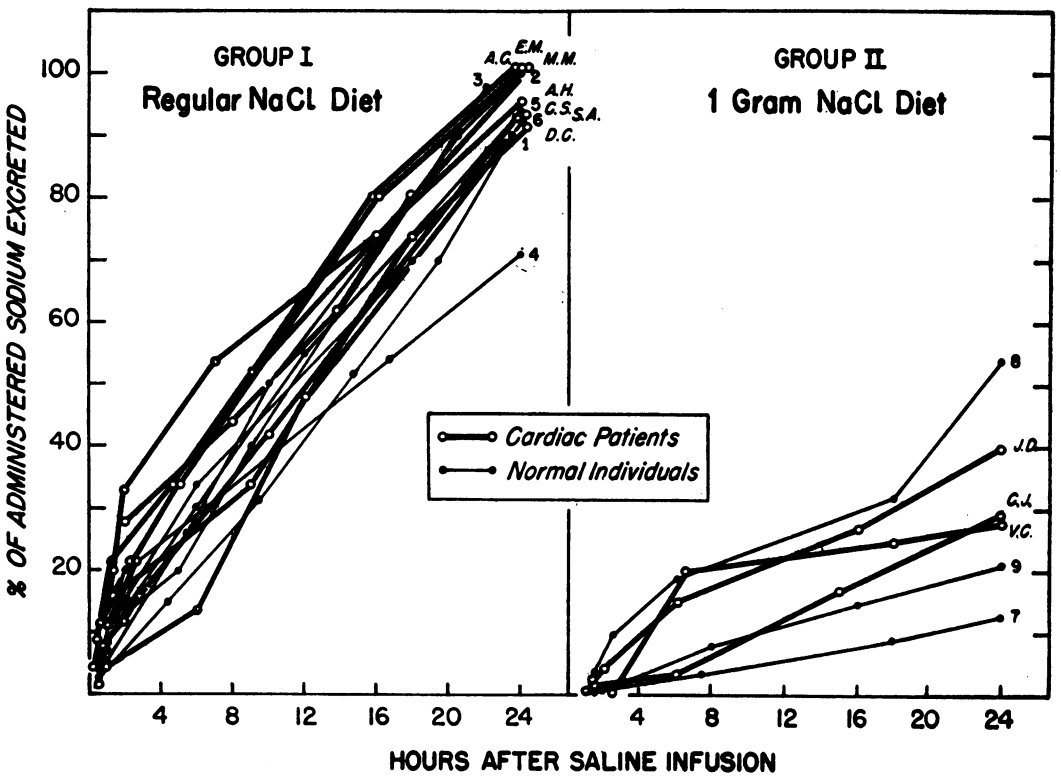

FIG. 1. URINARY EXCRETION OF SODIUM FOLLOWING THE INFUSION OF 300 ML. OF 5 PER CENT SALINE

grams of sodium chloride daily. The 24-hour urinary sodium excretion showed good concentration and a high recovery of the ingested salt, averaging 93 per cent for the group. All except patients A. F., S. A., C. J., and A. H. were followed carefully on an unrestricted salt diet for at least three months following this study and they continued to be edema free and showed no change in cardiac symptoms or signs.

Figure 1 shows graphically the excretion of sodium in this group following the infusion of 300 ml. of 5 per cent sodium chloride. Seven of the ten patients, like the normal controls, showed no delay in the excretion of sodium including even patient E. M. who developed cardiac asthma during the infusion. The three remaining patients, one of whom (V. C.) also developed acute pulmonary edema during the saline infusion, had previously been on a diet restricted in sodium and all three had a delay in excretion of sodium. This, however was comparable to that observed in three normal individuals who had likewise been on a limited sodium intake.

Hemodynamic functions

The cardiovascular and renal hemodynamic functions in this group of non-edematous cardiac patients are given in Table II for comparison with those in the edematous cardiac patients. A statistical analysis of the differences between these two groups is given in Table III.

Cardiac index and oxygen consumption. At rest the cardiac index was abnormally low and not significantly different in the two cardiac groups. During exercise the group without edema had a higher mean cardiac index (by 0.81 L. per min. per m^2) than the group with edema but this difference was not statistically significant. At rest and during exercise, the oxygen consumption and A-V O_2 difference likewise were not significantly different in the two groups. In response to exercise both groups had significant rises in cardiac index. The increase in this function, however, was significantly greater in the group without edema than the group with edema. This difference between the groups in response to exercise was not associated with a significantly different arteriovenous oxygen

TABLE III

Mean data and statistical analysis

	Cardiac index L./min./M²				Oxygen consumption ml./min./M²				A-V oxygen difference Vol. %			
	Rest	Exercise	Response to exercise	P	Rest	Exercise	Response to exercise	P	Rest	Exercise	Response to exercise	P
Group A	2.67±0.24	4.04±0.40	+1.33±0.21	<0.01	149± 7	376±33	+225±27	<0.01	5.99±0.51	9.79±0.72	+3.80±0.48	<0.01
Group B	2.69±0.30	3.23±0.25	+0.59±0.21	0.03	166± 9	311±25	+150±22	<0.01	6.81±0.80	9.92±0.97	+3.43±0.37	<0.01
Difference	−0.02±0.38	+0.81±0.47	+0.74±0.29		−17±11	+65±41	+ 75±35		−0.82±0.94	−0.13±1.21	+0.37±0.61	
Significance of Difference (P)	>0.9	0.1	0.02		0.2	0.1	0.05		0.4	>0.9	0.6	

	Arterial oxygen saturation %				Pressures (mm. Hg) Pulmonary arterial: Systolic				Pulmonary arterial: Diastolic			
	Rest	Exercise	Response to exercise	P	Rest	Exercise	Response to exercise	P	Rest	Exercise	Response to exercise	P
Group A	90±4	88±5	−1±1	0.4	61± 6	89± 8	+28±4	<0.01	35±4	49±4	+14±3	<0.01
Group B	88±4	81±7	−2±2	0.2	80± 8	108± 9	+27±6	<0.01	46±4	63±6	+16±3	<0.01
Difference	+2±6	+7±9	+1±2		−19±10	−19±12	+1±7		−11±6	−14±7	−2±4	
Significance of Difference (P)	0.8	0.4	0.6		0.07	0.1	0.9		0.06	0.07	0.6	

	Pressures (mm. Hg): Pulmonary arterial (mean)				Right ventricular end diastolic				Systemic arterial (systolic)			
	Rest	Exercise	Response to exercise	P	Rest	Exercise	Response to exercise	P	Rest	Exercise	Response to exercise	P
Group A	45±4	66± 6	−21±4	<0.01	9±1	16±2	+7±1	<0.01	134± 9	162±14	+28± 8	<0.01
Group B	58±5	79± 8	+21±3	<0.01	22±1	30±3	+9±3	0.02	155±12	181±21	+31±12	0.05
Difference	−13±7	−13±10	−0.1±5		−13±2	−14±4	−2±3		−21±15	−19±25	−3±15	
Significance of Difference (P)	0.08	0.2	>0.9		<0.01	<0.01	0.5		0.2	0.5	0.9	

	Pressures (mm. Hg): Systemic arterial (diastolic)				Systemic arterial (mean)				Pulse rate Beats/min.			
	Rest	Exercise	Response to exercise	P	Rest	Exercise	Response to exercise	P	Rest	Exercise	Response to exercise	P
Group A	77± 3	92± 6	+15±5	<0.01	99± 5	119±11	+21± 7	0.02	84±3	126±4	+41±5	<0.01
Group B	88±10	94±10	+11±8	0.2	111±10	123±13	+18± 8	0.07	88±5	109±4	+26±5	<0.01
Difference	−11±10	−2±12	+4±9		−12±11	−4±18	+3±11		−4±6	+17±6	+15±7	
Significance of Difference (P)	0.3	0.9	0.6		0.3	0.8	0.8		0.5	0.02	0.06	

	Clearances vol./min./1.73 m²: PAH				Inulin			
	Rest	Exercise	Response to exercise	P	Rest	Exercise	Response to exercise	P
Group A	323±28	205±24	−106±25	<0.01	99±6	70±11	−29±11	0.03
Group B	255±33	177±27	−60±16	0.01	95±5	70± 7	−20± 5	<0.01
Difference	+68±43	+28±36	−46±29		+4±8	+0.1±13	−8±12	
Significance of Difference (P)	0.1	0.5	0.1		0.6	>0.9	0.5	

difference, but was associated with a significantly larger increase in oxygen consumption in the edema free than in the edematous group. Two cardiac patients without edema (D. C. and A. C.) who clinically had much less cardiac insufficiency than the rest of the patients in the study exercised so vigorously that they had by far the largest increases in oxygen consumption. If these two patients are excluded from the statistical analysis, the differences in both cardiac index and oxygen consumption between the groups in response to exercise lack statistical significance, the P values being .07 and .2, respectively. The arterial oxygen saturation at rest, during exercise and the changes in response to exercise did not differ significantly between the two groups. Although this measurement was reduced at rest, it did not change significantly with exercise.

Pulmonary arterial pressure. At rest and during exercise, the average systolic, diastolic and mean pulmonary arterial pressures were elevated in both groups, but were 11 to 19 mm. Hg lower in the group without edema than in the group with edema. The differences between the groups, however, lacked statistical significance at the 5 per cent level. The significant increases in pulmonary arterial pressures which occurred in both groups in response to exercise, were not significantly different from each other.

Right ventricular end-diastolic pressure. In the cardiac group without edema the right ventricular end-diastolic pressure at rest was slightly elevated whereas in the edematous group it was strikingly elevated. The difference was highly significant statistically. During exercise likewise the right ventricular end-diastolic pressure was significantly higher in the group with edema than the group without edema. In response to exercise both groups had significant increases in the right ventricular end-diastolic pressure which were not significantly different from each other.

Systemic arterial pressure. The average systolic, diastolic and mean arterial pressures at rest, during exercise and the changes in response to exercise were not significantly different between the groups. The increases in all of the components of the systemic arterial pressure were significant only in the non-edematous cardiac group.

Pulse rate. Statistical analysis showed that the pulse rates, which were not significantly different at rest, were significantly higher during exercise in the non-edematous than in the edematous group. The rise in pulse rate in response to exercise, however, just lacked being significantly different in the two groups.

Renal clearance measurements

PAH clearance. In both cardiac groups the renal plasma flow was reduced at rest. In response to exercise both groups had further decreases in this function which were statistically significant. The average PAH clearances at rest and during exercise were respectively 68 ml. per min. per 1.73 m^2 and 28 ml. per min. per 1.73 m^2 higher in the group without edema than in the group with edema. However, these differences between the groups (both at rest and during exercise) lacked statistical significance.

Inulin clearance. In both cardiac groups the glomerular filtration rate, which was reduced at rest, was significantly further depressed during exercise. The inulin clearance at rest, during exercise, and the change in response to exercise were not significantly different between the groups.

DISCUSSION

Cardiac patients with signs and symptoms of pulmonary congestion but with little or no evidence of "right-sided heart failure" do not necessarily develop salt and fluid retention when placed on a moderately high sodium intake. A majority of such patients, most of whom had valvular heart disease, were also found to have no obvious defect in the excretion of sodium when loaded acutely with hypertonic saline. Past studies, however, indicate that cardiac patients with previous "right sided failure" may have a persistent disturbance in sodium excretion even after "compensation" (2, 5). Since in the present study sodium excretion was determined only in cardiac patients without a history of peripheral edema, the previous findings do not necessarily conflict with the present results.

A number of the cardiac patients who tolerated a moderately high salt diet without developing edema had many hemodynamic as well as clinical findings considered to be indicative of severe cardiac insufficiency. In addition to pulmonary hypertension, their circulatory abnormalities included a reduction in cardiac output and a de-

crease in renal plasma flow and glomerular filtration rate. However, in none was the right ventricular end-diastolic pressure elevated above 14 mm. Hg. This latter hemodynamic function was the most consistent one which differentiated the cardiac group who had no evidence of salt and water retention from the group with such retention as indicated by the clinical finding of peripheral edema. In every one of the "salt-retaining group" right ventricular end-diastolic pressure was above 15 mm. Hg. Neither at rest nor during exercise were the cardiac output, pulmonary artery pressure, systemic arterial pressure, renal plasma flow and glomerular filtration rate consistently or significantly different in the two groups.

The present findings do not lend support to the "forward failure" concept as the predominant cause of edema formation in congestive heart failure. Rather they are more consistent with the "backward failure" concept in that they suggest that a critical elevation of the right ventricular end-diastolic pressure and peripheral venous pressure is the more important determining factor. However, it is obviously possible that reductions in cardiac output and glomerular filtration rate may also operate to increase the renal retention of sodium and water. Studies in experimentally induced heart failure also indicate that retention of salt and water occurs primarily as a result of the elevation of the venous pressure (6, 7).

Although venous hypertension may signal the danger of edema formation in congestive heart failure, edema may not form without an ample dietary intake of sodium chloride. A number of cardiac patients, while having a marked and persistent elevation of the venous pressure, have been observed to be edema free during a restricted intake of sodium. However, on increasing the sodium intake, these patients have developed salt retention and peripheral edema. The studies of Relman and Schwartz (8) may have a bearing on these observations in that they suggest that the action of salt retaining hormones, which appear to be increased in congestive heart failure (9, 10) are affected by the sodium content of diet.

SUMMARY

Cardiac patients who had many clinical and hemodynamic findings of congestive heart failure but no history of peripheral edema were found to tolerate a moderately high sodium intake without developing edema or salt retention. Many in the group likewise showed no impairment in sodium excretion when infused with 5 per cent saline. The most consistent hemodynamic measurement that differentiated this group from a similar cardiac group with peripheral edema was the finding of a lower right ventricular end-diastolic pressure. This finding supports the concept that salt retention in congestive heart failure may be initiated primarily by a critical rise in the venous pressure rather than by a decrease in cardiac output or glomerular filtration rate.

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