Effects of Low-sodium Diet and Spironolactone on Portal Pressure in Patients with Compensated Cirrhosis

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The aim of this study was to investigate the hemodynamic effects of spironolactone associated with a low-sodium diet (n = 14) or a low-sodium diet alone (n = 9) in patients with compensated cirrhosis and portal hypertension. Spironolactone significantly reduced the plasma volume. This effect was associated with a significant reduction in the hepatic venous pressure gradient, from 17.6 ± 3.6 mm Hg to 15.3 ± 3.5 mm Hg (−13% ± 13%; p < 0.01). Azygos blood flow (−20% ± 20%), cardiac output (−16.2% ± 10.5%) and mean arterial pressure (−9% ± 9%) also decreased significantly. However, there were no significant changes in hepatic blood flow. Patients receiving low-sodium diet alone experienced a mild but significant reduction in hepatic venous pressure gradient (−6.3% ± 6%) and in mean arterial pressure (−4% ± 5%). There were no significant changes in cardiac output and in hepatic or azygos blood flows. This study indicates that low-sodium diet plus administration of spironolactone reduces portal pressure and azygos blood flow in patients with compensated cirrhosis. Low-sodium diet alone only produces mild effects that are likely to be clinically irrelevant. (HEPATOLOGY 1994;19:1095-1099.)

Several clinical and experimental studies have shown that portal hypertension is associated with an expanded plasma volume (1-4). It has been recently shown that plasma volume expansion results from sodium retention promoted by the systemic vasodilation induced by portal hypertension (5).

Plasma volume expansion probably contributes in part to the increased portal pressure. This perception is suggested by the fact that plasma volume expansion worsens portal hypertension (2, 6, 7), whereas plasma volume depletion, achieved by either diuretics (8-12) or low-sodium diet (13), decreases portal pressure in patients with cirrhosis (8-12) and in experimental models of portal hypertension (13). In addition, recent studies suggest that increased plasma volume plays an important role in the development of the high cardiac output and hyperkinetic circulatory syndrome associated with portal hypertension (5).

The aim of this study was to investigate, in patients with compensated cirrhosis and portal hypertension, the hemodynamic effects of continued spironolactone administration associated with a low-sodium diet or of a low-sodium diet alone.

PATIENTS AND METHODS

The study was performed in 23 patients with cirrhosis and portal hypertension admitted to the Liver Unit, Hospital Clinic and Provincial of Barcelona, for the evaluation of portal hypertension. All patients gave their written informed consent to participate in the study after full explanation of the purpose of the study. The procedures were reviewed and approved by the Clinical Investigation Committee of the Hospital Clinic i Provincial of Barcelona. Thirteen patients were men and 10 were women. The mean age was 57 ± 11 yr (mean ± S.D.). The cause of cirrhosis was nonalcoholic in 17 patients and alcoholic in 6 patients. All the alcoholic cirrhotic patients had abstained from alcohol for at least 6 mo. All patients had varices on endoscopy but none had bled from the varices. No patient had present or past ascites or edema. The absence of ascites was confirmed by ultrasonography. No subject was receiving vasoactive drugs or diuretics. Additional clinical data on these patients are shown in Table 1.

Patients were studied after an overnight fast. With the patients lying on a bed in a relaxed atmosphere, an intravenous cannula (Venflon-2 18G; Viggo AB, Helsingborg, Sweden) was inserted in an antecubital vein, and a blood sample for standard liver function tests, BUN, serum creatinine, serum electrolytes, plasma renin activity (PRA) and the plasma concentrations of aldosterone, atrial natriuretic factor (ANF) and antidiuretic hormone (ADH) was obtained 40 min later, without disturbing the patient. Furthermore, a 24-hr urine collection was performed to measure electrolytes. Samples for hormonal measurements were centrifuged (4,000 rpm) at 4° C and stored at −80° C until assayed. Immediately after the blood samples were obtained, a venous catheter introducer

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TABLE 1. Clinical data on the 23 patients studied

Parameters	LowNa + Spir (n = 14)	LowNa (n = 9)
Age (yr)[a]	58 ± 11	57 ± 11
Sex (M/F)	10/4	3/6
Etiology (alcoholic/nonalcoholic)	4/10	2/7
Bilirubin (mg/dl)[a]	1.4 ± 0.5	1.1 ± 0.5
Albumin (gm/L)[a]	39 ± 5	36 ± 4
Prothrombin ratio (%)[a]	83 ± 10	83 ± 16
Child-Pugh score[a]	5.6 ± 0.6	5.4 ± 0.7
Esophageal varices	14	9
Previous variceal bleeding	0	0

LowNa, low-sodium diet; *Spir*, spironolactone.
[a]Data expressed as mean ± S.D.

(USCI International Inc., Burlington, MA) was placed, while the patient was under local anesthesia, in the right femoral vein by the Seldinger technique. This procedure allowed us to advance, under fluoroscopy, first a 7F balloon-tipped catheter (Medi Tech; Cooper Scientific Corp, Watertown, MA) into the main right hepatic vein. Wedged (occluded) and free hepatic venous pressures (WHVP and FHVP, respectively) were measured by inflating and deflating the balloon. Afterwards a Swan-Ganz catheter (Edwards Laboratory, Los Angeles, CA) was placed into the pulmonary artery to measure cardiopulmonary pressures and cardiac output (thermodilution), and then a 7F coronary sinus continuous thermal dilution catheter (Webster Laboratories, Inc., Baldwin Park, CA) into the azygos vein to measure azygos blood flow as previously described (14). Arterial pressure was measured with an automatic sphygmomanometer (Dinamap; Critikon, Tampa, FL), and heart rate was derived from the continuous EKG monitoring. Plasma volume was measured by indicator dilution using ^{125}I-labeled human serum albumin (15). Hepatic blood flow was measured during a continuous infusion of indocyanine green (ICG) (Serb, Paris, France), prepared in a solution containing 2% human serum albumin, infused intravenously at a constant rate of 0.2 mg/min. After an equilibration period of 40 min, four sets of simultaneous samples of peripheral and hepatic venous blood were obtained for the measurement of hepatic blood flow, the hepatic clearance of ICG and the hepatic intrinsic clearance by following previously reported methods (16).

All parameters were measured at least in duplicate, and permanent tracings were obtained on a multichannel recorder (7754B; Hewlett-Packard, Waltham, MA). Portal pressure was estimated from the hepatic venous pressure gradient (HVPG), the difference between WHVP and FHVP. Systemic vascular resistance (SVR) (dyne · sec · cm^{-5}) was calculated as (MAP − RAP)/CO × 80 in which *MAP* indicates mean arterial pressure (millimeters of mercury), *RAP* indicates right atrial pressure (mm millimeters of mercury Hg) and *CO* indicates cardiac output (liters per minute).

PRA was determined by RIA (Clinical Assays; Baxter, Cambridge, MA) of generated angiotensin I after 20-min incubation at pH 7.4 and and 37° C in conditions of inhibiting further conversion of angiotensin I. Plasma aldosterone, ANF and ADH concentrations were measured by RIA. Serum electrolytes were measured by flame photometry (Instrumentation Laboratory, Ascoli Piceno, Italy). Normal values of PRA, aldosterone, ANF and ADH in our laboratory are 1.3 ± 0.2 ng/ml · hr, 10.5 ± 1.1 ng/dl, 6 ± 1 fmol/ml and 1.0 ± 0.2 pg/ml, respectively (17).

After completing the baseline investigation, all patients were given a low-sodium diet containing approximately 50 mEq/day of sodium. The first group (14 patients, patients 1 to 14) were also given spironolactone orally (100 mg/day). The second group (nine patients, patients 15 to 23) continued to receive only the low-sodium diet. In both groups a second hemodynamic study was performed at 2 mo.

On the day of the second hemodynamic study all measurements were performed by following an identical protocol as in the first study. In the spironolactone group, the patients took their dose of spironolactone at 8 AM, and measurements were performed 2 to 4 hr later (18).

The results are reported as mean ± S.D. The paired Student *t* test and the coefficient of correlation were used in the statistical analysis of the results. Statistical significance was established at $p < 0.05$.

RESULTS

Baseline Data. All patients had severe portal hypertension. This condition was associated with a high azygos blood flow and cardiac output and a decreased mean arterial pressure and systemic vascular resistance (Table 2). There were no significant differences in age, sex, cause of cirrhosis or liver function between patients treated with spironolactone plus low-sodium diet and with low-sodium diet alone (Table 1). Hemodynamic parameters were also similar except that patients receiving low-sodium diet alone exhibited a significantly higher systemic vascular resistance, hepatic clearance and intrinsic clearance of ICG and a significantly lower cardiac output than those who were also receiving spironolactone (Table 2).

Long-term Effects of Spironolactone and Low-sodium Diet on Plasma Volume and Systemic Hemodynamics. Patients who received low-sodium diet alone experienced a significant reduction in daily sodium excretion (from 113 ± 50 to 45 ± 14 mEq/day; $p < 0.01$). Plasma volume showed a mild, nonsignificant decrease (Table 3). There were no significant changes in cardiac output, systemic vascular resistance, cardiopulmonary pressures or heart rate, but mean arterial pressure exhibited a slight, albeit significant, reduction (−4% ± 5%, $p < 0.05$) (Table 2). Continuous spironolactone administration induced significant decreases of plasma volume, cardiopulmonary pressures and cardiac output (Table 2). Despite a significant increase in systemic vascular resistance, mean arterial pressure

TABLE 2. Hemodynamic effects of low-sodium diet plus continuous spironolactone administration or low-sodium diet alone in patients with compensated cirrhosis and portal hypertension

	LowNa + Spir		LowNa	
	Basal	2 mo	Basal	2 mo
Heart rate (beats/minute)	75 ± 10[a]	72 ± 9	73 ± 12	73 ± 12
MAP (mm Hg)	94 ± 12	85 ± 11[b]	94 ± 13	90 ± 12[c]
RAP (mm Hg)	3.5 ± 2	1.8 ± 1[b]	2.6 ± 1.9	2.5 ± 1.5
PAP (mm Hg)	13 ± 2.8	10 ± 2.2[b]	12 ± 2.5	11.6 ± 3
PCP (mm Hg)	7.6 ± 2.3	4.4 ± 1.5[b]	6.8 ± 3.1	6 ± 3
CO (L/min)	8.6 ± 2.2	7.3 ± 2[b]	6.6 ± 2[d]	6.4 ± 2
SVR (dyne · sec · cm $^{-5}$)	899 ± 282	1,007 ± 391[c]	1,178 ± 310[d]	1,167 ± 304
WHVP (mm Hg)	23.9 ± 4	20.8 ± 3.5[b]	22 ± 5.4	20 ± 5.4[c]
FHVP (mm Hg)	6.4 ± 2.0	5.5 ± 2.3	5.2 ± 1.6	4.4 ± 1.8[c]
HVPG (mm Hg)	17.6 ± 3.6	15.3 ± 3.5[b]	16.7 ± 4	15.7 ± 4.2[c]
HBF (L/min)	1.33 ± 0.5	1.24 ± 0.5	1.59 ± 0.5	1.44 ± 0.4
ICG extraction	0.27 ± 0.13	0.28 ± 0.10	0.32 ± 0.12	0.35 ± 0.14
HCl ICG (ml/min)	217 ± 66	211 ± 80	301 ± 111[d]	311 ± 143
ICl ICG (ml/min)	259 ± 89	251 ± 105	374 ± 158[d]	399 ± 217
AzBF (L/min)	0.58 ± 0.2	0.46 ± 0.2[c]	0.54 ± 0.2	0.51 ± 0.2

LowNa, low-sodium; *Spir*, spironolactone; *MAP*, mean arterial pressure; *RAP*, right atrial pressure; *PAP*, pulmonary artery pressure; *PCP*, pulmonary capillary pressure; *CO*, cardiac output; *SVR*, systemic vascular resistance; *HBF*, hepatic blood flow; *HCl*, hepatic clearance; *ICl*, intrinsic clearance; *AzBF*, azygos blood flow.

[a]Data expressed as mean ± S.D.

[b]$p < 0.01$ vs. baseline.

[c]$p < 0.05$ vs. baseline.

[d]$p < 0.05$ vs. LowNa + *Spir*.

TABLE 3. Changes in the endogenous vasoactive systems, body weight, hematocrit, renal function and electrolytes after long-term treatment with spironolactone plus low-sodium diet or low-sodium diet alone

	LowNa + Spir		LowNa	
	Basal	2 mo	Basal	2 mo
Hematocrit (%)	39.6 ± 5[a]	40.9 ± 5	37.7 ± 4	36.7 ± 4
Body weight (kg)	71.1 ± 0.9	70.3 ± 1	71.0 ± 1.8	69.5 ± 1.5
PRA (ng/ml · hr)	0.5 ± 0.5	3.4 ± 3.0[b]	0.2 ± 0.3	0.3 ± 0.2
PA (ng/dl)	9.8 ± 4.8	53 ± 29[b]	9.8 ± 8.7	10.2 ± 6.9
ANF (fmol/ml)	19.4 ± 6.3	11.4 ± 7.8[b]	21.4 ± 12.9	21.5 ± 11.9
ADH (pg/ml)	1.2 ± 0.2	1.7 ± 0.6[c]	3.1 ± 3.3	1.6 ± 0.6
Plasma volume (L)	3.68 ± 0.8	3.34 ± 0.7[c]	3.23 ± 0.6	3.05 ± 0.4
BUN (mg/dl)	15 ± 5	22 ± 9[b]	15 ± 4	15 ± 4
Creatinine (mg/dl)	0.9 ± 0.2	1.0 ± 0.3	0.8 ± 0.1[d]	0.7 ± 0.2
Serum Na (mEq/L)	140 ± 3	138 ± 3	139 ± 2	141 ± 2
Serum K (mEq/L)	3.8 ± 0.6	4.4 ± 0.6[b]	3.8 ± 0.3	3.9 ± 0.2

LowNa, low-sodium; *Spir*, spironolactone; *PRA*, plasma renin activity; *PA*, plasma aldosterone.

[a]Data expressed as mean ± S.D.

[b]$p < 0.01$ vs. baseline.

[c]$p < 0.05$ vs. baseline.

[d]$p < 0.05$ vs. LowNa + *Spir*.

exhibited a mild but significant reduction (−9 ± 9%; $p < 0.01$). Heart rate did not change (Table 2).

Long-term Effects of Spironolactone and Low-sodium Diet on Endogenous Vasoactive Systems and Renal Function. Low-sodium diet alone did not cause significant changes on endogenous vasoactive systems, renal function and serum electrolytes (Table 3). However, the plasma volume depletion induced by the addition of spironolactone to the low-sodium diet was associated with significant increases in PRA, plasma aldosterone concentration and plasma ADH, whereas plasma ANF decreased significantly (Table 3). Moreover, spironolactone caused significant changes in renal function and serum electrolytes. BUN and serum potassium increased, whereas plasma creatinine and serum sodium did not change (Table 3). Body weight and hematocrit did not change significantly in either group (Table 3).

Long-term Effects of Spironolactone and Low-sodium Diet on Splanchnic Hemodynamics. Administration of spironolactone produced a significant reduction of the HVPG (mean decrease, −12.6 ± 13%; $p < 0.01$) (Table

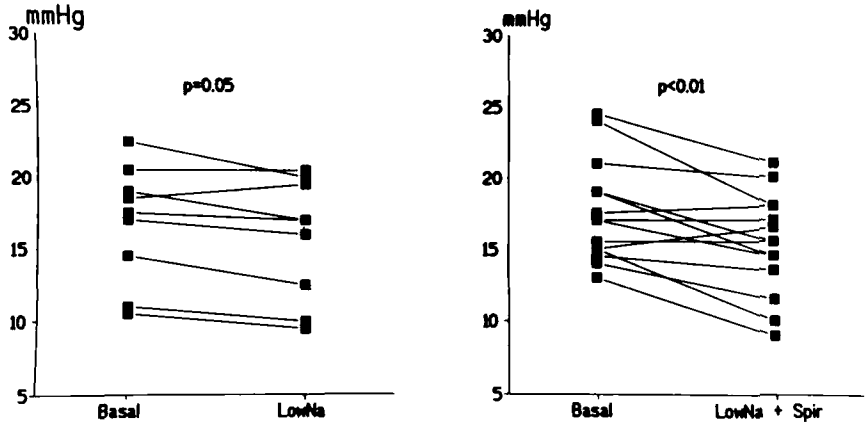

FIG. 1. Individual data on the effects of low-sodium diet alone *(LowNa)* or associated with spironolactone *(LowNa + Spir)* on the HVPG.

2). This resulted from a significant reduction in WHVP. FHVP also decreased, although this change did not reach statistical significance ($p = 0.1$) (Table 2). Low-sodium diet alone caused a mild but significant reduction in HVPG ($-6.3 \pm 6\%$; $p = 0.05$). This change was not significantly different from that caused by spironolactone. WHVP and FHVP also decreased significantly (Table 2). The individual changes in HVPG are shown in Figure 1.

Azygos blood flow decreased significantly after administration of spironolactone ($-20 \pm 20\%$, $p < 0.05$), but not after low-sodium diet alone. Hepatic blood flow, hepatic clearance of ICG and hepatic intrinsic clearance did not change significantly in either group (Table 2).

There was a significant correlation between the changes in plasma volume and the changes in cardiac output caused by spironolactone ($r = 0.68$, $p < 0.01$). The reduction in HVPG was not correlated with changes in plasma volume or any other parameter.

DISCUSSION

The results of our study clearly show that continued administration of spironolactone significantly reduces HVPG in patients with compensated cirrhosis and portal hypertension. These findings confirm previous studies (8-12) showing that plasma volume depletion decreases portal pressure in portal hypertension, which reinforces the idea that an increased plasma volume contributes to maintain—and probably aggravates—portal hypertension (2, 6, 7, 18). The mean reduction in HVPG caused by spironolactone (13%) compares well with that produced by propranolol, which usually ranges between 10% and 18% (19-23). However, contrary to propranolol (24), spironolactone did not cause significant changes in hepatic blood flow and liver function, as evaluated by measurements of the hepatic and intrinsic clearance of ICG. Patients receiving low-sodium diet alone did not exhibit such marked changes. HVPG showed just a mild reduction (-6%). This change, although statistically significant, may be clinically irrelevant, taking into account the relationship between the extent of HVPG reduction and clinical efficacy (20). Previous studies have suggested that to achieve effective protection from the risk of variceal bleeding, HVPG shall decrease below 12 mm Hg (20) or at least by 20% (25). Thus a 6% decrease appears far from what is desirable. In addition, contrary to spironolactone, low-sodium diet alone did not significantly reduce the azygos blood flow, a parameter that reflects blood flow through portosystemic collaterals and esophageal varices (14, 22). Actually, a marked reduction in azygos blood flow is thought to represent a major beneficial effect from propranolol therapy (18, 22).

One of the mechanisms by which spironolactone may decrease HVPG is by reducing the circulating blood volume and therefore the splanchnic blood volume. In addition, spironolactone may decrease HVPG by reducing portal blood flow, as suggested by the 20% reduction in azygos blood flow. This fall in azygos blood flow suggests splanchnic vasoconstriction in response to the decrease in effective volume. It should be noted in that regard that continuous administration of spironolactone promoted marked changes in endogenous vasoactive systems. PRA, aldosterone and ADH levels increased, whereas ANF decreased. These changes reflect a decrease in the effective blood volume and may modulate the hemodynamic effects of spironolactone (15, 17). It is likely that activation of the renin-angiotensin system and ADH, which are powerful splanchnic vasoconstrictors, may explain at least in part the decrease in portal-collateral blood flow.

It is likely that the mild decrease in HVPG observed in patients receiving low-sodium diet alone was also a result of a decrease in extracellular fluid volume, although the decrease in plasma volume failed to reach statistical significance. Indeed, in experimental models of portal hypertension (13), low-sodium diet alone caused a significant reduction in plasma volume. The milder effect of sodium restriction observed in the present study may be explained by the fact that in experimental models it is possible to decrease sodium ingestion much more than what is acceptable in compensated cirrhotic patients (approximately 50 mEq/day in the present series). The mild effects of such sodium

restriction on effective blood volume are further documented by the lack of changes in endogenous vasoactive systems.

Patients receiving a low-sodium diet alone had a slightly better liver function and less hyperkinetic circulation than patients treated with spironolactone. However, it is unlikely that a low-sodium diet alone would have greater effects in the latter group, because the sodium depletion was mild and because patients with more advanced disease usually show less marked responses to portal hypotensive agents (21, 22, 26).

Our study also shows that administration of spironolactone caused a significant decrease in cardiac output. This result was directly correlated with the changes in plasma volume after spironolactone. These data support the concept that an increased plasma volume is a major determinant of the increased cardiac output, a component of the hyperkinetic circulatory syndrome of patients with cirrhosis and portal hypertension (5).

Despite the moderate decrease in arterial pressure and the activation of endogenous vasoactive systems caused by spironolactone, there were no relevant changes in kidney function. BUN and serum potassium showed a significant increase, but the final values remained within the normal range of our laboratory, and no change was noted in plasma creatinine or serum sodium. Therefore, our data suggest that it is unlikely that continuous treatment with spironolactone may produce clinically significant deleterious effects on kidney function in compensated cirrhotic patients.

It is not unusual to begin propranolol treatment to prevent variceal bleeding in patients who are receiving a low-sodium diet and spironolactone because of present or past ascites. In that context spironolactone treatment may be a confounding factor that has not been adequately considered when the clinical or hemodynamic response to pharmacological therapy is analyzed.

In summary, this study indicates that low-sodium diet plus administration of spironolactone reduces portal pressure and azygos blood flow in patients with compensated cirrhosis and therefore may be useful in the pharmacological treatment of portal hypertension.

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