The Effect of Long-term Treatment With Spironolactone on Variceal Pressure in Patients With Portal Hypertension Without Ascites

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The effect of spironolactone on esophageal variceal pressure (VP) in patients without ascites was investigated. VP was assessed using a noninvasive endoscopic gauge. Spironolactone was administered during a 6-week period at a dosage of 100 mg/d. This treatment decreased VP from 16.8 ± 1.9 (SD) to 14.1 ± 2.7 mm Hg ($P < .001$) in a group of 12 patients and from 18.6 ± 2.1 to 13.7 ± 4.1 mm Hg ($P < .01$) in another group of 8 patients who still had high VP despite chronic intake of propranolol. In both groups, placebo administration to 12 and 8 comparable patients did not significantly alter VP. Spironolactone induced a significant reduction of plasma volume (42.1 ± 5.5 to 36.1 ± 6.6 mL/kg body weight, $P < .01$) and of the concentration of α-atrial natriuretic peptide (α-ANP) (39.8 ± 22 to 27.7 ± 20 pg/mL, $P < .01$); in addition, a pronounced increase in plasma renin activity (PRA) (1.1 ± 0.9 to 7.5 ± 3.4 ng/mL/h, $P < .001$) was induced by the treatment. No significant changes in systemic hemodynamics were observed during the studies. Severe side effects were not observed except for a high incidence (55%) of painful gynecomasty in the male patients. In conclusion, chronic spironolactone administration effectively lowers VP, even in patients under chronic propranolol therapy. The combination of propranolol and spironolactone deserves further study as a prophylactic therapy of variceal hemorrhage, but development of gynecomasty might be a problem. Finally, we confirmed the reproducibility of VP measurements with the noninvasive gauge in chronic conditions. (HEPATOLOGY 1996;23:1047-1052.)

Bleeding from esophageal varices still represents a major cause of death in patients with cirrhosis.[1] Therefore, medical treatment to prevent variceal bleeding is receiving much attention. Of the medical agents currently in use to prevent variceal bleeding, propranolol remains the agent most extensively validated.[2] It is generally accepted that β-adrenergic blockers decrease the risk of variceal bleeding by reducing pressure and flow in the portal and variceal system. Reinforcing this concept is the observation that a decrease of the hepatic venous pressure gradient to less than 12 mm Hg under propranolol treatment, protects from variceal bleeding and increases the rate of survival.[3] However, it also became clear that nonselective β-adrenergic blockers fail to prevent variceal bleeding in a substantial number of patients; as such the search for additional or alternative agents has to continue.[4]

Most patients with portal hypertension have an expanded plasma volume, associated with a peripheral vasodilatation, which is characteristic of the syndrome of portal hypertension.[5] An agent reducing the plasma volume might thus exert a beneficial effect on portal and variceal pressure. Preliminary studies in humans seem to show that chronic intake of the diuretic agent spironolactone, an antagonist of aldosterone, decreases plasma volume as well as portal vein pressure,[6,7] whereas chronic administration of furosemide did not profoundly affect the portal pressure.[7]

The decisive factor that may determine variceal rupture is the tension in the wall of the varix.[8] Variceal pressure (VP) is one of the factors determining the wall tension and can be appropriately measured by a pressure-sensitive gauge.[9]

In the present study, we investigated whether chronic intake of spironolactone reduces VP in patients with portal hypertension without ascites, and whether it also exerts a beneficial effect on VP in patients under propranolol therapy.

PATIENTS AND METHODS

Patients. Forty-five patients with portal hypertension due to various causes, esophageal varices at least 4 mm in diameter, and without a history of variceal bleeding or of recent hepatic decompensation were investigated. The absence of ascites was evaluated clinically. In the first part of the study, we investigated 27 patients who did not yet receive any prophylactic therapy (group 1). For the second part, 18 patients, treated chronically with propranolol at a median daily dose of 80 mg (range, 5-120 mg) as primary prophylaxis of variceal

Abbreviations: VP, variceal pressure; PRA, plasma renin activity; α-ANP, α-atrial natriuretic peptide.

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bleeding, were selected; these patients received therapy with propranolol for at least 3 months (mean, 15 months; range, 3-37 months). They were selected for this study when their VP under propranolol treatment still exceeded 14 mm Hg, suggesting insufficient response to the β-blocker.[10] All of them had varices of at least 5 mm and were in a steady-state with respect to β-blockade, as reflected by a pulse rate of 64 $\pm$ 7 beats/min. In group 2, baseline VP measurements, before starting propranolol therapy, had only been performed in a small number of the patients and, therefore, not reported. None of the patients in both groups had received diuretics for at least 1 month before the study.

All patients of groups 1 and 2 were treated during 6 weeks in a randomized way with either spironolactone 100 mg/d orally or with placebo, administered in identical tablets. The medication was administered once daily at breakfast. All patients were on a free diet throughout the study. In group 2, the dosage of propranolol was not altered during the study. Concomitant medication remained unchanged during the study. Compliance was assessed by counting the remaining tablets at each visit. Randomization was performed by the method of sealed envelopes, and the code was not broken until the end of the study. Informed consent was obtained from each patient, and the study protocol had been approved by the local ethical committee.

Procedures. All measurements were performed before and after 6 weeks of continuous oral administration of spironolactone or placebo. Assessment of plasma volume and VP was performed 3 and 5 hours, respectively, after the last intake of medication. Blood pressure, pulse rate, and blood samples were obtained in the supine position 4 hours after the last intake of drug. At that time, body weight was also recorded.

Measurement of plasma volume and determination of plasma renin activity (PRA) and of plasma α-atrial natriuretic peptide (α-ANP) were restricted to the first 15 patients of group 1.

Measurement of VP was performed under endoscopy by using a previously described noninvasive technique (Varipress; Labotron, Barcelona, Spain).[9-11] The recording of capsule pressure was considered satisfactory when fine venous fluctuations at a stable level, superimposed on the respiratory cycle, were recognized in the absence of pronounced luminal contractions and with a basal luminal pressure not exceeding 5 mm Hg.[11] Capsule pressure and free esophageal luminal pressure were calculated as the mean of the upper and lower level of the fluctuations. Free esophageal luminal pressure was regarded as the zero level. VP was calculated by obtaining the difference between the capsule pressure and the free esophageal luminal pressure. The mean of at least four satisfactory measurement periods was used to define VP. Calculations were performed by a computer; the interobserver variability for the calculation of VP was 4%. All patients received premedication with 2.5 to 7.5 mg diazepam and 40 mg *n*-butylscopolamine intravenously.

At the moment of VP measurement, the size of the varix was estimated by comparing the varix with the size of the pressure gauge. The maximal diameter of the varices was recorded.

The blood pressure was recorded by a sphygmomanometer attached to the right arm of the patient, who was in the supine position, taking into account Korotkoff phases I and V for systolic and diastolic blood pressure. The values were expressed as the mean of three consecutive readings. A 24-hour urine collection, obtained the day immediately before the investigation, was used for the calculation of the baseline salt excretion.

PRA was detected by radioimmunoassay.[12] α-ANP levels were determined by radioimmunoassay after extraction of freshly obtained plasma on a SEP-PAK-18 cartridge column (Millipore Corp., Milford, MA), as described previously.[13] Normal levels of PRA range from 0.40 to 2.78 ng/mL/h for a sodium excretion of more than 100 mmol/24 h. Normal values of plasma α-ANP obtained after the patient has been in a supine position for 5 minutes and for a urinary sodium excretion exceeding 100 mmol/24 h, are between 13 and 34 pg/mL

Plasma volume was assessed by the radiolabelled albumin dilution technique. The examination was performed by measuring radioactivity in four consecutive samples of blood obtained every 3 minutes and beginning 6 minutes after the intravenous injection of 250 μCi radiolabelled albumin (Technescan HSA, Mallinckrodt Medical, Holland). Normal values in our laboratory range between 27 and 42 mL/kg body weight.

Statistical Analysis. The results are reported as mean $\pm$ SD. Statistical analysis of the results was performed using paired Student's *t* test to evaluate the significance of comparisons with baseline within each group, whereas the analysis of variance was used for comparison between groups. Significance was considered $P < .05$.

RESULTS

Five patients were withdrawn from the study before the code was broken. In three of these patients, a second satisfactory VP recording could not be obtained. The other two patients belonged to the spironolactone group and stopped the medication because of side effects; one patient complained of anorexia and the other one developed diarrhea with a concomitant increase of serum potassium level of up to 5.5 mmol/L.

The clinical characteristics of the 40 patients in the study are summarized in Table 1. There were no significant differences in the group treated with placebo or with spironolactone with regard to age, cause of portal hypertension, severity of liver disease, and baseline mean urinary sodium excretion; there were more females in the spironolactone-propranolol group. Three of the nine males who received spironolactone had serious problems with gynecomasty during the study and stopped taking the drug immediately after the study period of 6 weeks. Spironolactone treatment was continued after the study in the patients who received active drug, but two other male patients later decided to interrupt the drug also because of gynecomasty.

Patients Not Treated With Propranolol. Figure 1 shows the individual changes in VP in 12 patients treated with placebo in comparison with the values obtained in 12 patients under long-term spironolactone treatment (100 mg/d for 6 weeks). Long-term administration of placebo did not cause changes in VPs (16.1 $\pm$ 3.0 mm Hg at baseline and 16.2 $\pm$ 3.3 mm Hg after 6 weeks), in variceal size (7 $\pm$ 2 mm at baseline and 7 $\pm$ 2 mm after 6 weeks), or in other variables (Table 2). In contrast, chronic intake of spironolactone caused a significant reduction in VPs (16.8 $\pm$ 1.9 mm Hg at baseline to 14.1 $\pm$ 2.7 mm Hg [$P < .001$] after 6 weeks).

TABLE 1. Clinical Characteristics of the Patients

	Placebo	Spironolactone	Placebo + Propranolol	Spironolactone + Propranolol
Number of patients	12	12	8	8
Age (yr)	54 ± 15	55 ± 14	57 ± 9	55 ± 9
Sex (M/F)	8/4	7/5	5/3	2/6
Origin of portal hypertension				
Alcohol	5	4	1	1
Cryptogenic	3	4	2	3
Viral induced	0	3	4	3
Primary biliary cirrhosis	3	0	0	1
Portal thrombosis	1	1	1	0
Child-Pugh class	6 ± 1	7 ± 2	7 ± 1	7 ± 2
Urinary sodium excretion (mmol/24 h) at baseline	110.5 ± 32.5	101 ± 42.5	Not performed	Not performed

NOTE. Values are expressed as numbers or mean ± SD.

However, in 4 patients no significant decrease of VP was obtained during chronic spironolactone intake. Overall, variceal size was 7 ± 2 mm at baseline and 6 ± 2 at 6 weeks' treatment (not significant). A sharp increase in PRA levels was observed in all patients who were administered spironolactone ($P < .001$).

Baseline plasma volume was increased or at the upper limit of normal in all our patients (Table 2). In contrast to the placebo group, spironolactone induced a significant decrease in plasma volume (mean ± SEM) of 14% ± 3% ($P < .001$). This effect was less obvious in two patients. However, there was no direct correlation between the decrease in plasma volume and the decrease in VP in the individual patient. Plasma α-ANP concentration decreased significantly in the patients receiving spironolactone treatment ($P < .01$) but not in the placebo group. No significant changes were observed in other biochemical parameters or in systemic hemodynamics (Table 2).

Patients Receiving Propranolol Therapy. Figure 2 shows the individual changes of VP in 16 patients receiving long-term propranolol therapy; 8 of them received a 6-week additional treatment with placebo and 8 with spironolactone 100 mg/d. The mean VP decreased significantly from 18.6 ± 2.1 mm Hg to 13.7 ± 4.1 mm Hg in the spironolactone group ($P < .01$). In the patients treated with placebo, no significant change was observed; the mean VP before treatment and at the end of treatment was 17.2 ± 1.9 mm Hg and 16.1 ± 3.4 mm Hg, respectively (not significant). As shown in Fig. 2, almost all patients except one in group 2 responded to spironolactone administration with a significant decrease in VP (mean ± SEM) of 23% ± 6% ($P < .001$). No significant changes were observed with regard to the variceal size (7 ± 2 and 6 ± 2 mm in the placebo and 7 ± 2 and 6 ± 2 in the spironolactone group at onset and after 6 weeks, respectively), the mean arterial pressure (99 ± 10 and 90 ± 20 mm Hg in the placebo and 96 ± 11 and 93 ± 14 mm Hg in the spironolactone group), or to the pulse rate (64 ± 6.5 and 65 ± 7.0 beats/min in the placebo and 67 ± 8 and 64 ± 6 beats/min in the spironolactone group).

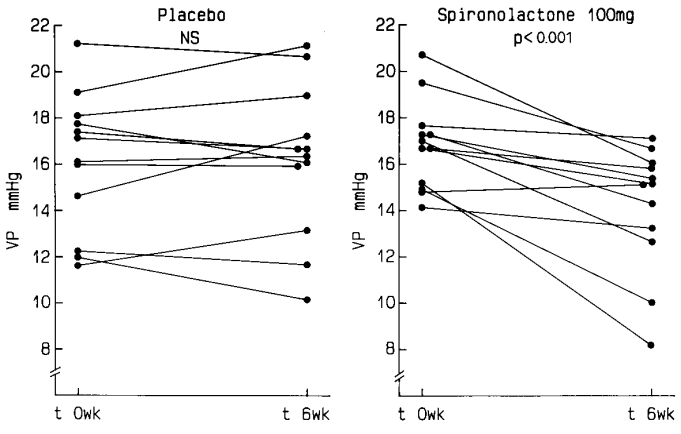

FIG. 1. Changes in VP after 6 weeks' administration of placebo (n = 12) or spironolactone (n = 12) in a group of patients with portal hypertension without ascites not treated with propranolol.

DISCUSSION

The pharmacological treatment of portal hypertension is based on the assumption that a sustained reduction in portal vein pressure can reduce the incidence of hypertensive complications.[3] β-Adrenergic receptor blocker agents can decrease portal pressure and prevent variceal bleeding.[14] However, a reduction of hepatic venous pressure gradient to less than 12 mm Hg is only obtained in a small number of patients; the latter pressure reduction is thought to be required to efficiently prevent variceal hemorrhage.[3] Another inconvenience of the treatment with propranolol is the finding that side effects leading to cessation of therapy occurs in 3% to 27% of patients.[15] Additional agents are thus required.

Most of the drugs investigated reduce portal pressure by provoking splanchnic vasoconstriction and a reduction of portal tributory blood flow. However, portal hypertension is also characterized by an increase in

TABLE 2. Systemic Hemodynamics, Circulating Plasma Volume, and Biochemical Parameters Before and After Long-Term Administration of Spironolactone

	Normal Range	No. of Patients	Placebo (n = 12) t_0	Placebo (n = 12) t_{6wk}		No. of Patients	Spironolactone (n = 12) t_0	Spironolactone (n = 12) t_{6wk}	*P*
Heart rate (beats/min)		12	77 ± 8	78 ± 12	NS	12	80 ± 18	81 ± 14	NS
Mean arterial pressure (mm Hg)		12	95 ± 12	87 ± 6	NS	12	97 ± 17	96 ± 14	NS
Body weight (kg)		12	79.3 ± 20.0	79.9 ± 20.5	NS	12	74.1 ± 16.7	75.6 ± 16.0	NS
Plasma volume (mL/kg body wt)	27-42	6	42.02 ± 2.20	45.14 ± 6.30	NS	6	42.11 ± 5.52	36.13 ± 6.69	.01
Plasma α-ANP (pg/mL)	13-34	6	37.9 ± 22.7	48.7 ± 28.8	NS	6	39.8 ± 22.1	27.7 ± 20.0	.01
PRA (mg/mL/h)	0.40-2.78	6	1.9 ± 0.9	1.4 ± 0.7	NS	6	1.1 ± 0.9	7.5 ± 3.4	.001
Serum sodium (mmol/L)	135.0-145.0	9	140.1 ± 2.0	139.0 ± 2.5	NS	9	139.9 ± 4.4	136.2 ± 5.6	NS
Serum potassium (mmol/L)	3.5-5.0	9	3.75 ± 0.18	3.85 ± 0.40	NS	9	3.95 ± 0.30	4.20 ± 0.30	NS
Serum bicarbonate (mmol/L)	22.0-32.0	9	26.3 ± 1.9	26.9 ± 3.2	NS	9	26.2 ± 2.8	24.7 ± 4.0	NS
Serum chloride (mmol/L)	96.0-106.0	9	104.9 ± 1.9	104.0 ± 2.6	NS	9	105.3 ± 4.0	101.9 ± 5.5	NS
Serum ureum (mg/dL)	20-45	9	25 ± 9	26 ± 6	NS	9	25 ± 7	32 ± 11	NS
Serum creatinine (mg/dL)	0.70-1.35	9	0.92 ± 0.13	0.96 ± 0.22	NS	9	0.91 ± 0.15	0.98 ± 0.12	NS
Hematocrit (%)	0.40-0.54	9	39 ± 5	40 ± 5	NS	9	41 ± 6	42 ± 6	NS
Serum albumin (g/dL)	3.5-5.0	9	3.81 ± 0.50	3.72 ± 0.38	NS	9	3.73 ± 0.58	3.78 ± 0.56	NS

NOTE. Data given as means ± SD.

plasma volume, the extent of which correlates with the degree of the disease.[5] Moreover, acute expansion of the plasma volume by albumin or by blood transfusion can increase portal pressure, which might lead to variceal rebleeding.[16] Plasma volume expansion may represent the link between vasodilatation and the development of the hyperdynamic state.[17] Reduction in plasma volume could thus constitute an alternative method to treat portal hypertension. It has recently been reported that chronic administration of spironolactone in patients with cirrhosis without ascites leads to a significant reduction of the hepatic venous pressure gradient.[6,7] It was suggested that the decrease in portal pressure was related to volume contraction.

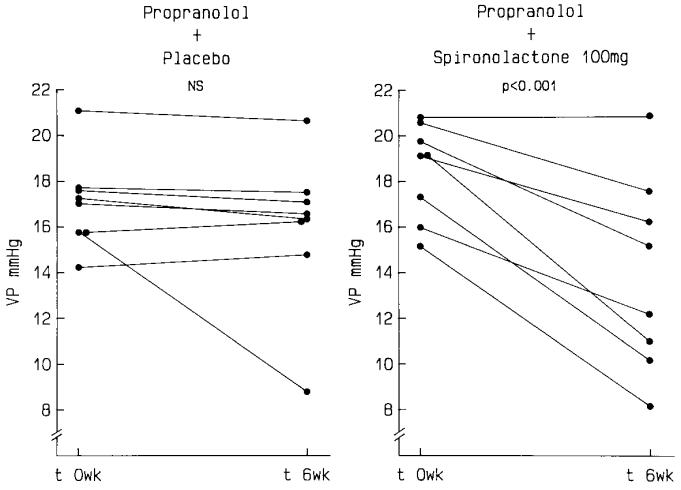

FIG. 2. Changes in VP after 6 weeks administration of placebo (n = 8) or of spironolactone (n = 8) in a group of patients already under propranolol therapy administered as primary prophylaxis of variceal bleeding.

Because VP seems to bear a close relationship to the risk of variceal bleeding[18] and because pharmacological agents may act differently on portosystemic collaterals,[19] we investigated in this placebo-controlled study the effect of chronic spironolactone directly on VP. In our group of previously untreated patients a significant overall mean decrease in VPs of 16% was observed by chronic spironolactone administration; this is in agreement with the reduction in hepatic venous pressure gradient and in azygos blood flow reported.[6,7] The changes in VPs occurred together with a reduction in plasma volume of 14% and with activation of the renin activity; the latter hormone is known to induce splanchnic vasoconstriction. This confirms earlier reports suggesting that a decrease of the body sodium content by administration of spironolactone triggers vasoactive mechanisms that decrease splanchnic blood flow.[7] Spironolactone did not decrease VPs in 4 patients who did not receive propranolol (and in 1 who received propranolol). A similar occurrence of so-called nonresponders to spironolactone was observed by Okumura et al.[6] in 2 of 16 patients and by Garcia-Pagan et al.[7] in 4 of 14 patients when measuring wedged hepatic venous pressure gradient. In 2 of 4 nonresponders, plasma volume, PRA, and α-ANP determinations were available; an increase in PRA levels and a decrease in α-ANP levels were observed in both. Plasma volume decreased in 1 patient and remained unaffected in the other patient. The baseline natriuresis was not different between responders and nonresponders. However, the small number of patients does not allow us to draw conclusions about possible characteristics of nonresponders.

In the second part of the study we showed that chronic spironolactone administration induced a decrease in VP in this selected group of patients who still presented large varices and increased levels of VP,

despite treatment with propranolol. This is of importance, because recently we could show in cirrhotic patients that administration of propranolol during a 3 month-period caused a mean decrease of VP of only 17%.[10]

The findings that a diuretic agent decreased VP in patients receiving long-term β-blockade differ from the results of Sogni et al.,[20] who showed that a bolus injection of the diuretic agent furosemide had no effect on hepatic venous pressure or on azygos blood flow in patients receiving chronic propranolol therapy. This difference could theoretically be caused by the mode of administration of the diuretic substance: bolus or chronic administration. However, the difference is probably related to the agent used. Indeed, Okumura et al.[7] also failed to observe a decrease in hepatic venous pressure gradient in patients during chronic administration of furosemide, in contrast to results obtained with chronic spironolactone intake. The beneficial effect of spironolactone on portal pressure and VP might be related to a direct hemodynamic effect on the splanchnic circulation and not be mediated by a decrease in plasma volume.[22] Furosemide lowers plasma volume, at least in short-term administration, but fails to decrease the hepatic venous pressure gradient in cirrhotic patients who are receiving β-adrenergic antagonists.[20,21] Furthermore, we could not ascertain an individual relationship between the decrease in plasma volume and in VP. Similarly, Okumura et al.[6] did not find a direct correlation between the changes in circulating plasma volume and hepatic venous pressure gradient. Further studies concerning the way of action of spironolactone are required.

The beneficial effects of spironolactone on portal pressure, on azygos flow,[7] and on VP, as is shown in this study even in patients under a stable treatment with β-blocking agents, suggest that long-term combination therapy of propranolol and spironolactone should be explored in the treatment of portal hypertension, especially because negative influences on systemic hemodynamics or kidney function were not observed. Furthermore, the drug is well known to prevent the formation of ascites, a condition that appears to diminish the efficacity of the propranolol therapy.[23] However, widespread long-term use of spironolactone in male patients without ascites might be problematic, because a considerable amount of our male patients developed serious gynecomasty.

In the present study, we showed a beneficial effect of chronic spironolactone intake on VP and plasma volume irrespective of other hemodynamic changes. The data are in accordance with previous studies showing an effect of the drug on splanchnic hemodynamics in patients with portal hypertension. This occurred in our study both in previously untreated patients and in patients under chronic propranolol therapy. Finally, we again confirmed the reproducibility of VP measurements with the noninvasive gauge in chronic conditions.[10]

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