



STENOSIS OF THE INFERIOR VENA CAVA AVOIDS LIVER HYPERTROPHY IN RATS WITH CHRONIC PREHEPATIC PORTAL HYPERTENSION

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ABSTRACT

The influence that the stenosing ligation of the infrahepatic inferior vena cava in the development of the portosystemic collateral circulation and in the liver lobular weight distribution has on the systemic hemodynamic alterations has been studied in rats having one year of evolution with prehepatic portal hypertension. Portal hypertension (Group III) causes redistribution of the liver lobes weights in 33.3% of the animals (subgroup IIIb) with hypertrophy of the posterior liver lobes, atrophy of the anterior liver lobes and splenomegaly and a decrease in the incidence of mesenteric venous vasculopathy; the latter being characterized by a significant dilation and tortuosity of the superior mesenteric vein branches. Coexistence of portal hypertension and stenosis of the inferior vena cava (Group IV) prevents hypertrophy of the anterior liver lobes, produces liver atrophy and also increases the incidence of mesenteric venous vasculopathy in 40.9% of the animals (subgroup IVb). It can be concluded that the systemic hemodynamic alterations which are caused by the stenosis of the inferior vena cava worsen the chronic evolution of prehepatic portal hypertension in the rat as it avoids the compensatory hypertrophy of the posterior liver lobes and increases the incidence of mesenteric venous vasculopathy.

INTRODUCTION

The experimental model that is used most frequently to study the pathophysiology of prehepatic portal hypertension is the one which consists in performing a portal stenosing ligation in the rat 4. In this experimental model, it has been shown that the mechanisms which contribute to the development and maintenance of portal hypertension change during its evolution 6,28,31. The sudden increase in portal venous resistance secondary to the stenosing ligation of the portal vein causes portal hypertension during the first days of the evolution; however, a new stage is begun on the eighth day and is characterized by the development of portosystemic shunts, a decrease of the portal resistance until control values and an increase of the splanchnic venous flow, all of which contribute to the maintenance of an increased portal pressure 28,31. It has been described that the splanchnic hyperdynamic circula-

tion disappears at 6 months of evolution, however portal hypertension persists, among other factors because an increase in the resistance of the portosystemic collateral to the portal venous flow is developed 29.

Because the different mechanisms involved in the development of the experimental prehepatic portal hypertension make it possible to attribute different evolutive phases to this condition, its long-term study would be interesting since the mechanisms involved in its pathophysiology as well as the derived alterations would be more similar to those that have been described in the human being. In the clinical area, among other factors, all these alterations are secondary to the chronicity of portal hypertension 27.

In addition, it has been suggested that the initial increase in portal pressure immediately following portal vein stenosis may have permanent effects on the extent of collateral deve-

lopment 9,11. If so, those factors that act by reducing or increasing portal pressure would modify the evolution of this prehepatic portal hypertension experimental model 10,11,27. Thus, the hemodynamic changes which occur during the early period after portal vein stenosis may play an important role in the development of portal hypertension and hyperdynamic circulation 12. In order to provide evidences to support this hypothesis we have studied the influence of hemodynamic changes secondary to the infrahepatic inferior vena cava stenosis in the development of the portosystemic collateral circulation in rats with chronic prehepatic portal hypertension.

MATERIALS AND METHODS

The experimental procedures employed in this study are in accordance with the principles and practices of the 1986 Guide for the Care and Use of Laboratory Animals, published in Spain in the Royal Decree 223/1988 24.

ANIMALS AND EXPERIMENTAL DESIGN

Male Wistar rats (210-250g) from the Vivarium of the Complutense University of Madrid were used. All the animals had ad libitum access to food and tap water and were maintained at constant room temperature ($20 \pm 2^{\circ}\text{C}$), with a relative humidity of $65 \pm 10\%$ and artificial light-dark cycle of 12 h (08:00-20:00 h/20:00-08:00 h). They were divided into four groups: Control (Group I; n=6), simple stenosis of the inferior vena cava (SLC) (Group II; n=8), triple stenosing ligation of the portal vein (TSLP) (Group III; n=12) and TSLP and SLC (Group IV; n=22). All the animals were sacrificed by ether overdose at one year of the evolution and body (BW), liver (LW), liver lobes, spleen (SL), kidneys (KW) and testes (TW) weights were determined.

TRIPLE STENOSING LIGATION OF THE PORTAL VEIN (TSLP) METHOD

The rats were anesthetized with Ketamine Hydrochloride (Imalgene, Merial) (80 mg/Kg b.w.) and Xilacine (Rompún,

Bayer) (12 mg/Kg b.w.) i.m. A midline abdominal incision was performed and part of the intestinal loops was gently shifted towards the left side and covered with a wet gauze. The portal vein was dissected in all of its length and then three equidistant stenosing ligations were performed in its superior, medial and inferior portion. The stenoses were calibrated by a simultaneous ligation (4/0 silk) around the portal vein and a 20G needle which was removed when the ties were ended, thus allowing for the partial reexpansion of the portal vein 16. The intestinal loops were restored to the abdominal cavity and the abdominal incision was closed on two layers with catgut and silk (3/0).

STENOSING LIGATION OF THE INFRAHEPATIC INFERIOR VEIN CAVA (SLC)

The infrahepatic inferior vena cava was dissected above the drainage of the right renal vein and the stenosis was calibrated by a simultaneous ligation (4/0) around the vena cava and a 20G needle which was removed when the tie was ended. This allowed for partial reexpansion of the infrahepatic inferior vena cava.

PORTOSYSTEMIC COLLATERAL CIRCULATION STUDY METHOD

After anesthetic induction, a midline abdominal incision was performed and then the areas in which the collateral venous circulation is developed, that is, the splenorenal (superior, SSR, and inferior, ISR collateral splenorenal), gastroesophageal (paraesophageal collaterals, PE), colorectal (pararectal collateral, PR) areas and the hepatic hilum (portoportal, PP and accessory hepatic vein, AHV), were studied. The latter reached the hepatic hilum following a pathway between the left lateral and caudate hepatic lobes 1,25. After this, the mesentery was exposed to study if there was spontaneous dilation and tortuosity of the branches of the upper mesenteric vein (Grade II), if these alterations were induced by clamping the superior mesenteric vein for 1 to 2 minutes (Grade I) and, when there are no mesenteric alterations, either spontaneous

Table I.

INITIAL BODY WEIGHT (IBW, G), FINAL BODY WEIGHT (FBW, G), BODY WEIGHT INCREASE (BWI, G), LIVER WEIGHT (LW, G), SPLEEN WEIGHT (SW, G), KIDNEYS WEIGHT (KW, G) AND TESTES WEIGHT (TW, G) IN GROUP I (CONTROL), GROUP II (STENOSIS LIGATION OF INFERIOR VENA CAVA, SLC), GROUP III (TRIPLE STENOSING LIGATION OF PORTAL VEIN, TSLP) AND IN GROUP IV (TSLP ASSOCIATED TO SLC) AT ONE YEAR OF EVOLUTION.

GROUP	IBW (g)	FBW(g)	BWI(g)	LW(g)	SW(g)	KW(g)	TW(g)
II (SLC) (n = 8)	227.51±6.87**	653.13±93.26	421.34±98.01	14.59±1.51	0.90±0.16	2.92±0.32	3.92±0.47
III (TSLP) (n = 12)	216.48±62.50***	641.13±138.09	412.33±149.21	17.28±4.17	1.19±0.25**	3.46±0.96	3.75±0.44
IV (SLC+TSLP) (n = 22)	228.49±10.29**	637.38±71.24	408.89±75.73	14.17±3.32	1.25±0.36**	3.01±0.44	3.72±0.41

*P < 0.05; **P < 0.01; ***P < 0.001: Statistically significant value in relation to Group I

*P < 0.05: Statistically significant value in relation to Group II

ones or those occurring after the clamping of the superior mesenteric vein (Grade 0) 1.

STUDY OF THE COLLATERAL CIRCULATION OF THE ABDOMINAL WALL

Transillumination of the abdominal wall was used to observe if the dilation of the parietal veins had occurred on both sides of the midline incision.

STATISTICAL ANALYSIS

The body, liver, liver lobes, spleen, kidneys and testes weights were expressed as the mean (the standard deviation (SD). ANOVA and Newman-Keuls tests were used for the statistical comparison of these variables between all the Groups. Chi square test was used to compare the incidence of collateral circulation between Groups II and III. The results are considered statistically significant if $p < 0.05$.

RESULTS

All the portal hypertensive animals survived until 12 months of postoperative evolution when they were sacrificed by ether overdose.

BODY AND ORGAN WEIGHTS

The operated animals (Groups II, III and IV) show an increase of their body weight during their postoperative evolution which is similar to those belonging to the control animals (Group I). The Group III animals (TSLP) show an increase of the liver weight in relation to the other Groups, although this increase is not statistically significant (Table I). In the animals belonging to Groups III (TSLP) and IV (TSLP+SLC), the spleen

weight increases ($p < 0.05$) in relation to Groups I (C) and II (SLC) (Table I). In all the Groups studied, we have not found significant differences in the kidneys and testes weights (Table I).

The determination of the anterior (middle and left lateral lobes) (ML+LLL) and posterior liver lobes (right lateral and caudate lobes) (RLL+CL) weights make it possible to verify the existence of significant differences in these values between the animals belonging to Groups III (TSLP) and IV (TSLP+SLC). The anterior liver lobes of the rat normally make up from 65% to 70% of the total liver and therefore their resection, described by Higgins and Anderson 7, is considered as a 70% hepatectomy 23. However, in some rats of Groups III and IV, the ponderal ratio between the anterior and posterior liver lobes changes significantly. For this reason, both groups of animals were divided into two subgroups (a and b) according to whether the percentage of the anterior and posterior liver lobes weight was normal (subgroups a) or whether there were pathological changes (subgroups b).

In relation to the animals of Group III (TSLP), the animals which make up subgroup b show an increase ($p < 0.001$) in the posterior liver lobes (RLL+CL) weight percentage. In turn, the weight increase of the posterior liver lobes (13.75 (5.75g) is associated to an atrophy of the anterior liver lobes (ML+LLL) (3.97(1.54g) (Table II). The animals belonging to subgroup b of Group IV (TSLP+SLC) have liver atrophy (LW: 11.98 (2.16g) at the expense of the anterior liver lobes (ML+LLL: 6.27 (1.61g) and, consequently, the posterior liver lobes (RLL+CL) weight percentage increases (47.9 (5.99%).

PORTOSYSTEMIC COLLATERAL CIRCULATION

The study of the different types of portosystemic collateral circulation in the groups mentioned makes it possible to esta-

Table II.

LIVER WEIGHT (LW, G), ANTERIOR LIVER LOBES (MIDDLE AND LEFT LATERAL LOBES) WEIGHT (ALLW, G), POSTERIOR LIVER LOBES (RIGHT LATERAL AND CAUDATE LOBES) WEIGHT (PLLW, G) AND SPLEEN WEIGHT (SW, G) IN GROUP I (CONTROL), GROUP II (STENOSIS LIGATION OF INFERIOR VENA CAVA, SLC), GROUP III (TRIPLE STENOSING LIGATION OF PORTAL VEIN, TSLP) AND IN GROUP IV (TSLP ASSOCIATED TO SLC) AT ONE YEAR OF EVOLUTION.

GROUPS	LW(g)	ALLW		PLLW		SW (g)
		(g)	%	(g)	%	
I (C)(n = 6)	15.17±0.62	9.76±1.42	64.38±1.91	5.41±0.86	35.62±1.91	0.92±0.10
II (SLC)	17.89±4.89 ^b	3.97±1.54 ^{bie}	24.21±13.33 ^{bi}	13.75±5.75 ^{bie}	74.96±12 ^{bie}	1.26±0.24 ^{ah}
III (TSLP)	11.98±2.16 ^{ceg}	6.27±1.61 ^{bdfi}	52.09±5.99 ^{bdegi}	5.71±1.04 ^g	47.90±5.99 ^{bdei}	1.33±0.45 ^{ah}

Subgroup a: animals in which the percentage of the anterior and posterior liver lobes weight is normal.

Subgroup b: animals in which the percentage of the anterior and posterior liver lobes weight is pathological.

a: $p < 0.01$ in relation to Group II

b: $p < 0.001$ in relation to Group II

c: $p < 0.05$ in relation to Group IVa

d: $p < 0.001$ in relation to Group IIIb/IVa

e: $p < 0.001$ in relation to Group IIIa

f: $p < 0.05$ in relation to Group IIIb

g: $p < 0.001$ in relation to Group IIIb

h: $p < 0.01$ in relation to Group I

i: $p < 0.001$ in relation to Group I

blish changes in its frequency. In the rats with TSLP, in both subgroups a and b, the most common type of portosystemic collateral circulation is the paraesophageal type (PE) (subgroup a: n=8; 100% and subgroup b: n=4; 100%), followed by the superior splenorenal (SSR) type (subgroup a: n=7; 87.5% and subgroup b: n=3; 75%) and the inferior splenorenal (ISR) type (subgroup a: n=5; 62.5% and subgroup b: n=3; 75%) (Figure 1). In the rats with TSLP associated to SLC (Group IV) the most frequent types of portosystemic collateral circulation in subgroup b are the superior (SSR) and inferior splenorenal (ISR), as well as the pararectal (PR) one. In addition, the paraesophageal collateral circulation (PE) is less frequent in Group IV (TSLP+SLC) in relation to Group III (TSLP) (Figure 1).

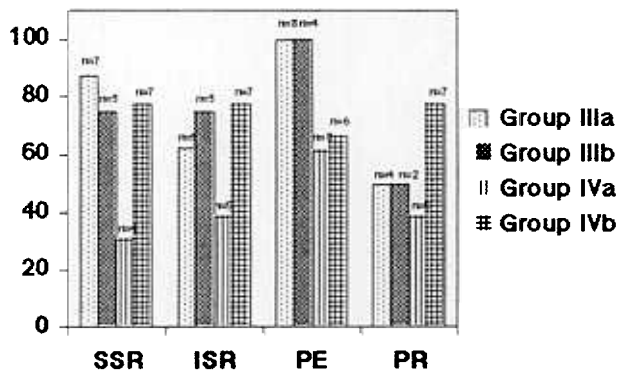


Figure 1.- Frequency of portosystemic collateral circulation in Group III (Triple Stenosing Ligation of Portal vein, TSLP) and in Group IV (TSLP associated to Stenosing Ligation of inferior Vena Cava) at one year of evolution. PE = Paraesophageal; SSR = Superior Splenorenal; ISR = Inferior Splenorenal and PR = Pararectal.

The portohepatic collateral circulation, represented by the accessory hepatic vein (AHV) is more frequent in Group IV (TSP+SLC) in relation to Group III (TSLP) and in Group IV, this circulation is predominately present in the subgroup IVb (Figure 2)

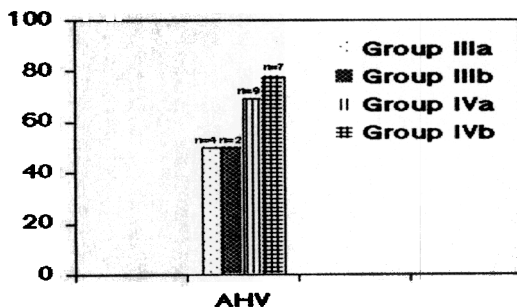


Figure 2.- Frequency of portohepatic collateral circulation in Group III (Triple Stenosing Ligation of Portal vein, TSLP) and in Group IV (TSLP associated to Stenosing Ligation of inferior Vena Cava) at one year of evolution. AHV = Accessory hepatic vein.

MESENTERIC VENOUS VASCULOPATHY

The incidence of mesenteric venous vasculopathy in Group III (TSLP) is superior in subgroup a in relation to subgroup b. In

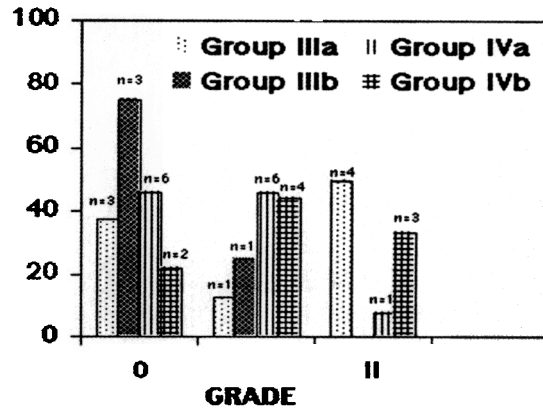


Figure 3.- Frequency of mesenteric venous vasculopathy in Group III (Triple Stenosing Ligation of Portal vein, TSLP) and in Group IV (TSLP associated to Stenosing Ligation of inferior Vena Cava) at one year of evolution.

turn, in Group IV (TSLP+SLC) it is more frequent in subgroup b in relation to subgroup a (Figure 3).

COLLATERAL VENOUS CIRCULATION IN THE ABDOMINAL WALL

The abdominal parietal collateral circulation (CCA) exists in 75% (n=6) of the animals belonging to Group II (SLC). In Group IV (TSLP+SLC) the abdominal parietal collateral circulation is more common in subgroup a (n=12; 92.3%) in relation to subgroup b (n=6; 66.6%).

DISCUSSION

In this study we have found two types of evolution in chronic prehepatic portal hypertension in the rat. Although the development of portosystemic and portohepatic collateral circulation is similar in both evolutive types, these types are different because of their incidence of mesenteric venous vasculopathy (Figure 3), and because of the lobular distribution of the liver weight (Table II).

The mesenteric venous vasculopathy is a gross anatomic finding which consists of the dilation and tortuosity of the superior mesenteric vein branches, which could be secondary to the increased portal venous inflow ("forward flow" theory), due to the increased portocolateral resistance to the portal blood flow ("backward flow" theory) or due to a combination of both causes 20. In the early evolutive phases (6 weeks) it has been proposed that one of the causes of the increased portal venous flow could be the inflammatory nature of the portal hypertensive enteropathy because we have verified a significant increase in the number of mast cells that infiltrate the duodenal mucosa and submucosa 5. The excessive release of mediators by the abundant mast cells which infiltrate the duodenal mucosa and submucosa could have, among other physiological effects, vasodilation and angiogenesis, two consequences which produce the increase in size and number of vessels and, thus, the vascular structural alterations which characterize the portal hypertensive vasculopathy 15,17.

In more advanced stages of this experimental model of prehepatic portal hypertension, it is not known if the intestinal parietal infiltration by mast cells and their mediators per-

sists, however, the decrease of the mesenteric venous vasculopathy incidence in the subgroup IIIb suggests that the long-term evolution post-TSLP is not uniform. Furthermore, the coexistence of the posterior liver lobes (RLL+CL) hypertrophy with the anterior liver (ML+LLL) atrophy is a surprising finding which makes it possible to establish a cause-effect relation between this liver lobular weight redistribution and the increase in the number of animals in which the mesenteric venous vasculopathy is not present (**Table II, Figure 3**).

If it is considered that the evolution is conditioned by the inflammatory nature of the alterations secondary to the increase of the portal pressure in this experimental model, it could be hypothesized that immunological mechanisms could be involved in the liver lobular ponderal changes. To be specific, the TNF- α increase in short-term portal hypertensive rats is one of the factors to which the hyperdynamic syndrome is attributed 13. It has been hypothesized that during the natural course of portal hypertension in portal vein-ligated rats, the increase in TNF- α , which increases NO synthesis, is at least partially responsible for the vasodilation found 13,14. This hypothesis is reinforced because the TNF synthesis inhibition reduces NO production and blunts the development of the hyperdynamic circulation and it also decreases the portal pressure in rats with prehepatic portal hypertension 14. The contribution of TNF to the development of the splanchnic hyperdynamic circulation seems to be important because it has been demonstrated that this cytokine causes a statistically significant dilation in second- and third-order arterioles and venules of the small bowel in rats 18 and, therefore it has also been involved in the production of mesenteric venous vasculopathy.

If this is true, the chronic exposure of the liver to the action of endogenous proinflammatory mediators of intestinal origin, like as TNF- α , in experimental prehepatic portal hypertension could be the cause of liver disease. In the TSLP rats with one year of evolution, these proinflammatory mediators could reach the hepatic parenchyma, either through the stenosed portal vein, through the accessory hepatic vein or by recirculation through the hepatic artery 26. Among the endogenous proinflammatory mediators, TNF- α , has emerged as a key factor in liver diseases, and particularly in the pathogenesis of fatty liver disease 22,30. In this case, hepatomegaly may be caused by hepatic accumulation of fat.

However, hepatomegaly in rats with prehepatic portal hypertension is secondary to posterior liver lobes (RLL+CL) weight increase because the anterior liver lobes (ML+LLL) are atrophied (**Table II**). Unpublished results have shown that the fatty infiltration of the liver occurs in rats with long-term prehepatic portal hypertension and therefore that the posterior liver lobes hypertrophy could be produced by selective fatty infiltration of these lobes (RLL+CL). It would be mentioned that this coexistence of posterior liver lobes hypertrophy with accumulation of fat within the liver cells has also been described after partial hepatectomy (68%) in the rat, although in this case the liver steatosis is a transient fact which is more intense 1-2 days after the operation 2.

In addition, in some animals with chronic prehepatic portal hypertension (subgroup IIIb), the steatosis and the posterior liver lobes (RLL+CL) hypertrophy could be a compensatory response to the anterior liver lobes (ML+LLL) atrophy. Consequently, a decrease in the portal pressure would be produced so that both the splanchnic hyperemia and mesenteric venous vasculopathy incidence also decrease. In essence, the

hepatic interlobular functional competition would cause a functional hepatectomy in these cases.

Furthermore, in TSLP rats the associated stenosis of the infrahepatic inferior vena cava increases the percentage of the animals with hepatic atrophy and dilation and tortuosity of the superior mesenteric vein branches, that is, the mesenteric vasculopathy (subgroup IVb). The hepatic atrophy is produced even though there is an increase of portal revascularization through the accessory hepatic vein.

All those animals having portal hypertension associated to a stenosis of the inferior vena cava develop either an extensive collateral circulation through the abdominal wall or a cava-cava collateral circulation which by-passes the stenosis. This would prevent the hyperpressure in the vena cava system. However, it is not possible to discard the fact that the acute venous hyperpressure which is produced by the stenosing ligation of the inferior vena cava prior to the establishment of an effective parietal abdominal drainage can influence the development of the portosystemic collateral circulation and especially the splenorenal and hemorrhoidal types by mechanical effects. The total diversion of venous return from the legs into the portal circulation by a portocaval shunt and a complete occlusion of the portal vein above the shunt produces shunting of blood through esophageal varices, via splenic and gastric veins was demonstrated in the dogs. Consequently, all the dogs developed esophageal varices and abdominal collateral veins 3-6 weeks after the operation 8. On the contrary, it has been shown in the present work that the coexistence of inferior vena cava stenosis reduces the incidence of portosystemic collateral circulation while the portohepatic collateral circulation, represented by the accessory hepatic vein, increases in animals with long-term prehepatic portal hypertension (**Figure 2**).

It has been accepted that the liver injury requires at least two "hits:" one that increases the exposure of the hepatocytes to TNF- α , and another one that interferes with the normal ability of the hepatocytes to protect themselves from TNF- α -induced cell death 30. The two-hit model is useful to explain the progression of fatty liver disease because the first hit, that is, the exposure increased of hepatocytes to TNF, may produce hepatic accumulation of fat 3,30, but renders the liver more vulnerable to a second insult because the hepatocytes became sensitized to the TNF-mediated cell death 30.

The application of this "two-hits" model to the evolution presented by the rats with TSLP associated to inferior vena cava stenosis could explain some of the alterations found (subgroup b) because portal hypertension (the first "hit") could induce fatty liver degeneration in these animals, thus sensitizing the hepatocytes to the systemic decompensation secondary to the inferior vena cava stenosis (second "hit"). In turn, this fact would favor hepatocytic death by necrosis or apoptosis and therefore the liver atrophy. If so, the reduction of the liver mass would increase the resistance to the portal flow with increased production of TNF- α and related inflammatory cytokines which, in turn, modulate the expression of enzymes such as inducible nitric oxide synthase that regulates the synthesis of vasoactive molecules which mediate the hyperdynamic systemic and splanchnic syndromes 19,21. The final result would be an increase in the portosystemic collateral circulation development and in the incidence of mesenteric venous vasculopathy.

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