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Original Article

LIVER REGENERATION AFTER PARTIAL HEPATECTOMY IN RATS SUBMITTED TO POST - HEPATIC PORTAL HYPERTENSION

Regeneração do fígado após hepatectomia parcial em ratos submetidos à hipertensão portal pós-hepática

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ABSTRACT - ***Background*** - The normal adult liver is quiescent and only a small percentage of its cells is subjected to cell division at any time, but can quickly initiate cell proliferation in response to a stimulus. This process can be triggered by partial hepatectomy. ***Aim*** - To evaluate the effect of portal hypertension caused by partial occlusion of hepatic venous drainage on regeneration of remnant liver of rats after partial hepatectomy. ***Methods*** - It was performed two-thirds hepatectomy in 50 adult male Wistar rats. The animals were divided into five groups: a control group and four study groups were subjected to different degrees of plication of inferior vena cava-hepatic above. After 240 hours of the stimulus for regeneration took place relaparotomy with measurement of portal pressure and inferior vena cava, and liver biopsy. Fragments were analyzed by immunohistochemistry for the markers Ki-67 and von Willebrand factor. The collagen deposition was evaluated by Masson's trichrome staining and liver function using serological markers. ***Results*** - Cell proliferation in animals subjected to partial hepatectomy and portal hypertension persisted in varying degrees higher when compared to the control group. The proliferation index for Ki-67 was higher in the groups submitted to the elevation of portal pressure. The expression of von Willebrand factor was markedly elevated after partial hepatectomy in groups with higher degree of portal hypertension. There was little collagen deposition in liver tissue in animals of the four groups with partial plication of the inferior vena cava above-liver, but the deposition was more intense in the group with lower portal pressure. ***Conclusions*** - Rats underwent 70% partial hepatectomy and portal hypertension, after 240 hours, presented: 1. delay in the regenerative process directly proportional to pressure levels in the portal system, 2. after ten days, there was the proliferation of hepatocytes proportionally more intense the higher the elevation of pressure in the porta, but extreme levels of portal pressure inhibit proliferation and liver regeneration; it has also been shown delayed angiogenesis influenced by the values portal pressure; 3. extreme portal hypertension produces an elevation of expression of factor VIII, suggesting sinusoid capillarization 4. the higher levels of portal pressure, the lower the amount of collagen deposited, it can be inferred that the increased portal pressure leads to delay in restoration of the extracellular matrix, 5. analysis of liver function showed that 70% partial hepatectomy after ten days, did not interfere with the physiology of the liver, which remained within normal limits; but, with portal hypertension, can happens functional impairment of the remnant liver during the regenerative process.

HEADINGS – Hepatic regeneration. Portal hypertension. Immunohystochemistry. Rats.

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RESUMO – ***Racional*** - O fígado adulto normal é quiescente e apenas uma pequena porcentagem das suas células é submetida à divisão celular em qualquer tempo, mas pode rapidamente iniciar a proliferação celular em resposta a um estímulo. Este processo pode ser desencadeado através da hepatectomia parcial. ***Objetivos*** - Avaliar o efeito da hipertensão portal provocada pela oclusão parcial da drenagem venosa hepática sobre a regeneração do fígado remanescente de ratos submetidos à hepatectomia parcial. ***Métodos*** - Foram realizadas hepatectomias a dois terços em 50 ratos Wistar machos adultos. Os animais foram divididos em cinco grupos: um grupo controle e quatro grupos de estudo que foram

submetidos a diferentes graus de plicatura da veia cava inferior supra-hepática. Após 240 horas do estímulo para regeneração realizou-se nova laparotomia com aferição das pressões portal e de veia cava inferior, além de biópsia hepática. Analisaram-se os fragmentos por imunoistoquímica para os marcadores Ki-67 e fator de von Willebrand. A deposição de colágeno foi avaliada pela coloração tricrômico de Masson e a função hepática através de marcadores sorológicos. ***Resultados*** - A proliferação celular nos animais submetidos à hepatectomia parcial e hipertensão portal de diversos graus persistiu mais elevada quando comparada ao grupo controle. O índice de proliferação para Ki-67 estava mais elevado nos grupos submetidos à elevação da pressão portal. A expressão do fator de von Willebrand estava acentuadamente elevada após a hepatectomia parcial nos grupos com maior grau de hipertensão portal. Houve pouco depósito de colágeno no tecido hepático nos animais dos quatro grupos com plicatura parcial da veia cava inferior supra-hepática, porém a deposição foi mais intensa nos grupos com níveis de pressão portal menores. ***Conclusões*** - Ratos submetidos à hepatectomia parcial a 70% e hipertensão portal, após 240 horas, apresentam: 1. atraso no processo regenerativo diretamente proporcional aos níveis pressóricos no sistema porta; 2. após dez dias, persiste a proliferação de hepatócitos proporcionalmente mais intensa quanto maior a elevação da pressão no sistema porta, porém níveis extremos de pressão portal inibem a proliferação, e, no estímulo para regeneração do fígado, demonstrou-se atraso da angiogênese influenciado pelos valores de pressão portal; 3. hipertensão portal extrema promove elevação da expressão de fator VIII, o que sugere capilarização dos sinusóides; 4. quanto mais elevados os níveis de pressão portal, menor será a quantidade de colágeno depositada, podendo-se inferir que o aumento da pressão portal ocasiona atraso na restauração da matriz extracelular; 5. a análise da função hepática evidenciou que a hepatectomia parcial a 70%, após dez dias, não interferiu com a fisiologia hepática, a qual permaneceu dentro dos limites da normalidade, mas com a hipertensão portal pode haver comprometimento funcional do fígado remanescente durante o processo regenerativo.

DESCRITORES - Regeneração hepática. Hipertensão porta. Imunoistoquímica. Ratos.

INTRODUCTION

The regeneration of the liver is a process involving hyperplasia (increased number of cells) and hypertrophy (increase in cell volume or protein content in the pre-replication). The concept of regeneration is widely used in literature, but liver regeneration is primarily a process of compensatory hyperplasia, which is driven more by functional requirements than anatomical ones. Most of the current knowledge on liver regeneration comes from studies performed in rats undergoing 70% hepatectomy. The partial hepatectomy is followed by enlargement of remaining liver segments, but not for the restitution of the original anatomy. The regeneration process is divided into three phases. It is understood as an early stage when the hepatocytes acquire the ability to replicate. Following, is the proliferation phase during which the number of liver cells increases seeking an appropriate amount for the restoration of function. Finally there is the level of termination, during which cell division is closed, after reaching the volume of cells needed for recovery of function. The proliferation of hepatocytes starts in the periportal (zone 1) after an interval of 24 hours and continues in the pericentral region (zone 3) for 36 to 48 hours. After three days, the liver histology is characterized by groups of hepatocytes with rudimentary vascularization. The invasion of these clusters of blood vessels similar to sinusoids occurs on the second day from the regenerative stimulus. Seven days in a typical lobular structure the liver is restored, but with lobes enlarged, which will be refurbished to its normal size[12].

The origin of the cells that replace those removed by the hepatocytes hepatectomy is the very mass of remaining hepatocytes that replicate without the participation of stem cells.

The normal adult liver is quiescent and only a small percentage of its cells is subjected to cell division at any time, but can quickly initiate cell proliferation in response to a stimulus. This process can be triggered by partial hepatectomy[13].

Liver regeneration after partial hepatectomy of 70% is one model for the regeneration of cells, organs and tissues. The complexity of reactions that signal the beginning and the end of this process has provided the paradigms for regenerative medicine. Many aspects of the signaling mechanisms involved in liver regeneration is under study[10].

With the aim of documenting concisely the presence and extent of hepatic regenerative activity, experimental models were created. Currently, the best stimulus for triggering liver regeneration is partial

hepatectomy, which involves surgical resection of the left lateral and median lobes of rat liver, thus preserving about 30% of the organ. In this model, the beginning of the process of reconstitution occurs after 12 to 16 hours, reaching the first peak of synthesis of deoxyribonucleic acid (DNA) after 24 hours of the regenerative stimulus, followed by another less intense by 36 to 48 hours. The recovery of liver mass removed happens within two to three weeks[7].

In addition to the proliferative capacity of hepatocytes, the critical functions for maintaining homeostasis is preserved, as the regulation of glucose levels, protein synthesis and plasma coagulation factors, bile secretion, urea cycle and degradation of toxins[4].

The process of liver regeneration after unleashed, can be assessed by various methods, such as liver weight, number of mitosis, the DNA components, the rate of synthesis of nuclear antigens assessed by immunohistochemistry, the expression of genes, variations in levels of serum proteins, serological, enzymatic determination of proliferation markers and flow cytometry[2].

Venoclusive diseases, among other situations, may alter the hepatic venous drainage, causing part of portal hypertension. Low output causes liver congestion and dilation in the microcirculation, altering the supply of nutrients and factors hepatotrophic. The effect is more intense in zone 3, often accompanied by atrophy of the hepatocytes. Injuries sinusoids can progress to fibrosis and liver failure, resulting in the loss of organ or graft implanted[9].

The objectives of this paper were to study the: 1. effect of portal hypertension on liver regeneration; 2. liver regeneration; 3. hepatic angiogenesis; 4. presence of collagen in liver tissue; 5. liver function.

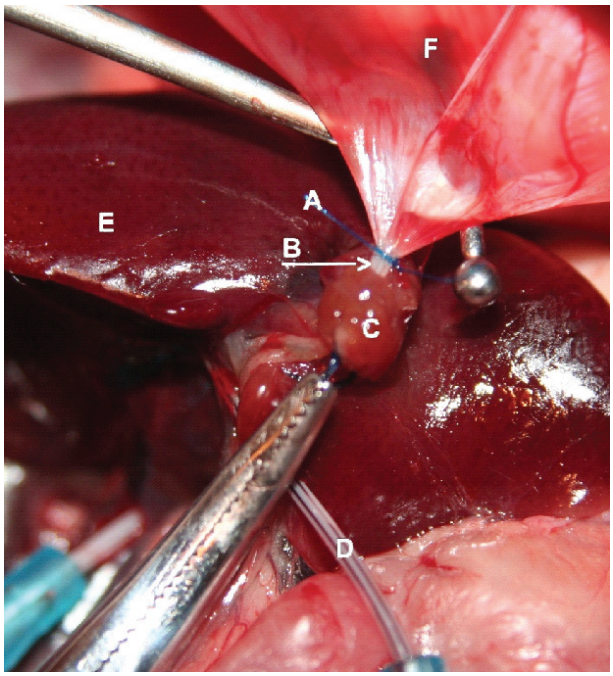
METHODS

The experiment was conducted at the Post-Graduate Program in Principles of Surgery of the University Evangelic Hospital/ Evangelic Faculty of Paraná, Curitiba, PR, Brazil. in the period between January 2007 and December 2010. Histology was done on Citolab - Laboratory of Clinical Cytology and Histopathology Ltda. The research project was approved by the Ethics Committee of the Evangelic Faculty of Paraná.

Was used 50 Wistar rats *Rattus norvegicus albinus, Rodentia mammalia* young adults, males, weighing between 242 and 348 g. The rats were divided into five groups of ten, randomly.

All underwent laparotomy and liver resection in 70% - median and left lateral lobes[7]. Also had the right portal vein and inferior vena cava above the renal veins punctured and measured portal pressure and inferior vena cava, keeping the venous puncture until the end of the surgical experiment. After removal of the punctures, it was made review the peritoneal cavity and abdominal wall was closed.

The control group (CTL) only underwent the surgical procedure. In group I, besides it, had plication of the inferior vena cava, supra-hepatic and right hepatic vein up to 25% increase in portal pressure and inferior vena cava pressure; group II, the same procedure with elevation up to 50%; group III, 75% and group IV, up to 100% (Figure 1).



NOTE: (A) inferior vena cava plication supra-hepatic; (B) inferior vena cava and supra-hepatic and right hepatic vein; (C) ligation of the resected lobes; (D) catheter into the portal vein; (E) right lobe of the liver. (F) diaphragm

FIGURE 1 - Plication of supra-hepatic inferior vena cava

After 240 hours of surgery another laparotomy was done, repeating puncture of the right portal vein and inferior vena cava above the renal veins and measurement of portal pressure and inferior vena cava, obtaining biopsies of the liver remaining and collection of 4 ml of blood. Then all animals were killed with a lethal dose of ether inhalation and immediately underwent total hepatectomy of the remaining liver.

The livers obtained from rats in group CTL were weighed, calibrated and measured their inferior vena cava above the hepatic. The resected animals in groups I, II, III, IV were weighed, and the caliber of their inferior vena cava above the hepatic was measured. Then, plication had been undone and the diameter of the inferior vena cava above the hepatic re-measured (Figure 2).

Liver biopsies collected at the second operation provided fragments of approximately 1 cm^3 immersed in buffered formalin. Then, this material was sent to the laboratory for processing, including, cutting the blocks for immunohistochemistry with histologic markers Ki-67

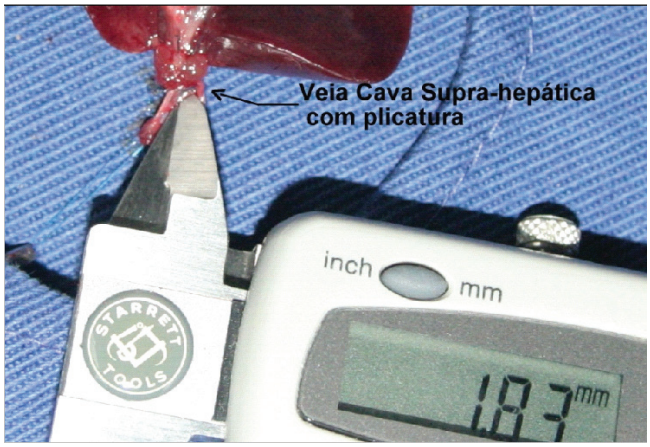


FIGURE 2 - Measurement of the diameter of the supra-hepatic vena cava plication

and factor VIII, and Masson's trichrome. Blood samples were collected in bottles sent to the specific laboratory to perform the biochemical and hematological disorders.

The results were evaluated using the software for Windows SPSS17 and comparisons, ANOVA, Kruskal-Wallis test and contingency table with chi-square.

RESULTS

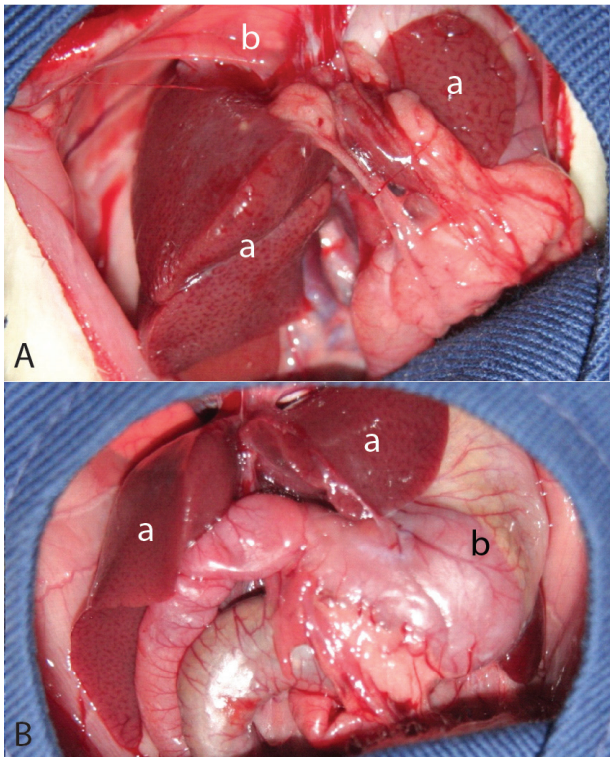
In the CTL group all animals survived; died two animals in group I between 96 and 144 hours, three from group II between 96 and 168 hours, two in group III between 96 and 120 hours, eight of group IV in the first 48 hours. All the dead animals had peritonitis. Also had peritonitis, at the time of re-operation, two animals in group I, one in group II and one in group III.

At the second operation, animals in the CTL group had their livers wine colored light, bright, with no signs of necrosis, bleeding when biopsied and showed few adhesions in the peritoneal cavity involving the liver (Figure 3A).

In group I, the rat had liver tissue with edema and bled after biopsy, had many adhesions in the peritoneal cavity including much in the surrounding liver. In group II, light aspect of liver congestion, dark wine color, with bleeding in the area of biopsy. In group III, congested liver appearance, dark color and a small wine heterogeneous vascularized site of biopsy. In group IV, liver looked congested, dark burgundy and heterogeneous, but with vascularization at the site of biopsy (Figure 3B).

With regard to initial body weight, no statistically significant difference between control group and the four study groups was found and the same happened with the final weight. Althought between the initial and final groups no significant differences were found, there was differences among all animals in the initial and final weight (p = 0.023).

With respect to the weights of liver resected,



NOTE: Appearance of the peritoneal cavity with little adherence (A) and congenital liver (B); (a) remnant liver, (b) stomach

FIGURE 3 - Liver from CTL and group IV after 240 hours

estimated, and the percentage of liver regeneration, no statistic significant difference was found (Table 1).

TABLE 1 - Differences between the weights of the liver and liver regeneration

Liver weight (g)		Sum of squares	df	Average square	F	p
Hepatectomy	between groups	5	4	1	2	0,113
	within groups	17	30	0,566		
	Total	22	34			
(Estimated)	between groups	9	4	2	2	0,112
	within groups	35	30	1		
	Total	44	34			
Regeneration	between groups	11	4	3	0,966	0,44
	within groups	86	30	3		
	Total	97	34			
Liver regeneration (%)	between groups	1.234	4	309	2	0,215
	within groups	6.000	30	200		
	Total	7.234	34			

It was noted that there is a significant difference in estimated liver weight/initial body weight in relationship to regenerated liver/final body weight of animals, but no difference was observed between the groups.

The descriptive values related to the initial pressure after hepatectomy or portal vein, the experimental pressure in the portal vein and portal vein pressure in the final ten days after the stimulus for regeneration are shown in Table 2.

TABLE 2 - Values of the initial portal pressure, experimental and final

	Groups	n	Average	Dp
Initial portal vein pressure	CTL	10	11,74	1,2322
	I	8	11,275	0,8844
	II	7	11,429	1,5063
	III	8	12,113	1,2766
	IV	2	12,6	1,1314
	Total	35	11,706	1,2175
Experimental portal vein pressure	CTL	10	11,74	1,2322
	I	8	13,937	1,0056
	II	7	16,743	2,1839
	III	8	20,7	2,1461
	IV	2	24,8	1,9799
	Total	35	16,037	4,3265
Vein end pressure	CTL	10	11,76	1,069
	I	8	11,763	0,9942
	II	7	13,8	1,4776
	III	8	16,35	1,2524
	IV	2	20,45	1,0607
		35	13,714	2,7517

There are differences with statistical significance for the measures of the initial portal pressure and portal pressure experimental (p = 0.00001), and there was interaction between groups and the initial measurement and experimental (p = 0.0001).

The proliferation index of hepatocytes, using the marker Ki-67, showed only a statistically significant difference between the CTL group and group II (p = 0.0121).

The proliferation index for endothelial marker FVIII related to angiogenesis through the comparison groups, was found that there are significant differences between them. Between the CTL group and the group I there was no significant difference (p = 0.207); between the CTL group and group II was found statistically significant difference (p = 0.002); between the CTL group and group III it was shown significant difference (p = 0.003); between the CTL group and group IV there was no statistically significant difference.

Masson's trichrome staining verified the deposition of collagen in the liver after 240 hours of regenerative stimulation. The figures relating to its presence and distribution within the groups showed no statistically significant difference among groups (p = 0.117).

The numerical values observed for ALT, AST, total bilirubin, direct bilirubin and indirect bilirubin showed no significant difference. Statistical analysis of the values obtained for alkaline phosphatase and gamma-glutamyl transpeptidase did not change significantly. The numerical values observed for glucose and APTT did not change significantly. There was significant difference in groups for cholesterol (p = 0.02), total protein (p = 0.008), albumin (p = 0.000) and globulin (p = 0.058). There were significant differences between groups for the variable time and prothrombin activity (p = 0.001).

DISCUSSION

The seeds of scientific curiosity for the presence of liver regeneration was planted in ancient Greece, when it was disclosed the Prometheus myth, where his liver was damaged and regenerated every day every night in order to undergo further injury the next day. The extraordinary capacity of this organ to achieve the full restoration after a serious injury is an attractive element to the ongoing search and investigation.

The process of liver regeneration can be experimentally induced by any intervention that promotes cell death or removal of liver tissue. The loss of functional units of the liver promotes a stimulus for cell proliferation in order to restore the original mass or necessary for homeostasis.

A 70% hepatectomy in rats[7] has been the most commonly used surgical model, because it is a simple and easily reproducible technique. In this study, the Wistar *Rattus norvegicus albinus, Rodentia mammalia* mammalia was used for its availability and having significant resistance to infection with low surgical mortality. In this study, the surviving animals had significant weight loss, ranging between 21.22% and 37.64% below the original body weight. The animals that died from peritonitis, died in the first seven days, and the greater the degree of portal hypertension, the lower the survival time after the start of the experiment.

In this evaluation it was noticed that the liver volume was restored within ten days for the animals that had only the regenerative stimulus by partial hepatectomy and the final appearance seemed an enhanced version of the portions not resected. But when the added factor of venous congestion, there was delay in recovery of mass. The hepatic venous congestion may manifest as a result of extensive resections, leaving little to restore the parenchyma, as occurs in hepatectomy for resection of tumors in liver transplants. In theses cases, the receptor receives an organ smaller than their needs when can be used the pyggback technique.

Venous congestion causes dilation of the vascular bed that returns to normal after recovery of the original liver mass, allowing the reduction of size to accommodate all the inflow portal. The present study found that stenosis performed in the right hepatic vein and inferior vena cava above the liver, provoked a regime of portal hypertension remained with venous congestion and vascular ectasia after ten days. Therefore, maintaining the partial obstruction to hepatic venous drainage keeps the intrahepatic venous congestion, even after the restoration of liver volume.

A two-thirds partial hepatectomy is sufficient incentive to increase the portal blood flow in two

or three times its basal volume, a fact that leads to injury of the microcirculation only ten minutes after resection of hepatic lobes median and left lateral. With the increase in portal blood flow in one vascular bed reduced, which causes increased vascular resistance, it is evident an increase in portal vein pressure by 30-40%[11], featuring a picture of portal hypertension. The control of portal pressure and portal blood flow in conditions close to physiological conditions is required, since low perfusion pressure may result in decreased hepatic volume due to the uneven distribution of blood flow within the liver, and perfusion with high pressure can cause an increase in intrahepatic vascular bed with consequent barotrauma of the parenchyma. This study showed that, after ten days of observations, it was still a situation of portal hypertension since, in both groups, the blood pressure values were lower than the basal pressure after liver resection, markedly in groups III and IV. On vascular bed in the hepatic sinusoids occurs pore fusion, forming large spaces that allow the exit of macromolecules into the perisinusoidal space. In the liquid overflowed the sinusoid are blood cells, fat molecules, nutrients and factors that contribute to the initiation and maintenance of the regenerative process. After 240 hours, the liver volume is close to the hepatic mass prior to surgical insult and the sinusoids resume their normal anatomical and physiological characteristics with small fenestrations[5]. However, sinusoids injuries can progress to fibrosis and liver failure, with the consequent loss of organ[9,14].

Add a complicating factor for hepatectomy for liver restoration, raises interest for scientific research. During regeneration, both growth factors such as metabolic changes may induce the initiation period. The expression of proto-oncogenes may be related to adaptive biochemical and nutritional changes that occur in hepatocytes after hepatectomy or can be induced by growth factors secreted by the liver or other organs. These adaptive reactions triggered together, the cascade of events that culminates in DNA replication. The proliferation of hepatocytes is predominantly regulated by autocrine mechanisms, from the release of growth factors for hepatocytes already started in the cell cycle to cell division, but also respond to growth factors produced by other liver cells, constituting the paracrine regulation. There is the participation of cells of other organs, promoting endocrine regulation. Therefore, during the period of proliferation, the progression of the process depends on mechanisms autocrine, paracrine and endocrine[8]. However, creating an obstacle to the venous drainage of venous congestion aggravates the liver and leads to elevation of portal pressure, above the values recorded after the removal of part of the functional mass of liver. The input of nutrients and growth factors that stimulate regeneration decreases. The restoration process occurs slowly, with persistence of proliferation for a longer time, accompanied by delays in angiogenesis and delay the restoration of the extracellular matrix[6,15].

This study was performed after two thirds partial hepatectomy, four different degrees of obstruction of hepatic venous drainage to assess the effect of portal hypertension resulting from the regeneration and a control group without obstruction of blood flow out of the liver. Considering the surgical aspect, the dissection of the right hepatic vein of rats after partial hepatectomy is technically difficult and high mortality rate. The partial obstruction of the drainage of the hepatic veins was induced by partial obstruction of the inferior vena cava cranial to the hepatic veins, as described in the literature[1], resulting in immediate elevation of portal pressure. Thus, the intention of provoking a framework for evaluation of portal hypertension, was obtained. Caval and portal pressures before hepatectomy were not measured and it was considered for analysis those measured baseline after removal of the median and left lateral lobes of the liver of the animal.

The animals showed weight loss by 16% after ten days of experiment. The weight recovery to preoperative levels occur between 25 to 28 days[7], and the results of this study are consistent with those presented in the literature.

The regenerative stimulus is followed by triggering the process of cell proliferation, initially by hepatocytes and then executed by the bile ducts, Kupffer cells and liver stellate cells and finally by sinusoidal endothelial cells. The potentiating effect of venous congestion, caused by the elevation of portal pressure by obstruction of hepatic venous drainage has the effect of delayed proliferative process as evidenced by the persistence number of mitotic cells and hepatocyte nuclei stained by Ki-67 in group II compared to the others. The higher the blood pressure level, the greater the delay in regeneration, but in Group III, showed up high levels of Ki-67, but no statistically significant difference to CTL, other than group IV which have not found a proliferation of hepatocytes after ten days.

After reducing the proliferation of hepatocytes, starts the vascular proliferation. Hypoxia in clusters of proliferating hepatocytes that stimulates angiogenesis in this study was assessed by von Willebrand factor. Very low levels of it showed delay in angiogenesis, as did the animals in group II. The expression of mRNA for factor VIII is strongly positive phase sinusoid capillarization and hepatic cirrhosis[3]. Thus, when the rates of proliferation of FVIII are is very high, representing capillarization of sinusoids, in which there is loss of fenestrations and with this loss distribution of nutrients, growth factors and substances that need to be metabolized in

hepatocytes, which may cause atrophy of the newly formed hepatocytes. In group III and IV the values of factor VIII suggests sinusoidal vessels capillarization.

The restoration of the extracellular matrix completes the process of regeneration of liver injured by presenting a new and functional liver tissue. The deposition of collagen is the reconstitution of extracellular matrix. No or low amounts of collagen showed delayed formation of new matrix and hence the delay in regeneration. In this study was observed that portal pressures greater than 25% of baseline value obtained with the two-thirds partial hepatectomy, causes delay of regeneration as evidenced in group II, even after 240 hours of regenerative stimulus, remained in the proliferative phase of hepatocytes insignificant with vascular proliferation and mild collagen deposition. For pressure levels above 50%, maintenance of portal hypertension in extremely high levels after ten days of the beginning of the experiment can cause changes in the microcirculation with consequent capillarization of sinusoids.

Resections of the liver can cause acute liver failure. In studies with 70% hepatectomy, the liver function tests remain within normal limits. This study showed that there was abnormal liver function in the remnant liver related to cholesterol levels, total protein, albumin and globulin and TAP. Transaminases ALT and AST, alkaline phosphatase, gamma glutamyl transpeptidase, glucose, APTT, and the excretion of bilirubin, were within normal values. The reference values for serum in this study were considered those obtained in the CTL group.

Liver regeneration is a clinically important process, but also an excellent model in regenerative medicine. Currently, there are many studies on the signaling pathways that contribute to the initiation and termination of the process of restoration of the liver and circulatory events including the contribution of other organs, but studies with hepatocellular carcinomas suggest other pathways that regulate the growth of hepatocytes. Research on regeneration may contribute to the understanding of adverse situations such as liver failure and even death after extensive liver resections. Therefore, liver regeneration remains the object of study and deep analysis in order to understand many liver diseases and thus contribute to decrease morbidity including human. The involvement of other organs in regeneration is the focus of extensive field research, the role of the pancreas and intestines. There is a need for more studies on nutrients that contribute to the acceleration of regeneration, such as glutamine and arginine. Nutritional supplementation before and after surgery on the liver can influence the results and represents a fertile field for research. As far as the mechanisms that stimulate proliferation, it is of vital importance to study the way it inhibits the regenerative event, perhaps contributing to the understanding and successful treatment of proliferative processes.

CONCLUSION

Rats underwent 70% partial hepatectomy and portal hypertension, after 240 hours, presented: 1. delay in the regenerative process directly proportional to pressure levels in the portal system; 2. after ten days, there was the proliferation of hepatocytes proportionally more intense the higher the elevation of pressure in the portal, but extreme levels of portal pressure inhibit proliferation and liver regeneration and it has also been shown delayed angiogenesis influenced by the values portal pressure; 4. the higher levels of portal pressure, the lower the amount of collagen deposited, it can be inferred that the increased portal pressure leads to delay in restoration of the extracellular matrix, 5. analysis of liver function showed that 70% partial hepatectomy after ten days, did not interfere with the physiology of the liver, which remained within normal limits, but, with portal hypertension, can happens functional impairment of the remnant liver during the regenerative process.

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