A modified microsurgical model for end-to-side selective portacaval shunt in the rat. Intraoperative microcirculatory investigations[1]

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ABSTRACT

PURPOSE: To investigate the intraoperative microcirculatory changes of the affected organs (small bowel, liver and kidney) during the making of a modified selective portacaval (PC) shunt.

METHODS: On ten anaesthetized Sprague-Dawley rats the selective end-to-side mesocaval anastomosis was performed, where only the rostral mesenteric vein is utilized and the portal vein with the splenic vein are left intact. Morphometric and microcirculatory investigations using a LDF device determining flux units (BFU) were carried out.

RESULTS: After completing the shunts the microcirculatory flux values did not recover in the same manner on the surface of the small intestine, the liver or the kidney. BFU values showed deterioration in the small intestine and in the liver ($p<0.001$). During the reperfusion the BFU values improved, but not in the same manner. The small intestine values left behind the kidney and liver data.

CONCLUSIONS: Technically, the advantages of the models include the selective characteristic, the mesocaval localization and the relatively easy access to those vessels. However, its major disadvantage is the time needed for positioning the vessels without coiling or definitive stretching. Intraoperative LDF may provide useful data on the microcirculatory affection of the organs suffering from hypoperfusion or ischemia during creating the shunts.

Key words: Portacaval Shunt, Surgical. Anastomosis, Surgical. Microsurgery. Microcirculation. Rats.

Introduction

Artificial porto-systemic shunts can be created by various techniques and localizations in case of underlying portal hypertension when other therapeutical ways are not effective[1-5], but these shunts may act as supportive tools in other surgical procedures (liver transplantation, small-for-size grafting)[6,7]. So these shunts still have important clinical relevance. While creating such artificial anastomoses, the surgical safety is an important aspects: patency, geometry and long-term effectiveness of these shunts have proved to be significant[8,9].

For analyzing the complex functional and morphological changes, numerous portacaval shunt models have been developed in rats, rabbits, dogs, pigs or even using simulation models[10-17]. Lee has made the first microsurgical portacaval shunt in the rat[10]. It was an end-to-side anastomosis model, which had been widely applied in variety of research models. Besides further refined models[3,15], side-to-side variation[1,3,11] and interpositioned H-graft methods are still used today. In case of selective portacaval shunt, one of the main branches of the portal venous system is connected directly into the inferior caval vein or drained into the left renal vein. The distal splenorenal shunt[4,12,14,19] is one of the example of such selective shunts. Based on the anatomical possibilities further selective portacaval shunts were created, such as the mesocaval localization[8,11,12,15,19-21].

In this study we describe a refined microsurgical model of a selective portacaval shunt model in the rat, where only the rostral mesenteric vein is utilized and the portal and lienal vein are left intact. Since portacaval shunt causes hemodynamic alterations (pressure-gradient differences, hepatic and splanchnic flow dynamic changes, selective redistribution of cardiac output)[3,18,20,22-25], we also aimed to observe the microcirculatory changes of the affected organs (liver, small intestine and right kidney) intraoperatively. Interestingly there is a lack of data in the literature about intraoperative microcirculatory changes in the organs that are affected by hypoperfusion or ischemia during creating of portacaval shunt.

Methods

Experimental animals and operative techniques

The experiments were approved and registered by the University of Debrecen Committee of Animal Research (permission Nr.: 6/2008. UD CAR), in accordance with the relevant Hungarian Animal Protection Act (Law XVIII/1998).

Ten Sprague-Dawley rats (bodyweight: 340.9 ± 24.52 g) were subjected to the study. The experimental animals were anesthetized using sodium-thiopental (60 mg/kg i.p., Thiopenthal, Biocheme GmbH, Austria). For microsurgical operations a Leica Wild M650 operative microscope was used, and video recordings were made. During the operation the rectal temperature was monitored (SEN-06-RTH1 Stick temperature probe, Experimetria Ltd., Hungary).

The microsurgical technique provided a design of a selective portacaval shunt, in which only the rostral mesenteric vein (rMV) was sutured, as end-to-side anastomosis, into the caudal caval vein (CCV), while the other main branch of the portal vein (gastrosplenic vein) was left intact (Figures 1 and 2).
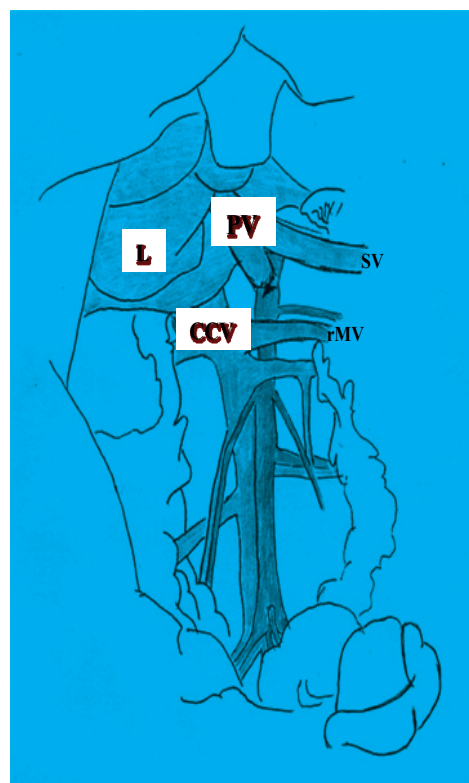

FIGURE 1 – Schematic drawing of the renewed, selective portacaval shunt model (drawing by Z. Klarik, with the main contours from Ref. 26, as a template).
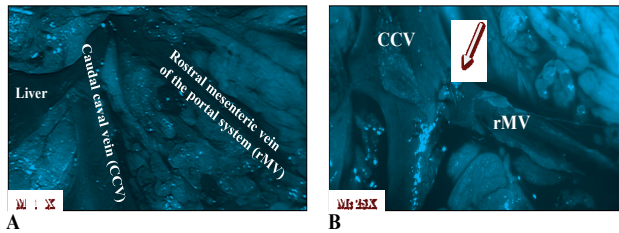CCV: caudal caval vein, PV: portal vein, rMV: rostral mesenteric vein, SV: splenic vein, L: liver.

FIGURE 2 – A: normal anatomical positions of the caudal caval vein (CCV) and the rostral mesenteric vein (rMV). **B**: the completed end-to-side anastomosis (arrow) between the rMV and the CCV at mesocaval localization. Magnification: x16 in A, x25 in B.

After median laparotomy and anteposition of the intestines, careful dissection of the portal vein (PV) and its tributaries were prepared.[26] The CCV was mobilized between the two renal veins. At the bifurcation of the portal vein the proximal part of the rMV was ligated with 8/0 braided silk. Clips were applied onto the intestinal part of the rMV and to the CCV proximally and distally. The rMV was washed out with physiological saline solution diluted with sodium-heparin (10%) and positioned toward the CCV in order to minimize the tension.

On the isolated anterior wall of the CCV, venotomy was performed with the length equal to the diameter of the mesenteric vein. The site of the venotomy was located as lateral as possible. Firstly, the posterior wall of the anastomosis was continuously sutured, while on the anterior wall simple interrupted sutures (6-7 stitches) were used with 10/0 polyamide monofilament suture material. After releasing the clips, the shunt patency was checked.

The intestines then were re-positioned and after completing the intraoperative microcirculatory measurements, the abdominal wall was closed in two layers.

Morphometric analyses of the shunts

The vessel geometry parameters were determined off-line from the video-recordings: outer diameter of the CCV and the rMV, as well as of the legs of the completed end-to-side anastomoses together with their angle. The offline measurements were carried out with Adobe Photoshop CS5 software. The angle of the anastomosis at the heel was measured with the same software. The axis of the veins was drawn and the angle was calculated where the lines were connected.

Intraoperative microcirculatory investigations

A non-invasive laser Doppler tissue flowmetry was used (LD-01 laser Doppler tissue flowmetry monitoring system,

Experimetria Ltd., Hungary) with a standard pencil probe (MNP100XP, Oxford Optronix Ltd., UK) placed on the surface of the liver's middle lobe, on the antimesenteric surface of a jejunum segment, as well as on the anterior surface of the right kidney. Based upon the Doppler shift effect when the laser beam is reflected from moving red blood cells, the device determines blood flux units (BFU), which were registered for 20 seconds after stabilization of the signal. Using single-channel laser Doppler flowmetry, it is important to set the standards for the evaluation[27,28-30], we have chosen the evaluation of the average BFU values of a standard time period of 20 seconds[30].

The laser Doppler measurements were carried out before (Base) and shortly after applying the clips, before and just after releasing the clamping (Reperfusion 0') as well as in the 30th minutes of the reperfusion (reperfusion 30').

Statistical analysis

Data are presented as mean ± standard deviation (S.D.), it is indicated if median ± standard error (S.E.) is shown. The comparison of intraoperative laser Doppler flowmetry data obtained from various measurement sites were carried out with Student's t-test or Mann-Whitney rank sum test, while the changes during the time-frame of experiment within measurement sites were analyzed by one-way ANOVA methods (Bonferroni's or Dunnett's test), depending on the data distribution. The significance level were considered when $p<0.05$.

Results

Technical experiences and morphometric data

The created mesocaval end-to-side venous anastomosis was functioning well; there were no bleeding at the site of the anastomosis. Its patency was maintained and no stenosis was observed. The operation time was 48.75 ± 11.26 min. The longest phase was the preparation and positioning of the vessels to be, providing situation without tearing, stretching or rupturing the intima. During the procedure (when clips were being applied) the changing of organs' color was well observable. The small intestine showed venous congestion and the liver became paler.

The presented geometry of the shunt occurred due to the anatomical localization of the given vessels, since there was a persisted risk of the rMV to tear at various angulation positioning. In order to minimalize such intraoperative complication, the

anastomosis could be created tension-free and at the angulation of 77.13 ± 5.84°.

The outer diameter of the rMV as well as the CCV dilated just above or below the shunt compared to the normal situation (state before applying the clips) (Table 1). Dilatation of the rMV was not significant, and the CCV diameter was increased significantly above (p<0.001 vs. normal; p=0.05 vs. anastomosis site) and below (p<0.001 vs. normal; p=0.004 vs. anastomosis site) the shunt.

TABLE 1 – Diameter of the caudal caval vein and the rostral mesenteric vein before and after completing the end-to-side anastomosis.

Vessel	Diameter [mm]		
	Before	After	
caudal caval vein	2.41 ± 0.15	above the anastomosis:	3 ± 0.36
		at the anastomosis:	2.44 ± 0.63
		below the anastomosis:	3.51 ± 0.61
rostral mesenteric vein	1.26 ± 0.19	1.4 ± 0.33	

Intraoperative microcirculatory investigations

The changes of blood flux unit (BFU) are shown on Figure 3. At base level the values of liver (32.64 ± 13.68), jejunum (35.83 ± 13.67) or kidney (36.14 ± 17.71) did not differ significantly among each other. When applying the clips according to the operative protocol, the intestinal BFU values as well as renal ones decreased, and as we expected, it was more expressed on the jejunum. After clamping the intestinal values (17.61 ± 9.09) were significantly lower compared to its base (p<0.001), as well as versus liver (29.13 ± 14.45, p<0.001) and kidney values (24.75 ± 10.86, p=0.001). Renal BFU decreased significantly compared to its base (p<0.001).
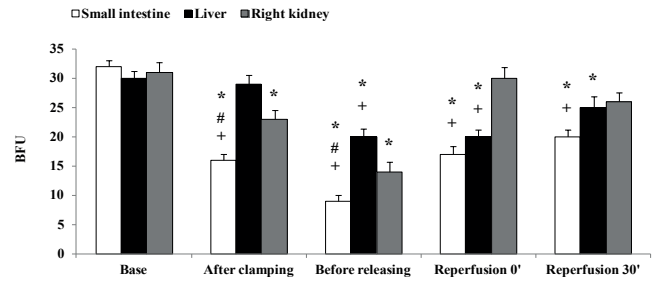

FIGURE 3 – Alterations of microcirculatory blood flux unit (BFU) measured on the surface small intestine (jejunum-part), middle lobe of the liver and on the right kidney. Median ± S.E., n=10.
* p<0.05 vs. Base (one way ANOVA test, Bonferroni's/Dunnett's), #p<0.05 vs. Liver; + p<0.05 vs. Kidney (t-test/Mann-Whitney RS test).

Just before releasing the clamps the lowered values were more expressed, keeping similar relations between the investigated organs (on the jejunum: 12.03 ± 9.19, p<0.001 vs. base and liver, p=0.036 vs. kidney; on the liver: 23.26 ± 13.37, p<0.001 vs. base, p=0.02 vs. kidney; on the kidney: 16.07 ± 10.91, p<0.001 vs. base).

Just after releasing all the clips, the BFU values started to increase, but not in the same manner in the organs. The renal BFU values recovered almost completely (31.87 ± 12.59), while intestinal values (21.26 ± 17.07, p<0.001 vs. base, p<0.001 vs. kidney) as well as hepatic BFU values (24.43 ± 12.06, p<0.001 vs. base, p<0.001 vs. kidney) were dropped behind the renal data. During the investigated reperfusion period, the intestinal values were remained lower compared to the hepatic values, however, the p values were close to the significance level (at reperfusion 0': p=0.059; at reperfusion 30': p=0.051).

Discussion

Experimental researches focusing on vascular anastomosis have high clinical importance hence the investigation of surgical safety, the morphological vascular changes and the long term effectives of these procedures are inevitable. Studying these aspects is necessary for a better understanding of the characteristic of such decompressive porto-systemic shunts[3,10,13,31].

The surgical management of these shunts is technically difficult, and because of these factors, variously localized portacaval shunts have been created since in the 1960s[3,12,19]. The purpose of the study groups was to describe new surgical methods to construct an anastomosis, where the technical difficulties (anatomical distance between the two vessels, shortness of the portal vein) can be overwhelmed. With the advance of microsurgery, these novel technique models could have been investigated in smaller animals and brought the possibility for

further development of the surgical protocols. Lee *et al.*[10] and Numata *et al.*[13] were the pioneers to describe portacaval shunt models in small laboratory animals, and observe changes in the presence of these anastomoses. Additionally, laboratory rats proved to be excellent models to study liver cirrhosis[11], as well as hepatic encephalopathy[31-33]. In those experiments the liver atrophy and regeneration[34], microvascular structural changes[35], as well as remote effects were studied. However, most of these shunts were non-selective types.

Numerous experiments focused on the comparison of the characteristics of the differently localized shunts[3,14,20]. In their study, Drapanas *et al.*[20] described pressure and flow measurements in the hepatic circulations and observed the changes following side-to-side and interpositional mesocaval shunt. By creating the side-to-side portacaval shunt the total portal blood flow ceased, while with the selective counterpart only 50% of the total blood was diverted. Schröder *et al.*[14] concluded that in case of distal spleno-caval shunt the blood drained from splenic vein does not significantly affect the liver compared to the non-selective portacaval shunt.

The presented end-to-side mesocaval anastomosis between the caudal caval vein and the rostral mesenteric vein is a renewed microsurgical model for creating a selective portacaval shunt. Although, the operative technique is not simple, due to the anatomical distances, but it gives the possibility to redirect the retrograde flow existing in case of portal hypertension back to the systemic circulation via bypassing the liver.

During the design of the surgical protocol our aim was to create a situation where we can minimize the tension between the structures. Therefore, additional vessel ligations were needed to further mobilize the mesenteric vein, so the approximation of the anatomical structures was under less tension. Using the applied suturing technique the veins were not stretched and the anastomosis was secure. At the toe of the anastomosis, the first knot of the continuous suture line was a surgical knot.

The advantages of the models include the selective characteristic (the gastrosplenic vein remains intact), the mesocaval localization, and the relatively easy access to those vessels. However, its major disadvantage is the time needed for positioning the vessels without coiling or definitive stretching it. It was also observed, that after completing the shunts the microcirculatory flux values did not recover in the same manner on the surface of the small intestine, liver or the kidney.

The mesocaval shunt is also a competent model to study hepatic encephalopathy and portal vein thrombosis. Several studies used portacaval shunts instead of pharmaceutical induction of encephalopathy to observe the neurological changes[31,36]. The described selective portacaval shunt created between the rostral mesenteric vein and the caudal vena cava with an end-to-side anastomosis differs in its surgical technique rather than its effect on the tissue and function of the liver from other previously known meso-caval shunt models.

Engelbrecht *et al.*[21] studied the effect of meso-caval shunts in rats where they created an end-to-side anastomosis with the ligation of the pyloric vein. To investigate the hepatotrophic factors in the liver, Rozga *et al.*[34] applied this shunt, however they only used continuous suture line. Jakab *et al.*[15] demonstrated a technique to exclude the possibility of stenosis during the microvascular mesocaval shunt anastomosis. By ligating the left and right branches of the portal vein and transecting at the ligations, they created a "cuff" and with that the diameter of the vessel increased. Jenkins *et al.*[23] studied the hemodynamic differences between total and selective portacaval shunts. They found that selective shunting (mesocaval H-graft) preserved liver blood flow to a greater extent than total portacaval shunting, while they had less marked effect on the wedge hepatic pressure.

Since the presence of any kind of portacaval shunts cause complex changes in the hemodynamic and the blood flow rate of the organs[16,17,22,37,38], it was also supposed, that the microcirculatory parameters may show early alterations even shortly after the operation[24,39-41].

Laser Doppler flowmetry is a well-known method to evaluate microcirculatory pattern of the tissues. With the necessary critical evaluation and standardized measurement conditions it is an easily applicable method for monitoring organ microcirculatory changes[27,28,30]. Intraoperative microcirculatory measurements of the affected organs with laser Doppler flowmetry during procedures where the portal circulation is selective decompressed is not well known in the literature, although it can prove to be beneficial in designing an innocuous surgical technique since the hypoperfusion and/or ischemia-reperfusion of the organs can influence the outcome of such shunts.

In this model we tested the microcirculatory blood flux units (an integral over erythrocyte velocity and number) on liver, jejunum and kidney surface. The deterioration of microcirculatory flow was present according to the blood flow cessation, based on the clip positions. After releasing the clamp, it was visible that the intestinal and hepatic values did not recover in the same manner compared to the renal values. Microcirculatory changes are widely studied being related to tissue hypoperfusion and ischemia-reperfusion. The deterioration of microcirculatory parameters can be originated from endothelial swelling, bleb formation,

vasospasm, interstitial edema, plugged leukocytes and platelets, and also with marked micro-rheological alterations (decreased deformability and enhanced aggregation of the erythrocytes)[41-43].

Concerning the follow-up of morphological and functional changes of artificial shunts, in a previous work we demonstrated significant hemodynamic and notable micro-rheological (red blood cell deformability and aggregation) alterations in case of artificial sapheno-saphenous arterio-venous shunt model in the rat[44]. In a recent study, we found aorto-portacaval differences in the certain hemorheological parameters (red blood cell aggregation, erythrocyte elongation index, osmotic gradient ektacytometry parameters)[45]. By the alterations of hemodynamic factors influencing blood flow, the hemorheological properties play an important role in the microcirculatory regulation[41]. Therefore, to understand the proper hemodynamic profile of these shunts and the microcirculatory pattern, further hemorheological examinations are planned.

Conclusions

In this model a selective portacaval shunt was achieved by anastomosing the rostral mesenteric vein into the caudal caval vein with a modified microsurgical technique in laboratory rat, where the shunts were well feasible and stable geometry was formed.

The intraoperative laser Doppler measurements provided useful information for the elaboration of a more secure surgical technique with the assessment of microcirculatory changes on the areas exposed to hypoperfusion and/or ischemia-reperfusion.

References

1. Blakemore AH. The portal shunt in the surgical treatment of portal hypertension. Ann Surg. 1948;128:825-41.
2. Donovan AJ. Surgical treatment of portal hypertension: a historical perspective. World J Surg. 1984;8:626-45.
3. Starlz TE, Porter KA, Francavilla A. The Eck fistula in animals and humans. Curr Probl Surg. 1983;20:687-752.
4. Sanyal AJ, Borch J, Blei A, Arroyo V. Portal hypertension and its complication. Gastroenterology. 2008;134:1715-28.
5. Orloff MJ, Vaida F, Haynes KS, Hye RJ, Isenberg JI, Jinich-Brook H. Randomized controlled trial of emergency transjugular intrahepatic portosystemic shunt versus emergency portacaval shunt treatment of acute bleeding esophageal varices in cirrhosis. J Gastrointest Surg. 2012;16:2094-111.
6. Huang JW, Yan LN, Chen ZY, Wu H, Lu Q, Xu YL, Prasoon P, Zeng Y. Hemi-portacaval shunt: a simple salvage maneuver for small-for-size graft during living donor liver transplantation: a case report. Chin Med J (Engl). 2011;124:2231-3.
7. Louwers LM, Bortman J, Koffron A, Stecevic V, Cohn S, Raofi V. Noncirrhotic Portal Hypertension due to Nodular Regenerative Hyperplasia treated with Surgical Portacaval shunt. Case Rep Med. 2012;2012:965304. doi: 10.1155/2012/965304.
8. Salam AA, Warren WD. Anatomic basis of the surgical treatment of portal hypertension. Surg Clin North Am. 1974;54:1247-57.
9. Rocko JM, Swan KG. The Eck-Pavlov connection. Am Surg. 1985;11:641-4.
10. Lee SH, Fisher B. Portacaval shunt in the rat. Surgery. 1961;50:668-72.
11. Henzel J, Turcotte JG, Child CG. The response of normal rats to portacaval shunt. A comparative study of end-to-side and side-to-side shunts. Arch Surg. 1963;86:342-8.
12. Warren WD, Zeppa R, Fomon JJ. Selective trans-splenic decompression of gastroesophageal varices by distal splenorenal shunt. Ann Surg. 1967;166:437-55.
13. Numata M. A modified technique to make a portacaval shunt in rats. Microsurgery. 1983;4:243-4.
14. Schröder R, Müller O, Bircher J. The portacaval and splenocaval shunt in the normal rat. A morphometric and functional reevaluation. J Hepatol. 1985;1:107-23.
15. Jakab F, Zaborszky A, Sugar I. 'Cuffed' portacaval anastomosis in rat. Acta Chir Hung. 1987;28:345-54.
16. Wang HS, Ohkohchi N, Enomoto Y, Usuda M, Miyagi S, Asakura T, Masuoka H, Aiso T, Fukushima K, Narita T, Yamaya H, Nakamura A, Sekiguchi S, Kawagishi N, Sato A, Satomi S. Excessive portal flow causes graft failure in extremely small-for-size liver transplantation in pigs. World J Gastroenterol. 2005;11:6954-9.
17. Garcia C, Gine E, Aller MA, Revuelta E, Arias JL, Vara E, Arias J. Multiple organ inflammatory response to portosystemic shunt in the rat. Cytokine. 2011;56:680-7.
18. Ho H, Bartlett A, Hunter P. Hemodynamic simulation for an anatomically realistic portal system. Med Image Comput Comput Assist Interv. 2011;14(Pt 1):347-54.
19. Erlik D, Barliai A, Shramek A. Porto-renal shunt: a new technic for porto-systemic anastomosis in portal hypertension. Ann Surg. 1964;159:72-8.
20. Drapanas T, Locicero J, Dowling JB. Hemodynamics of the interposition mesocaval shunt. Ann Surg. 1975;181:523-33.
21. Engelbrecht GH, van Hoorn-Hickman R, Keraan M, Meyers OL. Effect of mesentericocaval shunt upon globulin levels in the rat. Dig Dis Sci. 1981;26:1100-3.
22. Reynolds TB. The role of hemodynamic measurements in portosystemic shunt surgery. Arch Surg. 1974;108:276-81.
23. Jenkins SA, Baxter JN, Devitt P, Shields R. Effects of total and selective portasystemic shunting on hepatic haemodynamics and some aspects of liver function in the cirrhotic rat. Clin Exp Pharmacol Physiol. 1986;13:671-80.
24. Aller MA, Martinez V, Corcuera MT, Benito J, Traver E, Gómez-Aguado F, Vergara P, Arias J. Liver impairment after portacaval shunt in the rat: the loss of protective role of mast cells? Acta Histochem. 2012;114:301-10.
25. Melo VA de, Ceneviva R, Godoy ÁQ de, Santos JE dos, Melo GB de. Alterações bioquímicas e morfológicas após anastomose porto-cava e hepatectomia parcial. Estudo experimental em cães. Acta Cir Bras. 2003;18(3):245-9.
26. van Dongen JJ, van der Wal JC, Rensema JW, Everdsen M, Remie R. Brief anatomy of the rat. In: van Dongen JJ, Remie R, Rensema JW, van Wunnik GHJ, editors. Manual of Microsurgery on the Laboratory Rat. Part I. Amsterdam, New York, Oxford: Elsevier; 1990. p.35-60.
27. Obeid AN, Barnett NJ, Dougherty G, Ward G. A critical review of laser Doppler flowmetry. J Med Eng Technol. 1990;14:178-81.
28. Szijarto A, Hahn O, Lotz G, Schaff Z, Madarasz E, Kupcsulik PK.

Effect of ischemic preconditioning on rat liver microcirculation monitored with laser Doppler flowmetry. J Surg Res. 2006;131:150-7.

29. Hu W, Yang M, Chang J, Shen Z, Gu T, Deng A, Gu X. Laser Doppler perfusion imaging of skin territory to reflect autonomic functional recovery following sciatic nerve autografting repair in rats. Microsurgery. 2012;32:136-43.

30. Nemeth N, Kiss F, Klarik Z, Peto K, Vanyolos E, Toth L, Furka I, Miko I. Testicular ischemia-reperfusion may alter micro-rheological parameters in laboratory rats. Clin Hemorheol Microcirc. 2013 Jan 22 [Epub ahead of print].

31. Norenberg MD, Lapham LW, Nichols FA, May AG. An experimental model for the study of hepatic encephalopathy. Arch Neurol. 1974;31:106-9.

32. Olde Damink SW, Dejong CH, Deutz NE, Soeters PB. Effects of simulated upper gastrointestinal hemorrhage on ammonia and related amino acids in blood and brain of chronic portacaval-shunted rats. Metab Brain Dis. 1997;12:121-35.

33. Diaz-Gomez D, Jover M, del-Campo JA, Galindo A, Romero-Gómez M. Experimental models for hepatic encephalopathy. Rev Esp Enferm Dig. 2011;103:536-41.

34. Rozga J, Jeppsson B, Bengmark S. Hepatotrophic factors in liver growth and atrophy. Br J Exp Pathol. 1985;66:669-78.

35. McCuskey RS, Vonnahme FJ, Grün M. In vivo and electron microscopic observations of the hepatic microvasculature in the rat following portacaval anastomosis. Hepatology. 1983;3:96-104.

36. Bengtsson F, Bugge M, Brun A, Falck B, Henriksson KG, Nobin A. The impact of time after portacaval shunt in the rat on behavior, brain serotonin, and brain and muscle histology. J Neurol Sci. 1988;83:109-22.

37. Gustafsson BI, Wallin M, Delbro DS, Friman S. Nitric oxide-mediated effects on liver blood flow. Transplant Proc. 2005;37:3338-9.

38. Yagi S, Iida T, Hori T, Taniguchi K, Nagahama M, Isaji S, Uemoto S. Effect of portal haemodynamics on liver graft and intestinal mucosa after small-for-size liver transplantation in swine. Eur Surg Res. 2012;48:163-70.

39. Kusza K, Siemionow M. Is the knowledge on tissue microcirculation important for microsurgeon? Microsurgery. 2011;31:572-9.

40. Romalho FS, Fernandez-Monteiro I, Rosello-Catafau J, Perlata C. Hepatic microcirculatory failure. Acta Cir. Bras. 2006;21(suppl.1):48-53.

41. Popel AS, Johnson PC. Microcirculation and hemorheology. Ann Rev Fluid Mech. 2005;37:43-69.

42. Reffelmann T, Kloner RA. The no-reflow" phenomenon: Basic science and clinical correlates. Heart. 2002;87:162-8.

43. Vollmar B, Menger MD. Intestinal ischemia/reperfusion: microcirculatory pathology and functional consequences. Langenbecks Arch Surg. 2011;396:13-29.

44. Hever T, Nemeth N, Brath E, Toth L, Kiss F, Sajtos E, Matyas L, Szaszko J, Drimba L, Peitl B, Csiki Z, Miko I, Furka I. Morphological, hemodynamical and hemorheological changes of mature artificial saphenous arterio-venous shunts in the rat model. Microsurgery. 2010;30:649-56.

45. Klarik Z, Kiss F, Miko I, Nemeth N. Aorto-porto-caval micro-rheological differences of red blood cells in laboratory rats: Further deformability and ektacytometrial osmoscan data. Clin Hemorheol Microcirc. 2013;53:217-9.

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