Morphological and functional alterations induced by portal vein ligation

PhD thesis

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Introduction:

Hepatobiliary malignancies are rather common and their incidence shows an increasing tendency worldwide. Primary liver cancer, which predominantly comprises hepatocellular carcinoma, is the sixth most common malignant tumour and the third leading cause of cancer related deaths. However, liver malignancies are in most instances of secondary nature and mostly provoked by an underlying colorectal cancer. Hepatectomy is the only curative option for long-term survival in patients with primary or secondary liver malignancies. Unfortunately, to achieve tumour-free margins, extended liver resection (removal of four or more liver segments) is usually required. The excessive removal of hepatic parenchyma, however, often leads to posthepatectomy liver failure, due to an insufficient volume of the remnant liver – also known as the future liver remnant (FLR). In recent years, numerous surgical procedures have been developed in order to increase volume and function of FLR, of which portal vein occlusion (PVO) techniques are the most frequently used. These surgical strategies are based on the unique regeneration capacity of the liver. The selective occlusion of portal vein branches of the tumorbearing liver lobes lead to the redirection of portal blood away from the liver lobes that are planned to be resected towards the anticipated FLR, resulting in FLR hypertrophy (liver regeneration). Meanwhile the liver lobes that are deprived of portal blood undergo atrophy. These liver volume manipulation techniques made hepatic surgery much safer and expanded the indications for liver resection.

Although PVO techniques are increasingly used worldwide, a recently published systemic review demonstrated that almost 20% of the originally planned liver resections are cancelled after PVO, mainly due to the insufficient regenerative response and the unfortunate progression of the primary disease. The high rates of unsuccessful cases raised several important concerns regarding the PVO induced regenerative process.

Objectives:

The main goal of the present study was to establish a small animal model of portal vein occlusion (portal vein ligation (PVL)) and to assess the induced hemodynamical-, morphological- and functional alterations. In our experiments we sought answer to the following questions:

1.) Could the ligation of the portal vein branches supplying a significant part of the liver (70-80-90%) be safely and reproducibly carried out in rats? What are the effects of different degrees of PVL on the extent of liver regeneration and on portal pressure? Is there a possible correlation between the induced alterations such as portal pressure and the intensity of liver regeneration?

2.) What effect does PVL exert on systemic and splanchnic circulation and on liver microvascular blood flow?

3.) What kind of histological alterations are characteristic for portal vein ligation induced regenerative and atrophic processes, and how could the dynamics of these phenomena be characterized? What effect does PVL have on liver microstructure and lobar architecture?

4.) What is the effect of PVL on liver function? How does it change global liver function (as measured by laboratory and quantitative liver functional tests)? What changes occur in the excretory function (bile secretion, indocyanine green excretion) of the liver lobes? What kind of correlation is present, if any, between the alteration of functional capacity and the volume of the regenerating (non-ligated) liver lobes?

5.) Is NanoScan PET/MRI able to monitor the rapid volumetric alterations after PVL in small animals?

6.) What is the effects of PVL on FDG (2-deoxi-2-(18F)fluoro-D-glucose) uptake and glucose metabolism of the liver lobes?

Methods:

Animals

The experimental design was regulated in accordance with the National Institutes of Health guidelines for animal care and was approved by the Committee on Animal Experimentation of the Semmelweis University. Male Wistar rats weighing 200-250g were used.

Experimental design

I. Experiment: Assessment of the effect of different extent (70-80-90%) of portal vein ligation on liver regeneration (n=64).

II. Experiment: Assessment of the effect of portal vein ligation corresponding to 80% liver parenchyma on liver morphology (n=44).

III. Experiment: Assessment of the effect of portal vein ligation corresponding to 80% liver parenchyma on liver hemodynamics and functions, as well as on glucose metabolism (nanoScan PET/MRI) (n=42).

Operative procedure

Under general anesthesia, the median and left lateral liver lobes were carefully mobilized to reveal the portal pedicles. By using an operating microscope, the portal branches feeding the liver lobes designated for ligation were dissected and completely ligated. Great care was taken to avoid damaging the vulnerable hepatic artery and bile duct. Depending on experimental group order, the corresponding portal vein supplying the following lobes were specifically ligated: 70% PVL - median, left lateral lobes; PVL 80% - median, left lateral and caudal lobes; 90% PVL - right lateral, median and left lateral lobe. At the end of the procedure, the liver lobes were gently repositioned to obtain the anatomical setting, and the peritoneal cavity was closed in two layers by a running suture. Animals were returned to their cages until further examination. Rats were randomly allocated to groups based on the length of the recovery period (0, 1, 2, 3, 5, 7 days).

Assessment of morphological alterations

Liver weight measurement

Wet weight of liver lobes was measured separately using a laboratory scale. The relative weight of lobes to body weight (BW) was then calculated and expressed as grams of liver weight per 100 grams of BW.

Tissue edema

Following careful excision, liver lobes were immediately weighed (wet weight), placed in a drying oven heated to a temperature of +80°C and kept there for 3 days running. Liver lobes were then weighed once more (dry weight) and a wet/dry ratio was calculated: (wet weight–dry weight)/wet weight * 100.

Histological and immunohistochemical analysis

The excised liver samples were fixed in formalin and subsequently embedded in paraffin. Sections of 3-5 μm thickness were examined with light microscope after hematoxylin and eosin staining. Necrosis was graded as described by Suzuki. Apoptotic cell death and mitotic activity were determined by immunohistochemical staining. Primary antibodies against active caspase-3 and Ki-67 were used, respectively. To determine cellular glycogen content, periodic acid and Schiff (PAS) staining was used.

Liver lobule size determination

Hepatic veins were filled up through the inferior vena cava by a fluorescent dye containing a polystyrene resin. The liver surface was monitored by a stereomicroscope, and the filling was stopped when the resin has already filled up the sinusoids partially. The liver was removed and examined with inverted microscope. On the surface pictures, the interlobular borders were outlined by the resin in the sinusoids. Circumference and surface area of the lobules were determined with ImageJ program.

Assessment of hemodynamics

Mean arterial pressure, portal vein pressure

Blood pressure was measured by an invasive blood pressure monitoring system via the cannulated right carotid artery. Portal pressure was determined by directly puncturing the portal vein.

Liver microcirculation

Liver microcirculation was assessed using a laser Doppler monitor. Surface probes were placed on fixed locations of the livers. At least four measurements were performed at different sites of the lobes (5 min for each), and the mean of the measurements was calculated.

Assessment of functional alterations

Conventional laboratory blood tests

Serum levels of alanine aminotransferase, aspartate aminotransferase, albumin, and total bilirubin (tBil) were determined with an automated clinical chemistry analyzer.

ICG-clearance test

Indocyanine green (ICG) plasma disappearance rate (PDR) and retention rate (R15) constants were determined by means of ICG densitometry using a commercially available analyzer (PC5000 LiMON). ICG (1.5 mg/ml) was injected at the dose of 1 ml/kg via the right jugular vein. After a registration period of 6 min, the device calculated PDR and R15.

Bile production and biliary ICG excretion

To determine bile production and biliary ICG excretion of the liver, selective biliary drainage was performed. Bile was collected from the ligated and non-ligated lobes separately into preweighed, light-protected test tubes. Bile volume from each collection was measured gravimetrically, assuming a specific gravity of 1.0. Bile production was normalized to both body weight (ml/min/kg BW) and liver weight (ml/min/g liver). After measurement of the bile volume, the samples were centrifuged. The supernatant was diluted with distilled water and analyzed for ICG concentration using spectrophotometer at 805 nm. Maximal biliary

ICG concentration (C_{max}) and the corresponding time (T_{max}) were determined from the concentration curves. Furthermore, the biliary ICG excretion rate (ICG_{EX}) was expressed as a percentage of excreted ICG at the first 20 min from the injected dose.

Glucose metabolism (PET/MRI)

Images were acquired with a nanoScan PET/MRI sequential animal imaging system. In the PET experiment 6.561.0 MBq of FDG diluted in a total volume of 0.2 ml was injected into the tail vein. PET data was collected in a three-dimensional acquisition mode. The MRI images (matrix size 1406140; 0.5 mm; 30 slices; 1.3 mm; gap 0.5 mm) were acquired for 50 minutes with T1-weighted (SE2D; TR/TE 800/10 ms; FOV 70 mm; NEX 4) and T2-weighted (FSE2D; TR/TE 4733/ 60 ms; FOV 70 mm; NEX 2) sequences. PET volumes were reconstructed using a three-dimensional Ordered Subsets Expectation Maximization (3D-OSEM) algorithm. Reconstructed, reoriented and coregistered images were further analyzed with Fusion and VivoQuant dedicated image analysis softwares by placing appropriate Volume of Interests (VOI) on the organs. Two volume of interests were delineated manually slice by slice on each T1 weighted scan. One VOI represented the ligated liver lobes and the other characterized the non-ligated liver lobes. For volumetric analysis, the built-in VOI statistics of the VivoQuant software was used. For FDG uptake, the standardized uptake value (SUV) was calculated. The mean SUV for ligated and non-ligated liver lobes were selectively recorded. The mean SUV of the corresponding liver lobes was expressed in relation to a reference tissue SUV (cardiac left ventricle; SUV_{VOI}/SUV_{CLV}) and to the mean liver SUV (SUV_{VOI}/SUV_{Liver}).

Statistical analysis

Normality and homoscedasticity of the data were tested. Statistical analysis was performed with the analysis of variance test and the Bonferroni correction post hoc test. Differences were considered significant when $P < 0.05$. Calculations were performed with IBM SPSS Statistics 2.0 software.

Results:

I. Experiment - the effect of different degree (70-80-90%) of portal vein ligation

Liver weight alterations

Mortality remained zero throughout the whole experiment. The total liver weight did not significantly change in any of the different experimental groups. In contrast, the weight of non-ligated liver lobes significantly increased from 1.50±0.13, 1.00±0.12, 0.50±0.05g/100g BW to 3.30±0.2, 3.20±0.21, 2.10±0.22g/100g BW in the PVL-70%, PVL-80%, and PVL-90% groups, respectively. In parallel, the weight of the ligated lobes continuously decreased until the end of the experiment. In the PVL-90% group the regeneration ratio of the non-ligated liver lobes increased in a higher extent compared to that of seen in the PVL-80% ($p<0.001$) and PVL-70% ($p<0.001$) groups.

Mitotic activity

In the non-ligated liver lobes, the number of mitotic hepatocytes reached its peak 48 hours following ligation in the PVL-70% and PVL-80% groups, while in the PVL-90% group the mitotic activity of cells was the most intense on postoperative day 1. At his time point, the number of mitotic cells was significantly higher in the PVL-90% group (96±3,46 positive cells/visual field), than in the PVL-80% (54,67±4,04 positive cells/visual field) or the PVL-70% (31,33±4,04 positive cells/visual field) group.

Portal vein pressure

PVL provoked an immediate and steep increase of portal pressure in each of the experimental groups (PVL-70%: 17.12±2.03mmHg, PVL-80%: 19.8±1.05mmHg, PVL-90%: 28.39±3.6mmHg). The acute portal hypertension in the PVL-90% group significantly exceeded the values measured in groups PVL-80% ($p<0.001$) and PVL-70% ($p<0.001$). The increment in portal pressure strongly correlated with the volume of liver parenchyma

affected by the ligation (r=0.932), confirmed by the Pearson product-moment correlation coefficient.

Spleen weight

Spleen weight showed a significant increment in each group. The gain of spleen weight was the greatest in the PVL-90% group, which exhibited significantly higher spleen weights than groups PVL-80% and PVL-70%.

II. Experiment - Assessment of morphological alterations

Macroscopic appearance of the liver - weight changes

After the operation, the ligated lobes darkened, followed by the formation of small necrotic lesions on the liver surface during the first few days. By the end of the experiment (168^{th} hour), they were reduced to firm remnants. Alongside the atrophy, compensatory hypertrophy of the non-ligated lobes could be observed. The non-ligated lobes appeared fragile and light-coloured; the contours of the central veins were easily identifiable. Although the total liver weight remained unchanged, the weight of non-ligated lobes significantly increased after the operation and reached a plateau between the fifth and seventh days at approximately 329% of the preoperative value (0.97±0.08g/100gBW vs. 3.28±0.09g/100gBW). On the other hand, ligated lobes considerably shrunk and reached about 29% of their original weight by the end of the experiment (3.17±0.39g/100gBW vs. 0.86±0.19g/100gBW).

Tissue edema

A mild (insignificant) increase in tissue wet/dry ratio was notable in both the ligated and non-ligated liver lobes, with the peak on the fifth postoperative day (non-ligated day 0: 72.08±1.62% vs. day 5: 73.13±1.23%, ligated day 0: 71.98±1.52% vs. day 5: 73.76±2.25%).

Liver histology

In the ligated liver lobes, extensive coagulation necrosis occurred around the central veins one day after the operation. The

necrotic areas became significantly reduced in size at postoperative days 2 and 3. Seven days after the ligation, necrosis could not be observed anymore, while the normal hepatic architecture recovered. The number of apoptotic hepatocytes also increased rapidly after the operation and reached its peak on postoperative day 2 (54±8.39 positive cells/visual field). Apoptosis was most frequently present at the boundary between necrotic and non-necrotic areas and remained elevated until the 7th postoperative day. On the other hand, portal vein ligation led to an increased mitotic activity in non-ligated lobes with peak response on the second day (142.33±18.88 positive cells/visual field). Then the number of proliferating hepatocytes gradually declined, and on the fifth day, the incidence of mitosis did not significantly differ from that of seen before the operation. Liver slides showed a moderate, homogeneous glycogen staining before the operation (non-ligated: 2.20±0.27, ligated: 2.30±0.27). One day after ligation, PAS positive glycogen granules almost completely disappeared in ligated lobes (0.70±0.27) and the glycogen content of cells returned to baseline level only by the 5^{th} day (2.00±0.50). In contrast, the PAS staining in non-ligated liver lobes revealed no significant alterations compared to the baseline level in any examined time points.

Liver lobule size

Weight gain of the non-ligated lobes was associated with 1.52- and 2.35-fold increase in the average circumference and surface area of the liver lobules, respectively. By contrast, the lobules of ligated lobes shrunk considerably, and the lobular circumference and surface area decreased 0.32- and 0.54-fold, respectively.

III. Experiment - hemodynamic and functional alterations

Hemodynamic alterations

Mean arterial pressure remained around the baseline level during the experiments. Portal pressure increased significantly 1 day after the operation (20.42±1.65mmHg, $p<0.01$) and remained elevated until the seventh day (12.54±1.91mmHg, $p=0.02$).

Microcirculatory blood flow of the non-ligated lobes increased immediately after portal vein ligation and remained elevated until the third day (158±35.80AU vs. 278.91±24.46AU). On the fifth day, it returned to the values detected before the operation. In contrast, in ligated lobes, the microcirculatory flow decreased by almost 50% (199.83±29.26AU vs. 113.89±31.9AU) after the operation. Then a gradual recovery was observed, and on the third day, the microcirculatory flow of the lobes did not differ significantly from the preoperative value.

Laboratory blood tests

No significant alterations were observable regarding the serum total bilirubin and albumin levels. Portal vein ligation, however, resulted in a transient elevation of transaminases that peaked after the first day and normalized on the third day.

ICG-clearance test - global liver function

Portal vein ligation resulted in a significant reduction in PDR and a transient rise in R15 levels. The liver's clearance function was the lowest around the second day, but a gradual recovery was observable thereafter, and on the fifth day, the PDR and R15 values did not show significant difference from the preoperative level.

Bile flow - segmental liver function

Bile production normalized to body weight showed a sharp increase in non-ligated lobes, as a result of which bile production of the lobes reached about 380% of the preoperative value on the seventh day (23±5.1µl/min/bwkg vs. 87.49±7.42µl/min/bwkg). By contrast, in ligated lobes, the bile production per body weight kilogram gradually decreased until the seventh day (76.34±8.,4µl/min/bwkg vs. 17.95±3.17µl/min/bwkg). When bile production was normalized to liver weight, the bile flow of non-ligated lobes significantly increased, with peak response visible on the second day (1.48-fold increase: 2.24±0.25µl/min/g liver vs. 3.3±0.36µl/min/g liver). On the contrary, bile production of the ligated lobes showed gradual decrease until the third day (0.7-fold

decrease: 2.15±0.15µl/min/g liver vs. 1.52±0.33µl/min/g liver). Between the fifth and seventh days, the bile production per gram liver returned to almost the preoperative level both in ligated and non-ligated lobes.

Biliary ICG excretion

C_{max} and T_{max} were determined via analysis of the biliary ICG concentration curves. In non-ligated lobes, T_{max} was significantly prolonged (18.33±2.58perc vs. 28.33±5.16perc, p=0.003) and C_{max} was significantly reduced (0.34±0.01mg/ml vs. 0.28±0.03mg/ml, p=0.049) 2 days after the operation. Thereafter, a gradual recovery was observed, and on the seventh day, T_{max} and C_{max} returned to the preoperative level. On the first 2 days, the biliary ICG concentration curves of ligated lobes changed similarly to the curves seen in case of the non-ligated lobes. However, after the second day, T_{max} and C_{max} did not become normalized and remained significantly inferior as compared with the preoperative values. The biliary ICG_{EX} of the total liver became temporarily impaired after the operation, showing the lowest value on the second day (29.23±2.98% vs. 15.17±1.22%, p<0,001). Thereafter, the excretory function of the liver gradually recovered, reaching preoperative levels on the fifth day. The ICG_{EX} of the non-ligated lobes did not change significantly during the first 2 days. After the second day, the ICG_{EX} of the lobes sharply increased and reached approximately 394% of the preoperative level on the seventh day. In contrast, the ICG_{EX} of ligated lobes gradually decreased and reached about 10% of its preoperative value at the end of the experiment.

Comparison between morphological and functional regeneration of non-ligated liver lobes

When the alterations in liver weight and liver function (bile production and ICG excretion) were compared, there were noticeable discrepancies between the morphological and functional regeneration of non-ligated lobes. The increment (% from the baseline) in bile production was more pronounced than the alteration in liver weight at any examined time point. By contrast, the increase in ICG

excretion proved to be smaller than the weight gain during the first 2 days. From the third day, however, ICG excretion increased more expressively than liver weigh.

III. Experiment - alterations in glucose metabolism (PET/MRI)

MRI volumetry

The volume of liver lobes changed parallel with liver weights. The volume change, based on MRI volumetry, correlated well with the weight change derived from autopsy ($r=0.842$; $p<0.001$).

Glucose metabolism - FDG PET scan

Dynamic PET scans revealed altered FDG kinetics characterized by prolonged tracer elimination in both ligated and non-ligated liver lobes. The alterations in time-activity curves of ligated lobes were more remarkable compared to the non-ligated lobes. Before PVL the liver showed homogenous tracer biodistribution. After PVL, FDG uptake within the liver shifted towards the ligated lobes. The SUV_{VOI}/SUV_{CLV} showed a significantly increased FDG uptake in ligated liver lobes. That value reached its peak on the second postoperative day and returned to almost baseline levels by the seventh day. In non-ligated lobes, the SUV_{VOI}/ SUV_{CLV} ratio also increased, but with a significantly lower extent compared to the ligated lobes. The increment in FDG uptake of non-ligated lobes reached a statistically significant level on second and third postoperative days only, as compared to the baseline. SUV_{VOI}/SUV_{Liver} in ligated lobes significantly increased compared to that of in non-ligated liver lobes with the maximal level on the second postoperative day. Then on the seventh postoperative day the SUV_{VOI}/ SUV_{Liver} returned to baseline levels and the lobes of liver exhibited similar FDG uptake pattern once again.

Conclusions:

1.) The ligation of portal veins proved feasible and reproducible in rat even when affecting high parenchymal volumes. Different degrees of portal vein ligation were followed by an immediate

increase in portal pressure, which accelerated in accordance with the amount of liver volume affected by PVL. The experienced pressure increment revealed a correlation between the concomitant mitotic response and the intensity of growth of the non-ligated lobes. Consequently, our results support the anticipated role of portal hypertension (circulatory alterations) concerning the induction and regulation of liver regeneration.

2.) Although the systemic circulation was not affected by portal vein ligation, considerable alterations were seen in splanchnic hemodynamics. Proximal to the ligation (backward effect) the portal pressure and the shunt circulation significantly increased, while the liver microcirculatory blood flow also changed (forward effect). In contrast to the microcirculatory disorder seen in ligated liver lobes, the blood flow of non-ligated lobes multiplied after PVL. These circulatory changes, however, proved to be transient. Due to the rapid volumetric alterations of liver lobes, the liver adapted to the altered circulatory circumstances, and by the end of the experiment, a new steady-state condition has developed.

3.) The total liver mass remained essentially unchanged after PVL, which can be traced back to the balance of the atrophy of ligated lobes and the hypertrophy of non-ligated lobes. Atrophy of ligated liver lobes was dominantly caused by centrolubolar necro-apoptotic cell death, while in non-ligated liver lobes an increased mitotic activity of hepatocytes was seen. In rats, the above mentioned histological changes reached their peak between the 24^{th} and 48^{th} hour after PVL, meanwhile normal liver morphology would already be recovered by the $120\text{-}168^{th}$ hours. Based on these data, the atrophic-hypertrophic complex induced by PVL seems to be complete within one week in rats. Portal vein ligation caused a significant alteration in liver microstructure as well. The lobules of ligated liver lobes shrunk considerably and the lobular circumference and surface area decreased 0.32 and 0.54 fold, respectively. By contrast, the weight gain of the non-ligated lobes was associated with a 1.52 and 2.35 fold increase in average circumference and surface area of the liver lobules, respectively. Based of this observation,

hypertrophy of the preexisting liver lobules is primarily responsible for the regenerative liver growth after PVL.

4.) According to the routine laboratory parameters, global liver function remained stable after PVL. Nevertheless, the ICG clearance test indicated substantial impairment of total liver function within the first 72 hours after the operation. Based on this, the ICG clearance test indicates the functional state of the liver more reliably, than conventional laboratory blood tests. Portal vein ligation resulted in a significant impairment of excretory function of ligated liver lobes, indicated by bile secretion and ICG excretion. In contrast, in non-ligated liver lobes the biliary ICG excretion was impaired only temporarily, and after the peak of cell division (48^{th} hour) the secretory function of the lobes sharply increased. This observation indicates that liver regeneration is initially promoted at the expense of the liver function. After the peak of cell division, however, an overcompensatory response was manifest in the non-ligated lobes, during which the lobar liver function underwent more dramatic changes as compared with the respective liver weight. Consequently, the functional capacity of the liver shifted towards the regenerating lobes in a greater extent than would have been expected according to the volumetric alterations, resulting in an inhomogeneous functional distribution within the liver.

5.) The volume change, based on MRI volumetry, correlated well with the weight change derived from autopsy. Based on this, the NanoScan MRI seems to be a suitable method to noninvasively asses the rapid volumetric alterations of the liver induced by surgical interventions in small laboratory animals.

6.) Both the atrophic and regenerative processes were characterized by increased FDG uptake. The maximum uptake value of FDG coincides in time with the peak of PVL induced histo-morphological alterations (i.e. necrotic-apoptotic cell death and mitosis). These data may indicate the increased energy demand and subsequently enhanced glucose metabolism of the liver lobes during the PVL induced atrophic and regenerative processes.

List of publications:

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IF: 1,936

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1. Szijártó A*, Fülöp A*, Turóczi Zs, Garbaisz D, Dudás E, Szabó J, Nánási R, Kupcsulik P (2011) Rupturált hasi aorta aneurysma kísérletes modellje. A folyadék reszuszcitácó technikai megfontolása. Aneszteziológia és Intezív Terápia 41(2):61-70.

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