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ORIGINAL ARTICLE

Tissue injury of the remnant liver following radiofrequency-assisted partial hepatectomy

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Summary

Purpose: *To evaluate remnant liver tissue damage in a pig model of radiofrequency (RF)-assisted liver resection employing either the sequential coagulate cut (SCC) Belgrade technique using a monopolar RF electrode or the one using the bipolar Habib-4x device.*

Methods: *Sixteen pigs underwent either a) resection of part of the left lateral and left median hepatic lobes employing the SCC (SCC group), the Habib-4X (H group) or the "crush-clamp" technique (CC group) or b) sham operation (Sham group). Forty-eight hours later, tissue specimens were excised from the right lateral hepatic lobe for histopathological examination and immunohistochemical assessment of tissue injury, mitosis and inflammation.*

Results: *Histopathologic lesions, apoptotic activity, HSP 40 and TNFa expression were more intense, while mitotic activity was less prominent in the SCC group technique compared to H group. Comparison between CC and H groups suggested the pivotal role of partial hepatectomy (PH) per se in the changes noted in H group.*

Conclusion: *The Habib-4X liver resection technique proved to be less injurious in the remnant liver tissue after PH compared to the SCC technique.*

Key words: *liver, liver resection, radiofrequency, tissue injury*

Introduction

Partial hepatectomy (PH) is considered the method of choice for the treatment of primary or metastatic liver tumors. It is also performed in cases of living donor liver transplantation, trauma or benign liver disease. However, transection of the densely vascularized liver parenchyma is a major concern for surgeons due to increased intra-operative bleeding. When traditional techniques of liver resection are applied, such as the "crush-clamp" technique, reduction of haemorrhage is usually achieved by transient occlusion of the portal vein and hepatic artery blood flow, known as Pringle maneuver [1]. Subsequently, the ischemia-reperfusion insult resulting from vascular occlusion has adverse effects on liver histology and hepatocyte regenerating capacity [2]. Impaired liver volumetric and functional restoration poses a high risk of poor post-operative outcome especially in the presence of chronic hepatic disease [3].

During the past few years, technological advances in surgical equipment have enhanced the safety of liver resection procedure by minimizing intra-operative haemorrhage without necessitating the use of Pringle maneuver even for non-anatomic resections. Radiofrequency-assisted liver resection (RFLR) is among the techniques com-

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monly used in liver surgery. The main concept of this technique is based on RF ablation of the hepatic tissue prior to transection. This is accomplished by transition of high frequency (around 500 kHz) alternating electrical current through the hepatic tissue after having inserted a specially designed electrode into the hepatic parenchyma. This causes oscillation of ions of the tissue surrounding the electrode which leads to friction, local rise of temperature and finally to coagulative necrosis of cells [4]. Consequently, transection of the ablated tissue can be achieved with minimum haemorrhage. In the clinical setting, the two most commonly employed RFLR techniques are the SCC Belgrade technique in which a monopolar electrode is used [5] and the one using the bipolar Habib-4X device [6].

According to animal studies, liver radiofrequency ablation (RFA) causes mild tissue injury to the non-ablated hepatic parenchyma [7,8]. Moreover, PH induces inflammation of the remnant hepatic tissue which plays a pivotal role in the "priming phase" of the liver regeneration process [9]. To this end, RFLR, a combination of RFA and resection of liver parenchyma, was evaluated in terms of the effects on remnant hepatic tissue. In the present experimental study, the techniques of SCC and Habib-4X for liver resection were compared on the basis of tissue injury, mitotic activity and inflammatory response of remnant liver tissue in a pig model.

Methods

Animals

Sixteen Landrace pigs, 3-4 months of age, weighing 20-25 kg were used in the study. The animals were housed individually in slatted-floor stainless steel kennels under controlled environmental conditions (22-25oC room temperature, 40-60% relative humidity and 12-hr photoperiod). They were provided with 1 kg of commercially available standard pig pellets (code 21, EL.VI.Z., Xanthi, Greece), twice a day, and tap water *ad libitum*. The facilities were in accordance with P.D. 160/91 which complied with the Directive 86/609/EEC which was the legislation in force at the time of experimentation.

Experimental design

The animals were randomly assigned to 4 groups of 4 pigs each and were subjected either to a) midline laparotomy and resection of part of the left lateral and left median hepatic lobes using the SCC (SCC group), the Habib-4X (H group) or the "crush-clamp" technique (CC group) or b) sham operation (Sham group). Forty-eight hrs post-operation, a hepatic tissue specimen was excised from the right lateral hepatic lobe for histopathologic examination and immunohistochemical evaluation of apoptotic and mitotic activity and the expression of heat shock proteins 40 (HSP40) and 60 (HSP60), interleukin-6 (IL-6), tumor necrosis factor-α (TNFα) and nuclear factor-κB (NFκB). Finally, the animals were euthanized by intra-cardiac injection of KCl under general anesthesia. The experimental protocol was approved by the Animal Care and Use Committee of the local veterinary service since it was in accordance with the requirements set by PD 160/91 which complied with the Directive 86/609/EEC which was the legislation in force at the time of experimentation.

Animal preparation

Animals were deprived of food and water for 24 and 6 hrs, respectively, before induction of general anesthesia by intramuscular injection of a ketamine (33 mg/kg) - xylazine (2 mg/kg) - atropine (0.05 mg/kg) mixture. After endotracheal intubation, they were connected to a anesthesia-mechanical ventilation machine (Avance ®/Datex Ohmeda/Madison, WI, USA). Initial settings of the ventilator (12 breaths per min, 300 mL tidal volume) were adjusted, if needed, to maintain end tidal CO_2 ($ETCO_2$) between 35 and 45 mm Hg as measured automatically in the expired gas. Anesthesia was maintained by administration of sevoflurane (2-3% in oxygen). Animals were placed at dorsal recumbency on a heated-surface operation table. Their back was clipped in order to attach a self-adhesive grounding pad (SCC group). Their abdomen was clipped and disinfected with povidone iodine 10% solution. A lateral aurical vein was catheterized for intravenous fluid administration. A femoral artery was catheterized via the ipsilateral medial saphenus artery for arterial pressure monitoring (S/5 Compact Critical Care Monitor ®/Datex Ohmeda).

Surgical operation

After a 15 cm midline laparotomy was performed subxiphoidally, the left lateral and left median hepatic lobes were recognized and mobilized. Resection of the lobes was performed at 10 cm from their free end applying the SCC (SCC group), Habib-4X (H group) or CC technique (CC group). Hepatic lobes were only mobilized in the sham-operated animals. The abdominal wall was then closed in layers using No 1 polyglactin sutures. Post-operatively, animals were injected intramuscularly with oxytetracycline (Terramycin long acting/Phizer) at a dose of 20 mg/kg.

SCC technique

In order to perform the SCC liver resection technique, a Radionics Cool-tip RF Ablation System ® (Valleylab/Tyco Healthcare/Gosport, UK) was used comprising of a radiofrequency generator of 480 KHz/200 W maximum power, a peristaltic perfusion pump, a return pad and a single shaft, 15 cm long, needle electrode with a 2 cm long exposed tip. The radiofrequency generator was set at manual mode. A transection line was marked prior to resection. The electrode was inserted

into the hepatic parenchyma, parallel and near to the liver surface across the transection line. Alternating electrical current of 50-100 W power was transmitted until ablation of the tissue was achieved. The exposed electrode tip was sequentially positioned into the liver parenchyma under direct vision, several mm in each sequence, without the device switching off. An ablated zone with a 1 cm radius was formed in around 8-10 sec. Large diameter vessels were identified and ligated instead of delivering additional RF energy. Transection of hepatic tissue was performed at the middle of the ablated zone using a single scalpel. The procedure continued in depth down to the exposed tip of the electrode and until transection was complete and then repeated along the transection line until complete resection of the lobe segment was achieved. During ablation, the tip of the electrode was internally cooled by continuous perfusion of ice-cold distilled water delivered by the peristaltic perfusion pump.

Habib-4X technique

In order to perform the Habib-4X technique, a radiofrequency generator 1500X (RITA Medical Systems®, Inc. California, USA) and the Habib-4X bipolar radiofrequency device (HabibTM-4X Open Surgery Bipolar Resection Device ®) were used. The latter comprised of two couples of opposing needle electrodes, 6 cm in length, set at a 2x2 rectangular arrangement. The generator was set at auto mode. A transection line was marked prior to resection. The electrodes of the device were introduced into the hepatic parenchyma perpendicularly to the liver surface. Alternating current of 50-100W power was delivered until ablation of tissue was achieved at a radius approximately 1 cm around each electrode. The procedure was repeated along the transection line until an ablation zone was created. Ablated tissue was then transected across the transection line at the middle of the ablated zone using a single scalpel until resection of the liver segment was achieved.

CC technique

According to the CC technique, the liver parenchyma was transected after tissue had been crushed using Kelly forceps. Blood and bile vessels were then ligated using No 2-0 polyglactin suture. The procedure was repeated across the transection line until resection of the liver segment. Pringle maneuver was not applied during resection.

Calculation of resected liver to total liver parenchyma ratio

The ratio (percentage) of the resected liver parenchyma (ResLP) per total liver parenchyma (TLP) was calculated according to the following equation:

% ResLP = ResLP weight x 100 / TLP weight

where TLP weight = ResLP weight + remnant liver parenchyma (RemLP) weight.

The resected liver lobe segments were weighed immediately after resection to obtain ResLP weight. Remnant liver was excised and weighed at autopsy (48 hrs post-operation) to obtain RemLP weight. Calculations were approximate since remnant liver weight at 48 hrs should be different from that at the time of resection.

Calculation of ablated liver left in situ to total liver parenchyma ratio

The ratio (percentage) of the ablated liver parenchyma (ALP) left *in situ* per remnant liver parenchyma (RemLP) was calculated according to the equation:

% ALP = ALP volume x 100 / RemLP volume

where ALP volume = transection surface of ResLP x depth of ablated rim on remnant liver

The transection surface of the ResLP was measured immediately after resection by taking an imprint of the transection surface on paper; the surface of the imprint was scanned and then measured using a special software (AutoCAD 2013/Autodesk). The depth of the ablated rim left *in situ* on the remnant liver was 10 mm. Weight measurements of RemLP were converted to equivalent volume measurements assuming that liver parenchyma density was 1 g/mL.

Histopathology-immunohistochemistry

Liver tissue specimens were excised from the right lateral lobe, fixed in formalin 10% solution and embedded in paraffin according to standard procedures. Histopathologic examination was performed in 4 μm hematoxylin-eosin stained sections under a Nikon Eclipse® 50i light microscope (Tokyo/Japan). The endpoints evaluated were hyperemia, steatosis, inflammatory infiltration, edema, distention of bile ducts and necrosis. Lesion severity was graded according to the following scoring system: 0, none; 1, mild; 2, moderate; 3, severe. Lesion severity scores were added to obtain the histopathologic score.

Four μm sections of representative blocks from each case were obtained for immunohistochemical assessment. They were deparaffinized, dehydrated and treated with 0.3% H_2O_2 for 5 min in methanol to prevent endogenous peroxidase activity and immunostained using the UltraVision HRP/DAB kit (TP-125-HL/ Thermo Scientific, Waltham, MA, USA) according to the manufacturer's instructions. They were then incubated with the anti-phospho-histone H3 (Ser-10) rabbit polyclonal antibody (Santa Cruz Biotechnology/Dallas, Texas, USA), the HSP40 rabbit polyclonal antibody (Acris Antibodies/San Diego, CA, USA), the HSP60 rabbit polyclonal antibody (Acris Antibodies), the IL-6 rabbit polyclonal antibody (Santa Cruz Biotechnology), the TNFα rabbit polyclonal antibody (Acris Antibodies) or the NFκB mouse monoclonal antibody (Santa Cruz Biotechnology) in 1:500, 1:250, 1:250, 1:500, 1:200 or 1:500 dilution, respectively. Immunohistochemical tissue expression of antibodies was graded in terms of density and extent of the presence of positively stained cells according to the following scoring system: 0, none; 1, mild; 2, moderate and 3, intense.

Apoptotic cells were detected employing the terminal deoxynucleotidyl transferase (Tdt)-mediated deoxyuridine triphosphate biotin nick-end labeling (TUNEL) technique. For this purpose, the Deadend Colorimentric

TUNEL system (G7130, Promega/Madison, WI, USA) was used according to the manufacturer's instructions. Control slides were incubated for the same period with non-immunized rabbit serum (negative controls). Positive controls were also set up during the process. In order to avoid overestimation of apoptosis, positive cells were considered only those that exhibited both morphologic features of apoptosis on light microscopy (cytoplasmic fragmentation and nuclear condensation) and positive TUNEL staining for fragmented DNA. Apoptotic cells were detected at 40X magnification under a light microscope and counted in 10 random optical fields. The total number of apoptotic cells was divided by the number of optical fields to obtain the apoptotic index.

Mitotes count was performed in 10 high power fields (X40) for each section under a light microscope. The total number of mitoses was divided by the number of fields to obtain the mitotic index.

Statistics

Before the beginning of the study, a sample size calculation was performed with a 80% power and α error set at 0.05 (two-sided) [10]. We estimated that a maximum of 4 pigs per group would be required to detect a difference of 0.6 in apoptotic index, 1.2 in HSP expression score and 1.2 in IL-6 expression score with 0.3, 0.6 and 0.6 standard deviations, respectively. Normality of data was tested using the Shapiro-Wilk test. Data that followed normal distribution were subjected to analysis of variance (ANOVA) and multiple comparisons among groups were made using the Least Significance Difference test. Data that followed non-normal distribution were subjected to the Kruskal-Wallis test and comparisons between pairs of groups were made using the Mann-Whitney U test. A $p<0.05$ was considered statistically significant.

Results

All animals survived during the experimental period. The percentage of ResLP per TLP was 20.6 ± 6.2%. The percentage of the ALP left *in situ* per RemLP was 6.9 ± 2.0%.

Histopathologic findings

The histopathologic score was significantly increased in SCC and CC groups, but not in H group, compared to sham operated animals. This was significantly higher in SCC group than that in H group (Table 1). However, this increase was attributed to only mild hyperemia, inflammatory infiltration, oedema and bile ducts distention (Figure 1).

Apoptotic and mitotic activity

Apoptotic activity was significantly increased in all PH groups as compared to sham operated animals. Apoptotic index in SCC group was significantly higher than that in H and CC groups (Figure 2). Mitotic activity was significantly increased in all PH groups as compared to sham operated animals. Mitotic index in SCC group was significantly lower than that in H and CC groups (Figure 2).

Heat shock proteins

The expression of HSP40 was increased in all PH groups compared to sham operated animals. HSP40 expression was intense in SCC and CC

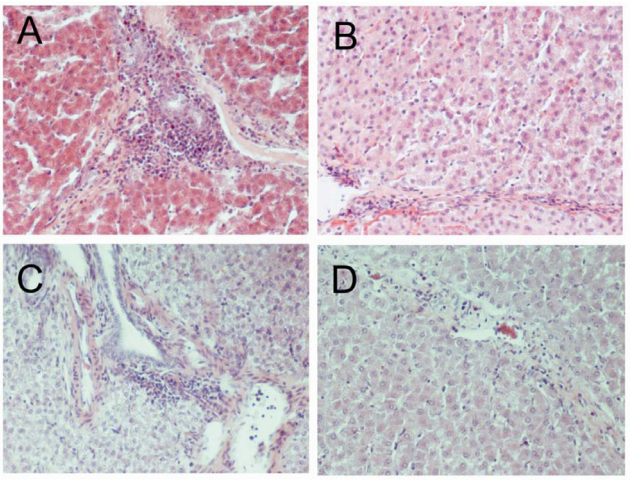

Figure 1. Remnant liver tissue sections after partial hepatectomy employing the "sequential coagulation-cut" **(A)**, Habib-4X **(B)** or "crush-clamp" technique **(C)** or after sham operation **(D)**. Partial hepatectomy groups are characterized by mild hyperemia, inflammatory infiltration, oedema and bile ducts distention. Hematoxylin-eosin staining; magnification x40.

Table 1. Severity degree of histopathologic lesions (mean ± standard deviation, n=4) in remnant liver tissue after partial hepatectomy using the "sequential coagulation-cut" (SCC group), the Habib-4X (H group) or the "crush- clamp" technique (CC group) or after sham operation (Sham group).

Group	*Hyperemia*	*Steatosis*	*Inflammatory infiltration*	*Oedema*	*Bile ducts distention*	*Necrosis*	*Histopathologic score*
SCC	1.0±0.0	0.2±0.4	1.2±0.4	0.8±0.4	1.0±0.0	0.0±0.0	4.1±0.7
H	0.5±0.6	0.0±0.0	0.5±0.6	0.3±0.5	0.3±0.5	0.0±0.0	1.5±1.9
CC	1.3±0.5	0.0±0.0	1.3±0.5	0.8±0.5	1.0±0.0	0.1±0.3	4.4±1.3
Sham	0.6±0.5	0.0±0.0	0.3±0.4	0.0±0.0	0.0±0.0	0.0±0.0	0.9±0.5

Histopathologic score: SCC vs H, p=0.002; SCC vs CC, p=0.686; SCC vs Sham, p<0.001, H vs CC, p=0.002; H vs Sham, p=0.644, CC vs Sham, p<0.001

groups, while moderate in H group. The expression score in H group was lower compared to that in SCC group (Figure 3). The expression of HSP60 was increased in all PH groups compared to sham operated animals but did not differ among those groups. The expression in these groups was moderate (Figure 3).

Inflammatory response

IL-6 tissue expression was increased in all PH groups compared to sham operated animals. The expression was intense in H group and mild in SCC and CC groups. IL-6 expression score in H group was higher than that in SCC group (Figure 4). TNFα tissue expression was increased in all PH groups but did not differ among those groups. Expression was intense in SCC group, while moderate in H and CC groups (Figure 4). Activated NFκB tissue expression increased in all PH groups but did not differ among those groups. The expression was moderate in all PH groups (Figure 4). Resection of hepatic parenchyma *per se* played a pivotal role in the inflammatory response noted in the RF-hepatectomy groups since expression of inflammatory biomarkers in these groups did not differ from that in CC group.

Discussion

Liver regeneration following PH is considered a fundamental prerequisite for functional restoration of the organ and hence for a favorable postoperative outcome [11]. Since this process takes place in the remnant liver tissue, an ideal PH technique should cause minimum liver tissue injury. RFLR techniques combine PH with liver RFA. There is evidence that each separate procedure causes mild tissue injury and inflammatory response to the remnant liver parenchyma [7-9] and therefore one would expect that their combination had similar effects. According to the results of the present comparative experimental study, PH em-

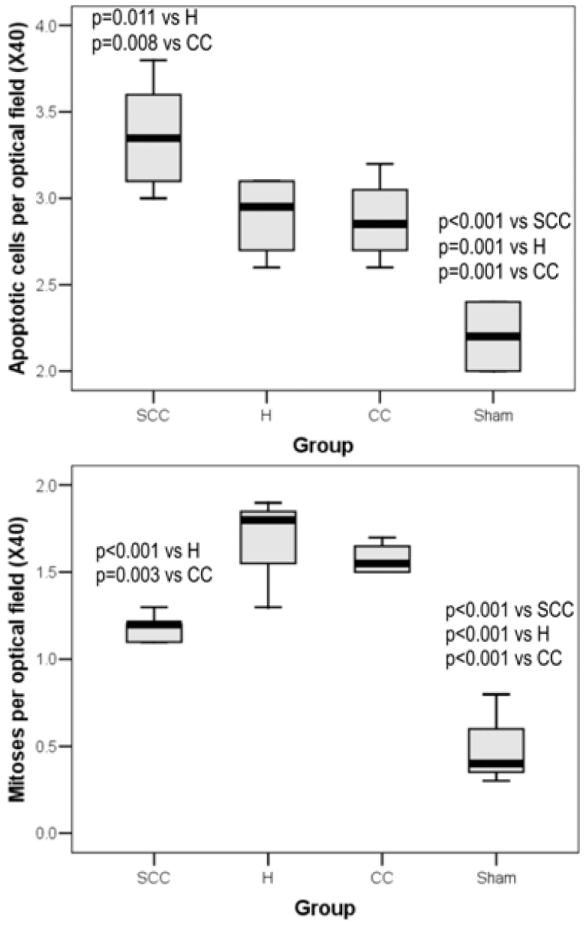

Figure 2. Apoptotic and mitotic indices of remnant liver tissue after partial hepatectomy using the "sequential coagulation-cut" (SCC group), the Habib-4X (H group) or the "crush-clamp" technique (CC group) or after sham operation (Sham group). Horizontal lines denote median values; boxes denote the interquartile range; whiskers denote minimum and maximum values.

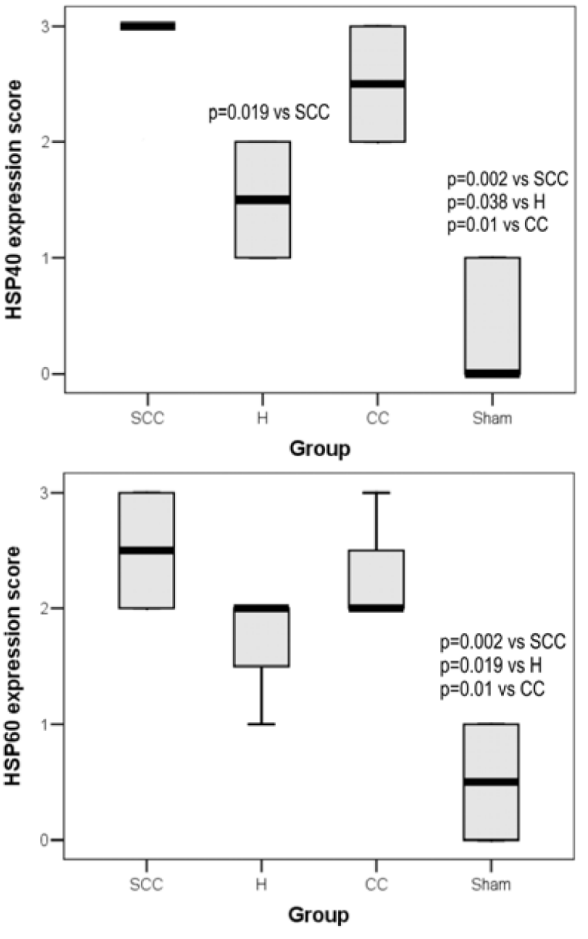

Figure 3. HSP40 and HSP60 tissue expression score in remnant liver tissue after partial hepatectomy using the "sequential coagulation-cut" (SCC group), the Habib-4X (H group) or the "crush-clamp" technique (CC group) or after sham operation (Sham group). Horizontal lines denote median values; boxes denote the interquartile range; whiskers denote minimum and maximum values.

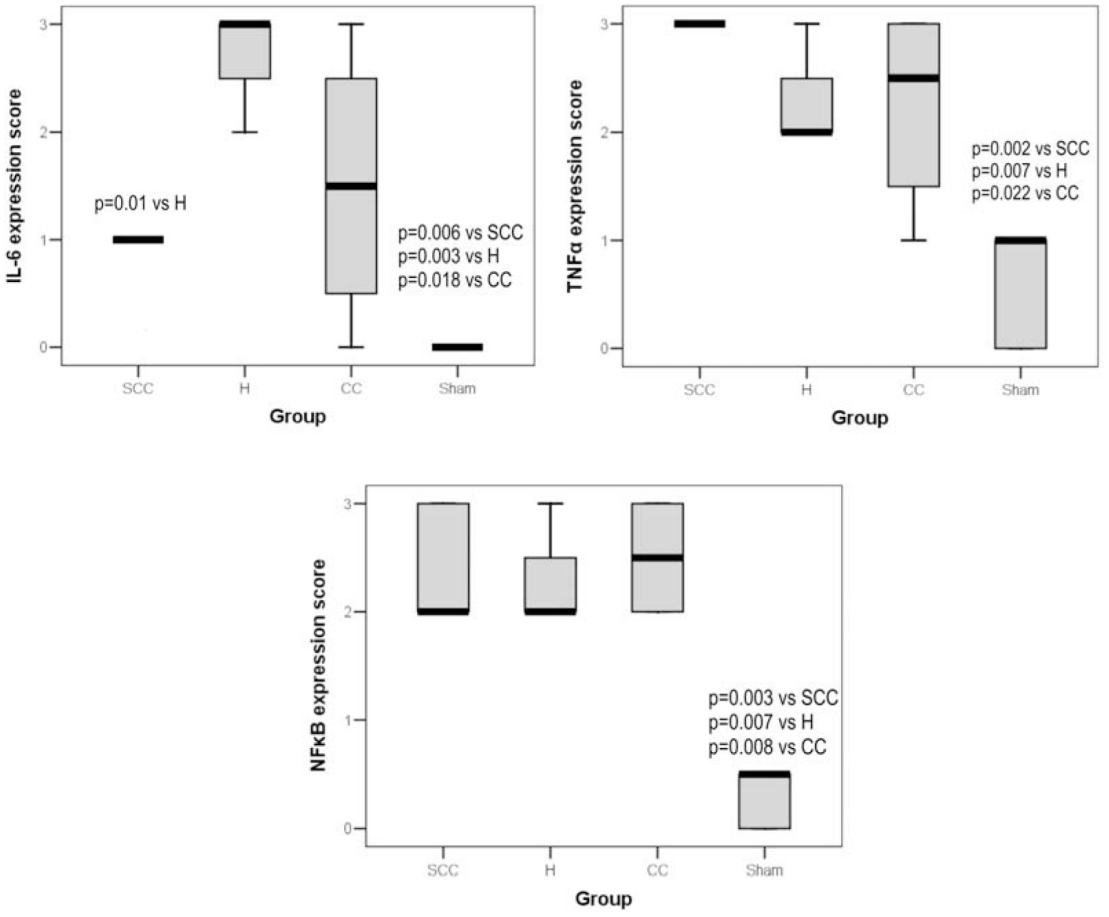

Figure 4. IL-6, TNFα and NFκB tissue expression score in remnant liver tissue after partial hepatectomy using the "sequential coagulation-cut" (SCC group), the Habib-4X (H group) or the "crush-clamp" technique (CC group) or after sham operation (Sham group). Horizontal lines denote median values; boxes denote the interquartile range; whiskers denote minimum and maximum values.

ploying two different RFLR techniques had various impact on remnant liver tissue. Evaluation of the histopathologic profile, HSP expression, apoptotic and mitotic activity, as well as local inflammatory response favored the employment of the Habib-4X over the SCC Belgrade technique.

PH *per se* induces local inflammatory response in the remnant liver tissue as an integral part of the priming phase of the liver regeneration process which corresponds to the passage of quiescent hepatocytes into the cell cycle (G_0 to G_1). A cytokine network is initiated through binding of TNF to its type 1 receptors in Kupffer cells leading to activation of NFκB in non-parenchymal cells, production of IL-6 and activation of signal transducer and activator of transcription 3 (STAT3) in hepatocytes [9].

RF-assisted PH resembles liver RFA in that a) radiofrequency energy is transmitted to the liver parenchyma to be transected and b) an ablated tissue rim is left *in situ* in order to facilitate hemostasis of the transection surface. According to an experimental study, RFA of 18% of total liver mass in rabbits using a monopolar RFA device conferred tissue injury in the non-ablated liver parenchyma [7]. Histopathologic lesions at 48 hrs post-ablation included portal infiltration, hyperemia of sinusoidal space, oedema and haemorrhage of moderate severity, while only mild steatosis, cholangitis and necrosis [7,8]. In the present pig model, liver resection involved almost 20% of total liver mass, while the ablated tissue rim left *in situ* corresponded to approximately 7% of remnant liver mass. Histopathologic examination of the remnant liver tissue at 48 hrs post PH employing the SCC technique revealed lesions of only mild severity which included hyperemia, infliltration of inflammatory cells, oedema and distention of bile ducts, while there were no lesions after application of the Habib-4X technique.

Tissue damage was further documented by assessing the expression of HSPs 40 and 60. Heat shock proteins are a family of proteins produced from cells in response to stressful stimulants, such as ischemia, heat, oxidative stress, pH change, toxins, infection and inflammation in order to protect cells [12]. HSPs 40 and 60 have been shown to act as molecular chaperone proteins maintaining the

integrity of cellular proteins when exposed to environmental changes. In the present study, PH induced overexpression of HSPs with HSP40 upregulation being more prominent in the SCC group. HSP40 acts primarily by stimulating the ATPase activity of HSP70 [13].

A local inflammatory response was evoked in the remnant liver tissue after application of either RFLR technique, as demonstrated by upregulation of activated NFκB and pro-inflammatory cytokines IL-6 and TNFα. It has to be mentioned though that IL-6, besides regulating inflammation by inducing production of acute phase proteins in the liver [14], also exerts anti-inflammatory, anti-apoptotic and hepatocyte survival properties [9,15]; it has been shown to be hepatoprotective in a rodent model of liver ischemia-perfusion via downregulation of TNFα production [15]. Taken these data together, one could justify the less pronounced apoptotic activity noted in the Habib-4X group which was combined with an intense IL-6 tissue expression and a moderate upregulation of TNFα. On the other hand, expression of IL-6 in the SCC group was mild, while that of TNFα intense. Differences in inflammatory response were also reflected on hepatocyte mitotic activity which was less prominent in the SCC group at 48 hrs post-PH. Nevertheless, we believe that a study conducted at a longer follow-up period involving serial assessments of hepatocyte mitotic activity and residual liver volume would provide more solid evidence on the liver regeneration process.

In order to clarify the contribution of PH *per se* on the changes noted, a separate group of animals was subjected to liver resection of equivalent parenchymal volume employing the "crush-clamp" technique which does not require the use of external energy. For reasons of comparison, Pringle maneuver was not applied during resection. Comparison with the findings of the Habib-4X group underscored the pivotal role of PH *per se* on the changes noted, downgrading the significance of RF energy-induced effects after application of this technique. Interestingly, histopathologic lesions and HSP40 expression were more intense in the "crush-clamp" group compared to the Habib-4X group. This could be attributed to the fact that avoidance of temporary vascular occlusion increased intra-operative haemorrhage which may have aggravated tissue damage [16].

Differences on the impact of RFLR techniques on liver tissue pathology highlighted safety issues associated with the use of monopolar versus bipolar electrodes in electrosurgical tissue coagulation. In the Habib-4X technique, the path of the electrical current is confined mainly to the tissue included between the opposing electrodes of the bipolar device. On the other hand, in the SCC technique, in which a monopolar electrode is used, current passes from the electrode to the tissue and through the patient to the return pad to complete the electrical current circuit. Since the entire body of the patient is in the circuit, current diverses to other parts of the body as well, besides the target tissue to be coagulated. Uncontrollable diffusion of electrical current poses a risk of damaging adjacent tissues when using monopolar electrosurgical devices due to capacitive coupling, a phenomenon that refers to establishment of electrical current in tissues not directly in contact with the active electrode [17].

The present experimental study compared two contemporary RFLR techniques in terms of remnant liver tissue damage. It provided sufficient evidence that the Habib-4X technique is less tissue-injurious on the residual liver parenchyma compared to the SCC Belgrade technique. This effect was associated with the type of electrode (bipolar versus monopolar) used for electrosurgical tissue coagulation prior to transection. One, however, must not oversee the significant merits of the SCC technique, which include energy saving manipulations due to the versatile use of the electrode under direct vision, efficient control of intra-operative bleeding even for non-anatomical liver resections, simplified surgical manipulations, tissue-sparing resections, as well as short operating and ICU time [5]. Yet, the surgeon would be more confident when using energy-based devices if collateral damage of adjacent tissues was avoided. Advanved technology instruments interfaced with electrosurgical units, such as the active electrode monitoring system, may address safety issues related to the use of monopolar electrodes in electrosurgery, by continuously monitoring and shielding against the occurrence of stray electrical currents [17,18]. Furthermore, additional studies are required to determine the potential adverse effects of RFLR techniques on tissues of adjacent as well as remote organs.

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Conflict of interests

The authors declare no confict of interests.

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