NEW MINIMAL INVASIVE THERAPEUTIC OPTIONS IN THE MANAGEMENT OF ACUTE AND RECURRENT ESOPHAGUS VARICEAL BLEEDING

PhD Thesis

By

László Benkő MD

Head of the Doctoral School: Judit Nagy MD, DSc

Supervisor: Elizabeth Rőth MD, DSc

Consultants:Elizabeth Rőth MD, DSc, Jan Danis MD, PhD, Dénes Lőrinczy DHabil, DSc

University of Pécs, Department of Surgical Research and Techniques

Hungary

Pécs

2007

I. INTRODUCTION

Portal hypertension is the most life-threatening complication of liver cirrhosis. The portal gradient exceeding 16 mm of mercury results in portosystemic collaterals. The esophageal varices present most important collaterals between portal and systemic blood circulation. Unfortunately, their tendency to rupture significantly increases the mortality rate for liver cirrhosis patients. The incidence of esophageal varices varies depending on the liver cirrhosis stage, from 40% for Child A to 85 % for C (average, 50%). A bleeding event occurs in 10% to 30% of patients within 1 year, with 40% of bleeding recurrences happening within the 6 weeks. Mortality from bleeding varicose veins increases up to 30% depending on the liver insufficiency. After acute treatment of the bleeding, the aim of the therapy is to prevent a subsequent bleeding event. Surgical treatment of portal hypertension was introduced by Whipple in 1945, with the performance of the first Pavlov-Eck fistula for a human. In the 1970s, azygoportal disconnection became popular. However, this procedure was associated with high mortality rate. In the past 10 years, the surgical procedures increasingly lost their significance due to widespread use of sclerotherapy or banding and the introduction of nonoperative interventional procedures such as TIPS. The TIPS implantation is accompanied with low procedural mortality. However, encephalopathy after the procedure seems to be a major problem. Moreover, the failure rate of TIPS is a high as 77% in the first year after implantation .

II. AIMS AND HYPOTHESIS

1. At first the aim of the study was to prove the suitability of venous closure by means of bipolar feedback thermal vessel sealing “in vitro” and on porcine model, and to show the feasibility of a new, minimally invasive procedure - the laparoscopic azygoportal disconnection – for treating artificially created portal hypertension on a new animal model.

   Further, the aim was to show the feasibility of the azygoportal disconnection operation using a bipolar feedback controlled sealing, the LigaSure Atlas Sealing System® in the human clinical practice.
2. The aim of the second part of this study was to show the safety and usefullness of a new self-expandable metal stent designed for the acute therapy of variceal bleeding and to compare the reaction of the esophageal wall on the new stent with the stent used for benign or malignant stenosis of the esophagus.

Finally we examined the effectiveness of this special stent in case of emergency in patients whose bleedings could not be managed by use of intensive medical treatment and endoscopy.

III. LAPAROSCOPIC DEVASCULARIZATION OF THE STOMACH AND THE DISTAL ESOPHAGUS WITH A BIPOLAR FEEDBACK CONROLLED SEALING SYSTEM IN A PORCINE MODEL

The azygo-portal devascularization methods, developed first by Sugiura in the 1960s, were accompanied with high perioperative mortality. Nevertheless, surviving patients revealed reduction of the encephalopathy as well as diminished rebleeding rates. Moreover, encephalopathy becomes less pronounced after the disconnection of azygoportal collaterals. The laparoscopic approach is less invasive, causing a significantly minor intra-operative trauma despite being safe with respect to venous closure and as well as in avoiding the intra- or post-operative bleeding.

III/1. Animals and methods

Twenty landrace pigs, mean weight 31.95 kg, range 28 to 35 kg, were used in the study in two groups. The initial surgery was performed to establish a portal hypertension. Fourteen days after the first intervention, all pigs underwent laparoscopic azygoportal disconnection. In the first group (n=6) additional punction the portal vein was performed and the portal pressure was measured simultaneously with the intrasplenic pressure record. The animals of the second group (n=14) were undergone the same procedure without pressure measurements. The surviving animals were sacrificed 4 weeks after the initial surgery and an autopsy was performed.

Surgical procedure I. (establishing the portal hypertension): The pneumoperitoneum was established with the Veres needle (CO_2 gas, 8 mmHg), and the first 10 mm trocar for the camera (10 mm, 30° Optic, Storz, Tuttlingen, Germany) was introduced through the umbilicus. The second (10 mm) and the third trocars were placed sub-costal and in the hypogastrium, both left for the insertion of the Clip applicator (Endoclip II, Tyco/Healthcare) and of the device for measurement of the portal vein pressure, respectively. Finally, a 5 mm trocar was positioned in the right hypogastrium. The spleen was punctured in all operated pigs transcutaneously and the intrasplenic pressure was recorded. To prove correlation between portal and intrasplenic pressure, the additional puncture of the portal vein close to the hepatic hilus, was performed in six of 20 animals. The portal vein pressure was recorded simultaneously. On a subgroup of six pigs, additional puncture of the portal vein was performed and the portal pressure was measured simultaneously with the intrasplenic pressure recorded. To establish the hypertension, the portal vein was carefully dissected and a clip was positioned at a right angle to its

longitudinal axis to achieve narrowing of the lumen. The clip was adjusted until the expected intrasplenic pressure>16 mmHg was achieved.

Surgical procedure II. (devascularization): Two weeks later, the pigs were reoperated laparoscopically using the same trocar sites beginning with the measurement of the intrasplenic portal pressure. The abdominal cavity was inspected for dilated collateral veins. The left gastric artery stem was separated from the veins intended for disconnection with a dissector before these were sealed and transsected by the use of LigaSure-ATLAS instrument. The veins of the lesser omentum were completely divided. The branches of the gastric coronary vein and the dilated esophageal veins were also dissected and separated. The procedure was continued by disconnection of the short gastro-splenic veins at the greater curvature site of the stomach. Finally, the esophagus was dissected 3 to 4 cm transhiatal. After the procedure was completed, the intrasplenic pressure was measured again by puncture of the spleen. An autopsy was performed 2 weeks after the second surgery.

III/2. Results

The experiment could be completed in all but four animals: two pigs died during the introduction of the first anesthesia. The third one died because of decreasing the pneumoperitoneum too fast by opening all gas outlets at the trocars at the same time. The fourth animal died after the second operation because of a necrosis and perforation of the gastric and esophageal wall on the second post-operative day after the second operation.

First Group (Model, 6 Pigs): The mean operation time was 23 min (range 14–33). Five pigs survived the first and the second procedure without any intra- or post-operative complication. The portal vein pressure increased as expected and the intrasplenic pressure rose in parallel. Autopsy showed correctly placed clips with partial occlusion of the portal vein without portal vein thrombosis in all pigs

Second Group (14 Pigs): The mean operation time was 30.2 min (range 17–60). There were 12 pigs that survived the first and 11 the second operation without any complication. Two pigs died during the introduction of anesthesia; one pig died immediately post-operatively because of a cardiac arrest because of decreasing the pneumoperitoneum too fast. There was no intra- or post-operative bleeding during all operations; all veins could be dissected and sealed by means of the LigaSure-ATLAS device safely.

All pigs developed dilated collateral veins along the smaller and greater curvature up to 3 to 4 mm in diameter as an indicator for the portal hypertension. At autopsy we found in all pigs a well clipped portal vein and histological a fine sealing zone of the veins. In summary of the results, 17 pigs out of 20 could be evaluated for the procedure, 16 developed hypertensive collaterals and survived the disconnection operation.

IV. LAPAROSCOPIC AZYGO-PORTAL DISCONNECTION PROCEDURE WITH A BIPOLAR FEEDBACK CONROLLED SEALING SYSTEM IN HUMAN

Safety and efficiency in the experimental model had encouraged us to applicate this method on five patients with bleeding esophagus varices. Laparoscopy was performed after all other procedures either failed to prevent recurrent bleeding or were refused by the patient.

IV/1. Patients and methods

Five men, ages 41 to 64 years, were admitted to the hospital (General Hospital Linz, Austria) with repeated variceal bleeding (2nd to 11th event) and liver cirrhosis stage Child-Pugh B and C in two patients, respectively. The liver damage was caused by chronic alcohol consumptions. The remaining patient had myeloproliferative syndrome with prehepatic portal hypertension, which was treated originally by means of a Linton shunt. One patient had undergone the TIPS procedure 27 months before admission. For the next patient, the TIPS had failed to create a shunt, and the remaining two patients refused the portocaval shunting.

After blood, saline, glucose, amino acid substitution hepatoprotective therapy, and the like liver function was conditioned to the Child-Pugh stage A in one and B in two patients. In one patient with stage C with permanent ascites, the liver function remained unaffected by the therapy. In all five patients, endoscopy, abdominal ultrasound B scan, color Doppler were performed, and in the three patients, CT scan, X-ray and angiography were performed to evaluate the collaterals. Laparoscopic azygoportal disconnection was performed after all other procedures either failed to prevent recurrent bleeding or were refused by the patient.

Surgical procedure: Five ports were positioned on the upper abdominal wall. After the camera was introduced, the veins in the lesser omentum were divided using the vessel sealing equipment (LigaSure-Atlas 10-mm sealing-cutting device) in all patients. The stomach coronary vein was visualized, and all proximal branches toward the esophagus, and the short gastric vessels of the gastrosplenic ligament were divided by the LigaSure-Atlas device. The diaphragm hiatus was opened, and the distal 10 cm of the esophagus was dissected through the hiatus. The paraesophageal venous collaterals were divided, and the remaining esophageal varices were occluded with transmural stitches positioned in four to five levels of the distal, exposed esophagus. In one patient with stomach fundus varicosis, a fatty pad of cardia was removed. The surgery was completed in all five patients with a hiatus reconstruction and fundoplication according to the Toupet technique. The drains were positioned in the mediastinum, the subhepatic and subphrenic spaces and removed after ascites production ceased (2-14 days after surgery).

IV/2. Results

All the patients survived the surgery. The mean duration of the procedure was 115 min on average (range, 85-230 min.). One port-site bleeding was occurred 6 hours after surgery and this bleeding required laparoscopic revision and a port access resuture. The postoperative intermediate care unit stay was 8 hours for all but one patient, who remained for 24 hours. Oral fluid intake was started 24 h after the surgery. The total mean hospital stay was 17.6 days (range, 11-36 days). One patient died 9 months postoperatively because of chronic alcohol intoxication.

During a postoperative follow-up period of 9 to 30 months, no esophagus variceal bleeding was recorded. One gastric mucous bleeding episode was noted in a patient with portal hypertensive gastropathy, which required a blood transfusion 9 months after surgery. In this patient alcohol consumption resulted in liver insufficiency (Child C accompanied with irreversible ascites) 15 months after the operation. The patient refused a liver transplantation and died 16 months after surgery. For all but one patient, complet remission of the esophagus varices was recorded. In the remaining patient, with varices stage 4 according to Paquet, stage 2 of the varices was achieved postoperatively. The remaining varices were banded 8 months postoperatively during endoscopic surveillance. In the next two patients also a stomach fundus varices was eliminated completely by proximal devascularization of the stomach.

V. EXAMINATION OF THE ESOPHAGUS AFTER IMPLANTATION OF TWO DIFFERENT SELF-EXPANDABLE STENTS IN ANIMAL EXPERIMENT

Variceal bleeding is now more commonly treated pharmacologically and/or via endoscopes with sclerotherapy, or band ligation. In some cases bleeding cannot be stopped despite combination of endoscopic and drug therapy, especially in patients after several procedures of sclerotherapy or band ligation leading to sclerosis of the mucosa. The inflatable balloons still have a place however, even if it is simply used to save time in preparation for more definitive treatment, or in case of persistent and recurrent bleeding despite of previous drug therapy and of course in case of immediate primary acute haemorrhage. This method can cause the pressure necrosis of the esophagus, after 48-72 hours. Patients usually should be intubated and ventilated mechanically to prevent pulmonary infection or aspiration.

Consequently, no effective method of treatment is available until now, which would guarantee high grade of patient wellness during the conditioning and investigation phase until the definitive treatment could be introduced. Therefore we searched an alternative method to compress the bleeding varices. The placement of self-expanding metal stents for palliation of

malignant esophagus strictures and esophago-tracheal fistulas are effective and safe. The fact that we haven't found any report in the literature about SEMS application in acute variceal bleeding had encouraged us to use stents usually used for esophageal malignancy in an emergency situation of varix bleeding instead of balloon tampon at the ambulance and furthermore develop a special stent for this individual indication.

V/1. Animals and methods

Design of the stents and the delivery systems: The new self expandable, covered metal stent (stent-1) with the introducer set was designed to be an effective and learnable method in the treatment of the acute phase of esophageal varix bleeding until the definitive therapy could be introduced. Stent SX-Ella-Danis (ELLA-CS Company, Hradec Kralove, Czech Republic) is a nitinol (nickel-titanium) monofilament woven wire mesh stent with flared ends preventing of the migration, and a polyurethane inner coating layer. The stent has a length of 105 mm, a body diameter of 21 mm, and a diameter of flare ends of 28 mm. The midstent (body of the stent) and the two ends have Pt/Ir radiopaque markers, to keep visible on the x-ray examination after the successful implantation or in fortuitous case of migration. Movable stainless steel wires with Au marker were placed on the two ends ensuring the possibility of position correcting or make easier removing after the management. The SX-Ella-Danis stent has a special delivery system with active length of 60 cm, and body diameter of 22 French, that allows a placement without radioscopy or even endoscopic control.

The other full-covered self-expandable stent (stent-2) is the FerX-Ella-Boubela (ELLA-CS Company, Hradec Kralove, Czech Republic) esophageal stent (diameter 21 mm, length 105 mm), designed primary for the iatrogenic treatment of malignant strictures in the esophagus. This stent is made of stainless steel that has a great corrosion resistance and good radiopacity, which is increased by radiopaque golden markers. The covering of the stent is made of polyethylene. Delivery system of this stent is equipped with an inflatable balloon for the easier positioning.

The experiment was carried out in two groups. In the first group (stent-1), the new self-expandable stents (SX-Ella-Danis) were introduced into the distal esophagus of seven mongrel dogs. After the correct positioning of the stent with an inflated balloon at the distal end of the introduction set, the stent was released by pulling the sheath back. Delivery system was removed after the procedure. In the second group (stent-2) seven mongrel dogs were undergone the same procedure, using the FerX-Ella-Boubela stent. After the successful stenting the correct position of the stents was identified with gastroscope and x-ray examination in both groups. Tissue oxygen saturation of the esophagus was monitored with the Inspectra Tissue Spectrometer and the StO_2 data were recorded before the intervention and after the procedure at the proximal end, and the middle part of both stented esophagus segments in all animals. A watery consumption food diet was administered from the first postoperative day to reduce the risk of early stent migration. 10 days after the procedure the

esophagus was inspected for mucosal injury due to the local pressure of the stent, and the possible necrosis of the esophagus wall. Histological examinations and DSC measurements of the esophagus walls were performed.

V/2. Results

The stents could be easily inserted with the special introducer in all cases. There was no bleeding or perforation by the introduction of the stents. Correct position of the stents was observed on x-ray examinations after successful implantation in all animals. Stents were well tolerated based on watery food consumption from the second post operation day and normal behaviour in both group. We observed stent migration into the stomach in one case of each group. This caused no perforation or mechanical ileus and removing could be performed by endoscopes without any complication. The stents in the other dogs have been found in the correct position without serious macroscopical esophageal injury.

Macroscopic examination of the esophagus in the group stent-1 showed wall thickening and a touch of inflammation at the sites where the free metallic wire ends clung into the mucosa. Wall thickening was observed alongside the stent in the group stent-2 without any sign of inflammation.

Microscopic examination of the distal esophagus was performed in all cases. At dogs from group stent-1 without stent migration, injuries were limited to the region of the uncovered metal skirts. Examination of the areas in contact with the covered middle part of the stent showed focal erosion of the mucosa exempt from inflammatory reactions. Samples from the group stent-2 with correct stent position, showed more explicit focal erosion of the esophagus wall alongside where the stents were situated.

StO2 data were showed significant ($p<0,05$) decrease in the group stent-2 in correlation with in the group stent-1 both examined oesophagus segment.

According to the denaturing experiments the surgical interventions result in a significant alteration both in the course of DSC scans, as well as in their thermal parameters compared to the healthy control. Using the stent-1 the final results are closer to the healthy control, but its all sample exhibit more stable thermal data (greater calorimetric enthalpy and higher melting temperature) as the control or stent-2. In case of stent-2 all the total calorimetric enthalpy data are smaller than that of the same control or stent-1 parameters (we did not separated the two melting processes because their structural background is yet not known).

VI. PRELIMINARY CLINICAL EXPERIENCE WITH THE NEW STENT IN THE MANAGEMENT OF ACUTE ESOPHAGEAL VARICEAL BLEEDING

Safety and efficiency in the experimental model had encouraged us to applicate this method successfully on 20 patients with bleeding esophagus varices.

VI/1. Patients and Methods

Between November 2002 and May 2005, some 11900 gastroscopies were carried out at Linz General Hospital. During this period, a total of 143 patients with variceal bleeding were treated. Pharmacological and endoscopic therapy did not provide adequate control of bleeding in 15 of the patients, and a SEMS was therefore inserted instead of using a balloon tamponade in these cases. In addition, five other patients with uncontrollable variceal hemorrhage were transferred from other hospitals; balloon tamponade treatment with Sengstaken-Blakemore tubes had been carried out in three of them. After the tamponade was withdrawn and ongoing bleeding was verified on endoscopy, a stent was introduced immediately. The other two patients were referred by a local endoscopy team and SEMS stents were implanted instead of a balloon tamponade to stop the bleeding. A total of 20 patients (18 men and 2 women) underwent SEMS placement to stop variceal haemorrhage.

All 20 patients had experienced several previous bleeding episodes despite previous endoscopic interventions. Previous treatments included band ligation, sclerotherapy, and balloon tamponade. The patients' mean age was 52 (range 27-87). Bleeding was caused by liver cirrhosis due to alcoholism, immunological or cryptogenic cirrhosis, or by gastric ulcer combined with bleeding esophageal varices. The Child-Pugh classification was B in eight of the patients and C in 12.

Stent implantation: The stents were inserted to treat acute ongoing beeding as follows. When sedation was necessary, intravenous midazolam was used, with flumazenil as an adjunct to reverse benzodiazepine-induced sedation. Three SEMS were inserted under intubation; 17 patients came to the endoscopic unit rapidly, allowing accurate treatment maximum 3 h after the first signs of bleeding. The first five stents were introduced using a guide wire with radiographic assistance to ensure correct placement of the stent across the gastroesophageal junction. Choo stents (diameter 18 mm, length 140mm) were used twice, Ella-Boubela stents (diameter 20mm, length 95 mm) three times. A new, special type of stent, the SX-Ella-Danis (diameter 25mm, length 135), especially developed for the treatment of acute variceal bleeding, were used in the 15 subsequent patients. The stents were inserted using special introducers that allow placement of the stent without radiographic or even endoscopic control. Esophagogastroscopy was carried out after stent implantation, and chest radiography was done up to 12 h later to verify correct positioning of the sent. Vasoactive drug therapy with somatostatin was discounted 12 h after stent placement.

VI/2. Results

Stent placement was successful and uncomplicated in all 20 patients, and the hemorrhage stopped immediately after implantation of the stent. One patient had bleeding from two sites, esophageal and gastric. The gastric site was identified after the esophageal variceal bleeding had been stopped by the implanted stent. This patient underwent total gastrectomy and an open azygo-portal disconnection as a final treatment.

In the remaining 19 patients, circulation stabilized within 2h. No recurrence of the bleeding from the esophagus or stomach during esophageal stenting. No local complications, such as aggravation of bleeding, perforation, or fistulization resulted from introduction of the stent. Stent igration to the stomach was observed in five patients (one of the two patients with Choo stents, two of the three patients with Ella-Boubela stents, and two of the 15 patients with Ella-Danis stents). The shift to the stomach was caused by a very low stent position. Stent dislocation was not accompanied by recurrent bleeding, and reposition was carried out easily with endoscopy in such cases.

In most of the patients (n=14), the stents remained in the esophagus for 5-7 days (range 2-14 days in the 20 patients). During this time, further diagnostic steps to optimize the management of the patients' illness and portal hypertension, such as laboratory tests, contrast-enhanced computed tomography of the abdomen, and magnetic imaging splenoportography scans, were undertaken. Accelerated diagnosis and rapid administration of secondary prophylaxis reduced the stenting period.

One patient had variceal bleeding following aortocoronary bypass surgery. Because of cardiac instability, the stent was left in the esophagus for 14 days. The postoperative recovery was uneventful, and the patient was discharged 24 days after surgery.

All of the stents were extracted using standard endoscopy and a foreign-body extractor to grasp the proximal loop of the stent, thus elongating and narrowing its skeleton. Stent removal was performed easily and without any complications. Only a slight impression can be seen after the extraction. One patient was found to have a small ulceration in the distal esophagus after the stent had been in position for 6 days. None of the other patients had any complications caused by stent or its removal, such as injury, or other throat problems. No recurrent bleeding or any other bleeding event was observed during the subsequent 30 days.
Despite arrest of hemorrhage, two of the patients died 3 and 5 days after stent placement, due to hepatic and multiple organ failure caused by the primary disease. The first patient (an 87-year-old woman with Child-Pugh grade C alcoholic cirrhosis) was transferred to our hospital with ongoing bleeding and an esophageal rupture caused by a Sengstaken tube used before the

stent procedure. SEMS stopped the bleeding, covered the ruptured esophagus, and prevented mediastinitis; death was caused by hepatic failure. Another patient (a 48-year-old man) died of hepatic failure. Neither of these two patients had recurrent bleeding from varices.

After the stent extraction, the remaining 18 patients underwent further treatment, with a high proportion of interventional and surgical therapy being necessary due to previous treatments for recurrent bleeding. For subsequent treatment of these patents, the main procedure used was TIPS insertion (n=5), endoscopic or interventional procedures (n=4), a radiographic interventional procedure (n=1), and embolotherapy with sclerosing agents in combination with coils, without further intervention (n=4). Three patients were placed on a liver transplantation list and treated with interventional and endoscopic methods.

VII. NOVEL FINDINGS

1. We could create a new, laparoscopic model of porcine portal hypertension by means of pre-hepatic block resulting from well-dosed clipping of the portal vein.

   The measurement of intrasplenic pressure is a feasible method for repeated monitoring of the portal hypertension.

   Laparoscopic approach and sealing of the venous collaterals by means of bipolar feedback controlled sealing system – LigaSure-ATLAS instrument – presents a safe and minimally invasive experimental method of laparoscopic azygoportal disconnection on the porcine model of portal hypertension.

   The novel laparoscopic azygoportal disconnection seems to be a reliable, less detrimental method for prevention of rebleeding from esophagus varices in human.
2. The new self-expandable stent is a safe and suitable solution without deterioration of the esophageal wall if the stent size is comparable with the oesophagus dimension of the experimental animal.

   Stent placement for variceal bleeding is an innovative technique which was found to be a safe and effective treatment for massive bleeding from esophageal varices in patients with liver cirrhosis.

VIII. ACKNOWLEDGEMENT

I would like to take this opportunity to thank for the overhelming support I have received from my supervisor Professor Elizabeth Rőth in completing this work. Her guidance and leadership has been a blessing.

I am also very thankful to Dr. Jan Danis, a good friend of mine, who has sent me on the way of surgical practice. Without his constructive ideas and advices this work would never have been born.

I would also like to acknowledge the help and assistance of all the staff at the Department of Surgical Research and Techniques in Pécs, without whom I would have been lost.

Special thanks to Professor Dénes Lőrinczy of the Institute of Biophysics for his valuable contribution to my work.

XI. PRESENTATIONS AND PUBLICATIONS

Publications releated to the thesis

1. Hubmann R, Bodlaj G, Czompo M, **Benkő L**, Pichler P, Al-Kathib S, Kiblbock P, Shamyieh A, Biesenbach G. The use of self-expanding metal stents to treat acute esophageal variceal bleeding.
   Endoscopy 2006; 38(9): 896-901. IF: 4,072

2. **Benkő L**, Danis J, Shamiyeh A, Czompo M, Gasz B, Ferencz A, Rőth E. A gyomor és az abdominális nyelőcsőszakasz laparoszkópos devaszkularizációja LigaSure® eszközzel sertés modellen
   Magy Seb. 2006; 59: 45-49.

3. **Benkő L**, Danis J, Czompo M, Hubmann R, Ferencz A, Jancsó G, Szántó Z, Zolyomi A, Könczöl F, Bellyei Á, Rőth E, Lőrinczy D. Differential scanning calorimetric examination of the oesophagus after two different self-expandable stents implantation. An experimental study.
   J Therm Anal Cal. 2006; 83(3): 715-720. IF: 1,648

4. Shamiyeh A, Hubmann R, **Benkő L**, Vattay P, Röth E, Tulipan L, Wayand WU, Danis J. Laparoscopic azygoportal disconnection procedure with a bipolar feedback controlled sealing system in a porcine model.
   J Surg Res. 2005; 130: 8-12. IF: 1,735

5. Hubmann R, Czompo M, **Benkő L**, Pichler P, Al-Kathib S, Kiblböck P, Shamiyeh A, Danis J. Use of esophageal stent – first experiences in treatment of bleeding varices „Pouzitie ezofágového stentu – Prvé skúsenosti v liecbe krvácajúcich varixov pazeráka"
   Provodná Práca, Lek Obz 2004; 53(12): 458-461.

Publications not releated to the thesis

1. Jancsó G, Cserepes B, Gasz B, **Benkő L**, Borsiczky B, Ferencz A, Kürthy M, Rácz B, Lantos J, Gál J, Arató E, Sinay L, Wéber Gy, Rőth E. Expression and protective role of heme oxigenase-1 in delayedmyocardial preconditioning.
   Ann NY Acad Sci. 2007; 1095: 251-261. IF: 1,789

2. Shamiyeh A, Danis J, **Benkő L**, Vattay P, Rőth E, Tulipan L, Shebl O, Wayand W. Effect of hyaluron derivate gel in prevention of postsurgical peritoneal adhesions-an

experimental study in pigs.
Hepatogastroenterology 2007; 54(76):1121-1124. IF: 0,756

3. Cserepes B, Jancso G, Gasz B, Rácz B, Ferencz A, **Benkő L**, Borsiczky B, Kürthy M, Ferencz S, Lantos J, Gál J, Arató E, Miseta A, Wéber G, Rőth E. Cardioprotective action of urocortin in early pre- and postconditioning.
Ann NY Acad Sci. 2007; 1095: 228-239. IF: 1,789

4. Gasz B, Lenárd L, Rácz B, **Benkő L**, Borsiczky B, Cserepes B, Gál J, Jancsó G, Lantos J, Ghosh S, Szabados S, Papp L, Alotti N, Roth E. Effect of cardiopulmonary bypass on cytokine network and myocardial cytokine production.
Clin Cardiol 2006; 29(7): 311-315.

5. Ferencz A, Rácz B, Gasz B, **Benkő L**, Jancsó G, Kürthy M, Rőth E. Intestinal ischemic preconditioning in rats and NF-kappaB activation.
Microsurgery 2006; 26(1): 54-57. IF: 0,711

6. Gasz B, Lenárd L, **Benkő L**, Borsiczky B, Szántó Z, Lantos J, Szabados S, Alotti N, Papp L, Rőth E. Expression of CD97 and adhesion molecules on circulating leukocytes in patients undergoing coronary artery bypass surgery.
Eur Surg Res. 2005; 37(5): 281-289. IF: 0,750

7. Ferencz A, Toldi J, Fehér Zs, Gasz B, **Benkő L**, Jancsó G, Rőth E. NF-kB activation after intestinal preconditioning.
Monduzzi Editore Press: Bologna 2005; 85-88.

8. Szántó Z, **Benkő L**, Gasz B, Ferencz A, Horváth ÖP, Molnár FT Rőth E. Politetrafluoroetilen alkalmazása hosszú szakaszú légcsőpótlásban.
Magy Seb. 2003; 56: 68-72.

9. Szantó Z, **Benkő L**, Gasz B, Jancsó G, Rőth E, Lőrinczy D. Differential scanning calorimetric examination of the tracheal cartilageafter primary reconstruction with continous suture. A preliminary study
Thermocimica Acta 2004; 417(1): 171-174. IF: 0,974

10. Gasz B, **Benkő L**, Jancsó G, Lantos J, Szantó Z, Alotti N, Rőth E. Comparison of inflammatory response following coronary revascularization with or without cardiopulmonary bypass.
Exp Clin Cardiology 2004; 9(1): 26-30.

11. Jancsó G, Cserepes B, Gasz B, **Benkő L**, Ferencz A, Borsiczky B, Lantos J, Dureja A, Kiss K, Szeberényi J, Rőth E. Effect of acetylsalicylic acid on nuclear factor-KB activation and on late preconditioning against infarction in the myocardium
J Cardiovasc Pharmacol. 2005; 46: 295-301. IF: 1,576

Abstracts

1. R. Hubmann, G. Bodlaj, M. Czompo, **L. Benkő**, P. Pichler, A. Al-Kathib, P. Kiblböck, A. Shamiyeh, M. Sedlak and G. Biesenbach. A new developed self-expanding metal stent as a treatment of acute esophageal variceal bleeding.
J Hepatol. 2006; 44(2): S12. IF: 4,931

2. J. Danis, R. Hubmann, M. Czompo, **L. Benkő**, P. Pichler, P. Kiblböck, S. Al-Kattib and A. Shamiyeh**.** Patient tailored laparoscopic azygoportal disconnection.
   J Hepatol. 2006; 44(2): S60. IF: 4,931

3. B. Cserepes, G. Jancsó, B. Rácz, B. Gasz, A. Ferencz, **L. Benkö**, B. Borsiczky, R. Füredi, S. Ferencz, M. Kürthy et al. Cell protective role of urocortin in myocardial pre- and postconditioning.
   J Mol and Cell Cardiol. 2006; 40(6): 959-960. IF: 3,872

4. **Benkő L**, Danis J, Ferencz A, Rácz B., Cserepes B., Lőrinczy D., Rőth E. Differential scanning calorimetric examination of the esophagus after 2 different stents implantation. Early results with a new stent, designed for the management of acute esophagus ariceal bleeding.
   Eur Surg Res. 2006; 38:143. IF: 0, 750

5. **Benkő L**, Danis J, Hubbmann R, Gasz B, Ferencz A, Rőth E. New method in the tratment of acute esophagus variceal bleeding. Early results with esophagus stenting in animal experimental model.
   Eur Surg Res. 2005; 37: 82. IF: 0.750

6. **Benkő L**, Danis J, Shamiyeh A, Gasz B, Ferencz A, Rőth E. Novel laparoscopic azygo-portal disconnection procedure with a bipolar feedback controlled sealing system in a porcine model.
   Eur Surg Res. 2005; 37: 59. IF: 0.750

7. **Benkő L**, Danis J, Compo M, Ferencz A, Jancsó G, Szántó Z, Rőth E. Stent beültetés, mint új lehetőség az akut nyelőcső varixvérzés kezelésében: korai eredmények és a nyelőcső kalorimetriás vizsgálata 2 különböző öntáguló stent beültetését követően.
   Magy Seb. 2005; 58: 280.

8. **Benkő L**, Danis J, Shamiyeh A, Wayand W, Rőth E. Laparoscopic devascularization of gastric varices with ATLAS-LigaSure in portal hypertensive porcine model (azygoportal disconnection)
   Magy Seb. 2003; 56: 137-168.

9. **Benkő L**, Danis J, Shamiyeh A, Wayand WU, Rőth E. Laparoscopic azygo-portal disconnection procedure with ATLAS-LigaSure in porcine model.
   Eur Surg Res. 2004; 36 (suppl 1): 1-148. IF: 0,706.

10. **Benkő L**, Danis J, Shamiyeh A, Wayand WU, Rőth E. New technique in abdominal sepsis management; vacuum assisted wound closure.
    Eur Surg Res. 2004; 36 (suppl 1): 1-148. IF: 0,706.

11. Rácz B., Reglődi D., **Benko L.**, Ferencz A., Cserepes B., Rőth E., Borsiczky B. The effects of adenylate cyclase activating polypeptide and the possible signalling pathways involved in chondrocytes during hyperosmotic conditions.
    Eur Surg Res. 2006; 38 (suppl 1):60. IF: 0, 750.

12. Cserepes B., Jancsó G., Rácz B., Gasz B., Ferencz A., **Benkő L.**, Rőth E. Cardioprotective effect of urocortin int he process of postconditioning.
Eur Surg Res. 2006; 38 (suppl 1):152. IF: 0, 750.

13. Gasz B, Jancsó G, **Benkő L**, Lantos J, Ferencz A, Lénárd L, Szabados S, Alotti N, Papp L, Rőth E. Change in cytokine balance during coronary surgery.
Shock 2005; 23: 68. IF: 2.542.

14. Ferencz A, Rácz A, Gasz B, **Benkő L**, Rőth E. Effects of brief ischemic preconditioning protocol to NF-KB activation in bowel cells.
Eur Surg Res. 2005; 37 (suppl 1): 102. IF: 0,750

15. Fodor B,. Gasz B, Rácz B, **Benkő L**, Rőth E, Borsiczky B. Intra-articular cytokine overload during acute haemarthrosis.
Eur Surg Res. 2005; 37 (suppl 1): 122. IF: 0,750.

16. Ferencz A, Rácz B, **Benkő L**, Rőth E. Rövid ciklusú ischémiás prekondícionálás hatása az NF-kB aktivációra bélsejtekben.
Magy Seb. 2005; 58: 282.

17. Lantos J., Jancsó G., Gasz B., **Benkő L.**, Borsiczky B., Rőth E. Sejtfelszini adhézios molekulák jelentősege a gyulladásos kórfolyamatokban: kisérletes és klinikai adatok tükrében.
Magy Seb. 2003; 56: 137-168.

18. Gasz B, **Benkő L**, Jancsó G, Lantos J, Alotti N, Rőth E. Hagyományos és pumpa nélkül végzett koszorúérműteteket követően kialakuló gyulladásos válaszreakciók összehasonlítása
Magy Seb. 2003; 56: 137-168.

19. Borsiczky B., Jancsó G., Gasz B., Lantos J., **Benkő L**., Rőth E. Végtagsérülésekhez társuló alapjelenségek kutatása – Izületi vérömleny patomechanizmusának vizsgálata
Magy Seb. 2003; 56: 137-168.

20. Gasz B, **Benkő L**, Jancsó G, Lantos J, Cserepes B, Alotti N, Rőth E. Comparison of invasivity in conventional and off-pump coronary artery surgery focusing on oxidative stress and inflammatory response parameters.
Exp Clin Cardiology 2003; 8: 78.

21. Szántó Z, **Benkő L**, Gasz B, Ferencz A, Molnár FT, Rőth E. Outcomes of different suturing techniques in tracheal replacement.
Eur Surg Res. 2003; 35: 241. IF: 0,939

22. Gasz B, **Benkő L**, Jancsó G, Lantos J, Alotti N, Rőth E. Biological benefit of the off-pump coronary surgery: Review of oxidative stress and inflammatory response parameters in conventional and off-pump cardiac surgery.
Eur Surg Res. 2003; 35: 241. IF: 0,939

23. Jancsó G, Lantos J, Gasz B, Borsiczky B, Szántó Z, **Benkő L**, Cserepes B, Rőth E. Does aspirin block the activation of Nuclear Factor-KappaB in the preconditioned myocardium?
    Eur Surg Res. 2004; 36: 1-148. IF: 0,706

24. Szántó Z, **Benkő L**, Gasz B, Lőrinczy D, Rőth E, Horváth ÖP. New method to evaluate different suture techniques on tracheal cartilage in primary airway reconstruction.
    Eur Surg Res. 2004; 36: 1-148. IF: 0,706

Presentations

1. **Benkő L**, Danis J, Ferencz A, Palov A, Fónagy E, Kasza G, Kollár L, Röth E. Öntáguló stent alkalmazása az akut nyelőcső várixvérzés kezelésében: kísérletes és humán eredmények.
   Magyar Sebész Társaság, Kísérletes Sebészeti Szekció XXI. Kongresszusa, Pécs, May 31-June 2 2007.

2. **Benkő L**, Danis J, Jancsó G, Cserepes B, Kasza G, Kollár L, Rőth E. Öntáguló stent, mint új lehetőség az akut nyelőcső várixvérzés kezelésében az állatkísérletes és humán eredmények tükrében.
   Magyar Sebész Társaság Kongresszusa, Budapest, September 6-9 2006.

3. **Benkő L**, Danis J, Ferencz A, Rácz B., Cserepes B., Lőrinczy D., Rőth E. Differential scanning calorimetric examination of the esophagus after 2 different stents implantation. Early results with a new stent, designed for the management of acute esophagus ariceal bleeding.
   XXXXI. Congress of the European Society for Surgical Research (ESSR), Rostock, Germany, 17-20 May 2006.

4. **Benkő L**, Danis J, Hubbmann R, Gasz B, Ferencz A, Rőth E. New method in the tratment of acute esophagus variceal bleeding. Early results with esophagus stenting in animal experimental model.
   XXXX. Congress of the European Society for Surgical Research (ESSR), Konya, Turkey, 25-28 May 2005.

5. **Benkő L**, Danis J, Shamiyeh A, Gasz B, Ferencz A, Rőth E. Novel laparoscopic azygo-portal disconnection procedure with a bipolar feedback controlled sealing system in a porcine model.
   XXXX. Congress of the European Society for Surgical Research (ESSR), Konya, Turkey, 25-28 May 2005.

6. **Benkő L**, Danis J, Compo M, Ferencz A, Jancsó G, Szántó Z, Rőth E. Stent beültetés, mint új lehetőség az akut nyelőcső varixvérzés kezelésében: korai eredmények és a nyelőcső kalorimetriás vizsgálata 2 különböző öntáguló stent beültetését követően.
   Magyar Sebész Társaság, Kísérletes Sebészeti Szekció XX. Jubileumi Kongresszusa, Hajdúszoboszló, September 8-10 2005.

7. **Benkő L**, Danis J, Compo M, Ferencz A, Jancsó G, Rőth E. Oesophagus stent , mint új lehetőség az akut nyelőcső varixvérzés kezelésében, az állatkísérletes és humán eredmények tükrében.
   MST, Endoszkópos Szekciójának Kongresszusa, Nagykanizsa-Zalakaros, November 3-5 2005.

8. **Benkő L**, Danis J, Shamiyeh A, Wayand WU, Rőth E. Laparoscopic azygo-portal disconnection procedure with ATLAS-LigaSure in porcine model.
   39 th Congress of the European Society for Surgical Research (ESSR), Athens, Greece, 12-15 May 2004.

9. **Benkő L**, Danis J, Shamiyeh A, Wayand WU, Rőth E. New technique in abdominal sepsis management; vacuum assisted wound closure.
   39 th Congress of the European Society for Surgical Research (ESSR), Athens, Greece, 12-15 May 2004.

10. **Benkő L**, Danis J, Czompo M. New method in the management of esophageal varix bleeding: „Danis – stent".
    New surgical methods in the 21.Century – Symposium, Losonc, Szlovákia, 20-21 May 2004.

11. **Benkő L**, Danis J, Shamiyeh A, Wayand WU, Rőth E. Laparoscopic devascularization of gastric varices with ATLAS-LigaSure in portal hypertensive porcine model /azygoportal disconnection/.
    Magyar Sebész Társaság Kongresszusa, Siófok, 11-13 September 2003.

Cumulative impact factor: 41,272
Impact factor of publication: 15,8
Impact factor releated to the thesis: 7,455