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

Studying in experimental and human

By

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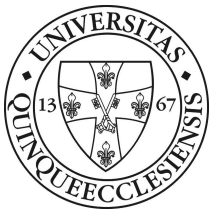

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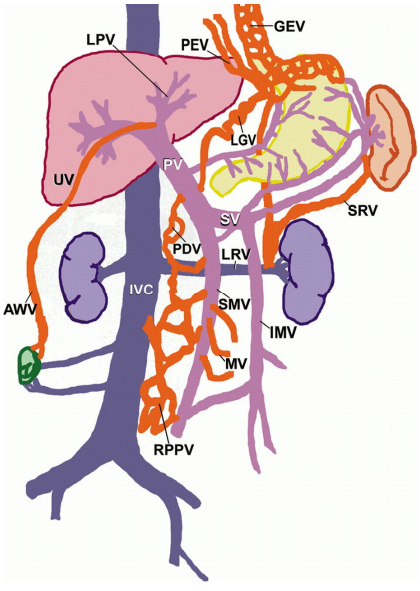
1. INTRODUCTION

Bleeding associated with portal hypertension is a major cause of morbidity and mortality in patients with cirrhosis. Although, over the past few decades, several new prophylactic and treatment options have evolved, the mortality rate of acute variceal bleeding and rebleeding still relatively high.

1.1. Surgical anatomy of the portal system

The portal vein is the termination of the splanchnic venous outflow and is formed by the junction of the splenic and superior mesenteric veins behind the neck of the pancreas. The portal vein is approximately 6-8 cm long and 1-1,2 cm in diameter. It runs in the free edge of the lesser omentum from the pancreas to the right end of the porta hepatis. The superior mesenteric vein forms from the draining jejunal and ileal veins, its major tributaries being the ileocolic, right colic and middle colic veins. The inferior mesenteric vein enters into either the superior mesenteric vein or the splenic vein while the coronary (left gastric) vein may enter into either the portal vein or the splanic vein behind the pancreas (**Figure 1.**).



AWV = abdominal wall vein
GEV = gastroesophageal vein
IMV = inferior mesenteric vein
IVC = inferior vena cava
LGV = left gastric vein
LPV = left portal vein
LRV = left renal vein
MV = mesenteric vein
PDV = pancreaticoduodenal vein
PEV = paraesophageal vein
PV = portal vein
RPPV = retroperitoneal-paravertebral vein
SMV = superior mesenteric vein
SRV = splenorenal vein
SV = splenic vein
UV = umbilical vein

Figure 1. Anatomy of the portal system

The other important surgical anatomy in portal hypertension is the venous anatomy of the gastroesophageal junction. Gastroesophageal varices are the classic collateral pathway that develops from the left gastric veins to the lesser and greater curves of the stomach. These veins run submucosally across the gastroesophageal junction up to the esophagus. Additional collateral pathways are found in the periumbilical area communicating with the umbilical vein, the retroperitoneum and between the inferior mesenteric vein and the haemorrhoidal venous plexus of the anal canal [1].

1.2. Classification and causes of portal hypertension

Portal hypertension is defined as an elevated pressure within some portion of the portal venous system. Portal hypertension is present if hepatic venous pressure gradient (HVPG) exceeds 12 mmHg. Normal venous pressure gradient is 5-10 mmHg that is sufficient to maintain a portal flow through the hepatic sinusoids of approximately 1liter/min.

Portal hypertension is classified by the site of obstruction as presinusoidal, sinusoidal and postsinusoidal portal hypertension (**Table 1.**). Presinusoidal portal hypertension may be either extra- or intrahepatic. Thrombosis of the extrahepatic portal vein or one of its major branches causes extrahepatic portal hypertension. Schistosomiasis and congenital hepatic fibrosis cause intrahepatic presinusoidal portal hypertension. In general, hepatocellular function is preserved in presinusoidal portal hypertension, which has implications for both prognosis and management. Cirrhosis causes sinusoidal portal hypertension, which is the most common cause of portal hypertension. The underlying etiology for cirrhosis is most frequently viral hepatitis or alcoholic liver disease. Other less common etiologies include sclerosing cholangitis, primary biliary cirrhosis, haemochromatosis, Wilson's disease or α-1 antitrypsin deficiency. Postsinusoidal portal hypertension is caused by hepatic venous outflow

obstruction either at the terminal hepatic venule level (venoocclusive diesease) or at the major hepatic vein or suprahepatic inferior vena cava level (Budd-Chiari syndrome) [2].

Table 1. Classification of portal hypertension

A. PRESINUSOIDAL

- extrahepatic:
    - portal vein obstruction (extrinsic compression, phlebitis, OC, coagulopathy, tumor invasion, pancreatitis, neonatal omphalitis)
    - dynamic: traumatic/neoplastic arterioportal fistula
    - segmental portal HTN: splenic/SMV occlusion
- intrahepatic (obstruction of portal venules):
    - congenital hepatic fibrosis
    - primary biliary cirrhosis
    - sarcoid
    - myelofibrosis
    - schistosomiasis
    - idiopathic noncirrhotic fibrosis
    - Wilson disease
    - reticuloendotheliosis
    - Felty syndrome
    - chronic malaria
    - toxic fibrosis (arsenic, copper, PVC vapors)

B. SINUSOIDAL

- cirrhosis
- sclerosing cholangitis

C. POSTSINUSOIDAL

- Budd-Chiari syndrome
- constrictive pericarditis
- congestive heart failure

1.4. Etiology and epidemiology of variceal bleeding

Varices form when portal hypertension causes dilatation of portosystemic collateral vessels. Blood may be shunted from the portal circulation into the systemic circulation. In case of esophageal and gastric varices, increased blood flow is noted in the azygos vein, on account of hepatofugal flow in the left gastric vein (or coronary vein) and short gastric veins (which collateralize with the splenic vein). If the hepatic venous pressure gradient (the difference in pressure between the portal vein and the hepatic vein) exceeds 12 mm/Hg, varices may form in the esophagus and stomach [3, 4]. In the esophagus, varices first arise at the gastroesophageal junction (**Figure 2.**).

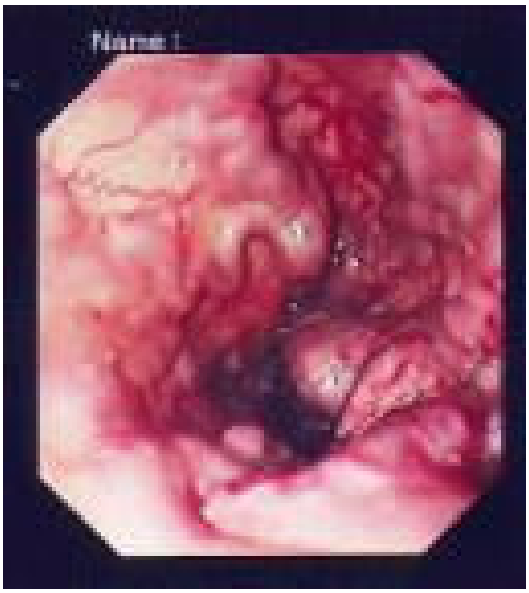


Figure 2. Esophagus varices (endoscopy, original magnification x10)

Local factors, including the amount of supporting esophageal tissue, may have an impact upon the diameter to which a superficial varix may dilate. Large varices, measured at more than 5 mm in diameter, have a greater predisposition to rupture spontaneously than small varices [5]. This, presumably, is a result of the increase in wall tension which occurs when varices increase in size [6]. It is now well appreciated that varices do not erode. Indeed, gastroesophageal reflux

does not appear to play a role in inducing variceal hemorrhage. [7].

Varices are identified in about 30% of patients with well-compensated cirrhosis and in 60% of patients with decompensated cirrhosis [8]. Small varices are at low risk of hemorrhage. It is estimated that varices will increase in size from “small” to “large” at a rate of 10–20% per year [8, 9]. Variceal bleeding occurs at a rate of 10–20% per year, when all patients with varices are considered [10, 11, 12], but rises to more than 20–30% per year in patients with large varices [5, 12]. This statistic takes on added importance with the knowledge that bleeding from varices is the cause of more than one quarter of all deaths in patients with cirrhosis [13]. Initial variceal bleeding stops spontaneously in 60–70% of patients [14, 15]. However, 17–42% of patients with early hemostasis will rebleed within 5–10 days of their initial hemorrhage [16, 17]. Variceal bleeding and early rebleeding are associated with a high mortality rate, estimated at about 40%. Exsanguinating hemorrhage itself is responsible for about 60% of deaths which occurs within 6 weeks of the initial hemorrhage. Recurrent bleeding is responsible for about 40% of late deaths [14]. Progressive liver failure and hepatorenal syndrome frequently complicate variceal bleeding and may result in death. These conditions are presumably precipitated by a state of decreased hepatic and renal blood flow. Thus, it is imperative that intravascular volume be maintained by aggressive resuscitation with fluid and blood products. However, care must be taken to avoid over-transfusion (above a hematocrit of 30%), as this may acutely worsen portal hypertension. Sepsis and, in patients with ascites, spontaneous bacterial peritonitis are frequently seen in the setting of variceal bleeding. Increasingly, there is interest in using selective intestinal decontamination (e.g., with norfloxacin 400 mg per nasogastric tube twice daily) in an effort to prevent serious infection in cirrhotic patients who develop gastrointestinal hemorrhage [18]. It has long been known that both early and late mortality following variceal bleeding are closely tied to a patient’s Child class at time of onset of bleeding [19–23]. (**Table 2**), has been modified to

include the international normalized ration (INR) readings for the prothrombin time. Patients with well-compensated liver disease receive a Child class A status. Patients who suffer from some degree of hepatic encephalopathy, ascites, jaundice or hepatic synthetic dysfunction, as marked by a depressed serum albumin or an elevated prothrombin time, have a Child class B or C status. Following variceal bleeding, 30-day mortality rates have been estimated at: less than 10% for Child class A, 30% for Child class B, and more than 45% for Child class C [21]. For patients who survive the initial variceal bleeding, the one-year mortality rate is estimated to be 50% when all patients with cirrhosis are considered [14]. When segregated by severity of liver disease, one-year mortality rates are estimated at: 24% for Child class A, 48% for Child class B, and 65–89% for Child class C [21, 22].

Table 2. Severity of Cirrhosis (Child-Pugh classification)

Variable	**Score** (5-6 = class A, 7-9 = class B, >10 = class C)		
	1 point	2 points	3 points
Encephalopathy	Absent	Mild / moderate	Severe or coma
Bilirubin (μ mol/l)	<34	34-51	>51
Albumin (g/l)	>3.5	2.8-3.5	<2.8
Prothrombin time (secs above normal)	1-4	4-6	>6

1.5. Management of acute variceal bleeding

For centuries, gastrointestinal bleeding has been recognized as a major cause of morbidity and mortality in patients with pathology of the portal circulation. By contrast, a fuller understanding of the pathophysiology of portal hypertension and variceal hemorrhage has occurred only over the past three decades. This has led to significant advances in therapies for the prevention and treatment of bleeding in portal hypertension. As more-effective therapies evolve, the role of the surgeon may be considered to be in question, or in evolution.

1.5.1. Historical Background

Early therapies for variceal bleeding were limited, and in the 1930s consisted of temporizing measures, such as balloon tamponade and rigid endoscopic sclerotherapy. Surgical treatment of portal hypertension was introduced by Whipple in 1945, with the performance of the first Pavlov-Eck fistula for a human. Portocaval and central splenorenal shunts became popular in the 1940s, but the long-term results of these total shunts were disappointing owing to a significant increase in hepatic encephalopathy and the risk of worsening liver failure. The use of vasopressin and improvements in balloon tamponade followed in the 1950s. The 1960s saw the introduction of new surgical approaches. The distal splenorenal shunt (DSRS) was introduced, which selectively decompressed gastroesophageal varices while maintaining portal perfusion to the liver. In the 1970s, azygoportal disconnection procedure became popular. Liver transplantation, successfully achieved by Starzl in 1967, has become the only therapeutic option to treat portal hypertension and address underlying liver disease simultaneously. In the 1980s, treatment moved to endoscopic therapies, with flexible scopes allowing sclerotherapy and then banding. This was soon followed by pharmacologic therapy with nonselective β-blockade for the prevention of bleeding. In the 1990's radiologists added to the useful treatment options for bleeding from portal hypertension, with the development of

the nonsurgical transjugular intrahepatic portosystemic shunt (TIPS) [23, 24]. This is a minimally invasive way of creating a shunt between the portal veinand the hepatic vein through the liver.

Treatment has evolved from surgery being the only option up through the 1970s to the wide range of options now available. Surgery has not vanished in treating these patients, however, but its role has changed.

1.5.2. Acute therapy

Patients with acute bleeding are best managed by a team including critical-care physicians, gastroenterologists, hepatologists, surgeons and interventional radiologists. During the acute episode, being able to carry out basic resuscitation is paramount, although over-resuscitation should be avoided. Endoscopic intervention with variceal banding in combination with pharmacotherapy, using octreotide by continuous infusion, will control acute variceal bleeding in >80% of patients. For the patient who continues to bleed actively, emergency TIPS is effective in stopping the bleeding. Emphasis is on exquisite patient care, with airway protection, careful fluid management, antibiotics and nutrition. Emergency surgical procedures are rarely indicated.

Patients with gastroesophageal varices who have had a bleeding episode should have elective interventions to prevent rebleeding, with endoscopic banding of varices that have bleed combined with nonselective β-blockade. For the 20% of patients who rebleed despite this primary therapy, decompression might be needed. The value of surgical rescue was shown in the 1980s [25], and this concept is still valid. The question at present is whether decompression is best done surgically or with TIPS. Nontransplant surgical data obtained in the past decade have promoted the use of DSRS, which works well for patients with refractory bleeding who have well-preserved liver function. The role of total portosystemic

shunts has virtually vanished. Devascularization surgery is reserved for patients with no surgical-shunt options. TIPS has, however, become widely used because of its ease of application. Data indicate that TIPS has a high stenosis rate (>50%) requiring redilation, and up to a 30% rate of encephalopathy [26]. Two randomized trials addressed the relative efficacy of TIPS or surgical shunt. The first of these compared TIPS with a partial (8 mm) portocaval shunt in an normal population, of whom 50% were Child–Turcotte–Pugh class C [27]. The surgical shunt performed better for control of bleeding, reduced the need for transplant, and improved overall shunt success rate, although survival was not significantly different. The second study compared DSRS with TIPS in Child–Turcotte–Pugh class A and B patients [28]. There was no significant difference in rebleeding rates (6% after DSRS and 9% after TIPS), encephalopathy or survival, but TIPS patients required significantly ($P < 0.001$) more reinterventions (83% of patients). In deed, TIPS cleared the surgical shunt in several cases, but the decision to decompress varices should still be made on an individual basis.

Clearly, the surgeon still plays a role in treating this group of patients, with liver transplant. It is end-stage liver disease, rather than variceal bleeding, that dictates the need for such surgery, which treats both portal hypertension and variceal bleeding with the additional advantage of restoring liver function. Not all patients are eligible, however, such as active alcoholics and those with concomitant disease, and the specific post-transplant risks of immunosuppression and infection must also be considered [29].

The role for surgery in bleeding portal hypertension has changed dramatically in the last few decades. Although there remains some role for surgical shunts, this has been markedly reduced. The use of liver transplantation as a treatment, however, has continued to grow. In the emergent setting, surgery is rarely needed. In the elective setting, DSRS provides

excellent long-term results for patients with stable liver disease and good liver function. Many patients are adequately treated with TIPS, but DSRS might be preferred for patients who cannot or will not comply with the follow-up investigations and interventions that are required for TIPS to achieve comparable long-term results to DSRS. Finally, TIPS has its greatest usefulness as a bridge to transplantation.

2. 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.

3. NEW MINIMAL INVASIVE METHOD FOR THE DEVASCULARIZATION OF THE STOMACH AND THE DISTAL ESOPHAGUS

(An experimental and clinical study)

3.1. Introduction

Bleeding from esophageal varices is a life threatening complication in patients with portal hypertension. Endoscopic interventions with sclerotherapy or endoscopic band ligature are considered the treatment of choice whereas emergency operations may be the last option, for they are accompanied with a high morbidity and mortality. Transjugular intrahepatic portosystemic shunt placement (TIPS) and surgical shunts are considered in case of recurrence. The TIPS procedure reduced significantly the procedural invasivity. However, the main problems remain dominant after such intervention: occlusion of the stent as well as encephalopathy. The azygoportal devascularization methods, developed first by Sugiura in the 1960s, were accompanied with high perioperative mortality [30, 31, 32, 33]. 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 [34] despite being safe with respect to venous closure and as well as in avoiding the intra- or post-operative bleeding [35].

3.2. Laparoscopic azygo-portal disconnection procedure with a bipolar feedback controlled sealing system in a porcine model

3.2.1. Insight into this study

The aim of the study was to examine *in vitro* and on porcine models the sufficiency of venous closure by means of bipolar feedback thermal vessel sealing and feasibility of a new, minimally invasive procedure, the laparoscopic azygoportal disconnection. Further, creating a portal hypertension in an animal model in pigs was necessary. The final aim was to show the feasibility of the azygoportal disconnection operation using a bipolar feedback controlled sealing, the LigaSure Atlas Sealing System. This sealing system was created for the safe closure of vessels, respectively arteries up to 7 mm [36].

3.2.2. Materials and methods

3.2.2.1. In Vitro Tests

The bursting strength was tested on 20 femoral veins of the pigs, with a body weight of 40 to 50 kg, that were harvested from a local slaughterhouse and were cannulated with Venflon TM 18GA 1.77IN; 1.2 × 45 mm max 80 ml/min (Becton Dickinson Infusion Therapy, Stockholm, Sweden) at its peripheral edge. The cannula was connected with a motor-powered, saline filled syringe at 37°C. The intraluminal pressure was detected by means of a transducer (LPD 102 TESLA; Czech Republic) inter-positioned between the cannula and the syringe.

The harvested vein, was shortened to 3 cm and protected by a PVC tube with corresponding diameter, and sealed on its central end by the use of the LigaSure-ATLAS instrument (10 mm, Tyco/Healthcare/Valleylab, 5920 Longbow Drive, Boulder, CO). The third intensity grade of the sealing was used.

The motor pump was adjusted for 1 ml saline/min and started 3 min after the sealing of the vein was finished. The maximal fluid pressure at which the sealed line leaked measured the strength of the secured vein edges. The same procedure was performed also with human veins harvested during leg varicose vein surgery. The procedural work-up of the human samples (saphenous veins) conformed to the Austrian and Upper Austrian autopsy law and has also been permitted by the Ministry of Health of the Austrian Government (BMGF; GZ: 92.600/0-I/B/8/04 from the 16th of January, 2004).

3.2.2.2. Animals

The presented study conforms to the Guide for Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH Publication W-85-23, revised 1996) and was approved by the local institutional committee on animal research of Pécs University (Hungary, BA 02/2000-29/2001). 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.

3.2.2.3. Anaesthesia

Anesthesia was induced with an intramuscular (i.m.) injection of azaperon (Stresnil 0,4 mg/kg, Jannsen CilagPharma, Vienna, Austria), and was maintained with Isofluran and N_2O

gas after oro-tracheal intubation. Perioperative antibiotic prophylaxis was given (Mezlocillin, 8 mg i.m. Baypen, Bayer, Leverkusen, Germany). A central venous catheter was placed in the right/left jugular vein and removed after surgery.

3.2.2.4. 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 (**Figure 3.**). The clip was adjusted until the expected intrasplenic pressure>17 mmHg was achieved [37]. Post-operative analgesia was administered with Metamizol (5 mg/kg body weight) intramuscularly on the first post-operative day.

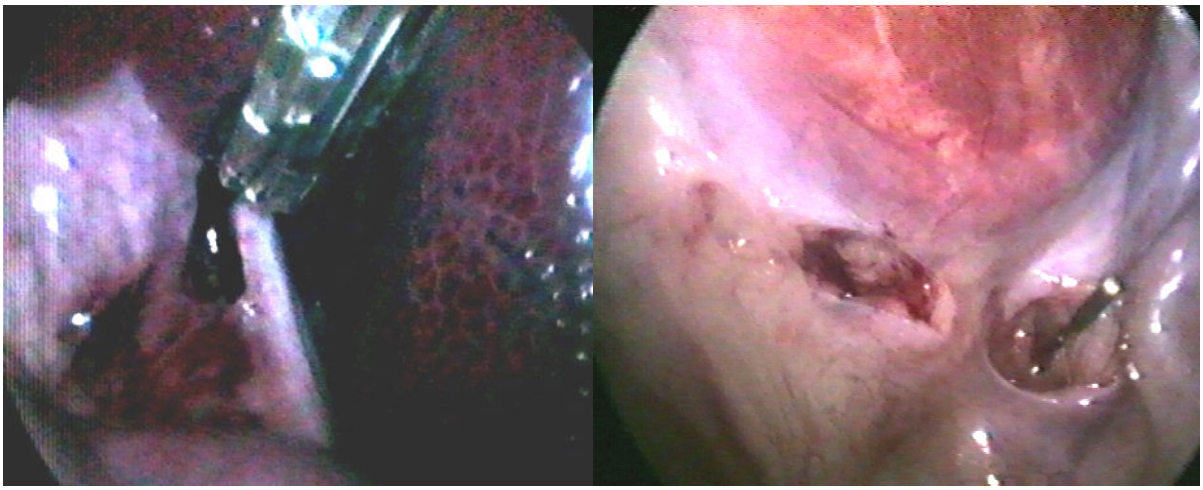


Figure 3. Laparoscopical clipping of the v. portae

3.2.2.5. 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 (**Figure 4.**).

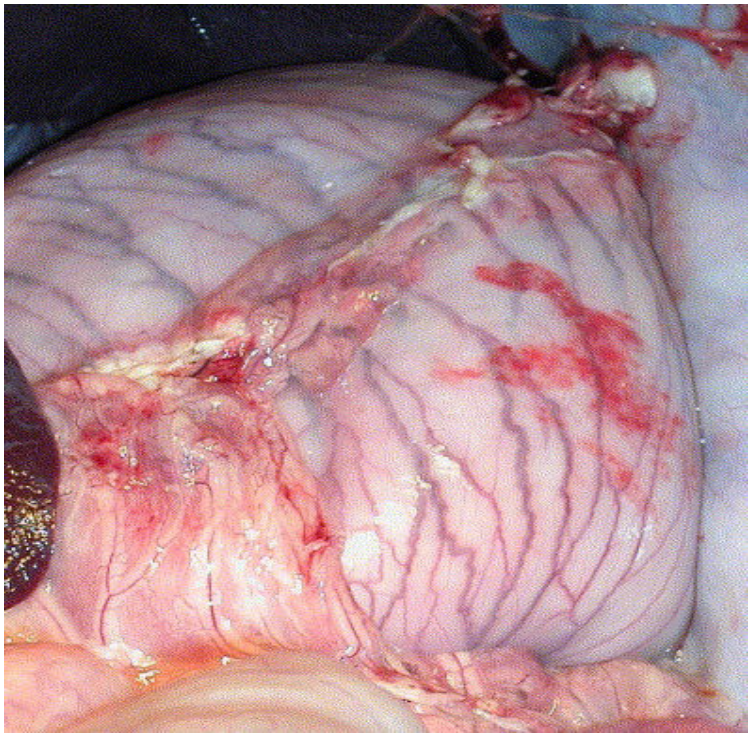


Figure 4. Situs after dissection (sealed veins along the greater curvature).

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 (Tyco/Healthcare/Valleylab). 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. Animals were anesthetised with azaperon (Stresnil) over dose and sacrified with intravenous injection of kalium-chloride solution. The abdominal cavity was inspected for esophageal varices, intra-abdominal bleeding, and possible necrosis of the dissected area of the stomach.

3.2.3. Results

The results of the *in vitro* experiment are summarized in **Table 3**. Diameters of both veins were comparable. Safe closure of the venous lumen could be achieved. The mean burst pressure of the porcine femoral vein was 121 ± 37 mmHg (mean ± SD); the human vein presented bursting pressure of 178 ± 44 mmHg (mean ± SD). These values are higher than the expected portal pressure in patients with portal hypertension. No primary leakage of the approximated and sealed line was observed.

Table 3. Bursting Pressure after Sealing of the Large Size Vein by Means of 10 mm Vessel Sealing Device LigaSure-ATLAS

	N	Mean bursting pressure (kPa)	SD (kPa)	Minimal bursting pressure (kPa)	Number of leakage
Porcine femoral vein	10	1.26	0.54	0.41	0
Human	20	1.75	0.47	0.66	0

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. The autopsy of this pig showed that we did not succeed in separating the left gastric artery, which was also sealed with LigaSure-ATLAS instrument.

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. The results of the portal and intrasplenic pressure measurements are summarized in **Table 4**. Autopsy showed correctly placed clips with partial occlusion of the portal vein without portal vein thrombosis in all pigs

Table 4. Intra-operative venous pressure in the first group

	Portal vein range	**Median**	**Intrasplenic pressure range**	**Median**
Before portal *versus* clipping	2–6	3.83	2–7	4.17
After portal *versus* clipping	17–27	22.67	18–26	22.33
2 weeks post-operatively	13–21[†]	18.80	13–24[†]	19.8

Results are set in mmHg at the first six pigs;
[†] one pig died.

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 (**Figure 5.**). At autopsy we found in all pigs a well clipped portal vein and histological a fine sealing zone of the veins (**Figure 6.**). None of the remaining 11 pigs had necrosis or perforation of the stomach or esophagus. 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.

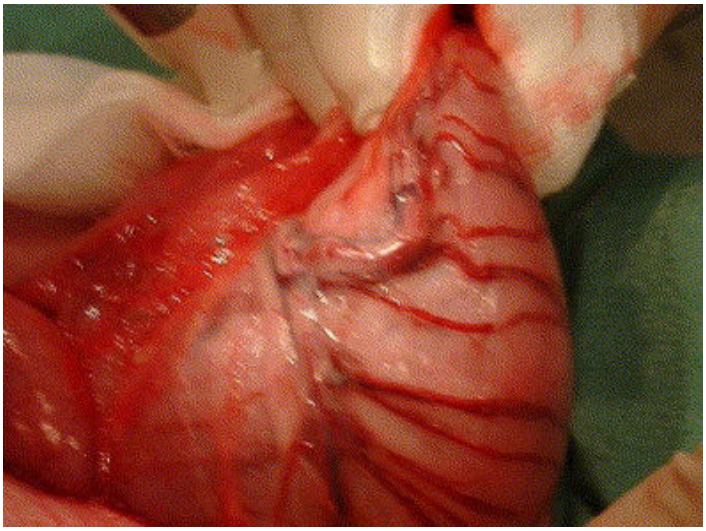


Figure 5. Dilated veins as a result of the portal hypertension

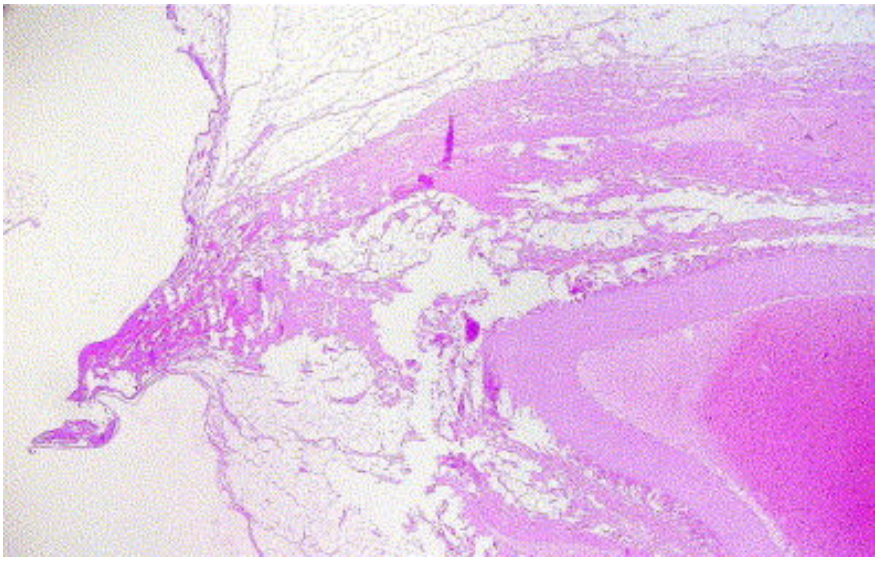


Figure 6. Histological examination of the sealed vein (H&E, original magnification x40)

3.2.4. Discussion

The crucial point of the devascularization technique is prevention of the brisk bleeding from the dilated vessels like enlarged azygoportal collaterals. LigaSure-ATLAS instrument was developed for laparoscopic surgery and experimentally tested on arteries before this technology was introduced in clinical practice. Although the data about venous closure are lacking, it could be proved that with this system veins up to 12 mm could be closed safely [38]. Kwok could show in his paper that with the LigaSure-ATLAS sealing system treatment of hemorrhoids grade 3 and 4 is feasible and safe [39]. Our observed *in vitro* results confirmed the safety of the sealed edge on pig (femoral vein) as well as human leg veins. There was no leakage after the sealing with the LigaSure-ATLAS instrument. However, a primary venous leakage on the pig model was reported after staple application [40]. In our experiment, the minimal burst pressure values detected were more than twice as high as the expected values in patients with portal hypertension. This result encouraged us to test this method in the porcine portal hypertension model experiment.

The hypothesis that the laparoscopic devascularization of the lower esophagus and the upper stomach is less invasive has to be tested by experimentation. To create a portal hypertension in an animal model, several possibilities are available:

1. Creation of liver cirrhosis by ligature of the common bile duct [41].
2. Micro particle embolization of the liver veins. This model only creates an acute portal hypertension but fails to create a permanent portal hypertension [37, 42, 43].
3. Partial clipping and well dosed clipping of the portal vein after laparotomy has been described [44, 45].

A potential problem is that a laparotomy is regularly accompanied by intra-abdominal adhesions. These could aggravate a subsequent surgery necessary for the testing of the operative technique. We developed a feasible model of porcine portal hypertension as the laparoscopic approach was completed with well-dosed pre-hepatic partial occlusion of the portal vein performed with the Endoclip II. With this technique we could maintain a permanent portal hypertension for at least 2 weeks with the development of high collaterals, which was proved in measurement of the intrasplenic pressure. Moreover, the intrasplenic pressure increased parallel with increased pressure in the portal vein. Thus, the intrasplenic pressure assessed through transcutaneously, video-assisted puncture of the spleen, presented a safe method for repeated monitoring of the portal hypertension in our experiment.

The LigaSure-ATLAS instrument guaranteed safe venous sealing on the portal hypertension porcine model. There was no intra- or post-operative bleeding and no conversion to open surgery. However, no vessels necessary for blood supply of the stomach should be injured, which may cause delayed perforation and death as we could observe in one pig (5%). Nevertheless, no differentiation between thermal injuries of the stomach wall resulting from energy conduction toward the stomach or extended arterial devascularization, resulting in leakage of the small curvature of the stomach was possible. However, in our experience, this complication should be avoided through two technical aspects: the company guarantees no thermal damage after a distance of 1.6 mm [36]. In a previous study we could prove that more than 2 mm far from the thermal energy source, no collateral damage of the solid tissue could be detected [46]. Thus, a safe distance of the LigaSure-ATLAS branches of at least 2 mm to the intestine serosa is recommended. Secondly, arteries should be separated and preserved during the dissection to avoid isochoric damage and necrosis.

The laparoscopic approach to the portocaval collaterals in our experiment gained some major advantages compared to Sugiura procedure and its modifications: The main target of the azygoportal disconnection was the branches of the gastric coronary veins, gastrosplenic veins, and paraesophageal veins in the mediastinum. No esophagus transsection was necessary; the paraesophageal veins could be occluded with LigaSure-ATLAS device without any serious bleeding event. A thoracotomy could also be avoided and completely replaced by the same laparoscopic transhiatal approach to the esophagus. No splenectomy was performed.

We conclude that in the *in vitro* study we could confirm the reliability of the bipolar feedback controlled sealing system LigaSure-ATLAS for the closure of the veins in animal with induced portal hypertension. This method seems to be applicable also in humans. The burst pressure of the vein harvested from humans ranked over the values expected in patients with portal hypertension.

3.2.5 Conclusion

In our experiment 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.

This procedure could give benefit to patients with esophageal variceal bleeding because of portal hypertension. These patients are usually high-risk patients in a bad condition with spoiled hemostasis. The main difference from the original Sugiura procedure is the lack of the esophageal transsection demanding a new anastomosis, which could result in a decreased morbidity. Because of the new hemostasis instruments, the operation can be done laparoscopically, which gives the patient all of the advantages of minimally invasive surgery. This procedure might be an effective and safe tool for an elective and emergency treatment of the esophageal variceal bleeding.

3.3. Laparoscopic azygo-portal disconnection procedure with a bipolar feedback controlled sealing system in human (preliminary experience with five patients)

3.3.1. Insight into this study

Liver cirrhosis leads frequently to the development of ascites and the formation of varicose veins in the esophagus. The introduction of the transjugular intrahepatic portosystemic shunt (TIPS) reduced the frequency of surgical shunt and disconnection procedures [47]. Recently, significant progress in laparoscopic technology enabled devascularization of the proximal stomach and distal esophagus in a less invasive way. We present a new surgical technique and preliminary results for five patients in whom a laparoscopic azygoportal disconnection was performed.

3.3.2. Patients and methods

3.3.2.1. Patients

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 (**Table 5.**). 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.

3.3.2.2. Surgical procedure

Five ports were positioned on the upper abdominal wall (**Figure 7**.). After the camera was introduced, the veins in the lesser omentum were divided using the vessel sealing equipment (LigaSure, 8LOC1038V Valleylab, LigaSure-Atlas 10-mm sealing-cutting device , LigaSure software Version 1.24, adjusted Grade 3) in all patients (**Figure 8.**). 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.

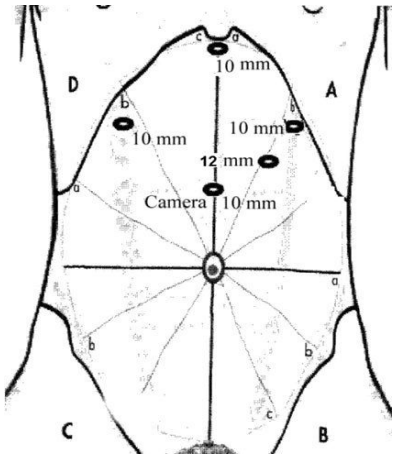


Figure 7. Position of the ports for the laparoscopic azygoportal disconection

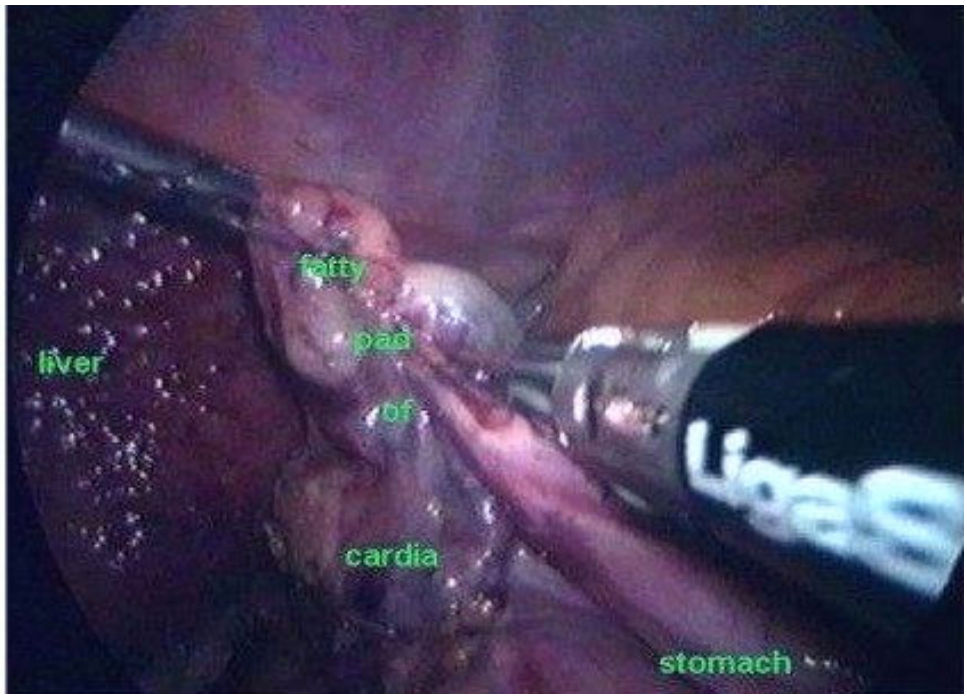


Figure 8. Sealing the vessels with the LigaSure-Atlas device (laparoscopy)

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).

Postoperatively, continuous somatostatin infusion (6 mg/24 hours), fluid substitution, diuretics, and amino acids were administered. Oral intake was started 24 hours after surgery.

At the patient interviews 3, 6, 9, and 12 months after surgery, blood sampling and endoscopical and ultrasound surveillance were performed. Thereafter, surveillance and health care were performed.

3.3.3. 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 (consumption of 1.4l vodka/day).

During a postoperative follow-up period of 9 to 30 months, no esophagus variceal bleeding was recorded (**Table 5.**). 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.

Table 5. Characteristics of patients who underwent laparoscopic azygoportal disconnection

Patient no.	Gender/age (years)	Prehistory	Variceal bleeding events	Liver cirrhosis/ child stage	Esophageal varices (Paquet stage)	Postoperative events
1	M/41	Alcohol 15 y TIPSS 4×	11	4 yr/B	2	No bleeding event Patient died after 9 mo liver insufficiency
2	M/51	Alcohol 8 y Pulmonary emboli 3 y Depression Tobago bronchitis Hiatus hernia	2	3 yr/B	2	No bleeding Hemorrhoids 7 mo Pneumonia 15 mo Leg varices 17 mo
3	M/58	Alcohol 20 y	8	5 yr/C	3	No variceal bleeding Congestion gastritis Died after 16 mo
4	M/50	Myeloproliferative syndrome Linton shunt, Cava filter	4	0	4	No bleeding, banding Left V. testicularis collaterals
5	M/64	Alcohol 14 y	3	4 yr/C	3 Fundus varices	No bleeding Ascites

3.3.4. Discussion

Portal hypertension is the most life-threatening complication of liver cirrhosis. The portal gradient exceeding 12 mm of mercury results in portosystemic collaterals. The esophageal varices present a 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 [48, 49, 50]. 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. Stratification of patients according the Child-Pugh classification was the consequence. Low-stage patients who survived the surgery profited from the proximal gastric devascularization through reduced rebleeding risk, good life expectancy, and a good quality of life without encephalopathy [51, 52].

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 [47, 53]. 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 [49, 54].

The hypothesis that laparoscopic devascularization of the lower esophagus and upper stomach is less invasive was tested by experimentation [55] and by small clinical studies in which devascularization was performed partly through minilaparotomy [56, 57, 58]. We previously reported our initial experience with the fully laparoscopic procedure performed on a patient after implantation of the TIPS [59]. The outcome of surgery for this patient was surprising, and this fact encouraged us to perform the next laparoscopic azygoportal disconnection procedures for patients without any chance of an alternative treatment.

We developed a totally new composition of surgical techniques (Danis procedure), which consisted of minimally invasive access that avoided a splenectomy and used a vessel-sealing technique with LigaSure-Atlas for dividing the short gastric vessels and Endo-GIA equipment for the branches of the gastric coronary vein. The distal esophagus also was approached by means of a minimally invasive technique through the hiatus esophagicus. To avoid a stricture, we did not perform any esophageal stapler transsection of the esophagus with our procedure, the stapling was replaced by transmural stitching of the distal esophagus. This may minimize a risk of esophagus leakage [59]. The procedure was completed with fundoplication according to the Toupet.

A transsection of the esophagus was reported in 1973 by Pugh. Moreover, liver function improved after an isolated esophagus transsection or devascularization [60, 61]. However, this particular step of the procedure remains controversial. During the Sugiura procedure, a circular stapler anastomosis has to be constructed in terrain that previously has been devascularized, which results frequently in leakage or stricture of the anastomosis [32, 33]. A transsection below the cardia may reduce the risk for stricture of the distal esophagus [62]. Theoretically, an alternative might be the Collis procedure, which reduces inflow from the area of the stomach fundus into the distal esophagus. The lineal stapler suture is performed in

the part of the stomach covered by the visceral peritoneum (serosa). In our institution, an ongoing pilot study is focused on technical variables of the laparoscopic azygoportal disconnection.

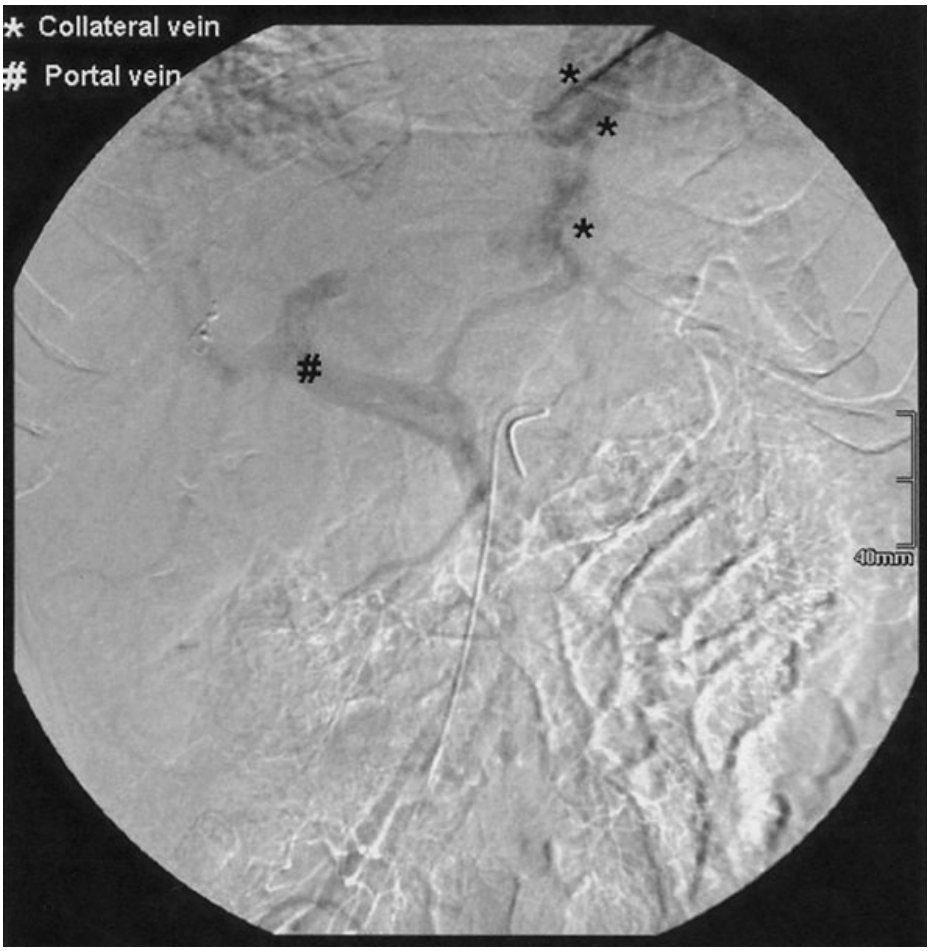


Figure 9. Splenoportography with the localized collateral vein toward the esophagus.

Another alternative is selective occlusion of the dominant collateral vein, which can be detected by angiography (CT scan, X-ray, or MRI) (**Figure 9.**). Laparoscopy makes it possible to identify such a solitary collateral vein. This procedure is less detrimental. However, an interventional occlusion of such dominant collateral during the angiography would then be the method of choice [63].

A final step of the procedure, a laparoscopic Toupet fundoplication, aims to restore the antireflux mechanism, which is likely to be destroyed by opening of the hiatus of the diaphragm and dissection of the distal esophagus and the stomach fundus during division of the venous collaterals. An alternative for controlling a gastroesophageal reflux could be proton pump inhibitors (PPIs). However, PPIs could negatively influence the cytochrome P450 (CYP) 2C19 of the liver in which the PPIs are metabolized [64].

3.3.5. Conclusion

All five of our patients survived the surgery very well, and the prospective follow-up period as long as 30 months confirmed the reduced varicose veins of the esophagus and the good quality of life experienced by the two patients who discontinued alcohol consumption. The novel laparoscopic azygoportal disconnection thus seems to be a reliable, less detrimental method for prevention of rebleeding from esophagus varices. However, our initial experiences must be confirmed in large prospective randomized studies comparing the laparoscopic procedure with other modern treatment methods such as beta receptor inhibitors, endoscopic intervention, or TIPS.

4. SELF-EXPANDABLE STENT FOR THE ACUTE TREATMENT OF ESOPHAGUS VARICEAL BLEEDING

(An experimental and clinical study)

4.1. Introduction

Acute esophagus variceal bleeding presents a life threatening complication of portal hypertension. Mortality after the first bleeding episode is up to 50%. After an initial haemorrhage, the frequency of recurrent bleeding ranges between 30-40% within the subsequent 6 weeks, and 70% of the patients die within the first year [48, 65]. Variceal bleeding is now more commonly treated pharmacologically and/or via endoscopes with sclerotherapy (EST), or band ligation (EBL) [66]. 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 [67]. 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 [68, 69]. 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.

4.2. Examination of the esophagus after implantation of two different self-expandable stents (experimental study)

4.2.1. Insight to this study

This study is proved the feasibility of the new stent designed for stop acute variceal bleeding, furthermore the destructive effect to the normal esophagus. The local pressure of the stents may result a decrease in the local microcirculation resulting in tissue damage. We aimed to demonstrate possible deformations of the tissue elements building up the esophagus after the implantation of two different stents.

4.2.3. Materials and methods

4.2.3.1. Design of the stents and the delivery system

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 (**Figure 10.**).

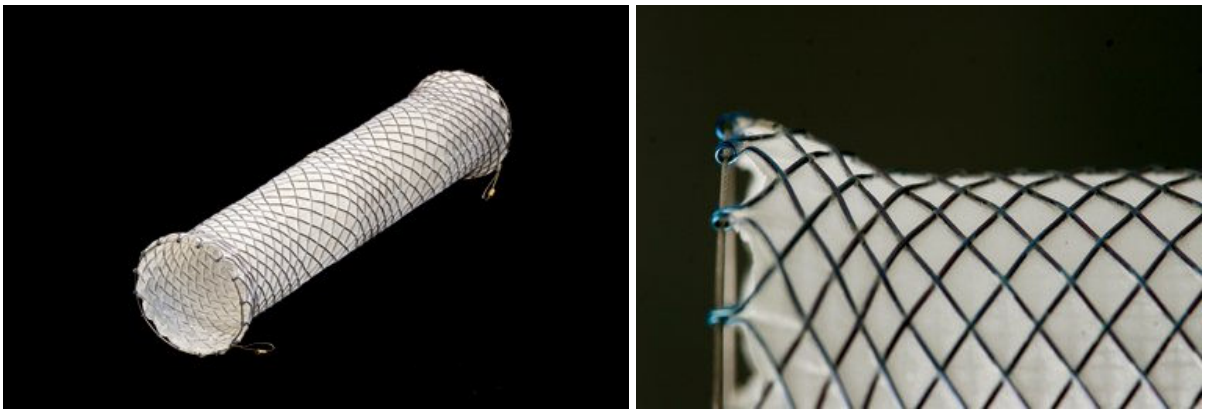


Figure 10. Design of the new stent (SX-Ella-Danis)

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 (**Figure 11.**).

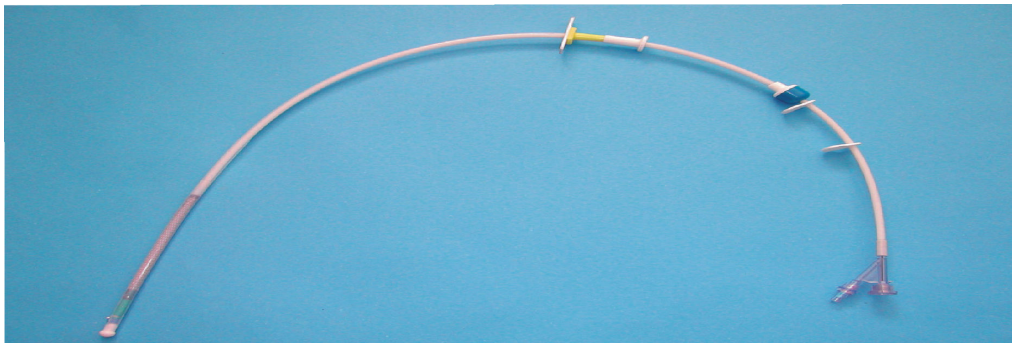


Figure 11. Design of the delivery system

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 (**Figure 12.**). Delivery system of this stent is equipped with an inflatable balloon for the easier positioning.

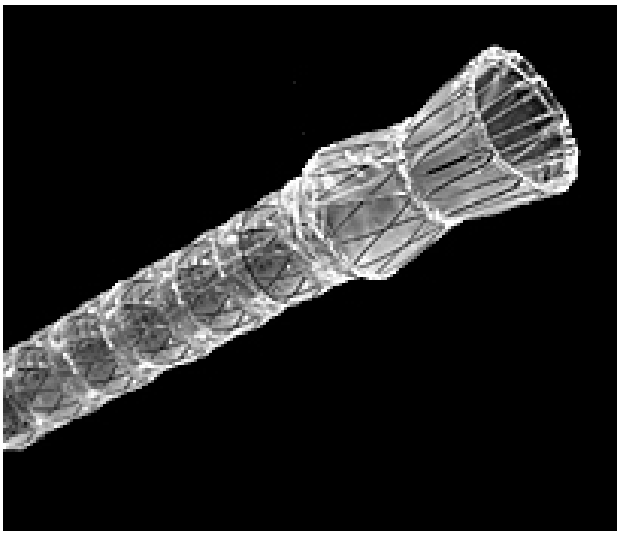


Figure 12. Design of the stent-2 (FerX-Ella-Boubela)

4.2.3.2. Animals

All experiments were in accordance to rules and regulations regarding the use of animals in medical research. The present study was approved by the local institutional committee on animal research of Pécs University (BA 02/2000-29/2001).

Fourteen adult mongrel dogs (five ♀, nine ♂, 9-32kg) were randomly selected and denied access to food prior to the procedure. After premedication with i.m. Droperidol (1,5 mg/Kg), Fentanyl (0,03mg/Kg) and Atropin (1mg), short anaesthesia was induced with i.v. Thiopental-sodium injection. Lidocain spray was sprinkled into the pharynx before the procedure in all animals.

4.2.3.3. Stent introduction

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 (mean body weight 24 kg) (**Figure 13.**). 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.

Figure 13. Introduction of the stent

In the second group (stent-2) seven mongrel dogs (with average body weight 26 Kg) 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. 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.

4.2.3.4. StO_2 measurement

Tissue oxygen saturation of the esophagus was monitored with the Inspectra Tissue Spectrometer-Model 325 (Hutchinson Technology Inc., Hutchinson, Minnesota USA) by means of a 15mm light emitting/collection head attached to an optical cable placed into the esophagus. 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.

Tissue oxygen saturation data were analysed with one-way analysis of variance (ANOVA). The level of significance was set at $P < 0.05$. The Micro Cal Origin (ver. 6.0) program (Microcal Software Inc., Northampton, USA) was used for graphical presentation.

4.2.3.5. Differential Scanning Calorimetric measurements

Differential scanning calorimetry (DSC) is a well-established method for the demonstration of thermal consequences of local and global conformational changes in biological systems [70], but it has never been used for the investigation of the esophagus.

The thermal unfolding of the healthy and stented esophagus preparations were monitored by SETARAM Micro DSC-II calorimeter. All experiments were conducted between 5 and 80 °C. The heating rate was 0.3 °K/min in all cases. Conventional Hastelloy batch vessels were used during the denaturation experiments with 850µL sample volume (oesophagus samples plus buffer) in average. Typical sample wet weights for calorimetric experiments were between 200 – 250 mg. DMEM-F12 (with admixtures) buffer was used as a reference sample. The sample and reference vessels were equilibrated with a precision of ± 0.1 mg. There was no need to do any correction from the point of view of heat capacity between sample and reference vessels. The repeated scan of denatured sample was used as baseline reference, which was subtracted from the original DSC curve. Calorimetric enthalpy was calculated from the area under the heat absorption curve by using two-point setting SETARAM peak integration.

After the follow up period the 15 cm long segment of the esophagus with the stent and the control normal wall above the involved area were removed, and carefully purified from tissue fragments. Esophagus samples were derived into mucosal and muscle tissue layer, to investigate separately the differences between the distinct tissue constituents and the whole wall.

All the esophagus samples weighted identically ca. 100 mg, that represents a 5 mm long, 5 mm wide segment with a height of 3 mm. Samples were washed 3 times in PBS (Sterile Phosphate-buffered saline, pH 7.4) in order to eliminate all tissue remnants. Samples were treated with DMEM-F12 solution (GIBCO lab) containing 10% (FBS) foetal bovine serum (HYCLONE lab), antibiotic, antimycotic solution (1U/ml penicillin, streptomycin, gentamycine and fungisone, GIBCO), non-essential amino acids (GIBCO), and sodium carbonate. All the individual samples were stored separately at 4°C, no longer than 24h. Then samples were subjected to calorimetric measurement**.**

4.2.4 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.

4.2.4.1. Examination of the esophageal wall

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, whereas the mucosa underlying the polyurethane membrane covering was smooth without signs of inflammatory or scarring (**Figure 14.**). Wall thickening was observed alongside the stent in the group stent-2 without any sign of inflammation.

Figure 14. Stented esophagus wall after 2 weeks (group stent-1)

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 (**Figure 15.**). 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.

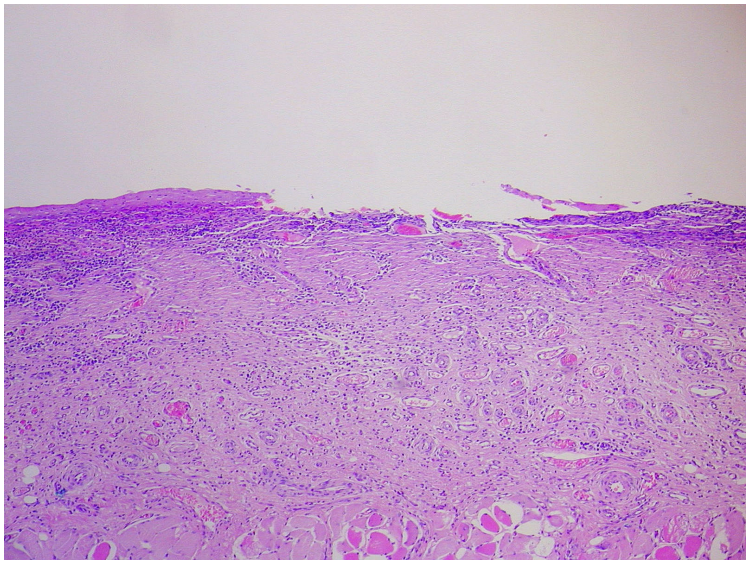


Figure 15. Focal erosion of the mucosa in group stent-1 (H&E, orig.magn. x100)

The microscopic investigation of the esophagus in the other specimens (2 dogs) with alternating stent position has found normal mucosa and did not show reactive or dysplastic changes.

4.2.4.2. StO_2 measurements

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. (**Figure 16.**)

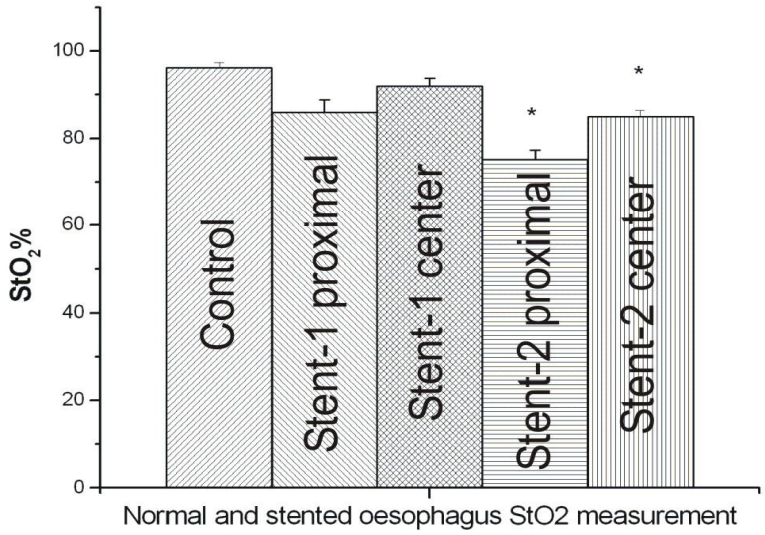


Figure 16. StO_2 measurements (*=p<0,05)

4.2.4.3. DSC measurements

According to the denaturing experiments the surgical interventions result in a significant alteration both in the course of DSC scans (**Fig. 17-19.**) as well as in their thermal parameters (**Table 6.**) 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). These findings clearly demonstrate that despite of the significant alterations caused by the surgical intervention, stent-1 seems to be a good choice to improve the general state of patients in gastrointestinal bleeding.

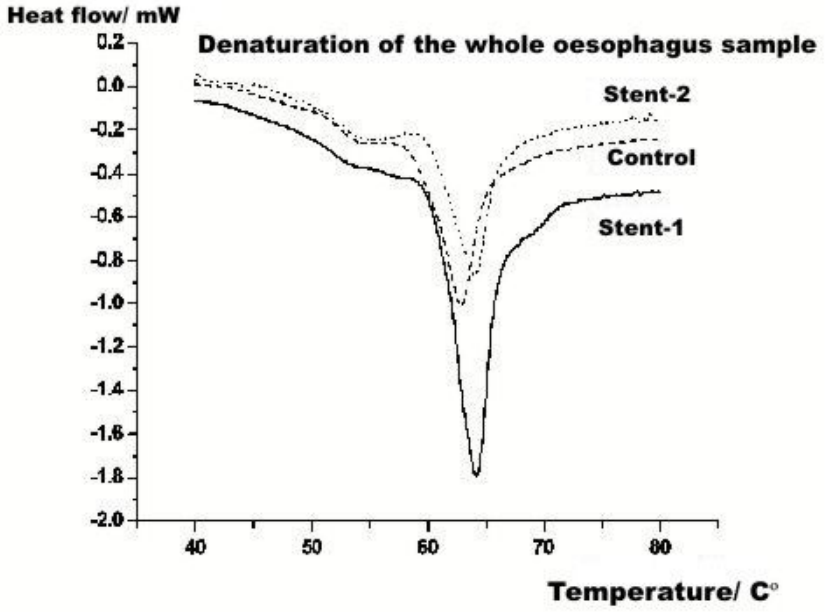


Figure 17. Thermal denaturation of healthy and stented dog whole esophagus wall

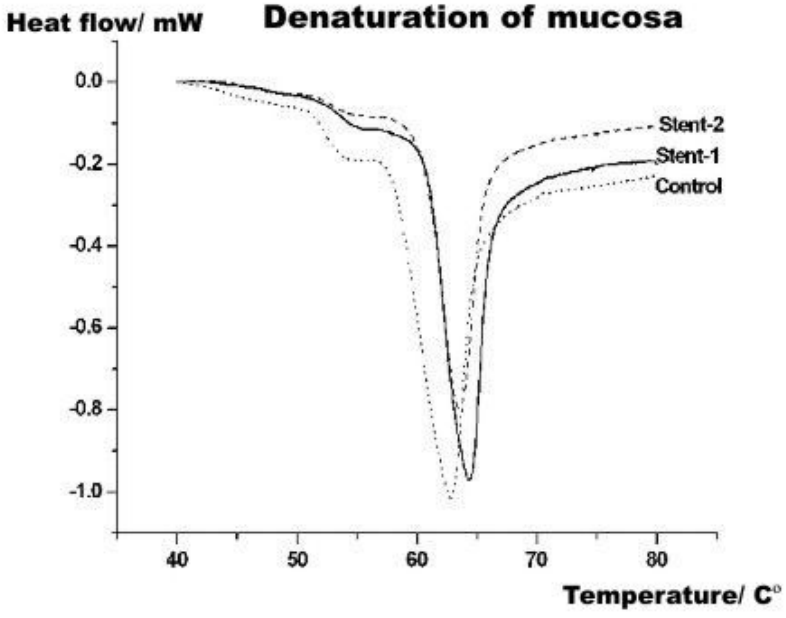


Figure 18. Thermal denaturation of healthy and stented dog esophagus mucosa

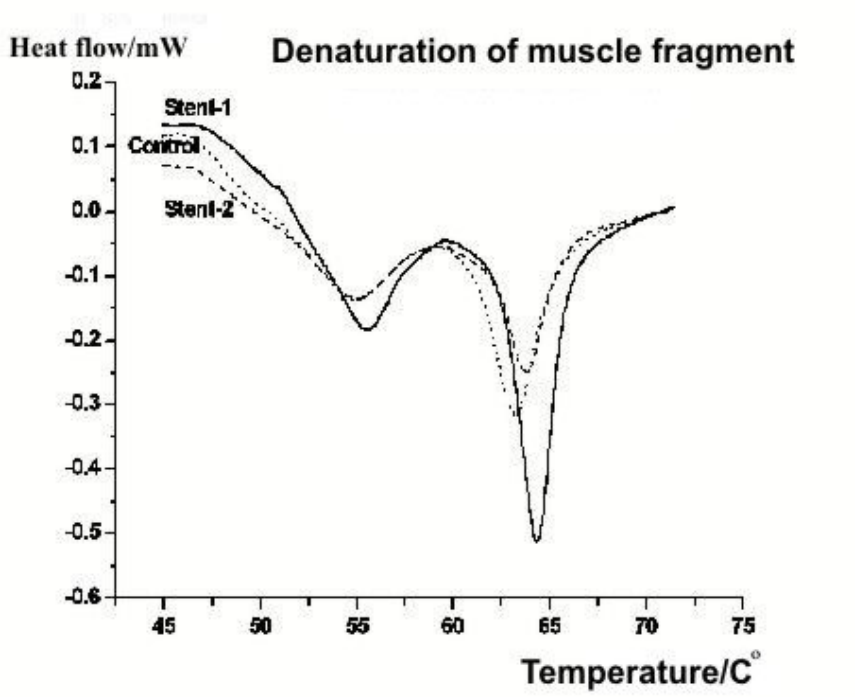


Figure 19. Thermal denaturation of healthy and stented dog esophagus muscle fregment

Table 6. Thermal parameters of denaturation of esophagus samples. Data are expressed in mean ± s.d., the calorimetric enthalpy is normalised to unit sample mass.

	Stent-1			Stent-2			Control		
	ΔH (J/g)	T_{m1}/ºC	T_{m2}/ºC	ΔH (J/g)	T_{m1}/ºC	T_{m2}/ºC	ΔH (J/g)	T_{m1}/ºC	T_{m2}/ºC
total sample	2±0.1	54.2±0.3	64.1±0.3	1.34±0.07	55.2±0.3	64±0.3	1.6±0.08	54.9±0.3	62.9±0.3
mucosa	0.9±0.05	55.6±0.3	64.3±0.3	1.15±0.06	55.6±0.3	63.6±0.3	1.2±0.06	54.8±0.3	62.8±0.3
muscle	1.13±0.06	55.5±0.3	64.3±0.3	0.97±0.05	55.1±0.3	63.8±0.3	0.95±0.07	54.9±0.3	63.2±0.3

4.2.5. Discussion

Massive bleeding from esophageal varices is the major cause of death in patients with portal hypertension. To decrease the amount of blood loss is very important, and immediate management is required. In the acute phase of bleeding, 25 % of the patients presenting with variceal haemorrhage continue to bleed, despite the acute drug or endoscopes therapeutic treatment [67]. These patients require further immediate intervention, usually a Sengstaken-Blakemore tube. The technique is successful in about 85% of cases, but the risk of recurrent haemorrhage following deflation is up to 50%. The device is uncomfortable for the patient and carries a 14% risk of serious complications, with 5% mortality; include aspiration pneumonia, esophageal rupture and mucosal ulceration. Complications appear to be more common when balloon are placed by inexperienced personnel [65, 71, 72].

Placement of conventional esophageal endoprosthesis and stents for palliation of obstructive esophageal carcinoma is safe and well established [68, 69]. In 1957 Vossschulte described the first surgical implantation of metal cylinder in the distal esophagus in the case of recurrent varix bleeding [73]. This method was not used again later on. In the beginning of the eighties palliative therapy of malignant strictures in the esophagus was revolutionized by the use of SEMS [74]. Nowadays, the stent placement in the gastrointestinal tract increases fast, due to the better clinical conditions of the patient after the insertion, and to the easier feasibility of this method. Our aim was to evaluate a new method for decrease or stop the blood loss to stabilize the haemodynamic parameters in the acute phase of varix bleeding as well as to preserve the patient general wellness during the treatment.

4.2.6. Conclusion

This experiment showed that the new self-expandable SX-Ella-Danis-stent is a safety and suitable procedure without deterioration of the esophageal wall when the stent size is comparable with the esophagus dimension of an experimental animal.

Safety and efficiency in the experimental model had encouraged us to apply this method successfully on fifteen patients with bleeding oesophagus varices. The long term goal is to show that expandable metal stent placement could be an effective way of decreasing or stabilising the acute bleeding from ruptured esophagus varices in cirrhotic patients until the effective therapeutic method (endoscopic band ligation, TIPS, etc.) would be introduced.

4.3. Preliminary clinical experience with the new stent in the management of acute esophageal variceal bleeding

4.3.1. Insight into this study

In case of acute variceal bleeding therapeutic strategies for stabilization of the cardiovascular system have priority. Additive therapy with antibiotics (norfloxacin or ciprofloxacin) leads to significant reduction of mortality and improve effectiveness of methods to control bleeding [75]. Standard therapy consists of terlipressin or octreotid and/or endoscopic therapy. This stops bleeding in 90% of the cases. It seems that medicamentous therapy is superior to sclerotherapy [76]. Regarding the band ligation there exist still no comparative studies for the acute bleeding. For the embolization with Histoacryl a comparative study is only present, which showed a significantly smaller rate of rebleeding with same rates of hemostasis, if the sclerotherapy and Histoacryl injections were combined (10 per cent versus 44 per cent with sclerotherapy alone during the first 10 months) [77]. In some cases bleeding cannot be stopped despite combination of endoscopic and medicamentous therapy, especially in patients after several procedures of sclerotherapy or band ligation leading to sclerosis of the mucosa with vulnerable mucosa [67]. In situations in which the standard treatment fails, balloon tamponade or emergency TIPS placement may be indicated [78]. Balloon tamponade is used if endoscopic interventions and vasoconstrictor therapy fail to control variceal bleeding. The techniques are successful in 90% of cases. Serious complications, with 5% mortality, include aspiration pneumonia, esophageal rupture and mucosal ulceration [71].

Coated self-expanding metal stents (SEMS) are a recognized means of treating esophageal malignancy [69]. SEMS can also be used to compress esophageal varices. When immediate hemostasis is not achieved using standard pharmacological and endoscopic therapy, we use

SEMS to arrest acute hemorrhage. An evaluation of effectiveness of SEMS placement in achieving hemostasis, demonstrating the safety of the method and avoiding complications with the procedure itself, led to the development of a specialized stent for exclusive use in patients with acute variceal bleeding.

The aim of this pilot study was to evaluate the use of self-expandable metallic stents to arrest uncontrollable acute variceal bleeding.

4.3.2.Patients and Methods

4.3.2.1. Patients

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. Vasoactive therapy (somatostatin) and antibiotic treatment were initiated when variceal bleeding was suspected [75]. After hemodynamic stabilization, endoscopy was carried out as soon as possible on a 24-h availability basis. An attempt was made in every patient to arrest the variceal bleeding by endoscopic therapy, and this was successful in 128 patients.

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 (range one to five; mean 2.4) despite previous endoscopic interventions. Previous treatments included band ligation (n=18; range, one to fie times), sclerotherapy (n=5; four patients with one procedure and one with two procedures), and balloon tamponade (n=6; range, one to three times). The patients' mean age was 52 (range 27-87). Bleeding was caused by liver cirrhosis due to alcoholism (n=11), immunological or cryptogenic cirrhosis (n=3), or by gastric ulcer combined with bleeding esophageal varices (n=1). The Child-Pugh classification was B in eight of the patients and C in 12 (**Table 7.**).

Informed consent was obtained from all but three patients who were in hepatic coma. After all established methods failed to stop bleeding; the stent procedure was use as a last resort.

4.3.2.2. Procedure

The stents were inserted to treat acute ongoing beeding as follows. When sedation was necessary, intravenous midazolam was used (at stepwise dosages of 2.5-10mg), 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 (**Table 7**.).

A new, special type of stent, the SX-Ella-Danis (diameter 25mm, length 135), was then developed in a collaboration with the company ELLA SX-Ella-Danis stents 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 (**Figure 20.**).

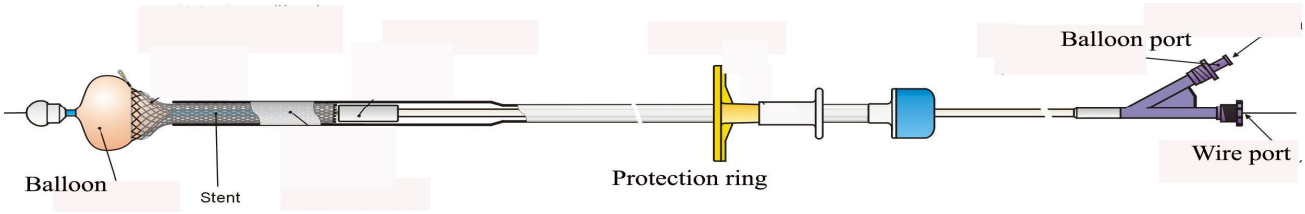


Figure 20. Design of the special introducer

The stent was situated just proximal to the positioning balloon in the funnel-shaped end. Correct insertion was accomplished by inflating the balloon at the distal end of the insertion device, to allow correct positioning when the balloon was retracted to the cardia before release of the stent. After release, the stent compressed the esophageal varices. The balloon was deflated and the set removed (**Figure 21.**).

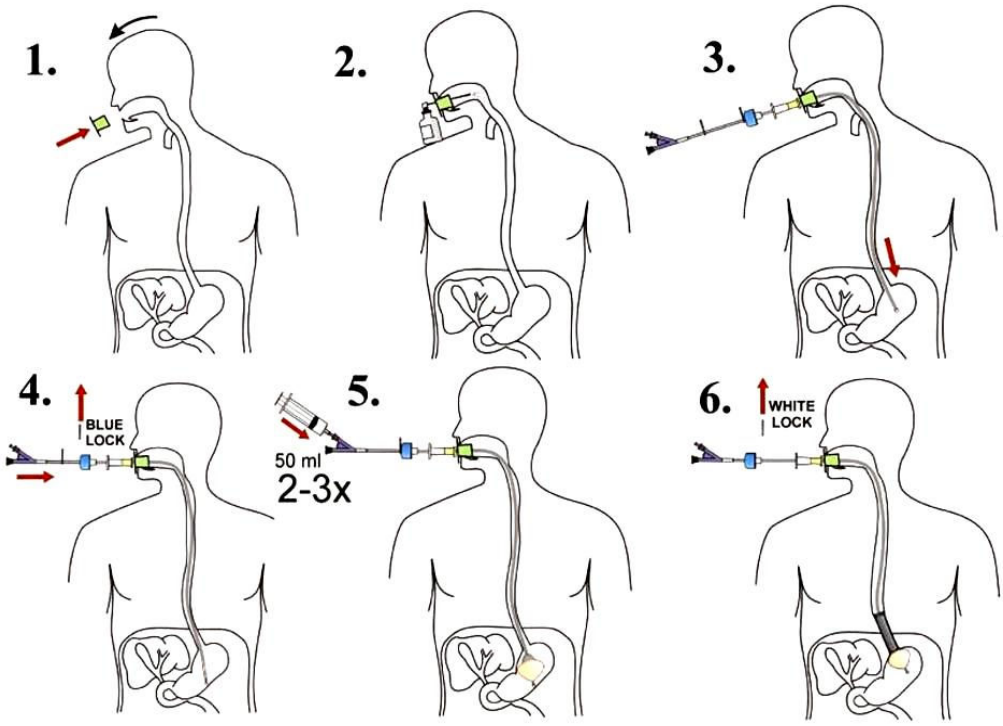


Figure 21. Steps of the introduction

Esophagogastroscopy was carried out after stent implantation, and chest radiography was done up to 12 h later to verify correct positioning of the sent (**Figure 22.**). Vasoactive drug therapy with somatostatin was discounted 12 h after stent placement. Cessation of hemorrhage was confirmed by subsequent gastroscopy.

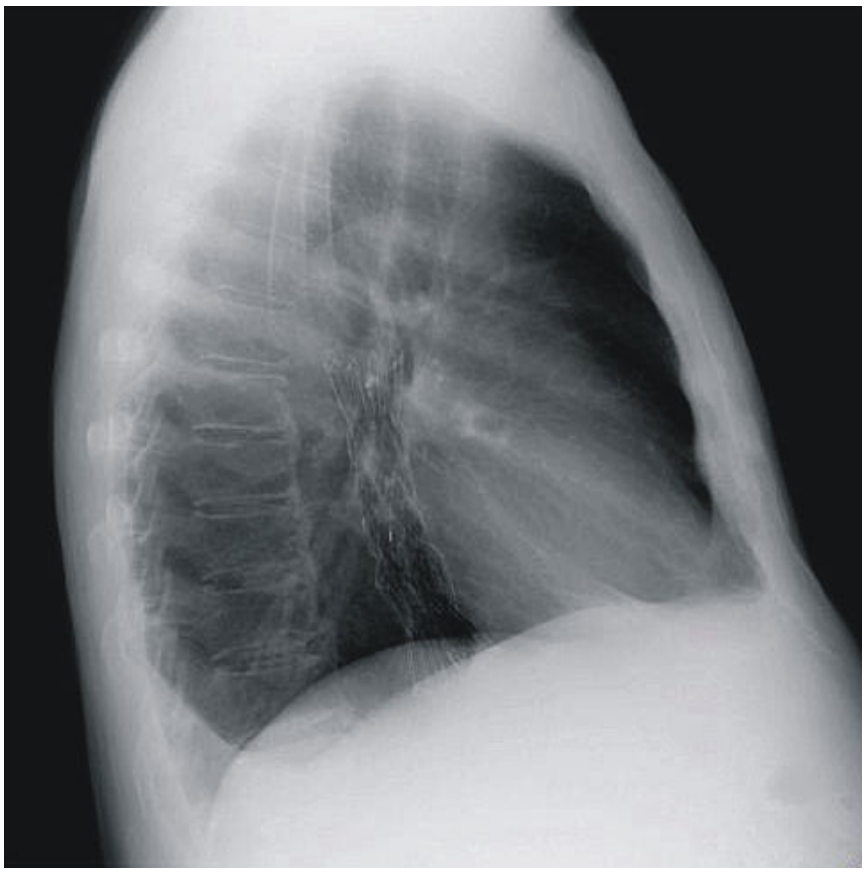


Figure 22. Radioscopy control of the correct stent position (stent Ella-Boubella)

After stabilization, the patient's upper body was placed in a slightly upright position (about 30°) in order to reduce the risk of reflux and aspiration. Liquid food and water were allowed 2 h after stent placement. After 1 day, all but the three comatose SEMS patients were able to take liquid or well-chewed food to avoid stent dislocation or occlusion. If there were signs of encephalopathy, l-ornithine-l-aspartate, lactulose, and neomycin were administered as needed.

4.3.3. Results

Stent placement was successful and uncomplicated in all 20 patients, and the hemorrhage stopped immediately after implantation of the stent (**Figure 23.**). 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.

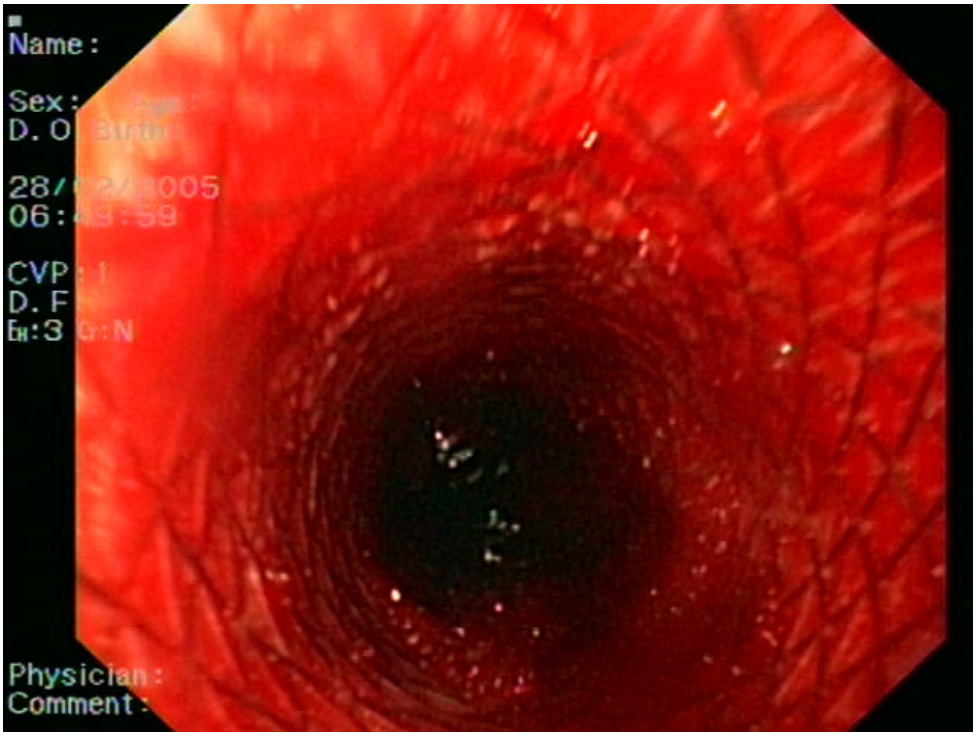


Figure 23. Succesful stent implantation into the bleeding esophagus on the control endoscopy

In the remaining 19 patients, circulation stabilized within 2 h. 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 (**Figure 24.**). 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.

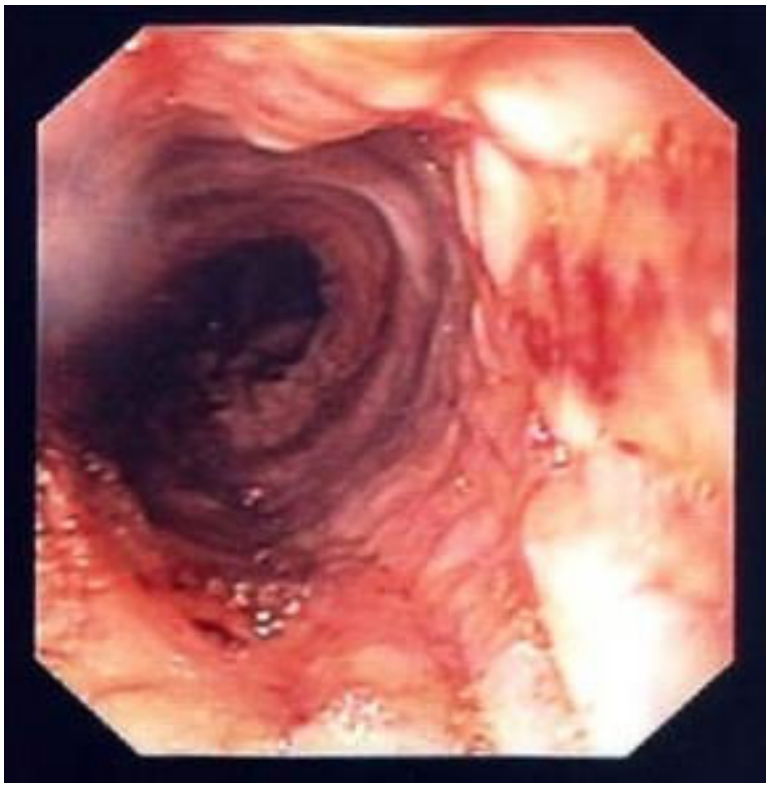


Figure 24. Esophagus after the stent extraction on the control endoscopy

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 (**Table 7.**).

4.3.4. Discussion

Acute variceal hemorrhage is the most lethal complication of cirrhosis. The reported mortality rate from variceal hemorrhage is 17 to 57 %. Management of varices can be categorized into three phases: Prevention of initial bleeding, management of acute bleeding, prevention of rebleeding. For the management of acute variceal hemorrhage a 24 hour endoscopy should be necessary to perform correct diagnosis and treatment by band ligation or sclerotherapy as well as pharmacologic therapy. Ideally, endoscopy should be carried out during the first 6h after admission [79]. Even in highly specialized centers with all possibilities of treatment balloon tamponade with all well-known problems and compilations cannot be avoided. It is used in about 5,5 % in first bleeding and 17,4% in rebleeding [65]. The results are supposed to be even worse in hospitals which cannot offer immediate treatment with all possibly necessary treatments as highly specialized interventional endoscopy or in dramatic situations acute TIPS. Balloon tamponade methods (Sengstaken Blakemore, Linton Nachlas, Minnesota) pursue the principle of compression for the cardiac or esophageal varices. They have all the same disadvantages: a) There are several uncertainties, concerning e.g. the filling with air or fluid, the filling pressure, and the modalities of fixation of the probe or the security of the probe to prevent from slipping into the stomach. b) The occlusion of the esophagus causes dysphagia, oral fluid supply is impossible, the patient is put at risk by aspiration of saliva and aspiration pneumonia. c) It is highly unpleasant for the patient, the nursing is costly. Manipulation by agitated patients leads to dangerous removal with a high risk of dislocation to the pharynx or even asphyxiation. d) Further or repeated endoscopic examination cannot be performed without repeated removal. Further diagnostic examinations are disturbed. e) Serious complications due to esophageal necrosis or other are published in several articles. [72, 80, 81, 82]

For all this mentioned reasons we searched for an alternative principle to compress the varices.

A surgical implantation of a metal cylinder in the distal esophagus was described Vossschulte first in 1957. [73] This method was not used again later on. In the beginning of the eighties palliative therapy of malignant strictures in the esophagus was revolutionized by the use of SEMS [74]. Secondary bleeding after introducing of Stents was more rarely than the calculated risk [83]. Despite, we haven't found any report in the literature about the use of stents for the therapy in variceal bleeding we were encouraged to use stents usually used for esophageal malignancy and develop a special stent for this individual indication. New methods always have the necessity to calculate the individual risk and advantages. Evaluating that the utilization of all conventional methods is obligatory the use of stents has substantial advantages:

a) There has to be a standardized expansion power and pressure to the esophageal wall which was optimized by our investigations in the development of the ELLA-Danis stent. b) Stent insertion is a standard procedure. c) The stent cannot be removed or dislocated by agitated patients. d) The lumen of the stents guarantees the physiologic drainage of saliva and makes even the feeding by oral fluid and food ingestion possible. This allows safety and high comfort for the patient. e) Immediate after insertion a detailed and repeated examination of the esophagus, cardia, stomach and duodenum as well as suction of gastric contents is available.

But there are well-known disadvantages due to stent application: a) For all established stents a radioscopy is necessary. This causes problems in acute bleeding by availability and hygienic reasons. b) Not optimal configuration of the stent causing distal migration or remaining of oral food at the wall. c) Risk of necrosis or fistulization. d) Necessity of stent extraction.

As we are of the opinion that the stent procedure for variceal bleeding has more benefits than risks we developed a special stent in several steps to minimize the problems and optimize the outcome. The stent is produced in a special winding according to the anatomic configuration of the esophageal varices especially in the distal 4 to 6 centimeters. Additional we developed a specific insertion device which makes radioscopy avoidable. This is guaranteed by the use of an inflatable balloon at the distal end which allows a correct location when the balloon is retracted to the cardia before setting the stent free. The stent is situated just proximal to the balloon in a funnel-shaped end, this enables a correct position although in the case of a hiatal hernia. The chosen length of the stent with 135 mm allows that the proximal end is distal of the aortic arch to avoid excessive tension. The cover is impermeable, smooth and situated inside, the outer side is rough. Both ends are equipped with a wire loop for extraction. This loop and the special winding lead to the elongation and narrowing of the stent during the extraction procedure. These modified and focused construction devices where tested for functionality and safety in animal trial, prior to use in human. They guarantee the highest grade of safety and reliability. There was an immediate stop of bleeding in all patients with variceal bleeding, which could not be managed by endoscopic or pharmacologic treatment options. In this setting stents where used as an alternative treatment to balloon tamponade. Most of the stents remained for 6 (one for 14) days in the esophagus. There where no early or late complications for a follow up period of 30 days. The stent application allowed a safe bridging from acute bleeding to perform all examinations and procedures to complete a definitive treatment without any rebleeding episodes. It guaranteed oral feeding at least by liquid without a high comfort for the patients and no additional nursing requirements.

4.3.5. Conclusion

Stent application for variceal bleeding is an innovative method which was used after carefully selection and evaluation for 20 patients in case of emergency and a high risk situation for mortality. This procedure caused no complications and lead to immediate stop of bleeding, a physiologic drainage of saliva was possible, and ingestion of fluid was performed about 2 hours later. During the treatment period and the follow up for 30 days there was no rebleeding episode in all patients. For the confirmation of this initial experience further studies including large number of patients have to be done.

5. NOVEL FINDINGS

1. In the first section of this thesis we examined the sufficiency of a new type venous closure by means of bipolar feedback thermal vessel sealing and the feasibility of a new, minimally invasive procedure, the laparoscopic azygoportal disconnection in animal model and also in human.

    - In the "*in vitro"* study we could confirm the reliability of the bipolar feedback controlled sealing system LigaSure-ATLAS for the closure of the veins in animal with induced portal hypertension.

    - 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. In the second section of this thesis we proved the feasibility of a new self-expandable metal stent designed for the treatment of acute variceal bleeding in animal experiment and also in human.

    - The new self-expandable stent is a safe and suitable solution without deterioration of the oesophageal 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

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8. PRESENTATIONS AND PUBLICATIONS

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Complete list of 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. (poszter)
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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. (poster presentation)
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8. **Benkő L**, Danis J, Shamiyeh A, Wayand WU, Rőth E. Laparoscopic azygo-portal disconnection procedure with ATLAS-LigaSure in porcine model.(oral presentation)
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