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Fully Covered Self-Expandable Metal Stent Placed Over a Colon Anastomosis in an Animal Model – A Pilot Study of Colon-Metabolism Over the Stent

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1. Abstract

1.1. Introduction: Anastomotic leakage in colorectal resection and primary anastomosis is a common and feared complication. Fully Covered Self Expandable Metal Stents (FCSEMS) have been used for treatment of anastomotic leakage. It is still unknown if FCSEMS affect anastomosis healing negatively by causing ischemia. In an animal study we investigated the metabolic effects over a FCSEMS covering a colon anastomosis.

1.2. Methods: 7 pigs were investigated with metabolic measurements with microdialysis after laparotomy, colon resection and anastomosis with stent placement. Measurements were sampled both the proximal and distal ends of the anastomosis, and from a reference catheter at the small intestine. Measurements of glucose, pyruvate, lactate and glycerol, Lactate Pyruvate (LP) ratio was determined at these three locations.

1.3. Results: Lactate increased during the study even at the reference catheter. Glucose increased initially distal to resection site but after anastomosis and stent insertion a small tendency for numerically declining values. LP ratio increased initially like glucose a minor decrease was noted after anastomosis and stent insertion. Glycerol levels were stable. Conclusion: The colon resection caused initially a hypermetabolism in the intestinal ends next to the ends next to resection site. This hypermetabolism neither deteriorated nor turned into ischemia during the initial postoperative course, but a start of hypoxemia cannot be excluded during the study and after the placement of a FCSEMS.

2. Introduction

Anastomotic leakage after colorectal surgery is a common and dreaded complication. The incidence of anastomotic leakage after colon-cancer surgery in Sweden in 2019 was reported by the Regional Cancer Center to 4.1%. 30-day mortality after acute operation is 6.1% and after elective surgery 1.4% [1]. In case of anastomotic leakage it is common practice to provide a stoma after resecting the anastomosis. In order to prevent the potentially fatal consequences of an anastomotic leak, such as peritonitis, sepsis and organ failure. A stoma not only causes discomfort, but further surgery may be required to close it, which can be complicated and not without risk [2, 3]. Many patients do not have their stoma closed due to reasons such as postoperative chemotherapy, impaired general condition, that it may be delayed due to a prioritizing of surgical resources. Enteral stents are being used as a nonoperative alternative for the treatment of benign and

malignant strictures in the gastrointestinal tract [4, 5]. Most recently, covered intraluminal stents have been successfully introduced to manage anastomotic leaks after esophagectomy, gastric bypass and gastric sleeve operations [6-8]. However there are a few clinical case reports and an animal study that describe the use of covered stents in colorectal anastomotic leakage [9-12]. Intraperitoneal Microdialysis (IPM) has been introduced as a promising method for prediction of surgical complications after gastrointestinal surgery [13-19]. IPM studies have been conducted in both animals and humans [20-22]. An increase of the intraperitoneal LP ratio is indicative of an increased anaerobic metabolism that may develop into inflammation, splanchnic hypoxia and ischemia [13-19]. This results in a disturbance of anastomosis healing. These early metabolic changes are detectable prior to several postoperative complications, such as anastomotic leakage and abdominal compartment syndrome [23]. Biochemical measurements have been analysed in subcutaneous and intraperitoneal locations [24]. Changes are observed only in the intraperitoneal measurements prior to complications, suggesting that major surgical complications are preceded by splanchnic hypoxia/ischemia and that the changes are possible to measure by IPM [13-19, 25-28](Figure 1). Furthermore it has been shown that obese and diabetic patients do not differ in the postoperative intraperitoneal lactate pyruvate ratio compared with control patients [24, 29]. FCSEMS could be an option in the early treatment of anastomotic leakage in colorectal surgery, if is shown not to be detrimental in anastomotic healing by, for example, causing ischemia at the anastomosis. The aim of this pilot animal study, is to investigate the local metabolic changes during the insertion of a fully covered self-expandable stent under a colon anastomosis.

3. Materials and Methods

3.1. Animals

In this study 7 healthy three-months- old domestic pigs of both sexes were used (a crossbreed between Swedish country breed, Hampshire and Yorkshire), with mean body weight 30,4 kg [26-34]. The pigs were housed at room temperature at a farm, with free access to standard porcine fodder before the experiment. They were kept in a 16-hour day and 8-hour night cycle. The experiment was approved by the Regional Animal Ethics committee in Linköping (ID 835-Dnr17869-2020). The study was conducted in accordance with the guidelines of the European Union for the protection of animals used for scientific purposes. The animal experimentation in this study is reported according to the ARRIVE guidelines [30].

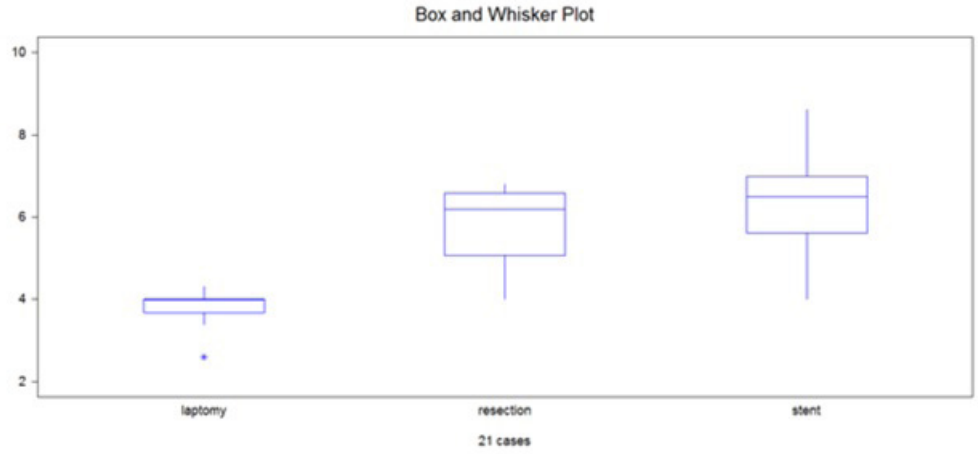


Figure 1: Box and Whisker plot from lactate at colon 1

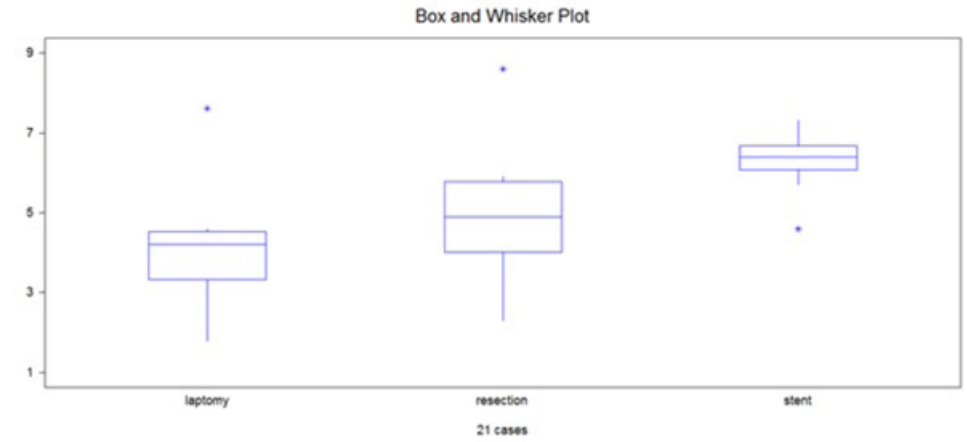


Figure 2: Box and Whisker plot from lactate at colon 2

3.2. Anesthesia, Fluid Administration, Ventilation and Euthanasia

Anesthesia was induced by tiletamine (6 mg kg-1, i.m.; Virbac, Kolding, Denmark), zolazepam (6 mg kg-1, i.m.; Virbac) and azaperone i.m. (4 mg kg-1). In addition, Atropine (1.5 mg, i.m.; Mylan, Stockholm, Sweden) was given. Propofol (1-2 mg kg-1, i.v.; Fresenius Kabi, Uppsala, Sweden) was given if needed. The experimental animals received two peripheral catheters (1.1 mm, VenflonTM Pro Safety, BD, Helsingborg, Sweden) in auricular veins. The animals were orally intubated in the prone position with a 6-mm endotracheal tube (Covidien, Tullamore, Ireland). Anesthesia was maintained. The depth of anesthesia was intermittently (every 5 minutes) monitored by pain response at the cleft of the back leg (Figure 3,4). No muscle relaxants were given. Ringer acetate(10 ml kg-1 h-1, i.v.; Fresenius Kabi) and 10% Glucose with 40 mM sodium and 20 mM potassium (0.5 ml kg-1 h-1, i.v.; Fresenius Kabi) were administrated, by volume pumps (Alaris GP, CareFusion), to substitute for fluid loss. The pigs were ventilated using volume-control ventilation mode (PV 501, Breas Medical AB, Sweden) to achieve arterial Pco2 of 5.0-5.3 kPa and Fio2 was adjusted to maintain arterial Po2 at 12-18 kPa. The animals were covered with a thermal mattress and a forced-air warming blanket was also used. At the end of the experiment euthanasia was performed with a rapid i.v. injection of 40 mmol potassium chloride (B. Braun, Danderyd, Sweden), and asystole and circulatory arrest were confirmed with ECG and blood pressure recordings.

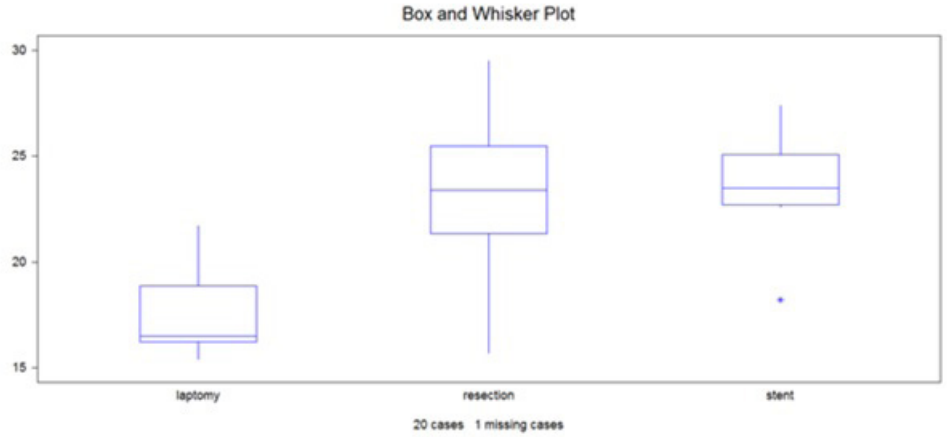


Figure 3: Box and Whisker plot from LP ratio at colon 1

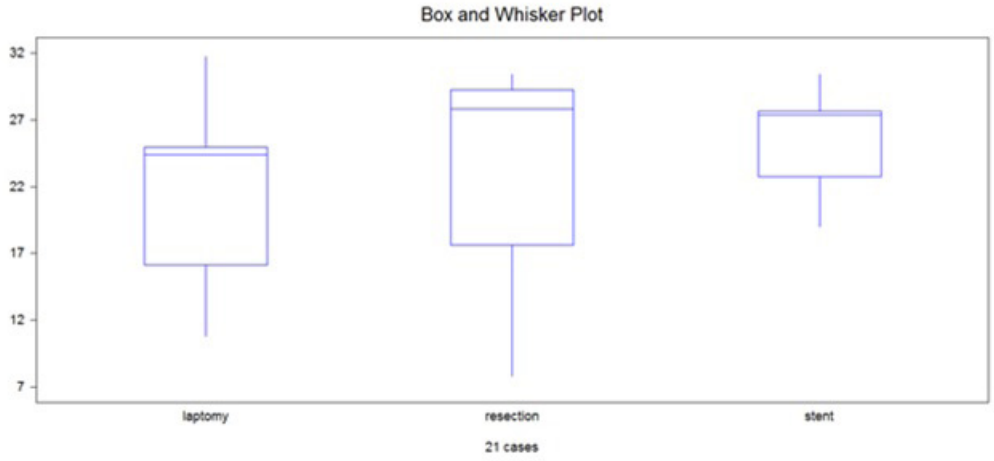
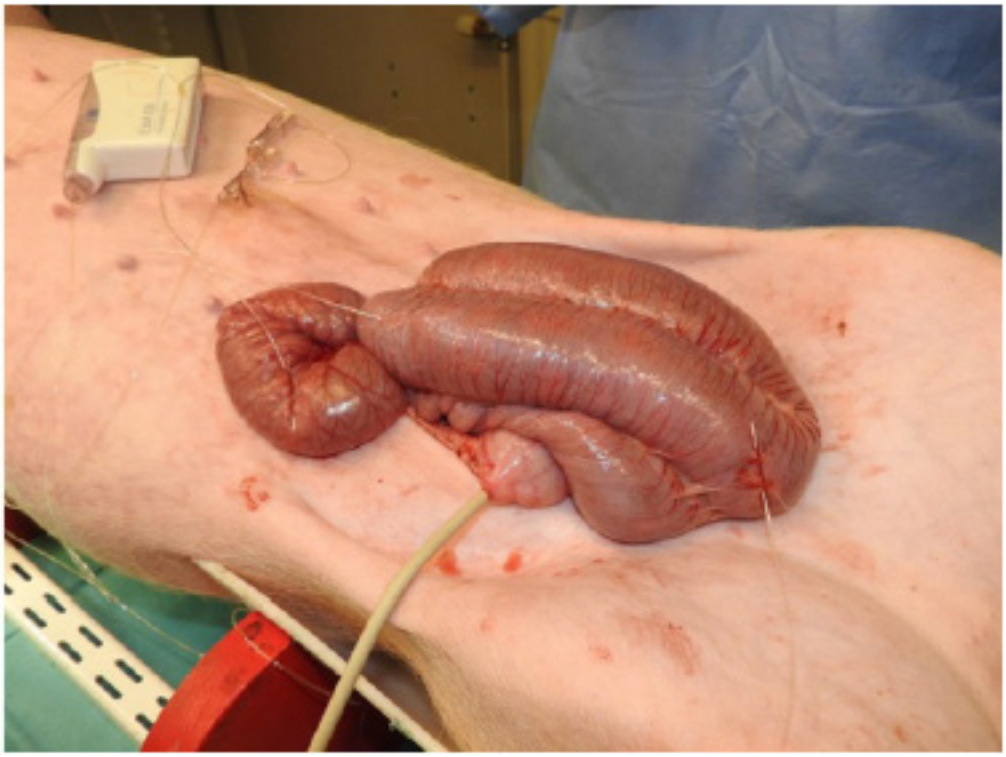


Figure 4: Box and Whisker plot from LP ratio at colon 2

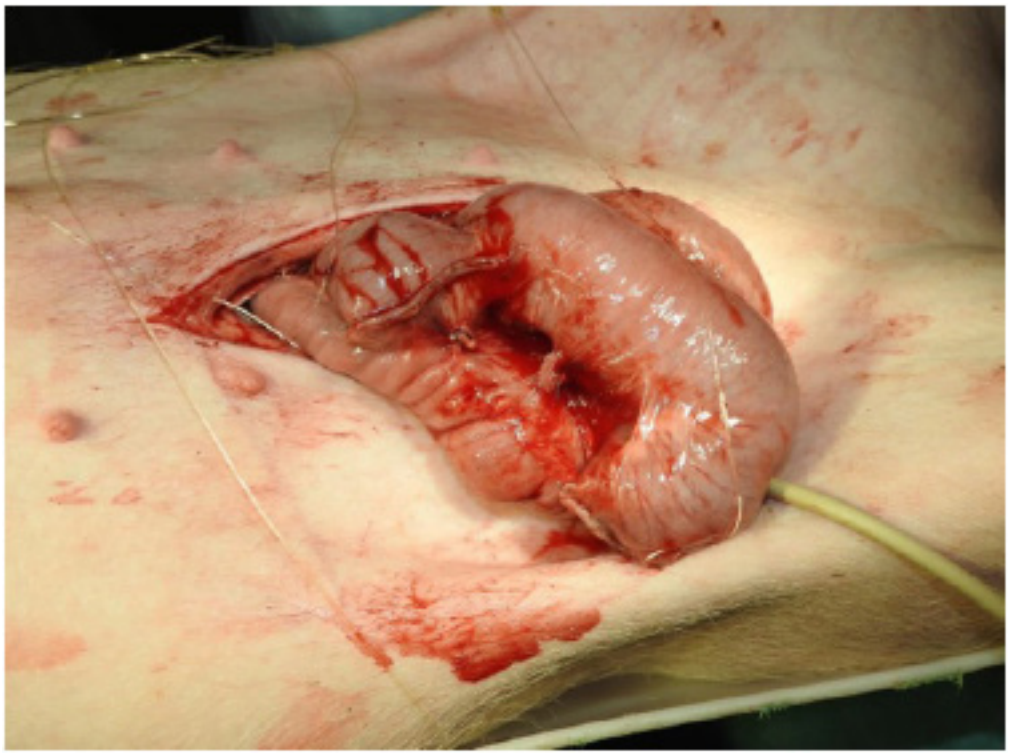
3.3. Surgical Preparation and Measurements

A 4 Fr introducer was placed in the right carotid artery, by open cutdown method, for the measurement of systemic blood pressure as well as blood sampling. The blood samples were analyzed for blood gases. A midline abdominal incision was performed. A 14 Fr Foley catheter was inserted in the urinary bladder and fixed with a purse-string suture. Three microdialysis catheters were placed intraperitoneally (M-dialysis gastrointestinal catheter 62). The first microdialysis catheter was sutured at the superior aspect of the descending colon a second microdialysis catheter was sutured in colon 20 cm distal from the first one. A third reference catheter was placed and sutured at the small intestine. After the laparotomy microdialysis

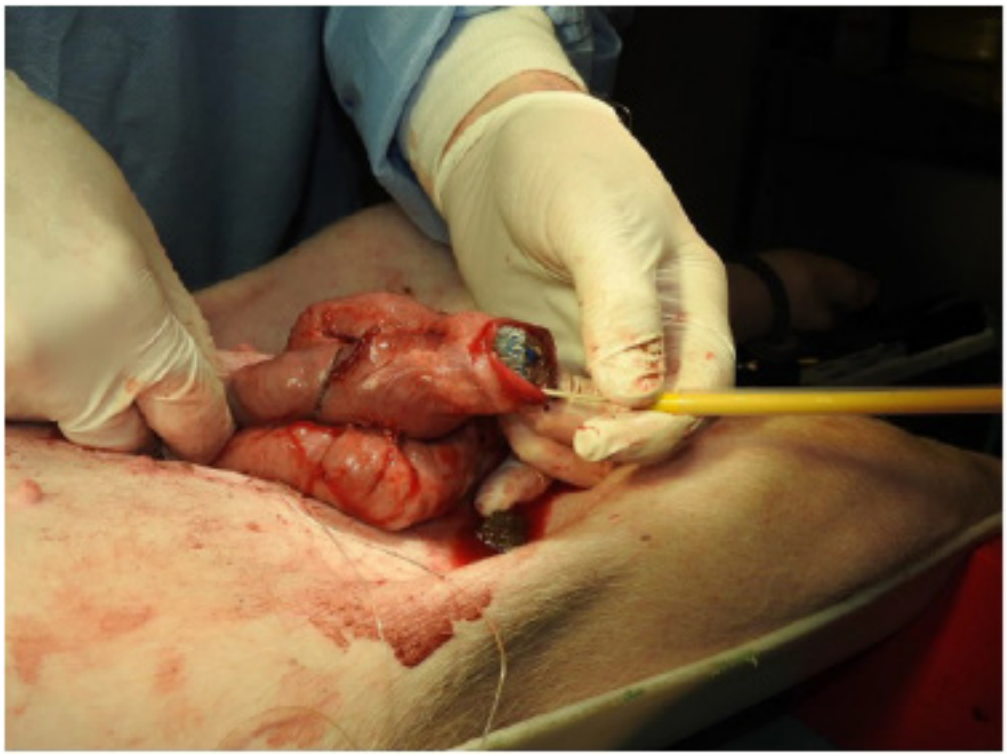
measurements were performed (Picture 1). At the second part of the experiment a colon resection between the first and second colon catheter close to the intestine was performed without disturbance of its vascularization. Microdialysis samples were gathered (Picture 2). Finally at the third part of the experiment an anastomosis between the colon stumps was constructed with circular staple 29 mm and a fully covered self-expandable metal esophagus stent, Hanaro (NES-28-110-070) by Olympus was placed over the anastomosis (Picture 3). Three syringe pumps (M-dialysis106 pumps) were used to propel a solution. The microdialysate was analyzed (M-dialysis ISCUS) for glucose, glycerol, pyruvate, lactate, and glycerol, and the lactate/pyruvate ratio was then calculated. The midline incision was sutured at the end of each procedure with a continuous suture.



Picture 1: Microdialysis catheters placement after laparotomy and an urinary catheter is placed into the urinary bladder.



Picture 2: Placement of microdialysis catheters after resection close to the anastomosis.



Picture 3: Insertion of the stent after the anastomosis is constructed. Microdialysis catheter are after closure of the intestine placed proximal and distal of the anastomosis over the stent.

3.4. Protocol

The animals were first operated with laparotomy. Three microdialysis catheters and the urine catheter were placed. An hour intervention free period. Three hours later, at the second phase of the experiment, colon resection was performed. At the third phase, 2 hours after the colon resection, anastomosis was constructed and the stent inserted. Blood pressure, pulse and urine production were measured after each phase of the experiment. At the same time, intraperitoneal samples were collected and analyzed immediately bedside. Blood samples were collected from the carotid artery and were analyzed for blood gases.

3.5. Intraperitoneal Microdialysis

Intraperitoneal Microdialysis (IPM) is a method that uses a double-lumen catheter with diameter of 0,9 mm placed between the small intestine loops free- floating. In this study microdialysis equipment from M-dialysis AB Stockholm Sweden have been used. At the end of this catheter there is a semipermeable membrane. Gastrointestinal catheter 20 kDa pores allow lactate, pyruvate, glucose and glycerol to filter through the membrane. A microdialysis pump provides a constant flow to the semi-permeable membrane, which facilitates the equilibrium of ringer dialysate with the extracellular tissue. This sample is collected in a little test tube called a microvial. The microvial is analyzed by a computer- assisted spectrophotometer. The analysis can be performed continuously with 20- min intervals between the sampling, time that is needed for the microvial to be filled with an adequate amount of fluid. The analysis of lactate, pyruvate, glucose and glycerol takes 7 minutes, which basically allows continuous monitoring of the balance between aerobic and anaerobic metabolism at the cellular level.

4. Statistical Analysis

Data are presented as median and interquartile range. In the statistical analysis, pairwise comparisons between groups were performed after the colon resection and after the anastomosis with the stent placement, using Kruskal Wallis test and ANOVA (Statistix 8®). A p-value less than 0.05 was regarded as statistically significant.

5. Results

5.1. Vital Parameters (Table 1)

Blood pressure was stable during the experiment with only small variations with an average- pressure of 80 mmHg. Small variations through the experiment could also be noted in the pulse frequency with approximate values of 90 beats/min. Urine production was stable throughout the experiment between 35 and 65 ml/h. No statistical differences could be seen in the vital parameters during the experiment.

5.2. Arterial Acid-Base Results (Table 2)

Completely stable arterial pH could be seen during the study (7.56) but a variation in Base Excess (BE) could be noted where it increases from 7.3 mmol/l after the laparotomy to 7.7 mmol/l after the colon resection. A decline was seen after anastomosis and stent insertion as BE decreased to 7.5 mmol/l. PO2 decreased during the experiment, started at 16.3 kPa, declined to 15.1 after resection, with a final value

of 14.3 mmol/l after stent insertion. Stable values were observed in measurements by 4.5 which were throughout the experiment. Arterial glucose is completely stable during the experiment with a value of 5.5 mmol/l and 5.4 during the 3 measurement observations. Gradually decreasing values can be noted in arterial lactate, after the laparotomy the median value of lactate is 1.6 mmol/l, which decreased to 1.5 after resection, and finally 1.3 after stent insertion.

Table 1: Vital parameters average bloodpressure (mmHg), pulse (beats/min) and urine production (ml/h) measured after laparotomy, resection and anastomosis with stent insertion. (Median values, Q1/Q3)

	laparotomy	resection	stent	p value
Bloodpressure	78	82	77	0.769
Q1/Q3	69/87	73/96	72/90	
Pulse	89	100	92	0.139
Q1/Q3	77/95	90/113	89/113	
Urine Production	35	65	50	0.994
Q1/Q3	30/85	25/70	40/55	

Table 2: Arterial acid base samples after laparotomy, colon resection and anastomosis with stent insertion. (Median values, Q1/Q3)

	laparotomy	resection	stent	p value
pH	7.56	7.55	7.56	0.708
Q1/Q3	7.55/7.58	7.5/7.59	7.5/7.6	
BE	7.3	7.7	7.5	0.772
Q1/Q3	6.6/8.2	6.8/8.4	6.7/10.1	
PO2	16.3	15.1	14.3	0.118
Q1/Q3	15.6/17.5	13.2/15.6	11./17.0	
PCO2	4.4	4.5	4.4	0.934
Q1/Q3	4.3/4.6	4.2/5.4	4.1/5.5	
Glucose	5.5	5.5	5.4	0.57
Q1/Q3	5.0/6.1	5.3/5.8	5.0/5.6	
Lactate	1.6	1.5	1.3	0.2248
Q1/Q3	1.3/1.8	1.2/2.3	0.9/1.8	

5.3. Microdialysis Results (Table 3)

Glucose colon 1 (proximal to colon resection) was 3.0 mmol/l after laparotomy then decrease to 2.9 mmol/l after colon resection, and further dropped to 2.5 mmol/l after stent insertion. This reduction was not significant (p=0.601). Glucose colon 2 (distal colon) started after the laparotomy similar to glucose colon 1 at 2.95 mmol/l but then increased after the resection to 4.3 mmol/l, after which almost a halving occured to 2.2 after the stent placement. Changes were, however, not significant (p=0.070). Glucose small intestine (reference catheter) after laparotomy gave a value of 2.4 mmol/l, which gradually increased to 3.9 mmol/l after resection and further increased to 4.3 mmol/l after stent insertion (p=0.853). Lactate colon 1 after laparotomy was 4.0 mmol/l and then increased to 6.2 mmol/l and 6.5 mmol/l after resection and anastomosis with stent insertion (p=0.035). Lactate colon 2 median value was 4.2 mmol/l after laparotomy, then increased to 4.9 mmol/l after colon resection and finally reached 6.4 mmol/l after anastomosis and stent placement. This increase was not significant with Kruskal Wallis test (p = 0.0549) but when tested with ANOVA a p-value of 0.046 was attained. Reference lactate at the small bowel started at 4.0 mmol/l after the laparotomy increased to 5.8 mmol/l after resection and further increased to 6.0 mmol/l after stent placement (p=0.161). Pyruvate colon 1 showed small differences in data values with 216, 232, and 226 μmol/l respectively at the three measurement occasions. At colon 2, slightly greater variation could be seen 185, 254 and 233 μmol/l respectively. At the small intestine the corresponding values were 180, 207 and 260 μmol/l respectively. Glycerol colon 1 was 61 μmol/l after laparotomy, dropped after resection to 49 μmol/l, with a slight recovery to 52 μmol/l after stent placement. At colon 2, stable values could be seen at 51, 51 and 54 μmol/l respectively. In the reference catheter of the small intestine, initial value of 78 μmol/l after the laparotomy was noted, declining sharply to 37 μmol/l after resection and stent insertion (p=0.400 and 0.756 respectively). Lactate Pyruvate ratio (LP ratio) colon 1. An LP ratio of 16.5 after laparotomy was detected which increased to 24.2 after resection, after which a certain decrease was noted after stent insertion to 23.5. The differences were proved significant (p=0.014). A similar pattern was seen in the LP ratio at colon 2. An initial value of 24.4 increased after resection to 27.8 decreased slightly after anastomosis and stent placement to 27.4. Large variations in values at the different locations lead, however, to no statistical significance (p=0.590). The reference catheter located in the small intestine shows a similar pattern as in colon 1 and 2, with an initial value of 23.1 increasing to 28.1 after the resection, but after stent insertion a regression to 22.6 (p=0.634).

Table 3: Microdialysis results at colon 1 (proximal to anastomosis), colon 2 (distal to anastomosis) and at the reference catheter at the middle of small intestine. (Median values, Q1/Q3)

	laparotomy	resection	stent	p value
Glucose colon 1	3	2.9	2.5	0.601
Q1/Q3	1.9/5.1	2.3/5.1	2.1/4.1	
Glucose colon 2	2.9	4.3	2.2	0.07
Q1/Q3	2.4/4.2	3.4/6.9	1.2/4.5	
Glucose small intestine	2.4	3.9	4.3	0.853
Q1/Q3	2.3/6.6	2.5/4.8	0.5/4.5	
Lactate colon 1	4	6.2	6.5	0.0035
Q1/Q3	3.4/4.0	4.6/6.7	5.0/7.0	
Lactate colon 2	4.2	4.9	6.4	0.0549
Q1/Q3	2.5/4.6	3.4/5.9	5.7/6.8	
Lactate small intestine	4	5.8	6	0.161
Q1/Q3	2.9/6.3	4.5/7.6	4.7/6.6	
Pyruvate colon 1	216	232	226	0.486
Q1/Q3	167/262	186/290	211/357	
Pyruvate colon 2	185	254	233	0.404
Q1/Q3	174/239	169/284	211/241	
Pyruvate small intestine	180	207	260	0.157
Q1/Q3	72/184	97/286	244/290	
Glycerol colon 1	61	49	52	0.4
Q1/Q3	40/95	20/62	44/59	
Glycerol colon 2	51	51	54	0.756
Q1/Q3	42/90	37/65	44/69	
Glycerol small intestine	78	37	37	0.14
Q1/Q3	32/143	17/75	26/47	
LP ratio colon 1	16.5	24.2	23.5	0.0144
Q1/Q3	15/19.4	21.3/29.5	22.6/265	
LP ratio colon 2	24.4	27.8	27.4	0.59
Q1/Q3	15.7/25.5	11.9/29.5	20.9/28.0	
LP ratio small intestine	23.1	28.1	22.6	0.634
Q1/Q3	19.8/35.0	21.3/78.2	19.7/27.0	

6. Discussion

An intraluminal covering stent has been shown to be a successful treatment for esophageal rupture [6-8]. Covering colon stents have been tested in anastomotic leakage after colon surgery and the preliminary results seems promising [9-12]. A leading cause of anastomotic leakage in colorectal surgery is ischemia in the proximal and/or distal intestine at the anastomosis, which gives rise to leakage several days after the operation. The purpose of this study was to observe how an intraluminal stent affects the intestinal metabolism in the intestinal wall proximally and distally of the anastomosis over a colon stent. Our study results shows that vital parameters as well as the acid base samples were stable during the experiment and showed no differences after laparotomy, resection or anastomosis/stent insertion. In the microdialysis response, several changes are found at the different measurement locations. Lactate increases significantly proximal to resection (colon 1), and distal to resection (colon 2), while at the reference catheter (small intestine) no significant increase can be detected but only a slight increase can be noted. The LP ratio increases significantly at colon 1, while at colon 2 a high level after laparotomy is noted. At both locations values further increases after the resection while a slight decrease occurs after anastomosis and stent insertion are performed. No significant differences at small intestine can be detected. Glucose measurements decreases slightly at colon 1 after anastomosis with stent insertion, while glucose measurements at colon 2 decreases more but not significantly after anastomosis and stent insertion. These values show a similar pattern as LP ratio, which increases after resection and then decreases after anastomosis and stent insertion. Pyruvate values shows a similar tendency as glucose values with the highest measurements after resection. Glycerol decreases numerically at the small intestine during the course of the experiment but is basically unchanged both proximally and distally to the anastomosis. In the cell's carbohydrate metabolism, glucose is transported into the cell in presence of insulin, where it is converted into pyruvate if oxygen is available, the reactions proceed through coenzyme A into the Krebs cycle and a large amount of energy in the form of ATP is recovered. In an anaerobic situation, pyruvate is converted to lactate and significantly less energy is recovered. The LP ratio reflects the current relationship between aerobic and anaerobic metabolism [31]. In an ischemic situation, the LP ratio is high, lactate is high and glucose approaches zero values. In a situation of hypermetabolism, glucose, lactate and LP ratio rise [5].

In colon 1 (proximal to resection and anastomosis) and colon 2 (distal to resection and anastomosis), our study shows a gradual increase in lactate from laparotomy to the resection, it increase further after the third phase of the experiment, with anastomosis and stent placement. The LP ratio increases from laparotomy to the resection stage, after which a minor regression is seen after anastomosis and stent insertion. The same pattern as the LP assays is seen in the glucose assays, glucose increases from laparotomy to the resection phase and then a decrease in glucose values is seen. At the reference catheter (small intestine) glucose, pyruvate and lactate increase successively while LP ratio increase after resection and a small decrease is noted after anastomosis and stent insertion. The metabolic changes in this study are interpreted as a hypermetabolism occurring both proximally and distally in the intestinal ends after a colon resection (even if the commencement of a hypoxic reaction distal to the anastomosis (colon 2) cannot be fully ruled out). Hypermetabolism does not deteriorate and does not turn into ischemia after anastomosis and stent insertion [28]. In the study, the anastomosis was done with a 25 mm circular stapler and the width of the stent was 29 mm, the stent having 14% greater width than the anastomosis, this should mean that the intestine next to the anastomosis is stretched and increased risk of ischemia and necrosis under the stent, but we have not noted such signs during the study period. The study has several limitations. Few experimental animals have been used and the study time has been limited to 9 hours, which may be considered as a short study time as most anastomotic leaks are found much later in the postoperative course. Nevertheless, we conclude that colon resection causes a hypermetabolism in the intestinal ends next to the resection site and at the small intestine, and that hypermetabolism neither deteriorates nor turns into ischemia during the initial postoperative course when a colon stent is placed intraluminally under a stapled anastomosis. However, an initial start of hypoxia most pronounced at the distal end of the colonresection cannot be excluded.

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