

The influence of epidural blockade on gut permeability in patients undergoing open surgical repair of abdominal aortic aneurysm

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Abstract

Background: Abdominal aortic clamping during aneurysm repair may cause a decrease in splanchnic blood flow and deterioration of gut barrier integrity. Epidural blocks have beneficial effects on vital organs during abdominal surgery, but sparse data are available on the influence on gut permeability during open aortic surgery. The aim of this study was to verify the hypothesis that epidural blocks may have beneficial effects on intestine permeability changes.

Methods: Seventy individuals undergoing elective open abdominal aortic aneurysm repair were randomly assigned to receive either balanced anaesthesia (continuous epidural and general anaesthesia, group E&G) or only general anaesthesia (group G). For group E&G, an epidural catheter was inserted into the epidural space before the induction of general anaesthesia. Ropivacaine was used for intraoperative and postoperative blocks. For both groups general anaesthesia was maintained with sevoflurane. For group G, analgesia was provided with remifentanyl. The assessments of gut function were based on measurements of the absorption and percentages of urinary excretion of four sugars (m 3-O-methyl-D-glucose, D-xylose, L-rhamnose and lactulose) and the lactulose/rhamnose (L/R) ratio.

Results: No intergroup differences were observed for sugar recovery or L/R ratio. Significant decreases in 3-O-methyl-D-glucose, D-xylose, and L-rhamnose recoveries were revealed in both examined groups when comparing the results obtained at 12 and 24 hours following the administration of anaesthesia. The rate of blood pressure decrease was significantly higher in group E&G.

Conclusions: Aortic clamping during open abdominal aortic repair led to unfavorable changes in intestinal permeability. Epidural block did not attenuate this deterioration.

Key words: aortic aneurysm, repair, open surgery; gut, barrier, assessment; anaesthesia, regional, epidural blockade

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Traditional open surgery remains the most common method of repairing abdominal aortic aneurysms, although the use of the endovascular technique is clearly increasing [1–3]. Major open aortic surgery, particularly the repair of ruptured aneurysms, is associated with a relatively high rate of complications [4]. Unfortunately, complications have been reported during scheduled procedures even in well-prepared patients, which have occurred due

to many factors. Aortic clamping may be responsible for many of these complications, including visceral ischemia. There are many reports of kidney injury following aortic clamping and its prophylaxis [5]. By contrast, sparse data are available regarding the influence of this procedure on gut blood flow and wall permeability. This procedure can have potentially dangerous consequences, such as toxin or bacterial translocation into the bloodstream. It has been

shown that longer periods of visceral ischemia in patients undergoing supraceliac cross-clamping are associated with higher levels of intraoperative CD11b expression, severe sepsis, and organ failure [6].

Open aortic surgery is frequently performed under balanced general and epidural anaesthesia, and epidural block is suitable for postoperative pain treatment, although its popularity has decreased in recent years [7]. Thoracic epidural anaesthesia (TEA) reduces cardiac and splanchnic sympathetic activities, thereby positively influencing the perioperative functioning of vital organ systems. TEA appears to reduce the occurrence of gut injury during major surgery as long as its systemic hemodynamic effects are adequately controlled [8]. No data are available from human studies regarding the influence of epidural blocks on gut permeability changes induced by abdominal aortic clamping.

The aim of this study was to verify the hypothesis that epidural blocks may have beneficial effects on intestinal permeability changes resulting from open surgical repair of abdominal aortic aneurysm.

METHODS

After obtaining approval from the Bioethical Committee of the Medical University of Gdansk and written informed consent from the study participants, 70 individuals were recruited to take part in this study. Patients were of both sexes and between 40 and 75 years of age and were already scheduled to undergo elective open abdominal aortic aneurysm repair. Patients with chronic intestinal diseases (e.g., Crohn's disease or ulcerative colitis), malabsorption syndromes, or chronic kidney disease were excluded. Patients were also excluded if they had any contraindications for an epidural block or did not agree to receive this type of anaesthesia.

A randomization scheme was generated using the generator of Wichmann and Hill, as modified by McLeod (available at <http://www.randomization.com>). Patients were randomly allocated to receive either balanced anaesthesia (continuous epidural and general anaesthesia, group E&G) or only general anaesthesia (group G). For group E&G, an epidural catheter was inserted into the epidural space (T10–11 to L1–2 levels) before the induction of general anaesthesia. After confirmation of correct catheter placement (injection of a test dose of 3–4 mL of 2% lidocaine and 15 minutes of observation), 1% ropivacaine was injected through the catheter at a dose of 0.8–1.2 mL per anaesthetized segment, followed by continuous infusion of 6–12 mL h⁻¹ of a 0.5% solution.

During the postoperative period, a 0.2% ropivacaine solution was used for epidural analgesia. The dose of local anaesthetic was adjusted individually according to the pain level of the patient. For group E&G, general anaesthesia

was maintained with 0.5–2.5 vol% of sevoflurane while the lungs were ventilated with a mixture of 33% oxygen and 67% nitrous oxide. Skeletal muscle relaxation was achieved with rocuronium bromide, using an intubating dose of 0.6 mg kg⁻¹, followed by continuous infusion of 0.3–0.6 mg kg⁻¹ hour⁻¹.

For group G, analgesia was provided with remifentanyl at an induction dose of 0.5–1 µg kg⁻¹, followed by continuous infusion of 0.3–0.6 µg kg⁻¹ min⁻¹ during the maintenance phase. Similar to group E&G, sevoflurane was used for the maintenance of general anaesthesia, and rocuronium bromide was used for muscle relaxation, and the same dosages were used for both groups.

Assessments of gut absorption and permeability were based on measurements of the absorption and percentages of urinary excretion of four sugars (mono- and disaccharides, including 3-O-methyl-D-glucose, D-xylose, L-rhamnose and lactulose).

A sugar solution containing 2 g L⁻¹ 3-O-methyl-D-glucose, 5 g L⁻¹ of D-xylose, 10 g L⁻¹ of L-rhamnose and 50 g L⁻¹ of lactulose, with an approximate osmolarity of 240 milliosmoles L⁻¹, was prepared by the hospital pharmacy on the day of anaesthesia administration. A dose of 2 mL kg⁻¹ of this mixture was administered through a nasogastric tube right after induction of anaesthesia. The urinary concentrations of the aforementioned saccharides were measured at the three following time points: during general anaesthesia administration and at 12 and 24 hours after induction of anaesthesia. At these time points, 3-hour urine collections were initiated through a urinary catheter, and 20-mL urine samples were obtained from these 3-hour samples. The samples were stored at -85 °C until further analysis.

Urine sugar concentrations were determined by gas chromatography (GC) and gas chromatography–mass spectrometry (GC/MS). Because sugars are highly polar and have low volatility, chemical derivatization was required before GC–MS analysis. Sugars were reduced with sodium borohydride (5 mg) in water (500 µL) for 12 hours at room temperature. Then, several drops of acetic acid were added to remove the excess borohydride. Next, acetic acid/methanol 1:9 (200 µL) was added, and the mixtures were dried under a stream of nitrogen to remove the boric acid. This procedure was performed three times with acetic acid/methanol (250 µL). After drying under vacuum over phosphorus pentoxide, dry pyridine (100 µL) and acetic anhydride (200 µL) were added, and the samples were incubated at 120 °C for 2 hours in a reacti-block. The reaction mixtures were dried under a gentle stream of nitrogen while adding toluene (500 µL, twice). The samples were dissolved in CH₂Cl₂ and injected (1 µL) into a gas chromatograph. The individual sugars in the test mixture showed the following constant response factors: 1.503 for 3-O-methyl-D-glucose, 0.844 for L-rhamnose, 1.196 for D-xylose (defined relative to D-ribose), and 0.750

for lactulose (determined relative to an internal standard, trehalose). This developed method can be used for qualitative and quantitative analyses of mono- and disaccharides in urine samples. However, the time required for analysis of one sample is too long, which precludes its clinical routine use. To optimize the derivatization procedure, reactions of mono- and disaccharides with hydroxylamine hydrochloride (100 µl) in pyridine were also performed (90°C for 1 h). The obtained oximes were then converted to silyl derivatives with *N*-trimethylsilylimidazole (100 µL, 90°C for 1 h). This method was rapid, sensitive, and easy to automate for the study of intestinal permeability in clinical practice. The validation parameters were acceptable for analytical work. Urine sample preparation procedure for analyses of mono- and disaccharides was also developed. DEAE Sephadex A-25 (200 mg) and washed ion exchange resin Amberlite XAD-2 (500 mg) were added to 10 ml of each thawed urine specimen for desalting. The mixture was vortex-mixed for 10 s and centrifuged for 10 min at 4000 rpm. The resulting supernatant was filtered through 0.45-µm (pore size) disposable syringe filters and lyophilized.

STATISTICAL ANALYSIS

A minimal sample size of 34 individuals per group was calculated assuming an alpha level of 0.05 and a beta level of 0.80 for the detection of a mean difference in the L/R ratio of 0.02, based on a study by Fujii *et al.* that reported a mean (SD) L/R ratio of 0.049 (0.008) [9].

Statistical analysis was performed using STATISTICA 10.0 PL software (Polish version) (StatSoft, Tulsa, OK, USA). The normality of the data distribution was verified using the Shapiro-Wilk *W* test, and the homogeneity of variance was verified using Levene's test. Comparisons were performed using two-sided analysis of variance (ANOVA) for repeated measurements with subsequent analysis of significant differences using a post hoc method (Tukey's honest significant difference (HSD) test) if appropriate or the chi-squared test (with the Yates correction if necessary). A $P < 0.05$ was indicative of a significant difference.

RESULTS

Demographic data and comorbidities are presented in Table 1. There were no significant differences in mean age, gender, or body mass among the three groups. Similarly, there were no differences in American Society of Anesthesiology (ASA) pre-operative status, the prevalence of coronary artery syndrome or brain stroke in anamnesis. The prevalences of diabetes and arterial hypertension were higher in group G ($P = 0.04$ for both diseases).

The aortic disorders that prompted the surgical procedures and coexisting vascular pathologies are shown in

Table 1. Patient demographics. Median (25th-75th percentile) or n (%) is shown

	Group E&G (n = 35)	Group G (n = 35)
Age (years)	69 (63–75)	68 (65–74)
Sex F : M	4 : 31	9 : 26
Body mass (kg)	78 (65–88)	78 (70–86)
ASA status; II : III	13 : 22	11 : 24
Comorbidities		
Arterial hypertension	23 (65.7%)	31 (88.6%)
Diabetes	4 (11.4%)	12 (34.3%)
Coronary disease	19 (54.3%)	18 (51.4%)
History of stroke	2 (5.7%)	3 (8.6%)

Table 2. Aortic disorders that led to surgical procedures

	Group E&G (n = 35)	Group G (n = 35)
Aortic aneurysm	24 (68.6%)	30 (85.7%)
Aortic aneurysm coexisting with aneurysm of one or both iliac arteries	10 (28.6%)	4 (11.4%)
Aortic aneurysm coexisting with stenosis of the iliac artery	1 (2.8%)	0
Aortic aneurysm coexisting with stenosis of the renal artery	0	1 (2.8%)

Table 3. Type of surgical procedure and duration of aortic cross-clamping. Median (25th-75th percentile) or n (%) is shown.

	Group E&G (n = 35)	Group G (n = 35)	<i>P</i> value
Aorto-aortic bypass	19 (54.3%)	27 (77.1%)	0.16
ABI	3 (8.6%)	3 (8.6%)	
ABF	9 (25.7%)	4 (11.4%)	
Ao-MI/MF	4 (11.4%)	1 (2.8%)	
Cross-clamping (min)	40 (31–52)	35 (28–44)	0.14

ABI — aortobiiliac bypass; ABF — aortobifemoral bypass; Ao-MI/MF — aortic bypass with one distal end in the iliac artery on one side and with the second distal end in the femoral artery on the other side of the body

Table 2. The type of surgical procedure and the duration of aortic cross-clamping are shown in Table 3. There were no significant differences among the types of procedures and the durations of aortic cross-clamping.

Intra- and postoperative events that could have influenced the results of the current study are shown in Table 4. Statistical analysis showed significant differences in the number of episodes of blood pressure drops between the groups ($P = 0.008$). There was no difference in the necessity for catecholamines during anaesthesia. The only catecho-

Table 4. Intra- and postoperative events with potential influences on the study results

	Group E&G (n = 35)	Group G (n = 35)	P value
Significant blood pressure decrease*	22 (62.8%)	12 (34.3%)	0.008
Need for catecholamines	8 (22.9%)	3 (8.6%)	0.09
Intestines removed from peritoneal cavity	5 (14.3%)	1 (2.8%)	0.09
Cross-clamping above renal arteries	1 (2.8%)	1 (2.8%)	1.0
Postoperative AKI	2 (5.7%)	1 (2.8%)	1.0

AKI — acute kidney injury; * A significant blood pressure decrease was defined as a decrease in systolic pressure to below 90 mm Hg that lasted for more than 15 minutes

Table 5. Sugar recoveries and lactulose/rhamnose (L/R) ratios for the studied groups, expressed as percentages of the intragastrically administered dose. Data are reported as medians (25th–75th percentiles). +12 and +24 hours indicate time after anaesthesia induction

	Group E&G	Group G
3-O-methyl-D-glucose		
+ 12 hours	4.55 (2.28–5.43)	5.09 (1.03–5.56)
+ 24 hours	0.95 (0.60–1.61)*	0.62 (0.59–1.75)*
D-xylose		
+ 12 hours	5.24 (4.76–6.62)	5.09 (4.10–5.47)
+ 24 hours	2.39 (1.93–2.72)*	2.54 (0.45–2.79)*
L-rhamnose		
+ 12 hours	1.09 (0.97–1.21)	1.18 (0.98–1.31)
+ 24 hours	0.34 (0.25–0.56)*	0.32 (0.20–0.72)*
Lactulose		
+ 12 hours	0.36 (0.13–0.57)	0.28 (0.12–0.48)
+ 24 hours	0.23 (0.11–0.25)	0.24 (0.09–0.45)
L/R ratio		
+ 12 hours	0.18 (0.11–0.56)	0.21 (0.10–0.43)
+ 24 hours	0.22 (0.15–0.64)	0.28 (0.17–0.65)

* $P < 0.05$ compared with the value at the 12th hour in the same group

lamine used was dopamine, the dose range of which was between 5 and 10 $\mu\text{g kg}^{-1} \text{min}^{-1}$.

In both examined groups, traces of 3-O-methyl-D-glucose, D-xylose, and L-rhamnose were detected in the urine samples collected during the first three hours of anaesthesia from 3 individuals in group E&G and 3 individuals from group G. No subjects exhibited detectable lactulose in their urine, which is why the lactulose results were not included in the analysis. The percent recoveries of the administered sugars and the lactulose/rhamnose ratio are presented in Table 5, for which no intergroup differences were observed. Significant decreases in the recoveries of 3-O-methyl-D-

glucose, D-xylose, and L-rhamnose were revealed in both examined groups.

DISCUSSION

The most important finding of this study is the lack of a significant difference in gut permeability in the patients anaesthetized either under epidural and general anaesthesia or solely under general anaesthesia.

Intraoperative abdominal aortic clamping is accompanied by many side effects involving various vital organs, such as hemodynamic disturbances with cardiac output drop and acute heart failure, decreased kidney blood perfusion and acute kidney injury, and acute spinal cord ischemia with persistent or transient neurological deficits [10]. Another organ that may suffer from hypoperfusion due to aortic clamping is the intestine [11]. Its integrity guarantees a proper barrier between the sterile peritoneal cavity and the intestinal contents that have been physiologically colonized by microorganisms. The loss of gut wall integrity may be the consequence of decreased splanchnic blood flow. Many studies have shown that this pathology may lead to endotoxemia and sepsis with serious clinical consequences, including multiorgan failure and death [12–14].

In the present study, gut permeability was assessed according to the absorption and urinary excretion of four saccharides, including 3-O-methyl-D-glucose, D-xylose, L-rhamnose and lactulose. These molecules undergo active carrier-mediated, passive carrier-mediated, transcellular and paracellular transport, respectively, in the small intestine. They are widely used as diagnostic tools to detect disturbances in these processes [15, 16]. It is believed that the most representative parameter of intestinal wall integrity is the L/R ratio, which is normally below 0.05 [17].

In the examined groups, traces of 3-O-methyl-D-glucose, D-xylose, and L-rhamnose were detected in the urine samples collected during the first three hours of anaesthesia administration in 3 individuals from group E&G and 3 from group G. No subjects had detectable lactulose in their urine. In a study by Malagon and colleagues [17], gut permeability was assessed using a similar method in children undergoing cardiac surgery with or without cardiopulmonary bypass. All of these sugars were detected in urine samples collected during the first three hours of the procedures; however, their concentrations were low. This difference may be explained by variations in the time required for gastric emptying in small children compared with older adults, especially when the adults suffer from comorbidities that influence gastric motility, such as diabetes and/or arteriosclerosis. At the 12th and 24th hour after sugar administration, they could be detected in the urine, but there were no significant differences in their levels between the groups. Minimally significant decreases in the 3-O-methyl-D-glucose, D-xylose, and

L-rhamnose concentrations were revealed at subsequent time points.

The obtained results did not confirm our hypothesis that epidural block may have beneficial effects on gut permeability disturbances induced by aortic clamping during abdominal aortic aneurysm repair. This hypothesis originated from a previous study stating that epidural block has favorable effects on intra- and postoperative intestinal function. These effects may be due to its influence on splanchnic blood flow, peristalsis improvement or intestinal shrinkage facilitated by surgery. Animal studies have indicated that epidural blocks increase mucosal blood flow in the intestines [18]. Additionally, the use of epidural block in animals with increased gut permeability has beneficial effects on gut function and splanchnic blood flow [19].

The potential beneficial effects of epidural block may have been attenuated by other factors that negatively influenced the gut barrier in our patients. The most probable influential factor was the higher rate of hypotension in group E&G, which was defined as a systolic blood pressure of below 90 mm Hg lasting for at least 15 minutes. Sympathetic block, which is an integral part of epidural block, and hypotension-induced hypoperfusion may lead to paradoxical side effects. This observation has been confirmed by other authors [20, 21]. Another unfavorable factor is the use of catecholamines, especially in patients with advanced atherosclerosis of the intestinal arteries, which is highly probable in individuals with aortic aneurysm. In group E&G, the rate of catecholamine infusion was relatively high (22.9%) although there were no significant differences compared with group G. However, the only catecholamine used was dopamine in the dose range of 5 to 10 $\mu\text{g kg}^{-1} \text{min}^{-1}$. Those doses should not produce substantial vasoconstriction, but this effect cannot be definitively excluded in the examined patients. Another reason for the surprising results may have been the intestinal positioning during surgery. In group E&G, the intestines were more frequently (but not significantly more frequently) taken out of the peritoneal cavity and covered by a drape. Lau *et al.* [22] have revealed that the surgical approach (extraperitoneal versus transperitoneal) used during elective aortic aneurysm surgery affects intestinal permeability and portal endotoxemia.

There are some limitations to the present study. The main limitation is that it was not conducted in a blind fashion. In our opinion, it was not ethically justifiable to place an epidural catheter in the examined patients in the control group and administer normal saline as a placebo. This opinion is in accordance with that of Cyna and Tan, who recently published an article in *Anaesthesia* [23].

In conclusion, aortic clamping during open abdominal aortic repair led to unfavorable changes in intestinal perme-

ability. Epidural block did not attenuate this deterioration, which may have been caused by the induced decrease in arterial pressure.

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