CRITICAL CARE

COMMENTARY

The role of thoracic epidural anesthesia in severe acute pancreatitis

Daniel Harper* and Clare E McNaught

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Abstract

In animal studies of severe acute pancreatitis, thoracic epidural anesthesia appears to enhance the splanchnic circulation, improve end-organ perfusion, and favorably influence mortality. The application of thoracic epidurals in the critically ill human patient is less clear. Methodological difficulties in reliably assessing mesenteric flow have hampered progress, and clinical concerns surrounding this potentially attractive therapeutic modality remain unanswered. Future research needs to focus on the impact of epidural anesthesia on basic human physiological parameters to help direct further randomized studies in human disease.

In recent years, researchers have examined a number of therapeutic modalities aimed at maintaining the splanchnic circulation, in the hope of modifying the host cytokine response to the insult causing pancreatitis. In the previous issue of *Critical Care*, Bachmann and colleagues [1] explored the hypothesis that regional sympathetic blockade, through the use of thoracic epidural anesthesia (TEA), may promote splanchnic flow and improve pancreatic oxygenation in a porcine model of severe acute pancreatitis (SAP). Acute pancreatitis is a common surgical emergency with an annual case incidence of 15 to 35 per 100,000 population. The recently published Revised Atlanta Classification has stratified the disorder into mild, moderate, and severe categories. SAP is associated with a mortality rate of up to 30% and is characterized by the persistence of a systemic inflammatory response 48 hours after the onset of the attack [2]. The pathophysiology of severe pancreatitis is yet to be fully elucidated, but inadequate pancreatic microvascular perfusion and hypoxia may play a significant role in early disease progression [3].

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In Bachmann and colleagues' well-designed study, severe pancreatitis was induced in 34 anesthetized pigs through an intraductal infusion of bile acid followed by ligation of the pancreatic duct. Animals were randomly assigned to receive SAP alone or SAP with a TEA infusion started 75 minutes after SAP was initiated. Over the course of a 6-hour period, pancreatic tissue oxygen tension and microcirculation were directly measured by using a polarographic probe and laser Doppler imager, respectively, after which anesthesia was ceased and the animals were closely monitored for 7 days prior to sacrifice. Reductions in tissue oxygenation and microcirculation were observed after induction of SAP in both groups, but perfusion and oxygenation significantly improved when TEA was started in the treatment group. In addition, survival was significantly greater in the TEA group than the control, which had mortality rates of 29.4% and 82.4%, respectively.

This study provides further support to the theory that changes in pancreatic microcirculation and tissue oxygenation contribute to the progression of SAP [4]. The beneficial effect of TEA in this study appeared to relate specifically to the effects of sympathetic blockade on the splanchnic circulation and not overall perfusion, as global indices of circulation such as cardiac output and blood pressure were tightly controlled. Standardization of intravascular volume replacement in each group was critical, as previous studies have shown that different intravenous fluid preparations can independently influence the outcome of SAP [5]. The position of the epidural catheter (T7/8) was confirmed by epidurogram both at the start of the procedure and after sacrifice. Definitive proof of epidural spread was not established, and so the extent of the sympathetic block and the involvement of the nervi accelerantes could not be assessed.

These results are undoubtedly interesting, but how applicable are they to our daily clinical practice? At present, controversy still exists as to the effects of thoracic epidurals on the human splanchnic circulation. Some

clinical trials, in which mesenteric blood flow was recorded directly, demonstrated a reduction in intestinal perfusion, which was not corrected with the administration of intravenous fluids alone. Conversely, other human studies demonstrated increases in hepatic blood flow and gastric mucosal blood flow by using surrogate markers of tissue perfusion. In animal models of shock and sepsis, TEA seems to have a protective effect in preventing splanchnic vasoconstriction, but the physiological response may be different in humans. Furthermore, research in humans has been hampered by the lack of a robust methodological technique to measure splanchnic flow non-invasively [6].

The use of TEA in patients with SAP poses further clinical problems. At what point in the disease course should the epidural be placed? What about the risk of coagulopathy and epidural hematoma, particularly in patients with a biliary etiology who may well be jaundiced? How long do you continue TEA, when the recovery from an episode of SAP can take weeks and there is evidence that infective complications increase with the length of time that epidurals are *in situ*? Hematological markers of infection may be raised due to the acute inflammatory response in pancreatitis, masking any signs of epidural-related sepsis. How do you detect symptoms of increasing back pain or deteriorating motor function when the patients may have impaired cognition or require invasive ventilation? Although some initial feasibility studies of TEA in SAP have been performed, the numbers of patients assessed are too low to show any meaningful difference in the significant, but rare, complications of TEA [7]. Despite this, as the risk of significant morbidity from SAP is so high, it may be reasonable to accept a small rate of TEA complications if a major reduction in mortality was confirmed.

The use of TEA in the acute clinical setting of SAP and sepsis remains a fascinating area of research. Reliable non-invasive measures of splanchnic perfusion require development to allow further evaluation of the effect of TEA on basic human physiological parameters and to help direct randomized trials in critically ill patients.

Abbreviations

SAP: Severe acute pancreatitis; TEA: Thoracic epidural anesthesia.

Competing interests

The authors declare that they have no competing interests.

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Effects of thoracic epidural anaesthesia on survival and microcirculation in severe acute pancreatitis: a randomized experimental trial

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Effects of thoracic epidural anaesthesia on survival and microcirculation in severe acute pancreatitis: a randomized experimental trial

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Abstract

Introduction

Severe acute pancreatitis is still a potentially life threatening disease with high mortality. The aim of this study was to evaluate the therapeutic effect of thoracic epidural anaesthesia (TEA) on survival, microcirculation, tissue oxygenation and histopathologic damage in an experimental animal model of severe acute pancreatitis in a prospective animal study.

Methods

In this study, 34 pigs were randomly assigned into 2 treatment groups. After severe acute pancreatitis was induced by intraductal injection of glycodesoxycholic acid in Group 1 (n = 17) bupivacaine (0.5%; bolus injection 2 ml, continuous infusion 4 ml/h) was applied via TEA. In Group 2 (n = 17) no TEA was applied. During a period of 6 hours after induction, tissue oxygen tension (tpO_2) in the pancreas and pancreatic microcirculation was assessed. Thereafter animals were observed for 7 days followed by sacrification and histopathologic examination.

Results

Survival rate after 7 days was 82% in Group 1 (TEA) versus 29% in Group 2: (Control) (P <0.05). Group 1 (TEA) also showed a significantly superior microcirculation (1608 ± 374 AU versus 1121 ± 510 AU; P <0.05) and tissue oxygenation (215 ± 64 mmHg versus 138 ± 90 mmHG; P <0.05) as compared to Group 2 (Control). Consecutively, tissue damage in Group 1 was reduced in the histopathologic scoring (5.5 (3 to 8) versus 8 (5.5 to 10); P <0.05).

Conclusions

TEA led to improved survival, enhanced microcirculatory perfusion and tissue oxygenation and resulted in less histopathologic tissue-damage in an experimental animal model of severe acute pancreatitis.

Introduction

Severe acute pancreatitis (SAP) is a life threatening disease with a high mortality despite improved treatment strategies. The incidence of severe acute pancreatitis increased during the last decades [1,2]. The progress from mild edematous, to hemorrhagic necrotizing form determines outcome [3-8]. Up to now, no causal treatment of pancreatitis is known. Though the pathophysiologic cascade of the development and progress is poorly understood, microcirculatory disturbances are considered to be a key factor [9,10].

The rationale of this trial is based on the generally accepted finding that an improvement of pancreatic microcirculation prevents the progression from mild edematous to severe necrotizing pancreatitis [3-7,11]. Different therapeutic interventions for improving pancreatic microcirculation have been evaluated in the last years [9,12-16]. Therapeutic efforts aim at saving injured tissue from infarction and necrosis by improving microcirculatory perfusion and oxygen supply. The main idea in our approach is sympathetic block by thoracic epidural anaesthesia (TEA) with consecutive redistribution of blood flood toward the splanchnic vessels [17]. This effect could be demonstrated in various trials [18-21]. In perioperative and experimentally induced hemorrhage positive effects due to epidural anaesthesia on gastrointestinal microcirculation could be demonstrated [22,23]. TEA further is reported to improve renal and gastrointestinal perfusion during endotoxemia [22,24,25]. This is also true for microvascular blood flow in the liver or ileal mucosa in other models of systemic inflammation [24,26]. Some first attempts also showed promising results for the use of TEA in pancreatitis demonstrating reduced liver injury, improved ileal mucosal capillary perfusion and survival as well as pancreatic microcirculation in the rat [26-28].

Another aspect is, that microcirculation is also dependent from macrocirculatory conditions and an adequate macrocirculation is an indispensible precondition. For evaluation of macrocirculatory conditions meaning of advanced hemodynamic monitoring has substantially increased in recent years in intensive care and perioperative settings [29]. In parts, results of this study have already been reported demonstrating the impact of two different treatment strategies for early goal-directed fluid therapy [30]. However, to date no data and final validation exist evaluating the therapeutic effect of TEA in severe acute pancreatitis during controlled hemodynamic conditions. We hypothesized that improvement of microcirculation due to redistribution of blood flow in the inflamed tissue by TEA would result in improved pancreatic microcirculatory conditions and outcome in severe acute pancreatitis.

Therefore, the aim of this study was to evaluate the therapeutic effects of TEA in an experimental model of severe acute pancreatitis. Primary outcome variable was survival after 7 days. Secondary outcome variables were pancreatic microcirculation and tissue oxygenation during the first six hours after induction as well as the extent of histopathologic tissue-damage.

Materials and methods

The study was approved by the Governmental Commission on the Care and Use of Animals of the City of Hamburg. The animals received care in compliance with the “Guide for the Care and Use of Laboratory Animals” (NIH publication No. 86–23, revised 1996) and experiments were carried out according to the ARRIVE guidelines [31].

Study design

The study was designed as prospective randomized trial in 34 German domestic pigs (German Hybrid). Animals were randomized to two different treatment groups: Group 1 (TEA, n = 17) received thoracic epidural anaesthesia after induction of severe acute pancreatitis. In Group 2 acute pancreatitis was induced, however no TEA was performed (Control; n = 17).

Anaesthesia and surgical preparation

After fasting overnight ketamine (10 mg/kg), azaperone (4 mg/kg), midazolam (15 mg) and atropine (0.0015 mg/kg) were administered for premedication. After preoxygenation induction of anaesthesia and orotracheal intubation were performed. Continuous infusion of fentanyl (0.05 mg/kg/h) and sevoflurane (Fet 2.0) were used for balanced anaesthesia. The animals were mechanically ventilated using tidal volumes of 10 ml/kg. Inspiratory oxygen fraction (FiO_2) was set at 0.35 and respiratory rate was adjusted to maintain endexperiatory pCO2 at 35–40 mmHg (Zeus, Draeger Medical Systems, Lübeck, Germany). Moreover a gastric tube was brought in position. For monitoring of heart rate and oxygen saturation a 5-lead electrocardiogram and pulse oximetry were used. Body temperature was kept constant using forced-air warming blankets.

Prior to beginning of further surgical preparation, animals randomized to Group 1 (TEA) were positioned on the right side and a thoracic epidural catheter was introduced between Th 7 and Th 8 under sterile conditions and radiographic control. The catheter was advanced 2 cm into the epidural space and correct positioning of the catheter was verified and documented by an epidurogram as goldstandard (Figure 1). For these purposes 5 ml of contrast agent were injected in the epidural space during fluoroscopy to exclude an intravascular position of the catheter. Thereby it was verified that a minimal spread over 6–8 segments was present and no misplacement of the epidural catheter had occured.

Figure 1 Epidurogram after placement of the epidural catheter.

All animals were placed in supine position and after thorough disinfection and sterile coverage, the femoral artery was canulated using a 5 F thermistor tipped arterial catheter (PICCO, PV 2015L20, Pulsion, Germany). Two central venous catheters were surgically introduced into the internal and external jugular vein, one for volume administration the other to enable injection of cold indicator for transcardiopulmonary thermodilution. Hemodynamic data were recorded using a PiCCOplus monitoring system (version 6.0, Pulsion Medical Systems, Munich, Germany).

Thereafter a transverse upper laparotomy was performed. A urinary catheter was placed directly into the bladder for urinary drainage and intraoperative accounting of urine. Pancreas and duodenum were mobilized and fixed at the laparotomy incision for intraoperative measurements, whereupon meticulous attention was paid to strainless positioning. After dissection and cannulation of the main pancreatic duct (Vasofix 0,8 mm, B. Braun, Melsungen, Germany) between pancreas and duodenal wall, a flexible polarographic measuring probe (CCP1, Licox, Kiel, Germany) was placed in the pancreatic head for continuous measurement of the tissue oxygen tension (tpO2) [32,33]. Laser-Doppler imager (Laser-Doppler Imager LDI2, Moor, Millway, UK), was installed to assess microcirculation in the pancreatic head. The laser is scattered by the tissue and moving blood cells in the capillaries, arterioles and venules. The moving blood cells cause frequency shifts that are processed to produce a color coded map of scanned area. The Laser-Doppler imager was positioned above the pancreas and the region of interest (pancreas) was marked in a color coded map of the corresponding image. The mean microcirculation in the region of interest was calculated automatically [9].

Hemodynamic management

In both groups hemodynamic management was carried out according to a defined treatment algorithm [30]. Ringer's solution and hydroxyethylstarch 6% 130/0.4 were administered at a fixed ratio of 2:1. The treatment algorithm for guidance of fluid therapy is presented in Figure 2. Hemodynamic data were assessed continuously during the entire procedure as well as with each point of measurement.

Figure 2 Algorithm for guidance of fluid therapy. Stroke volume variation (SVV), Cardiac Index (CI), mean arterial pressure (MAP).

Therapeutic intervention

Animals in Group 1 (TEA, n = 17) received thoracic epidural anaesthesia after induction of acute pancreatitis. Initially a bolus of 2 ml bupivacaine 0.5% was applied via the epidural catheter, followed by a continuous application at a fixed rate of 4 ml/h using an automated infusion pump (Pega® Plus, Venner Medical, Kiel Germany). Thereby we aimed for blocking 3 to 4 segments above and below site of insertion.

In group 2 (Control; n = 17), acute pancreatitis was induced while no TEA was performed.

Measurement and experimental protocol

After an initial equilibration baseline measurements (M0) were performed. Measurements included blood gas analysis, measurement of tissue oxygenation (tpO2) and microcirculation in the pancreatic head as well as thermodilution measurements for assessment of hemodynamic conditions. After completion of baseline measurements, in both groups severe acute pancreatitis was induced by intraductal infusion of 0.8 ml kg^{-1} glycodesoxycholic acid (10 mmol l^{-1}, pH 8, Sigma, Steinheim, Germany) during a period of 15 minutes as previously described, using an automated infusion system (Perfusor® fm (MFC), B Braun, Melsungen, Germany) to ensure a standardized infusion pressure and avoid pancreatic pressure necrosis [4,9,30,34]. Thereafter the cannula was removed and the pancreatic duct was ligated. 15 minutes (M1) and 75 (M2) minutes after completion of the intraductal infusion measurements were repeated. After M2 in animals randomized to Group 1 (TEA) a bolus of bupivacaine was applied via the epidural catheter, immediately followed by a continuous application at a fixed rate as described. After beginning of therapeutic intervention measurements were repeated every 60 minutes (M3-8). After completion of intraoperative measurements (M8) all catheters were removed except for the TEA catheter in Group 1 (TEA) as well as a central line, tunneled to the dorsal neck, for application of analgesic medication and blood gas sampling in the postoperative course. The abdominal cavity and incision of the neck were closed and anaesthesia was ceased. The animals were extubated and transferred to heated boxes in the animal facility. In animals randomized to Group 1 (TEA) the infusion pump for application of bupivacain via the epidural catheter during the postoperative observation interval was attached to the back using a special dressing.

Survival and postoperative observation

Animals were closely monitored for 7 days. Analgesics were given every 6 hours (piritamide 15 mg). Once a day blood samples for evaluation of pancreatic amylase, total bilirubin

(TBIL) liver enzymes (aspartate-transaminase (AST), alanine-transaminase (ALT)), leucocyte count, lactate, creatinine, prothrombin time (PT), and partial thromboplastin time (pTT) were taken via the central venous catheter and laboratory analysis was carried out. Hemoglobine, leucocytes and thrombocytes were counted with a fully automatic blood count analysis unit. TBIL was measured by spectral absorption while the measurement of ALT and AST was based on their enzyme activity.The concentration of amylase was measured by amylase activity enzyme kit (Abcam). Isotope dilution mass spectrometry was applied to analyze serum creatinine. PT and pTT were measured in a fully automated system as well. Moreover a porcine well-being was assessed in all animals [35].

Animals surviving the observation period were re-anaesthetized on the 7^{th} postoperative day, and sacrificed by fast injection of potassium chloride during deep anaesthesia. The correct positioning of the thoracic epidural catheter was reassured by another epidurogram. Postmortem examination was carried out and the pancreas was removed for histopathologic examination. In animals that died during the postoperative observation period postmortem examination, removal of the pancreas and the epidurogram were conducted immediately after diagnosis of death. Specimens of the pancreas were stored in 3.5% buffered formalin and routinely processed. They were embedded in paraffin and 5 µm slices were stained with hematoxylin and eosin. The slices were examined by an experienced pathologist blinded for the treatment (A.H.) using an established scoring system [9,30]. The median score of the histopathologic examination is based on the analysis of 10 high power fields (HPF) in four different slices.

Power calculation and statistical analysis

Primary endpoint of the trial was survival. Secondary endpoints were pancreatic microcirculation, tissue oxygenation and histopathologic tissue damage. A detectable difference of 25% versus 75% in survival was used to calculate group size. The calculated group size (using 5% alpha error and 80% power) was n = 17. SPSS® for Windows® (Version 13.0) (SPSS Inc., Chicago, IL) was used for statistical analysis. Survival curves were plotted using the Kaplan-Meier method, data were analyzed using the log-rank test. Assessment of Normal distribution was conducted using the Kolmogorov-Smirnov-Test. Descriptive analysis of parametric parameters is expressed as means and standard deviation. Ordinal data were expressed as median and range. For analysis of the difference between the groups in repeated measurements the variance analysis for repeated measurements (ANOVA) followed by a time-by-treatment-Interaction test was used. Additionally the area under curve was calculated during the intraoperative treatment interval (M2-M8). Differences between the treatment groups were analyzed using a one way ANOVA. Significance statements refer to p values of two-tailed tests that were less than 0.05.

Results

In both groups 17 animals were studied. There were no statistically significant differences between the different treatment groups. Mean body weight of animals in Group 1 (TEA) was 32.0 ± 7.5 versus 32.0 ± 6.9 kg in Group 2 (Control), while mean body length was 102 ± 5 cm and 102 ± 6 cm ($p > 0.05$).

Survival and postoperative observation

Overall survival after 7 days was 82.4% in Group 1 (TEA) versus 29.4% in Group 2 (Control) ($p < 0.001$). Survival data are presented in Figure 3.

Figure 3 Kaplan Meier Curve for survival of animals in the postoperative treatment intervall (TEA Group versus Control-Group).

During the postoperative course evaluation of the "Porcine Well-being Score" also demonstrated significantly better results in Group 1 (TEA) (Table 1).

Table 1 Scoring results of the porcine Wellbeing Score

Porcine Wellbeing Score		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	TEA	34 ± 13	35 ± 17	34 ± 17	35 ± 17	37 ± 18	37 ± 18	36 ± 18
	Control	28 ± 17	29 ± 20	27 ± 21	25 ± 22	23 ± 23	17 ± 22*	14 ± 22*

Data are presented as Mean ± Standard deviation. (Scoring Range: 0–50).
* representing statistically significant difference ($p < 0.05$).

Tissue oxygenation and microcirculation of the pancreas

In both groups (group 1 and 2) strong decreases of pancreatic microcirculation (Flux) and tissue oxygenation (tpO2) were detected after induction of severe acute pancreatitis. After beginning of TEA, pancreatic microcirculation improved in Group 1 (TEA) and a significant time by treatment interaction was detected in the variance analysis for repeated measurements ($p < 0.001$). Comparing the areas under the curve during the treatment interval a significantly enhanced pancreatic microcirculation was found in Group 1 (TEA) (1608.4 ± 374.4) versus Group 2 (Control) (1121.0 ± 510.) ($p = 0.003$) (Figure 4).Concerning the tissue oxygenation a significant time by treatment interaction was detected in the variance analysis for repeated measurements ($p < 0.001$) and when comparing the areas under the curve during the treatment interval a significantly better tissue oxygenation was found in Group 1 (Group 1 (TEA) 215 ± 64 in comparison to Group 2 (Control) 138 ± 90; $p = 0.007$) (Figure 4). The detailed course is presented in Table 2.

Figure 4 Microcirculation and Tissue Oxygenation (tpO2). a) pancreatic microcirculation and **b)** tissue oxygenation in the pancreatic head. (MP0 = before Induction of the acute pancreatitis, MP1 and 2 after Induction of the acute pancreatitis, MP3-8 during TEA. Mean and SD; Value in Flux (AU).

Table 2 Data on microcirculation, tissue oxygenation, hemodynamics, blood gas analysis and fluid balance

Parameter	*Group*	*M 0*	*M 1*	*M 2*	*M 3*	*M 4*	*M 5*	*M 6*	*M 7*	*M 8*
Tissue oxygenation [tpO_2 mmHg]	***1 (TEA)***	63,8 ± 14,1	40,2 ± 17,7	32,5 ± 11,4	36,3 ± 13,7	37,1 ± 12,2	36,8 ± 11,0	36,2 ± 10,5	35,2 ± 9,1	35,0 ± 9,1
	2 (Control)	64,2 ± 14,1	45,2 ± 21,4	32,4 ± 16,2	25,7 ± 15,9*	22,8 ± 15,6*	22,2 ± 15.9*	20,4 ± 15,0*	20,5 ± 14,3*	20.4 ± 14.2*
Microcirculation [Flux AU]	***1 (TEA)***	391,9 ± 82,8	253,3 ± 81,2	236,1 ± 55,1	288,9 ± 73,4	300,4 ± 68,5	276,2 ± 65,7	254,1 ± 73,8	249,9 ± 66,0	241,5 ± 97,0
	2 (Control)	408.5 ± 88.3	267.4 ± 103.4	233.2 ± 56.3	215.9 ± 104.9*	201.8 ± 108.1*	182.4.0 ± 90.0*	168.6 ± 89.0*	160.5 ± 80.7*	150.6 ± 85.7*
HR [min^{-1}]	***1 (TEA)***	90.5 ± 24.9	91.9 ± 24.5	95.4 ± 21.5	94.4 ± 19.9	97.7 ± 16.8	100.7 ± 16.3	99.4 ± 14.6	99.3 ± 10.3	99.4 ± 13.2
	2 (Control)	85.5 ± 13.8	85.4 ± 14.9	91.1 ± 16.6	95.5 ± 16.7	98.9 ± 15.0	101.0 ± 13.8	103.3 ± 14.7	102.6 ± 16.5	100.8 ± 11.3
MAP [mmHg]	***1 (TEA)***	72.5 ± 10.6	74.1 ± 11.5	76.8 ± 10.6	74.8 ± 8.7	74.9 ± 8.4	70.9 ± 7.2	67.2 ± 6.6	64.1 ± 5.3	62.2 ± 6.2
	2 (Control)	74.7 ± 10.4	73.3 ± 8.3	73.5 ± 9.4	73.4 ± 7.7	73.1 ± 11.2	69.6 ± 5.8	66.5 ± 6.7	64.2 ± 6.2	61.9 ± 6.8
CI [l/min]	***1 (TEA)***	4.7 ± 1.3	4.9 ± 1.3	5.2 ± 1.1	5.1 ± 0.9	5.0 ± 0.9	5.2 ± 0.9	4.8 ± 0.7	4.6 ± 0.5	4.7 ± 0.8
	2 (Control)	4.6 ± 0.8	4.6 ± 0.8	5.1 ± 1.1	5.1 ± 0.8	5.1 ± 0.9	5.1 ± 0.9	5.2 ± 1.0	5.2 ± 1.1	5.2 ± 0.9
SVV [%]	***1 (TEA)***	6.5 ± 2.7	6.2 ± 1.1	5.9 ± 1.0	5.9 ± 1.0	7.1 ± 1.9	7.1 ± 1.5	6.5 ± 1.5	7.1 ± 1.5	7.3 ± 1.5
	2 (Control)	6.6 ± 1.6	6.8 ± 1.6	6.1 ± 1.3	6.1 ± 1.3*	6.9 ± 1.8*	6.6 ± 0.9*	6.2 ± 1.6*	6.8 ± 1.7*	7.2 ± 2.6*
CVP [mmHg]	***1 (TEA)***	6.7 ± 1.9	6.6 ± 1.7	7.0 ± 1.9	6.6 ± 2.3	6.5 ± 2.2	6.4 ± 1.7	6.6 ± 1.8	6.7 ± 1.6	6.6 ± 1.9
	2 (Control)	7.2 ± 2.4	6.6 ± 1.9	7.1 ± 2.0	7.0 ± 1.7	7.1 ± 2.0	7.2 ± 2.2	7.8 ± 2.3	7.5 ± 2.6*	8.1 ± 2.9*
p_aO_2 [mmHg]	***1 (TEA)***	161.1 ± 67.7	147.8 ± 24.9	139.1 ± 14.7	137.1 ± 12.7	134.7 ± 16.5	131.1 ± 17.6	130.2 ± 18.0	126.8 ± 17.2	125.3 ± 17.3
	2 (Control)	159.2 ± 21.2	145.4 ± 16.8	141.1 ± 14.9	138.6 ± 16.7	128.8 ± 12.7	124.8 ± 18.2	122.4 ± 17.1	118.4 ± 16.6	115.9 ± 18.7
$ScvO_2$ [%]	***1 (TEA)***	72.8 ± 8.4	75.2 ± 8.3	73.9 ± 10.8	74.4 ± 11.7	73.6 ± 13.2	71.6 ± 12.6	71.3 ± 9.6	69.1 ± 9.3	65.6 ± 12.9
	2 (Control)	81.6 ± 9.9	77.5 ± 9.6	79.4 ± 9.8	77.3 ± 9.4	70.8 ± 12.3	73.6 ± 12.2	73.4 ± 11.0	74.8 ± 11.5	72.0 ± 12.5
Lactate [mmol/l]	***1 (TEA)***	0.9 ± 0.3	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
	2 (Control)	0.9 ± 0.3	0.9 ± 0.4	0.9 ± 0.4	0.9 ± 0.4	0.8 ± 0.3	0.7 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2
Colloids [ml]	***1 (TEA)***	59 ± 141	121 ± 193	397 ± 235	518 ± 203	676 ± 290	879 ± 367	1088 ± 434	1294 ± 460	1594 ± 560
	2 (Control)	0 ± 0	50 ± 132	174 ± 209	388 ± 172	538 ± 156	768 ± 225	1032 ± 171	1382 ± 269	1694 ± 420
Cristalloids [ml]s	***1 (TEA)***	757 ± 210	1047 ± 325	1268 ± 403	1518 ± 460	1844 ± 548	2347 ± 637	2756 ± 748	3232 ± 968	3606 ± 1103
	2 (Control)	621 ± 211	932 ± 292	1271 ± 335	1415 ± 363	1829 ± 357	2276 ± 370	2788 ± 501	3300 ± 663	3800 ± 794
Urine [ml]	***1 (TEA)***	297 ± 271	406 ± 370	579 ± 491	682 ± 552	1012 ± 702	1294 ± 833	1571 ± 1015	1868 ± 1166	2188 ± 1343
	2 (Control)	206 ± 228	335 ± 337	582 ± 559	762 ± 644	1065 ± 748	1424 ± 858	1876 ± 1013	2376 ± 1136	2844 ± 1305

Values for tissue oxygenation (tpo2 [mmHg]), microcirculatory flow (Flux [AU]), Heart rate (HR [min^{-1}]), mean arterial pressure (MAP [mmHg]), cardiac index (CI [l/min]), systemic vascular resistance (SVRi [dynes*sec/cm^5/m^2]), stroke volume variation (SVV [%]), central venous pressure (CVP [mmHg]), arterial partial oxygen pressure (p_aO_2 [mmHg]), central venous oxygen saturation ($ScvO_2$ [%]), lactate measured in arterial blood gas analysis [mmol/l], cumulative crystalloid infusion (ml), cumulative colloid infusion (ml) and urine output (ml). Data are presented as mean ± standard deviation. * representing statistically significant differenence between treatment groups ($p < 0.05$) at time of measurement. M 0: Before induction of the acute pancreatitis, M 1 and 2: After Induction of the acute pancreatitis, M 2–8: During treatment interval.

Histopathologic examination

Histopathologic tissue examination revealed a lower severity of acute pancreatitis in Group 1 (TEA) compared to Group 2 (Control). Overall histopathologic pancreatitis score was 5.5 (3–8) (Group 1 (TEA)) versus 8 (5.5-10) (Group 2 (Control)) ($p < 0.001$). Details on histopathologic scoring for acinarnecrois, fatty tissue necrosis, inflammation and edema in the pancreatic head are presented in Table 3.

Table 3 Histopathologic Scoring for severity of acute porcine pancreatitis

Histopathologic severity score of acute pancreatis					
Group	**Acinar necrosis***	**Fatty tissue necrosis***	**Inflammation**	**Edema***	**Overall***
Group 1 (TEA)	2 (0-3)	1 (0–2)	2 (0–2)	1 (0–2)	5.5 (3–8)
Group 2 (CONTROL)	3 (0-3)	2 (1–3)	2 (1–3)	1.5 (0.5-3)	8 (5.5-10)
	Acinar necrosis	Fatty tissue necrosis (in relation to plane)	Inflammation (plasma cells, lymphocytes and granolocyts outside parechymal and fatty tissue)	Edema	
	0 nil	0 nil	0 nil	0 nil	
	1 <10 single necrosis/lobule	1 <1/3 of plane	1 loose infiltrates (≤30 cells/HPF)	1 intralobular edema	
	2 ≥10 single necrosis/lobule	2 ≥1/3 to <2/3 of plane	2 moderate infiltrates (30–99 cells/HPF)	2 interacinar edema, ≥2 lobules	
* p<0.05	3 ≥1/3 of plane	3 ≥2/3 of plane	3 dense infiltrates (≥100 cells/HPF)	3 intercellular edema, ≥2lobules	

Data are presented as Median (Range); HPF: High power field.
Pancreatitis Score: 0 (no pancreatitis)- 12 (severe pancreatitis).
Histopathologic pancreatitis score (0-12Points) including acinar necrosis (0–3) fatty tissue necrosis (0–3), inflammation (0–3) and Edema (0–3).
*p<0.05 representing statistically significant difference.

Hemodynamics and fluid balance

Hemodynamic data on macrocirculatory conditions did not present any significant differences during the entire intraopaerative period. Neither norepinephrine nor epinephrine were applied in either of the treatment groups. Detailed data on hemodynamics and fluid balance are presented in Table 2. The amount of fluids infused also did not differ between the treatment groups.

Laboratory data

Neither arterial blood gas analysis during the treatment interval (M2-M8) nor analysis of pancreatic amylase, liver enzymes, bilirubin, leucocyte count, lactate, and creatinine, from the blood samples taken in the postoperative observation period did present any significant differences between the two treatment groups ($p > 0.05$); (Table 4).

Table 4 Laboratory results of analysis of hemoglobine, leucocyte count, thrombocyte count, prothrombin time (PT), partial thromboplastin time (PTT), creatinine, aspartate-transaminase (AST), alanine-transferase (ALT), pancreatic amylase and total bilirubin

	Group	M 0	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Hemoglobine [g/dl]	**TEA**	8.8 ± 0.6	8.6 ± 0.6	8.2 ± 0.6	8.7 ± 0.7	9.1 ± 0.9	8.6 ± 0.5	8.6 ± 0.5	8.4 ± 0.7	8.2 ± 0.8	9.7 ± 0.8	9.6 ± 1.4	9.3 ± 1.2	9.2 ± 1.4	9.4 ± 1.2	9.3 ± 1.2	8.6 ± 1.4
	Controll	8.6 ± 0.5	8.7 ± 0.5	8.1 ± 0.6	8.5 ± 0.4	8.7 ± 0.5	8.4 ± 0.7	8.5 ± 0.9	8.0 ± 0.9	7.8 ± 0.6	9.5 ± 0.5	9.4 ± 1.2	9.4 ± 0.9	9.3 ± 0.4	9.3 ± 1.6	10.0 ± 0.7	9.5 ± 1.0
Leucocytes [109/l]	**TEA**	9.2 ± 3.0	8.7 ± 3.9	10.8 ± 4.0	9.4 ± 4.5	11.9 ± 4.4	11.8 ± 3.4	11.0 ± 3.0	10.5 ± 3.4	9.5 ± 4.3	11.0 ± 4.0	15.1 ± 4.6	18.8 ± 6.8	17.0 ± 7.1	23.4 ± 7.4	24.1 ± 7.6	23.5 ± 7.2
	Controll	9.0 ± 3.4	11.3 ± 3.2	12.8 ± 5.3	11.9 ± 2.4	13.3 ± 3.1	12.8 ± 3.3	12.4 ± 3.8	11.6 ± 3.4	9.8 ± 4.3	11.4 ± 3.5	17.9 ± 4.6	18.2 ± 6.6	17.7 ± 3.9	21.5 ± 6.7	25.0 ± 2.4	21.2 ± 6.3
Thrombocytes [109/l]	**TEA**	279 ± 97	196 ± 40	263 ± 72	176 ± 13	202 ± 38	191 ± 15	198 ± 19	186 ± 29	266 ± 97	356 ± 148	337 ± 103	380 ± 140	417 ± 174	445 ± 191	408 ± 178	403 ± 151
	Control	322 ± 97	240 ± 41	296 ± 100	251 ± 32	237 ± 42	250 ± 40	233 ± 20	211 ± 18	272 ± 100	366 ± 99	321 ± 94	333 ± 63	361 ± 100	423 ± 164	353 ± 175	408 ± 101
PT [sec]	**TEA**	108 ± 9	110 ± 5	107 ± 8	112 ± 7	110 ± 6	113 ± 4	110 ± 7	110 ± 9	107 ± 10	94 ± 10	112 ± 8	109 ± 15	102 ± 12	98 ± 13	98 ± 11	94 ± 11
	Control	115 ± 8	108 ± 5	105 ± 23	107 ± 3	106 ± 5	104 ± 9	105 ± 5	101 ± 8	101 ± 11	97 ± 9	100 ± 31	112 ± 13	114 ± 14	104 ± 15	109 ± 11	98 ± 11
PTT [sec]	**TEA**	89 ± 16	79 ± 15	85 ± 24	81 ± 27	86 ± 10	91 ± 26	93 ± 15	76 ± 4	92 ± 30	134 ± 22	103 ± 40	109 ± 22	79 ± 42	97 ± 48	107 ± 48	43 ± 25
	Control	84 ± 21	81 ± 18	86 ± 27	84 ± 27	82 ± 19	90 ± 30	75 ± 19	88 ± 19	98 ± 19	121 ± 25	111 ± 30	100 ± 33	87 ± 41	69 ± 17	79 ± 27	58 ± 14
Creatinine [mg/dl]	**TEA**	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.2	0.8 ± 0.1	0.8 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	0.9 ± 0.4	1.0 ± 1.0	1.1 ± 1.3	1.2 ± 2.0
	Control	0.7 ± 0.1	0.8 ± 0.1	0.7 ± 0.1	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.3	0.8 ± 0.1	0.7 ± 0.1	0.7 ± 0.2	0.6 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.2	0.7 ± 0.1
AST [U/l]	**TEA**	38 ± 13	42 ± 22	38 ± 14	45 ± 18	48 ± 20	47 ± 19	51 ± 22	52 ± 18	60 ± 21	348 ± 220	116 ± 62	54 ± 25	40 ± 19	32 ± 15	30 ± 14	41 ± 48
	Control	34 ± 11	40 ± 12	40 ± 15	40 ± 13	43 ± 10	46 ± 13	51 ± 8	51 ± 13	58 ± 19	319 ± 116	86 ± 27	45 ± 12	33 ± 5	30 ± 4	29 ± 12	32 ± 9
ALT [U/l]	**TEA**	77 ± 15	80 ± 6	63 ± 13	77 ± 9	76 ± 5	70 ± 9	66 ± 4	63 ± 8	50 ± 8	111 ± 30	105 ± 25	93 ± 24	77 ± 24	74 ± 19	66 ± 16	49 ± 15
	Control	76 ± 13	70 ± 12	63 ± 11	62 ± 9	61 ± 11	55 ± 8	55 ± 9	47 ± 7	46 ± 10	115 ± 28	105 ± 21	88 ± 15	82 ± 9	81 ± 13	71 ± 13	50 ± 12
Amylase [U/l]	**TEA**	2155 ± 368	2606 ± 103	2388 ± 509	2808 ± 137	2960 ± 280	2895 ± 250	3011 ± 187	3045 ± 319	3153 ± 965	8726 ± 3736	8196 ± 4195	6745 ± 4591	4316 ± 2923	3966 ± 2930	3909 ± 3319	3225 ± 3886
	Control	1971 ± 432	2165 ± 476	2249 ± 814	2278 ± 556	2479 ± 541	2567 ± 699	2876 ± 953	2733 ± 978	3261 ± 1296	10186 ± 5195	9001 ± 6610	8472 ± 5937	8109 ± 7347	6726 ± 5501	10129 ± 6670	7926 ± 6196
Bilirubine [mg/dl]	**TEA**	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.1	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.4 ± 0.2	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
	Control	0.2 ± 0.1	0.2 ± 0.0	0.2 ± 0.1	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.3 ± 0.1	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0

M0 –M8: During intraoperative setting.Day1-Day7: Results of blood samples taken in the postoperative observation period.

Discussion

This study is analyzing the effects of thoracic epidural analgesia in severe acute pancreatitis in an experimental setting. We found that TEA improved survival as well as pancreatic microcirculation and tissue oxygenation resulting in reduced histopathologic tissue-damage. It is the first study assessing the effects of TEA during controlled hemodynamic conditions as comparable to an intensive care setting. This is a necessary prerequisite to reliably assess microcirculatory dysfunction and tissue oxygenation.

The rationale for the use of TEA in acute pancreatitis is that intestinal and hepatic perfusion is regulated by sympathetic and parasympathetic nerves. In healthy subjects the regulation of blood flow is optimized for maintaining metabolic stability. During resting circumstances the sympathetic tone is low and blood flow is mainly regulated by vagal tone activity. An increasing sympathetic activity resulting in an intestinal vasoconstriction and consequently reduced blood flow has been shown in acute stress and pain [28]. This is also true for systemic inflammation where an affection of microcirculation is present [22,36,37]. The effects of TEA have been analyzed in different experimental models. Adolphs and co-workers were able to detect an improved microcirculation after TEA during hemorrhage-induced impairment of intestinal perfusion [38]. Additionally, there are several studies in animals suffering from systemic inflammation demonstrating benefits for the use of TEA. Models using coecal ligation to induce severe systemic inflammation could demonstrate an improvement of sepsis induced alterations of hepatic blood flow as well as improved mucosal microcirculation in rats [24,26]. In a model of systemic inflammation during endotoxemia in an ovine model as well as in the rat, superior renal perfusion as well as an attenuation of impairment of gastrointestinal organ perfusion and improved microvascular mucosa perfusion could be demonstrated [22,24,25]. A study by Lauer et al. demonstrated, that TEA also improved pulmonary endothelial integrity in hyperdynamic sepsis [39].

Regarding TEA and pancreatitis data are rare. Up to now, only two feasibility studies using TEA in acute pancreatitis in humans have been published so far. In the first trial, it was shown that the use is safe and rate of complications is low, although no control group was investigated in this trial. In the second trial TEA was found to be superior in terms of pain management [40,41]. Overall no clinical data concerning the therapeutic effect of TEA in severe acute pancreatitis especially on improvement of outcome and survival are available. Since there is enormous experience in the clinical use of TEA in humans for major abdominal and thoracic surgery, as well as for acute and chronic pain management the implementation of TEA in the early treatment of severe acute pancreatitis appears possible if no contraindications are present. Nonetheless the idea of using TEA also in systemic inflammation and sepsis still is discussed controversially [42]. Up to now, three experimental trials analyzing the impact of TEA in acute pancreatitis in rats have been published. In a setting similar to ours Demirag and co-workers for the first time demonstrated an improved pancreatic microcirculation also using laser Doppler flowmetry as well as reduced histopathologic damage in a small series in the rat. However no survival data were available [27]. Freise et al. were the first analyzing the impact of TEA on survival in an experimental model of severe acute pancreatitis in the rat. Besides improved 7 day survival they found an increased capillary perfusion and lower Inflammation, while no significant difference regarding histopathologic damage was present [43]. Another study by Freise and coworkers analyzed the impact of TEA on the liver in acute pancreatitis. Here a reduction of the vasoconstriction of the sinusoids and reduced apoptosis was found [28]. These data are

completely in accordance with our findings, that applying TEA resulted in improved microcirclutation and oxygenation of the pancreas and finally better survival as well as less histopathologic damage in SAP. Moreover in our study the effects of TEA on survival could be evalutated in a model where TEA was applied continuously over a period of 7 days similar to a clinical setting, since animals were equipped with an automated infusion pump. To date for practical reasons no direct assessment of pancreatic microcirculation exists in awake animals. Nonetheless, the effect of sympathetic block by TEA is also demonstrated for awake animals [44]. In the animals included in this study no obvious signs of a motor block were present. Unfortunately there is no reliable and validated method to assess analgesic effects and a sensory block, such as a pain scoring system, available in pigs. Though for reasons of the experimental setupt not direct evaluation of sympathicolytic effect was carried out, the correct positioning of the epidural catheter was verified at the end of the observation period by performing another epidurogram. Therefore we can only postulate that the epidural catheter was in the correct position and that due to the application of bupivacaine a sympathetic block and a sensory effect were present and that the detected effects of TEA on pancreatic microcirculation and tissue oxygenation during the intraoperative treatment period are present during the entire protocol, thereby contributing to the superior survival. Our findings are therefore in accordance to the afore mentioned theoretical considerations and are in line with the positive effects in other models of systemic inflammation using endotoxemia or bowel perforation. What has to be considered is, that overall not only pancreatic microcirculation but also other aspects like improved intestinal mucosal perfusion with less gut barrier dysfunction and improved liver perfusion potentially might have contributed to improved survival in our setting. Since especially the liver also is involved in a multitude of physiologic processes and decisively contributes to the host's immune reaction in sepsis and inflammation [28].

Some other aspects need to be taken into consideration. With a view to the evaluation of effectiveness of the treatment of severe acute pancreatitis it is important, that a model is used that closely mimics the clinical situation with a high mortality in severe acute pancreatitis where the severity of the pancreatitis ensures that some animals survive but also that some animals die without treatment. In our setting a model of intraductal injection of bile acid in the main pancreatic duct followed by closure was used. The model closely represents the clinical situation of acute biliary pancreatitis caused by obstruction of the papilla by bile stone and has been established in previous trials [9,45-47]. Another advantage of the model is, that it allows a very high standardization, using standardized dosages and infusion pressures unlike other models suggesting to induce severe acute pancreatitis by ischemia, hypotension or indigestion of alcohol [48,49].

Another aspect is that in our study we cannot explicitly demonstrate the sympathetic block. Measurements of arterial plasma levels epinephrine and norepinephrine were not carried out and also thermal imaging was not possible for reasons of the experimental setup. When looking at hemodynamics we also could not find a significant impact due to onset of TEA. The level chosen at Th 7/8 for TEA will not result in relevant vasodilation of capacitance vessels, neither should there be a relevant effect on the nervi accelerantes. Therefore to our understanding it is not surprising that onset of TEA did not present with significant changes and result in significant differences of hemodynamic parameters.

In addition to the data presented we analyzed the effects of TEA in a small series of healthy animals as well, where no experimental induction of pancreatitis was carried out. In one group only surgical preparation was carried out, while in the other group surgical preparation

and TEA were performed. Most importantly it was shown that the pancreatitis is not caused by the experimental setting (except the intraductal injection of bile acid), surgical trauma or anesthesia or TEA. No differences regarding pancreatic microcirculation and tissue oxygenation were detected and no sign of pancreatitis or inflammation was found in the histopathologic examination.

An issue, worth to be discussed is the interval between induction of pancreatitis and beginning of treatment. In our study, the interval chosen was rather short. However to our understanding this seems to be adequate, because the direct intraductal injection of bile acid induces an acute pancreatitis within a few minutes, which is much faster than acute biliary pancreatitis found in the clinical situation [50,51]. In our experimental setting a severe acute pancreatitis was observed macroscopically in all animals prior to beginning of therapeutic intervention. If the interval between induction and beginning of the treatment is too long the effect of improvement of the pancreatic microcirculation may fail to appear when fulminate necroses are already present, as the rationale for the treatment approach is to improve microcirculatory perfusion and thereby save not yet irreversible injured tissue from infarction and necrosis [52,53]. This aspect should not be forgotten and similar to approaches for early goal-directed hemodynamic stabilization by fluid therapy in systemic inflammation it holds probably true, that the treatment intervall is short and TEA should be commenced as early as possible.

Concerning the animal model, pigs were chosen since in smaller animals no adequate hemodynamic monitoring and therapy is possible which is essential to rule out macrocirculatory effects on pancreatic microcirculation as potential confounding factors influencing the estimation of effects of TEA in our trial. The combination of invasive intrapancreatic measurement of tissue oxygenation and microcirculation by microvascular blood flow does not only allow a reliable assessment of the pancreatic microcirculatory conditions, it also allows evaluation of the amount of oxygen reaching the end organ. Although a substantial benefit of TEA in severe acute pancreatitis was detected in our animal model, the direct transfer of the results to humans is not proven. The conception of the trial with a 7 days observation period allowed evaluation of outcome for severe acute pancreatitis and in this regard represents a good model closely mimicking the clinical situation and an important basis for potential further prospective randomized clinical trials.

Another fact is that measurement of pancreatic tissue oxygenation and microcirculation was limited to a period of only six hours. For this reason we cannot make a definite statement on the effects of TEA on pancreatic microcirculation and tissue oxygenation in the later course. Nonetheless, the effects and differences are present at an early stage and TEA led to a significant improvement in survival and less histopathologic damage. This strengthens the assumption of our hypothesis that TEA has a relevant therapeutic effect in severe acute pancreatitis.

Conclusions

In conclusion, our data suggest, that application of TEA resulted in improved survival and lead to enhanced pancreatic microcirculation and tissue oxygenation resulting in reduced histopathologic damage in a model of severe acute porcine pancreatitis.

Key messages

- The use of epidural anesthesia in systemic inflammation is still controversial.
- The results of our study suggest there is a relevant improvement in pancreatic microcirculation and tissue oxygenation due to the use of TEA in severe acute pancreatitis.
- Further we could demonstrate, that this improvement due to TEA resulted in less histopathologic damage and improved survival.
- Further evaluation is required to transfer these promising results into clinical practice.

Abbreviations

ALT, Alanine transaminase; ANOVA, Analysis of variance; AST, Aspartate transaminase; Fet, Endtidal fraction; FiO_2, Inspiratory oxygen fraction; HPF, High power field; PT, Prothormbin time; pTT, partial thromboplatin time; SAP, Severe acute pancreatitis; TBIL, Total bilirubin; TEA, Thoracic epidural anesthesia; tpO_2, tissue oxygen tension.

Competing interests

The authors declare they have no competing interests.

Authors' contributions

KB, CT, DR and OM have made substantial contributions to conception and design, analysis and interpretation of data and have been involved in drafting and revising the manuscript. AG, TS and JI have been involved in analysis and interpretation of data and in drafting and revising the manuscript critically for important intellectual content. LT JS WB LH participated in the acquisition of data and execution of the experimental protocol. AH carried out the histopathologic examination. All authors read and approved the final manuscript.

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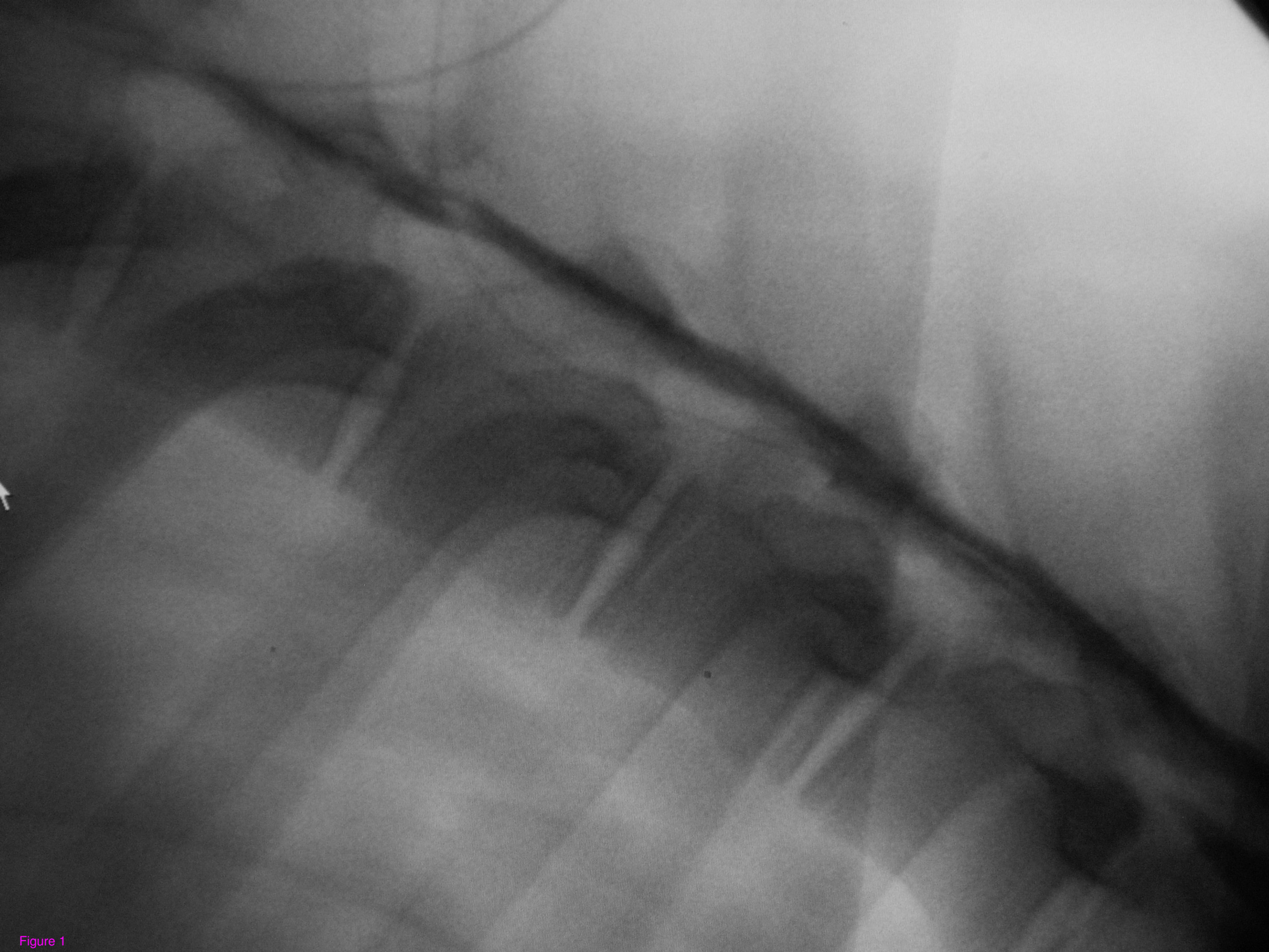

Figure 1

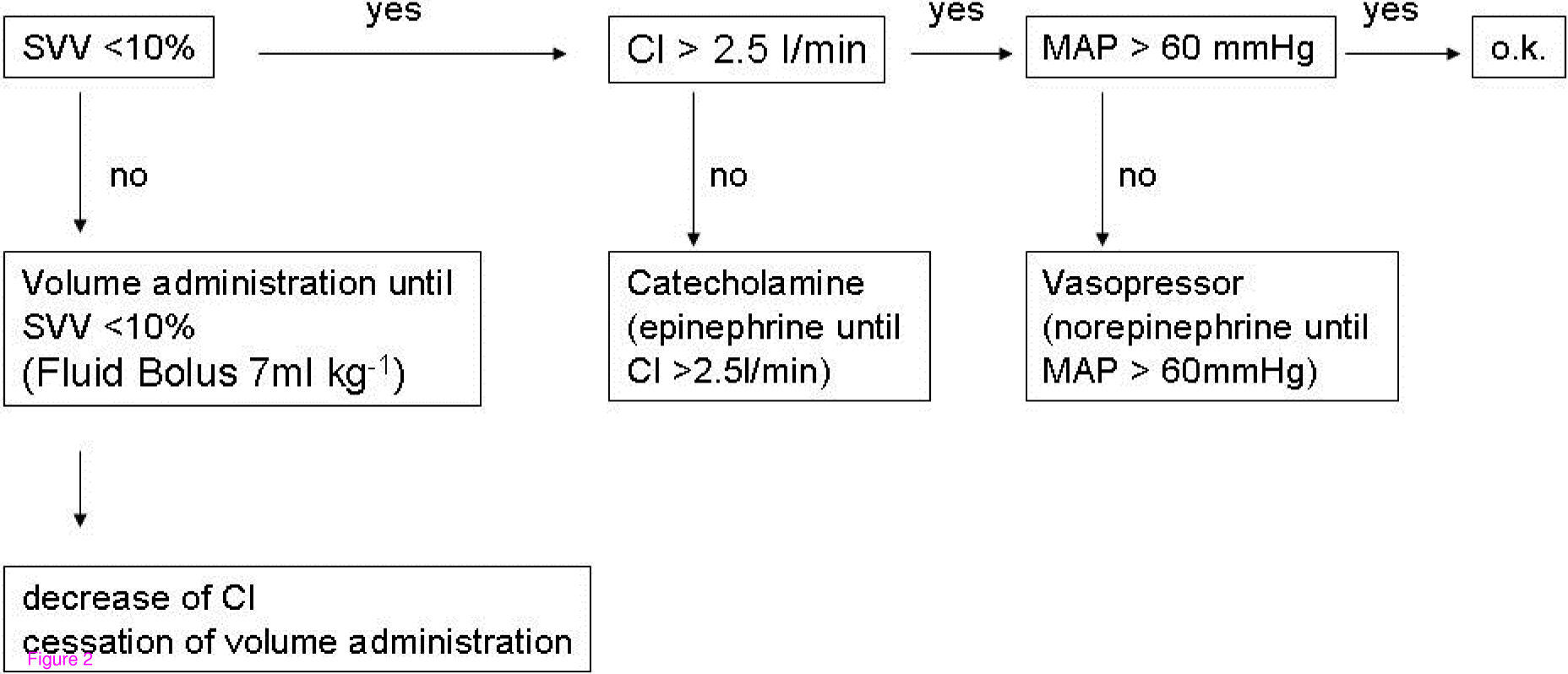
SVV <10%
yes
CI > 2.5 l/min
yes
MAP > 60 mmHg
yes
o.k.
no
no
no
Volume administration until
SVV <10%
(Fluid Bolus 7ml kg-1)
Catecholamine
(epinephrine until
CI >2.5l/min)
Vasopressor
(norepinephrine until
MAP > 60mmHg)
decrease of CI
cessation of volume administration

Figure 2

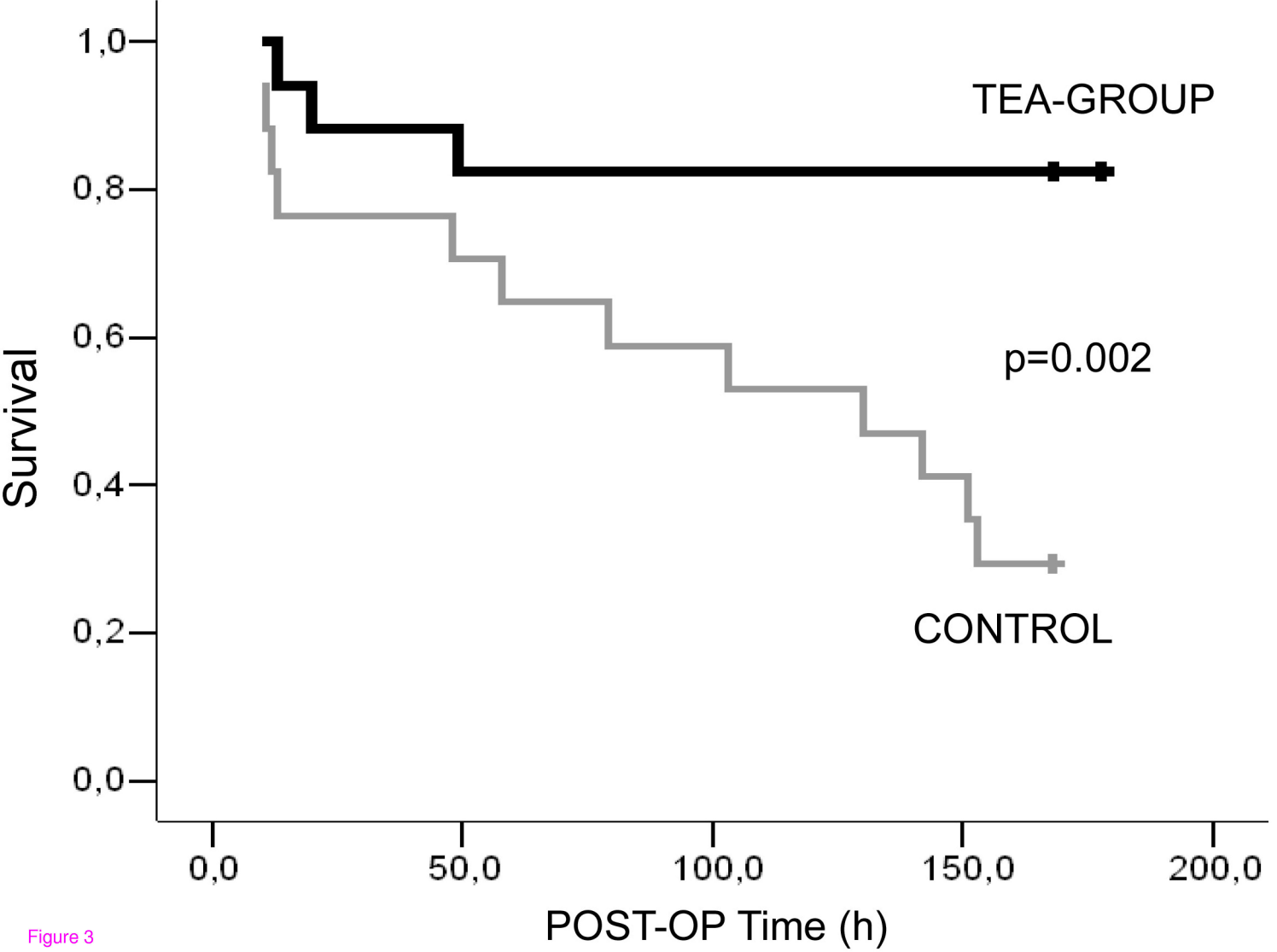
1,0
0,8
0,6
0,4
0,2
0,0
Survival
TEA-GROUP
p=0.002
CONTROL
0,0
50,0
100,0
150,0
200,0
POST-OP Time (h)

Figure 3

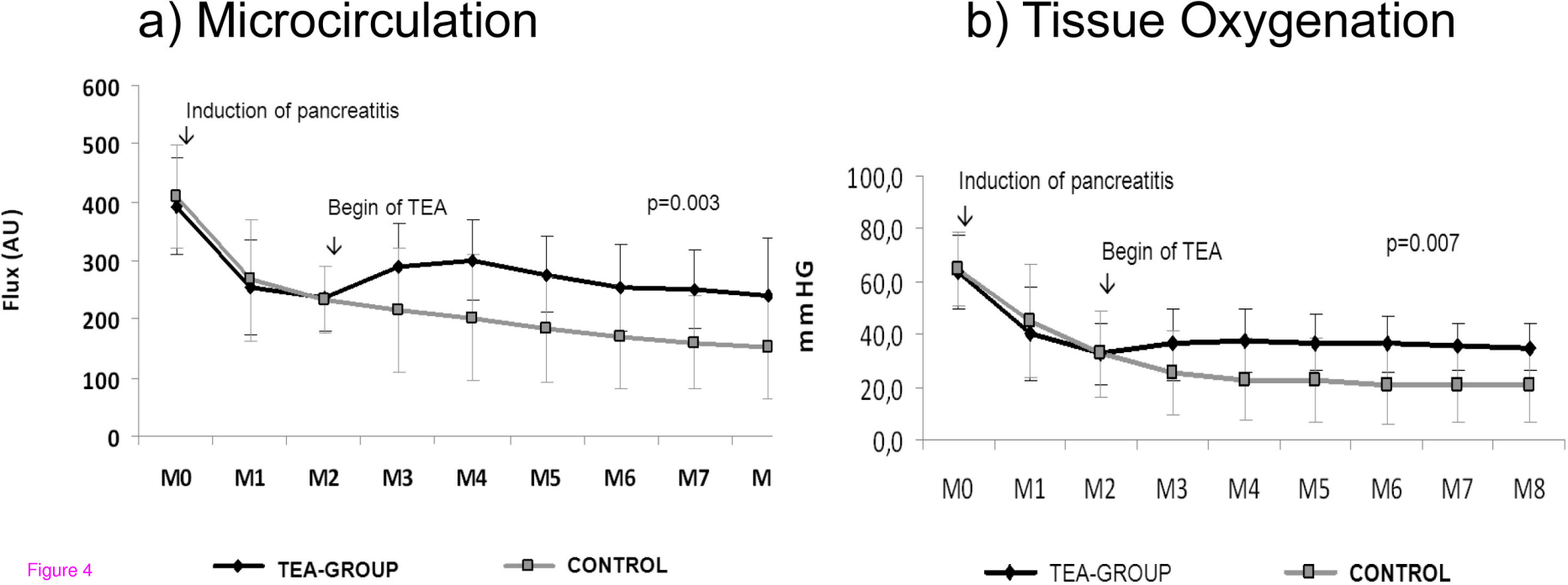
a) Microcirculation
Flux (AU)
600
500
400
300
200
100
0
Induction of pancreatitis
Begin of TEA
p=0.003
M0
M1
M2
M3
M4
M5
M6
M7
M
TEA-GROUP
CONTROL
b) Tissue Oxygenation
mm HG
100,0
80,0
60,0
40,0
20,0
0,0
Induction of pancreatitis
Begin of TEA
p=0.007
M0
M1
M2
M3
M4
M5
M6
M7
M8
TEA-GROUP
CONTROL

Figure 4