Elevated PEEP without effect upon gas embolism frequency or severity in experimental laparoscopic liver resection

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Abstract

Background. Carbon dioxide (CO_2) embolism is a potential complication in laparoscopic liver surgery. Gas embolism (GE) is thought to occur when CVP is lower than the intra abdominal pressure (IAP). This study aimed to investigate whether an increased CVP due to induction of positive end-expiratory pressure (PEEP) could influence the frequency and severity of GE during laparoscopic liver resection.

Methods. Twenty anaesthetized piglets underwent laparoscopic left liver lobe resection, being randomly assigned to either 5 or 15 cm H_2O PEEP (n=10 per group). During resection, a standardized injury to the left hepatic vein (VC) was created to increase the risk of GE. Haemodynamic and respiratory variables were monitored and online arterial blood gas monitoring and transoesophageal echocardiography (TOE) were used. GE occurrence and severity was graded as 0 (none), 1 (minor) or 2 (major), depending on the TOE results.

Results. No differences were found between the two groups regarding the frequency or severity of GE, during either the VC (P=0.65) or the rest of the surgery (P=0.24). GE occurred irrespective of the CVP–IAP gradient.

Conclusion. Mechanisms other than the CVP–IAP gradient seemed to contribute to the formation of CO_2 GE – knowledge of clinical importance to the anaesthesiologist.

Introduction

The complexity of liver surgery is increased by the addition of laparoscopy, among other things, due to the risk of gas embolism (GE). Reports on this complication have been published.[1 2] As use of laparoscopic liver surgery (LLS) has increased, so too has the need to predict and evaluate carbon dioxide (CO_2) embolism.[3-9] We previously showed a GE occurrence of 70% during LLS in an animal model; half of these cases gave rise to haemodynamic/respiratory disturbances.[10]

One condition thought necessary for GE to occur is the existence of a pressure gradient between the inside and outside of a blood vessel. [11-15] Thus, according to this theory, gas could migrate intravenously if the intra abdominal pressure (IAP) exceeds the intra luminal pressure in a wounded vessel. We have previously shown that the frequency and severity of GE was lower when IAP was 8 mm Hg than when IAP was 16 mm Hg; however, this came at the cost of increased blood loss at the lower IAP.[16] One easy method of increasing the intra luminal pressure in the liver veins, reflected by CVP,[17] is to use positive end-expiratory pressure (PEEP).[15 18 19 20]

We therefore hypothesized that an elevation of CVP, through increased PEEP, would affect the frequency and severity of GE during laparoscopic liver resection in a porcine model.

Methods

The study design and the care and handling of the animals were approved by the Ethics Committee on Animal Experiments in Uppsala, Sweden.

Animal preparation

Twenty Swedish country-breed piglets aged about three months, of both genders, were used in the study. The animals were fasted overnight with free access to water. Before leaving the farm, the piglets were intramuscularly (i.m.) injected with xylazine 20 mg ml-1 (2.2 mg kg-1) (Rompun® vet. Bayer, Leverkusen, Germany). For induction of general anaesthesia, the piglets were injected i.m. with 6 mg kg-1 tiletamine/zolazepam (both 50 mg ml-1) (Zoletil forte vet. ® Virbac, Carros, France), xylazine 20 mg ml-1 (2.2 mg kg-1) (Rompun® vet.), and atropine sulphate 0.5 mg ml-1 (0.04 mg kg-1). An intravenous (i.v.) injection of morphine hydrochloride 20 mg and ketamine 100 mg was administered as a bolus injection. A continuous i.v. infusion of a ketamine-containing agent, ketaminol 20 mg kg-1 h-1, pancuronium bromide 0.24 mg kg-1 h-1 and morphine hydrochloride 0.5 mg kg-1 h-1 was used to maintain anaesthesia. The piglets were placed in a supine head-up position at an angle of 5°, tracheostomized (7-mm tube) and mechanically ventilated (Servo Ventilator 900 C, Siemens Elema, Solna, Sweden) with O_2 in air (FiO_2 0.3) with volume-controlled ventilation and a PEEP of 5 cm H_2O. Minute ventilation was adjusted to maintain the arterial $PaCO_2$ within the range 5.0–5.5 kPa. No subsequent adjustment of ventilation was made. For half of the piglets PEEP was elevated to 15 cm H_2O after the preparations were made.

A pulmonary artery catheter (Swan-Ganz, CritiCath Ohmeda®, 7.5 French) and a central venous catheter (7.0 French) were placed in the right external jugular vein. Gelofusin (gelatine with electrolytes, Braun, Austria) was administered i.v. to the piglets in order to achieve a pulmonary capillary wedge pressure (PCWP) of 8–10 mm Hg before the start of the experiment and Ringers solution 8 ml-1 kg-1 h-1 was administered thereafter to compensate for external losses. During the first 30 post-operative minutes the piglets with a PCWP<8–10 mm Hg received Gelofusin i.v. until PCWP reached 8–10 mm Hg.

An arterial catheter (Boston Dickinson®, 18 G) was inserted into the external carotid artery and then threaded into the aortic arch to enable pressure monitoring and blood sampling. The position of all the catheters was confirmed by pressure tracing. For continuously monitoring arterial blood gases a second artery catheter (Boston Dickinson®, 20 G) was placed in an branch into the left external carotid artery for insertion of a ParaTrend® sensor (Trendcare® Monitoring System, TCM 7000®, Diametrics Medical, High Wycombe, UK) .

The right outflow tract of the heart was monitored continuously by transoesophageal echocardiography (TOE) (Sonos 1000 Ultrasound system, Omniplane Probe; Hewlett Packard, Aliso Uiejo, CA, USA). Both TOE and the surgical procedure were recorded on video for later review. After the experiment, the animals were euthanized under general anaesthesia with intravenous KCl.

Measurements and calculations

Temperature, electrocardiography, heart rate, arterial blood pressure, pulmonary artery pressure and CVP were continuously monitored (Marquette, Solar 8000, Hellige Systems, Germany) and recorded (AcqKnowledge 3.8.1 StatSoft® Scandinavia AB, Uppsala, Sweden). The CVP waveform consists of several peaks and descents of which the a-wave ($CVP_{a\text{-}wave}$) is the most prominent peak and the x-wave ($CVP_{x\text{-}wave}$) the nadir value (Fig. 1). The pressure gradients between $CVP_{a\text{-}wave}$ and AIP as well as between $CVP_{x\text{-}wave}$ and IAP were analyzed during the VC period, i.e. when the vein was cut and left open for 3 min.

PCWP was measured and cardiac output (CO) calculated using the thermodilution technique. As there is no body surface nomogram for piglets, we calculated Cardiac Index as CO/weight (kg); to indicate this difference we used the abbreviation CI_w instead of CI. Arterial blood gases (PaO2, $PaCO_2$ and pH) were continuously monitored and recorded. Mixed venous oxygen saturation (Sv_{O2}) was measured before start of the operation and at the end of the experiment. (ABL 300, Radiometer, Copenhagen, Denmark). End-tidal CO_2 (Et_{CO2}), peak inspiratory pressure (PIP) and dead space Vd/Vt [ratio of dead ventilation (Vd) to tidal ventilation (Vt)], alveolar dead space and physiological dead space were also recorded and calculated (CO_2SMO plus, Nova Metrix Medical Systems Inc., Connecticut, USA).

Operation technique

The liver resection was performed by two highly experienced surgeons. Pneumoperitoneum was established using a Veress needle, and the IAP maintained at 16 mm Hg with CO_2 at room temperature. Dissection was conducted on the left side of the liver with an Ultrasound dissector (CUSA Excel®, Valleylab Inc., Boulder, CO, USA) and a Vessel sealing system (LigaSure™, Valleylab Inc.). In the pig, the left hepatic vein is found approximately halfway through the resection of the left lobe. The vein was carefully dissected and a standardized venous cut (VC) of 6 mm was made into the anterior wall of the vein with scissors and then left open for 3 min before it was clipped with 10-mm clips (EndoClip™, Autosuture, CT, USA) on both sides of the cut. Thereafter division and full resection of the left lobe was performed. Haemostasis was checked and controlled during and at the end of the operation.

Experimental protocol

After completion of the preparations, no interventions were allowed for 30–45 min to achieve haemodynamic and respiratory stability. The animals were randomized into two groups for PEEP 5 (i.e. P5) (*n*=10) weighing 25.2 (2.2) kg [mean (standard deviation)] and PEEP 15 cm H_2O (i.e. P15) (*n*=10) weighing 25.5 (2.1) kg [mean (standard deviation)]. Baseline values were then obtained. For the P15 group, PEEP was increased to 15 cm H_2O followed by a new stabilization period and a second set of baseline values were collected. CO_2 pneumoperitoneum was established in both groups with a Veress needle, and the pressure maintained at 16 mm Hg. This was followed by another stabilization period and once more a set of baseline values were collected before the start of the surgery. Recordings were made every 5 min during the operation; except for PCWP and CO, which were recorded every 15 min. The systemic and pulmonary arterial pressures, end-tidal CO_2, temperature and PIP were recorded. Immediately after the surgery, a set of recordings was made before exsufflation of the pneumoperitoneum. For the P15 group, PEEP was lowered to 5 cm H_2O. After exsufflation, data were recorded every 10 min for 30 min.

Criteria for embolism

TOE videos were reviewed and analyzed blind by two of the authors. With TOE, white dots observed moving with the blood flow in the right outflow tract, were considered to be gas bubbles. A previously described scoring system was adapted for classifying the severity of each embolic episode.[10 21] These were classified as Grade 0 if <5 bubbles were seen at the same time, Grade 1 if ≥5 bubbles were seen at the same time but the right outflow tract was not completely obscured by bubbles, and Grade 2 if the outflow tract was completely filled with bubbles. The end of a GE period was set when followed by an interval of at least 10 s without any bubbles.

Data analyzes

Data handled by AcqKnowledge 3.8.1 (StatSoft®) were collected at a frequency of 200 Hz. Mean values for every minute during the experiment were selected, with the exception of the embolization episodes for which mean values every 15 s were chosen. The mean of the final four 15-s values recorded immediately before the start of the embolization were used as a baseline for analyzing changes. The time period analyzed was 2 min after the end of embolization, unless a new embolization occurred within this period. Analyzes of the variables focused on the times when GE was observed by TOE.

Statistical analyzes

The time period during the surgery was divided into two parts which were treated separately. The time from the beginning to the end of the surgical procedure except for the 3-min period of VC was considered as one part (Non-VC). The other part was the 3-min VC which was considered an isolated time period and thereby only one embolization event was possible. The changes in respiratory and haemodynamic variables were non-normally distributed and thus non-parametric tests were used. The Mann–Whitney *U* test was used to analyze differences between the treatment groups before operation and during the Non-VC period. Fisher's exact test was used to compare the severity of GE during the VC period between the P5 and P15 groups. Statistical significance was set at $P<0.05$.

Results

After establishment of pneumoperitoneum (16 mm Hg) before the start of the surgery, the physiological variables were assessed and compared. The groups differed in CVP, Pa_{CO2}, Pa_{O2}, CI_w and SvO_2 (Table 1). At baseline in P15 group CVP was 9(6-14) cm H_2O [median (minimum-maximum)] and after increase in PEEP to15 cm H_2O 10.5 (8-13) cm H_2O [median (minimum-maximum)] (P=0.97). After establishment of pneumoperitoneum, however, there was a difference in CVP between the P5 and P15 groups (p = 0.001) (Fig.2).

In five of 20 piglets there were no signs of GE during the whole procedure. In six of the animals GE occurred in the Non-VC or the VC period, and for the remaining nine piglets GE occurred in both periods of the operation (Table 2). Comparing the P5 and P15 groups in number and grade of embolic events, there were no differences either during the VC (P=0.65, Fisher's exact test) or the Non-VC periods (P=0.24, Mann–Whitney U test).

Three piglets in the P5 group and five in the P15 group showed no signs of GE during the VC period despite $CVP_{x\text{-wave}}$<IAP (Table 3). For the remaining seven piglets in the P5 group and two of the piglets in the P15 group, both the $CVP_{x\text{-wave}}$ and the $CVP_{a\text{-wave}}$ were <IAP while GE occurred during the VC. For the last three piglets in the P15 group showing GE during VC, both the $CVP_{x\text{-wave}}$ and the $CVP_{a\text{-wave}}$ were higher than the IAP. Two of these were classified as Grade 2 embolism.

The duration of surgery as well as the median occurrences of Grades 1 and 2 embolisms of the total operating time were compared; however, there were no differences between the two groups (Table 4).

Discussion

No differences were found between the P5 and P15 groups in the frequency or severity of GE during laparoscopic liver resection. During the Non-VC period, GE occurred in 60% of the animals, mostly as harmless Grade 1 episodes which is in accordance with our previous study.[10] Grade 2 episodes had negative effects on respiration as well as circulation.

By increasing PEEP, CVP was elevated and differed between the two groups after establishment of pneumoperitoneum. CVP is a variable influenced by many factors such as intrathoracic pressure, hydration and systemic venoconstriction. This is why it commonly varies over time during an operation. As gas flux is thought to be influenced by a pressure gradient, in this case the difference between CVP and IAP, the importance of CVP in the occurrence of GE was analyzed. It is essential to keep in mind that CVP is a calculated value. In reality this pressure consists of systolic and diastolic components with following phasic pressure variations. (Fig.1). It is these pressure peaks and valleys which represent the pressure gradients to compare with the AIP. In spite of an open vein and $CVP_{x\text{-}wave}$<IAP during the VC, eight of the 20 piglets showed no signs of GE. GE occurred irrespective of CVP higher or lower than the IAP. We compared not only the numbers of GE events between the groups but also the duration of surgery as well as the total time of occurrence of GE during the surgery. Neither was there a difference between groups P5 and P15 in the surgery duration nor in the occurrence of Grade 1 or Grade 2 embolisms.

The differences between humans and pigs, in terms of pulmonary structure and reactions that might influence the restoration of a disturbed ventilation-perfusion ratio, have previously been discussed in detail.[22 23] One concern with applying a PEEP as high as 15 cm H_2O was the negative effect upon the circulation illustrated by a decrease in CI_w and Sv_{O2}.[24] Even if the CVP in all animals in the P15 group was at least 16 mm Hg before the surgery started, it almost always decreased and varied in an unpredictable way (Fig. 1). It is unclear whether a further increase in PEEP could have stabilized CVP at a higher level than IAP without having a devastating effect on circulation. Schmandra and colleagues recommended an elevation of the CVP to a level permanently exceeding the IAP to reduce the risk of GE; however, they also reported that episodes of GE were detected when the CVP was both above and below the IAP.[25] Jayaraman and colleagues reported that the CVP–IAP gradient did not influence the occurrence of GE in a pig model during laparoscopic hepatectomy.[26] In the field of neurosurgery, many studies have been conducted concerning the problem of air entrance through non-collapsible venous channels. Different methods have been used to increase the pressure in the venous sinuses above atmospheric pressure, with a reduced frequency of air embolism reported.[18 27 28] In a recently published study, our group reported that the embolization grade and frequency were lower when applying an IAP of 8 mm Hg compared with one of 16 mm Hg.[16] The discussion is ongoing concerning the level of CVP, blood loss, IAP and the risk of GE why there still is a lack of accord in handling GE.[16 17 29]

The theory that the pressure gradient inside and outside a venous vessel alone is responsible for gas flux could not be supported in this trial. The filling pressure on the right side of the heart (i.e. CVP) was, as expected, elevated with an increased PEEP. During the VC, GE mostly occurred when IAP>CVP, but the opposite also occurred. Interestingly, all eight animals without GE during the VC had periods of a positive CVP–IAP gradient but with no signs of intravenous gas migration. The physics of gas flux is apparently influenced by the IAP, but this pressure does not seem to be balanced by the intravenous pressure. Thus other explanatory mechanisms must be sought.

CO_2 in blood reacts with water to form bicarbonate and 70% of the CO_2 is in blood transported as sodium bicarbonate. This chemical reaction is relatively slow in plasma, but is in the erythrocytes one of the fastest biological chemical reaction known, due to the present of the enzyme carbonic anhydrase. CO_2 is easily dissolved in blood due to the reaction with water and formation of bicarbonate (i.e. $CO_2 + H_2O \leftrightarrow H_2CO_3$) and is transported as sodium bicarbonate. According to Henry's law, the amount of gas dissolved in a liquid is directly proportional to the partial pressure of the gas in equilibrium with the liquid as long as the temperature is stable. Gas flux from higher to lower partial pressure and CO_2 therefore ought to migrate from the abdomen (with a high P_{CO2} due to pneumoperitoneum) into the veins of the liver where the blood has a lower P_{CO2}. However, in the heart the gas is seen as bubbles on the TOE. There is no reasonable explanation for the dissolved CO_2 coming out of solution when reaching the heart.

As long as there is a blood flow, gas can be transported along with the stream towards the heart. Respiration causes a rhythmic compression and decompression with an influence upon the liver parenchyma, the thoracic pressure and the central venous return. These changes in flow velocity and pressure might influence the ease of, and amount of, gas flux into the blood according to entrainment, a Venturi-like effect and thereby contribute to a risk of GE. An even and stable blood flow could therefore have a positive influence upon the frequency and severity of GE. Further studies are required to investigate whether the Venturi effect is important in this respect.

Summary: An increase in PEEP elevated the CVP when combined with pneumoperitoneum, but at the cost of a negative influence on the circulation. Despite a positive CVP–IAP gradient, GE occurred in this experimental study. There must therefore be other explanations for GE occurrence, irrespective of the CVP level. One explanation could be the Venturi effect, which might be exaggerated by the pressure and thereby flow changes caused by respiration. Future studies are required to explore the underlying mechanisms. For the anaesthesiologist, as well as the surgeon, it is important not to underestimate the risk of GE, despite a positive CVP–IAP gradient during laparoscopic procedures in the liver.

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Conflicts of interest
None declared.

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Figures

Fig 1. The CVP waveform with its five phasic events: the a-, c-, x-, v- and y-waves. Ventricular systole starts at the valley before c and ends at v.

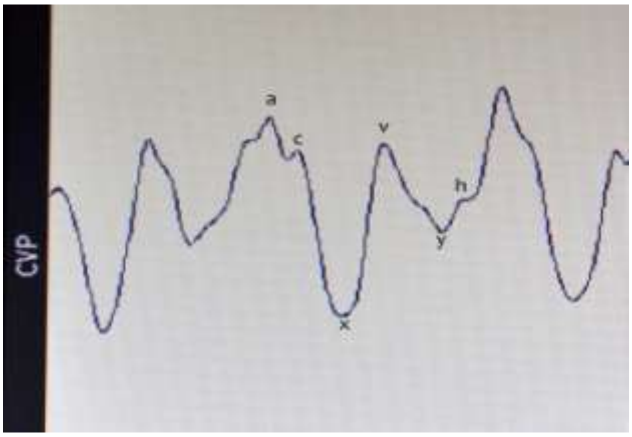
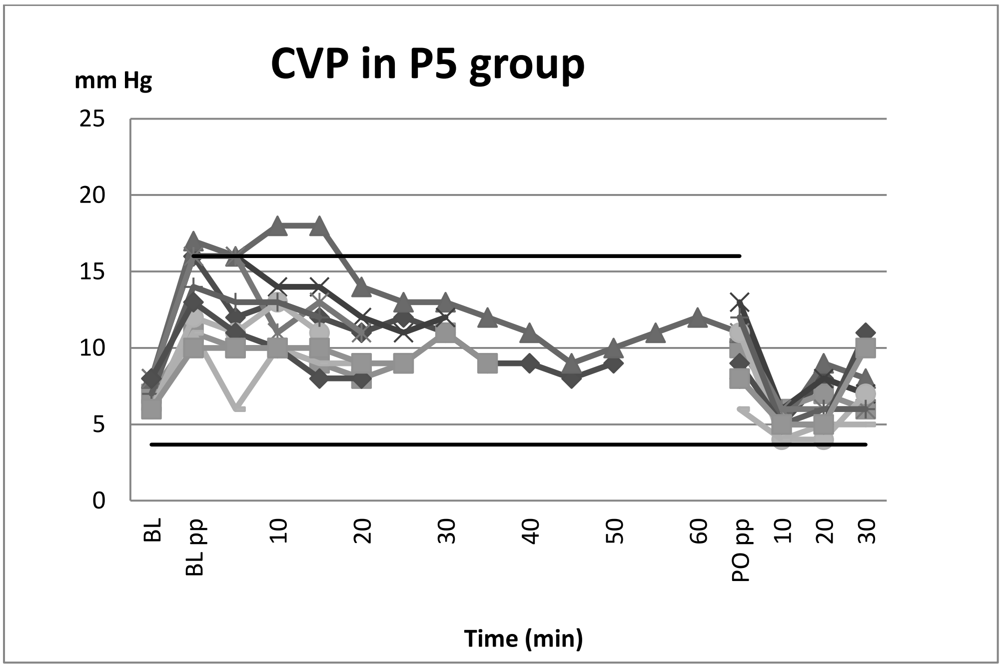
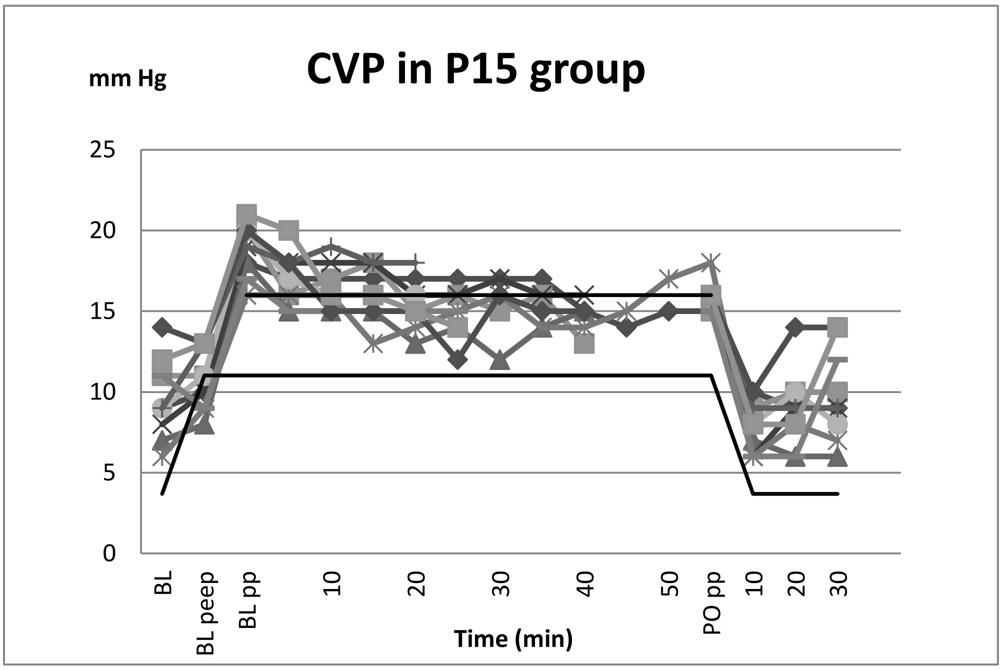


Fig 2. CVP in P5 and P15 groups during the surgery. BL = baseline, BLpeep = baseline after increasing PEEP to 15 cm H_2O, BLpp = baseline after establishment of pneumoperitoneum. POpp = Post-Operative values, before exsufflation of pneumoperitoneum. Depending on the varying lengths of surgery, most curves have a gap in the time interval before POpp. The top black line represents IAP (16 mm Hg) and the bottom black line PEEP (5 and 15 cm H_2O).





Tables

Table 1 Comparison between the P5 and P15 groups before surgery, after establishment of pneumoperitoneum. PEEP was measured in cm H_2O. *P*-values are calculated from a Mann-Whitney *U* test.

Variable	P5		P15		P5 vs. P15
	n	Median (min.–max.)	No	Median (min.–max.)	*P*-value
CVP (mm Hg)	10	14 (10–17)	10	19 (16–21)	0.001
pH	10	7.40 (7.32–7.45)	10	7.40 (7.39–7.48)	>0.1
Pa_{CO2} (kPa)	10	6.1 (5.8–7.4)	10	5.90 (5.5–6.5)	0.035
Pa_{O2} (kPa)	10	15.5 (8.4–20.1)	10	19.4 (10.9–24.4)	0.02
Et_{CO2} (kPa)	10	5.8 (5.2–6.4)	10	5.85 (4.5–6.6)	>0.1
Vd/Vt (ratio)	10	0.56 (0.44–0.66)	10	0.54 (0.40–0.63)	>0.1
CI_w ($l\ min^{-1} kg^{-1}$)	10	0.12 (0.10-0.20)	10	0.11 (0.08-0.15)	0.09
PCWP (mm Hg)	10	14 (6–18)	10	16 (14–20)	>0.1
Sv_{O2} (%)	10	64.7 (49.5–72.9)	10	55.8 (44.4–62.7)	0.02

Table 2 Number of embolic events and embolization grade (Gr.) before venous cut (Pre VC), after venous cut (Post VC) and during the venous cut (VC) periods for groups P5 and P15.

Pig n	Pre VC P5		VC P5		Post VC P5	
	Gr. 1	Gr. 2	Gr.1	Gr.2	Gr. 1	Gr. 2
2	6		1		2	
4					3	2
5			1		8	
7	1			1		
11	3			1	1	1
12	3		1		2	
13	5		1			
14			1			
19	-	-	-	-	-	-
20	-	-	-	-	-	-
Total	**18**	**0**	**5**	**2**	**16**	**3**

Pig n	Pre VC P15		VC P15		Post VC P15	
	Gr. 1	Gr. 2	Gr.1	Gr.2	Gr. 1	Gr. 2
1	-	-	-	-	-	-
3			1			
6	-	-	-	-	-	-
8	-	-	-	-	-	-
9	4				1	
10			1		1	
15				1	8	
16					2	
17				1		
18			1		3	
Total	**4**	**0**	**3**	**2**	**15**	**0**

Table 3 The lowest $CVP_{x\text{-wave}}$ (mm Hg) value measured during the VC period of the operation as well as the lowest $CVP_{x\text{-wave}}$ and highest $CVP_{a\text{-wave}}$ values during ongoing GE episodes during the VC period for P5 (*n*=10) and P15 groups (*n*=10). Embolization grade = Gr. IAP = 16 mm Hg

P5

Gr.	Lowest $CVP_{x\text{-wave}}$ during VC	Lowest $CVP_{x\text{-wave}}$ /highest $CVP_{a\text{-wave}}$ during ongoing GE
0	4	
0	7	
0	8	
1	4	6/11
1	8	8/12
1	6	6/12
1	8	8/12
1	7	7/11
2	10	11/14
2	9	8/13

P15

Gr.	Lowest $CVP_{x\text{-wave}}$ during VC	Lowest $CVP_{x\text{-wave}}$ /highest $CVP_{a\text{-wave}}$ during ongoing GE
0	8	
0	10	
0	14	
0	12	
0	14	
1	11	11/14
1	8	9/15
1	18	17/21
2	16	16/19
2	18	18/19

Table 4 Occurrence of Grade 1 and 2 embolisms in minutes during the surgery for all piglets in groups P5 and P15 respectively.

	P5 Median (min.–max.)	**P15 Median (min.–max.)**	***P*-value**
Total surgery time (min)	25 (16.5–65)	40.9 (21–53)	0.25
Total time of Grade 1 (min)	1.8 (0–4.8)	0.4 (0–5.8)	0.28
Total time of Grade 2 (min)	0 (0–3.7)	0 (0–2.9)	0.53