Gas embolism during laparoscopic liver resection in a pig model: frequency and severity

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Key points
- Gas embolism (GE) can occur during laparoscopic liver surgery.
- Laparoscopic liver surgery was carried out in pigs and GE was identified using transoesophageal echocardiography.
- Embolism occurred in most animals.
- About half the emboli resulted in mainly respiratory and some haemodynamic problems.
- Further studies in patients are required.

Background. Laparoscopic liver surgery is evolving rapidly. Carbon dioxide embolism is a potential complication. The aim of this work was to study the frequency and severity of gas embolism (GE) during laparoscopic liver lobe resection in a pig model and the resulting cardiovascular and respiratory changes.

Methods. Fifteen anaesthetized piglets underwent laparoscopic left liver lobe resection. Haemodynamic and respiratory variables were monitored, including systemic and pulmonary arterial pressures, end-tidal CO2, and pulmonary dead space. Online blood gas monitoring and a transoesophageal echocardiography (TOE) were used. GE was graded semi-quantitatively as grade 0 (none), grade 1 (minor), or grade 2 (major), depending on the TOE results.

Results. In 10 of 15 piglets, GE occurred. In total, 33 separate episodes of GE were recorded. All 13 episodes of grade 2 and three of grade 1 were serious enough to cause mainly respiratory, but also haemodynamic effects. Mostly, grade 1 GE caused only minor respiratory or haemodynamic changes. Most variables were affected during grade 2 GE; the most important were \( P_{aO2} \), \( P_{aCO2} \), end-tidal CO2, \( Vd/Vt \), and mean pulmonary arterial pressure.

Conclusions. GE occurred frequently during laparoscopic liver resection in this experimental study. Approximately half of the embolisms were serious enough to cause respiratory or haemodynamic disturbances or both. Pending further human studies, a combination of several monitoring techniques, with narrow limits for the alarm settings, will ensure correct interpretation of the complex physiological response to GE and reveal it early enough to alert the anaesthetist and the surgeon to the ongoing problem.

Keywords: embolism, air; liver; surgery, laparoscopic; swine

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Gas embolism (GE) from carbon dioxide is an acknowledged complication of laparoscopic surgical procedures.1 A report on this complication during laparoscopic liver resection was recently published.2 Laparoscopic liver surgery is a new approach that is evolving rapidly and its use is predicted to increase in the future.3–8 It differs in several fundamental ways from open liver surgery, a matter of major concern to anaesthetists. Open surgery implies a well-established risk of air embolism. During laparoscopic surgery, CO2 is used at a certain pressure, which also implies a risk for GE, although this is less harmful because of the solubility of CO2 in blood.9

The absence of GE during laparoscopic liver resection has been reported.5 7 10 This is a statement without any strong scientific support, since the monitoring techniques used are frequently not described and the occurrence of GE has not always been clearly defined. The true frequency of GE in laparoscopic liver surgery therefore appears unclear. In studies focused on evaluating the risk of GE, contradictory results have been obtained.11 12

The aim of this work was to study the frequency and severity of GE and the resulting cardiovascular and respiratory changes during laparoscopic liver lobe resection in a pig 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

Fifteen Swedish country-breed piglets aged about 3 months and of both genders, weighing 27.4 (1.7) kg [mean (SD)], were used in the study. The animals were fasted overnight.
with free access to water. 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.\(^{11}\) Virbac, Carros, France) xylazine 20 mg ml\(^{-1}\) (2.2 mg kg\(^{-1}\) (Rompun\(^{\circledR}\) vet. Bayer, Leverkusen, Germany), and atropine sulphate 0.5 mg ml\(^{-1}\) (0.04 mg kg\(^{-1}\)). An i.v. injection of morphine hydrochloride 20 mg and ketamine 100 mg was administered as a bolus injection. A continuous i.v. infusion of ketaminol 20 mg kg\(^{-1}\) h\(^{-1}\), pancuronium bromide 2 mg ml\(^{-1}\) (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 head-up position at an angle of 5\(^{\circ}\), tracheostomized (7 mm tube), and mechanically ventilated (Servo Ventilator 900 C, Siemens Elema, Solna, Sweden) with \(\text{N}_2\text{O} 70\%\) in air during the preparation. \(\text{N}_2\text{O}\) was discontinued after the preparation and at least 45 min before the start of the operation so as not to influence GE. Thereafter, the piglets were ventilated with \(\text{O}_2\) in air (\(\text{F}_{\text{io}2}\) 0.3) with volume-controlled ventilation and a PEEP of 5 cm H\(_2\)O. Minute ventilation was adjusted to maintain the arterial \(\text{P}_{\text{aCO}_2}\) within the range of 5.0–5.5 kPa. No subsequent adjustment of ventilation was made.

A pulmonary artery catheter (Swan-Ganz, CritiCath Ohmeda\(^{12}\), 7.5 Fr) and a central venous catheter (7.0 Fr) were placed in the right external jugular vein. Ringer’s solution was administered i.v. in order to achieve a central venous pressure (CVP) of 5 mm Hg before the start of the experiment and at a dose of 8 ml kg\(^{-1}\) h\(^{-1}\) thereafter to compensate for external losses. During the first 30 min after operation, the piglets with a CVP of <5 mm Hg received Ringer’s solution i.v. until CVP reached 5 mm Hg.

An arterial catheter (Boston Dickinson\(^{13}\), Franklin, Lakes, NJ, USA, 18 G) was inserted into the right external carotid artery and then threaded into the aortic arch for pressure monitoring and blood sampling. A second arterial catheter (Boston Dickinson\(^{13}\), 20 G) was placed via a branch into the left external carotid artery for insertion of a ParaTrend sensor (Trendcare Monitoring System, TCM 7000\(^{14}\), Diamedrix Medical Inc., Buckinghamshire, England).

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

**Operation technique**

The liver resection was performed by two well-experienced surgeons. Carbon dioxide pneumoperitoneum was established with use of a Veress needle and the intra-abdominal pressure (IAP) was maintained at 16 mm Hg. Dissection was made on the left side of the liver. The left hepatic vein was carefully dissected out and then closed with clips before division and full resection of the left lobe. Haemostasis was checked and controlled before the operation was ended. For further information concerning the operation details, see Eiriksson and colleagues.\(^{13}\)

**Measurements**

Temperature (\(T\)), ECG, heart rate (HR), arterial pressure, and pulmonary artery pressure were monitored continuously (Marquette, Solar 8000, Hellige Systems, Germany) and recorded (AcqKnowledge 3.8.1 StatSoft\(^{\circledR}\) Scandinavia AB, Uppsala, Sweden). Pulmonary capillary wedge pressure (PCWP) was measured, and cardiac output (CO) was calculated by thermodilution. Arterial blood gases (\(\text{Pa}_{\text{aCO}_2}\) and \(\text{Pa}_{\text{aO}_2}\)) and pH were continuously monitored and recorded (Paratrend, Trendcare Monitoring system, TCM 7000, Diamedrix Medical Inc., MN, USA). End-tidal \(\text{CO}_2\) (\(\text{eCO}_2\)), peak inspiratory pressure (PIP), the ratio of dead space volume to tidal volume (\(\text{Vd}/\text{Vt}\)), and alveolar dead space (\(\text{Vd}_{\text{alv}}\)) were calculated and recorded (\(\text{CO}_2\)SMO plus, Nova Metrix Medical Systems Inc., CT, USA).

**Experimental protocol**

After completion of the preparations, animals were left for 30–45 min with no interventions to allow haemodynamic and respiratory stability. Baseline values were then obtained and thereafter CO\(_2\) pneumoperitoneum was established with a Veress needle, and the pressure was maintained at 16 mm Hg. This was followed by a new stabilization period and a second set of baseline values was collected before the start of the operation. 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 \(\text{CO}_2\) temperature, and PIP were recorded. Immediately after the operation, a third set of recordings was made before exsufflation of the pneumoperitoneum; after exsufflation, data were recorded every 10 min for 30 min.

**Criteria for embolism**

TOE videos were reviewed by two independent observers. Analyses of the other variables were focused on the times when GE was observed by TOE. A previously described scoring system was adapted for classifying the severity of each embolic episode.\(^{15}\) With TOE, the white dots observed moving with the blood flow in the right outflow tract were considered as gas bubbles. These were classified as grade 0 if <5 bubbles were seen, grade 1 if ≥5 bubbles were seen but the right outflow tract was not completely obscured by bubbles, and grade 2 if the outflow tract was completely filled with bubbles (Fig. 1A–C). The end of a GE period was defined as a bubble-free interval of at least 10 s.

**Preset limits**

Physiological responses to CO\(_2\) embolism were defined as visualization of bubbles in the right ventricle or outflow tract of the heart on TOE concomitant with at least one of the following, occurring abruptly: a decrease in \(\text{Pa}_{\text{aO}_2} \geq 1.0\) kPa, an increase in \(\text{Pa}_{\text{aCO}_2} \geq 0.3\) kPa, a decrease in end-tidal \(\text{CO}_2 \geq 0.3\) kPa, or an increase in mean pulmonary arterial
When one of the above-mentioned variables exceeded the preset limits, all variable values at the same time point were analysed.

Data analysis

For data collected by AcqKnowledge 3.8.1, mean values for every minute during the experiment were calculated, except in the embolization episodes, during which mean values for every 15 s were chosen. In order to analyse changes, the mean of the final four 15 s values recorded immediately before the start of the embolism was used as a baseline value. The time period analysed was the first 2 min period after the end of embolism, unless a new embolism occurred during this time.

Statistical analysis

Non-parametric tests were used, as the changes in respiratory and haemodynamic variables were not normally distributed.

Within each grade of embolism, we used the median value of all observations for each pig as the variable value in the statistical tests, as repeated embolisms within a pig are dependent observations. In order to identify a significant change in respiratory and haemodynamic variables during an embolization episode, and before and after establishment of pneumoperitoneum, the Wilcoxon signed-rank test was used. The Mann–Whitney U-test was applied to compare the changes in respiratory and haemodynamic variables between embolization episodes of grades 1 and 2. Spearman’s rank order correlation was used to assess the relationship between the changes in respiratory and haemodynamic variables.

Results

When establishing pneumoperitoneum, most of the measured variables changed in relation to baseline values. $P_{aCO_2}$, end-tidal CO$_2$, MPAP, Vd/Vt, mean arterial pressure (MAP), CVP, and PIP increased, whereas $P_{aO_2}$ and HR decreased ($P<0.05$) (Table 1).

During surgery, 10 of the 15 piglets showed evidence of grade 1 or 2 GE. Of 33 episodes, 20 were of grade 1 and 13 were of grade 2. One of the five piglets with GE classified as grade 0 displayed pronounced respiratory and haemodynamic changes, including a decrease in $P_{aO_2}$ of 9.4 kPa, a decrease in end-tidal CO$_2$ of 1.0 kPa, an increase in $P_{aCO_2}$ of 1.2 kPa, and an increase in MPAP of 9 mm Hg.

Comparison between grade 1 and 2 GE

None of the circulatory or respiratory variables showed significant changes in response to the grade 1 embolism episodes. The episodes of grade 2 GE, on the other hand, resulted in significant changes ($P<0.05$) in all variables except PIP and HR (Supplementary Table S2).

The two grades were compared regarding the changes they caused in end-tidal CO$_2$, $P_{aO_2}$, $P_{aCO_2}$, MPAP, and Vd/Vt, and significant differences were found regarding all these five variables ($P<0.02$) (Supplementary Table S2).

When, on the other hand, data were analysed according to the preset limits, of the 20 grade 1 episodes, 17 caused no or only minor haemodynamic or respiratory changes that did not exceed these limits. In the remaining three grade 1 episodes, of which two lasted for an extended time of more than 1 min, end-tidal CO$_2$ exceeded the limits in all events, and $P_{aO_2}$ and $P_{aCO_2}$ exceeded the limits twice, whereas MPAP did not exceed the limit (Fig. 2A–H). Regarding grade 2 GE, the preset limits were exceeded in all episodes for $P_{aCO_2}$, in all but one for end-tidal CO$_2$ and in all but two for $P_{aO_2}$. MPAP was least affected (Fig. 2A–H).

On three occasions, $P_{aCO_2}$ was $<8.0$ kPa (range 6.1–7.9 kPa). Twice this was observed on repeated embolism within a short interval and once it was noted in association with an extended embolism period of 84 s.

MAP varied within a wide range of $-22$ to $+7$ mm Hg, with a decrease in all but two embolism periods, in both of which an increase was observed. The effect on CVP in all animals with grade 1 or 2 varied between $-4$ and $+2$ mm Hg. The mean CVP preceding grade 1 and 2 GE was 9 mm Hg (range 7–11 mm Hg, grade 1; and 8–12 mm Hg, grade 2). In four of the five grade 0 piglets, the CVP range was 5–12

Fig 1 (A–C) Examples of definitions of GE grade 0 (A), grade 1 (B), and grade 2 (C). The right outflow tract of the heart (ROT) is visualized by TOE. (A) An arrow indicates a gas bubble seen as a white rounded spot. (C) An arrow indicates a compact mass of gas bubbles filling ROT.
mm Hg, but in one animal, it ranged from 15 to 18 mm Hg. In five episodes, CVP decreased just before the start of GE: in four of these episodes (both grades 1 and 2 GE) it decreased by 1 mm Hg and in one episode (grade 2 GE) by 2 mm Hg. In all these cases, the decrease was thus transient. In the other episodes, CVP was stable or increased just before the start of GE.

Except for MAP and CVP, during grade 2 embolism, there were generally strong correlations between all variables. The strongest correlation was between PaCO2 and MPAP (r=0.97; n=7) and between PaCO2 and end-tidal CO2 (r=0.99; n=7), whereas the weakest correlation was found between Vd/Vt and end-tidal CO2 (r=-0.72; n=7). With grade 1 embolisms, the correlations were less uniform. The strongest correlations were seen between PaCO2 and PaO2 (r=-0.94; n=7) and between PaO2 and Vd/Vt (r=-0.86; n=6), whereas the weakest correlation was found between PaO2 and MPAP (r=0.00; n=7). Correlations with embolism interval were strongest for PaO2 and PaCO2 regarding grade 1 embolization (r=0.79; n=7 for both variables) and for PaCO2 and MPAP regarding grade 2 embolization (r=0.89; n=7 for both variables).

**Discussion**

GE during experimental laparoscopic liver lobe resection was observed in 10 out of 15 piglets. Fifty per cent of these episodes were serious enough to cause mainly respiratory but even haemodynamic changes. Most episodes of grade 1 embolism appeared to be harmless. The variables mostly observed in 10 out of 15 piglets. Fifty per cent of these episodes were serious enough to cause mainly respiratory but even haemodynamic changes. Most episodes of grade 1 embolism appeared to be harmless. The variables mostly affected during grade 2 GE were PaCO2, PaO2, end-tidal CO2, Vd/Vt, and MPAP.

The changes in end-tidal CO2 were rapid and sometimes of short duration and thus could easily be missed in the operating theatre. Even if this technique is easy to apply and is considered a standard anaesthesia monitoring technique, narrow limits for alarm settings are needed to alert the anaesthesiologist.

According to the preset limits, MPAP was the least affected of the haemodynamic variables after GE. The lung vessels are compliant and can accommodate a large increase in blood volume with only a small increase in pressure, as about 40–50% of the pulmonary vascular bed has to be obstructed before the pulmonary artery pressure increases to ensure blood flow through the lung. Monitoring of CO and PCWP did not appear to be clinically useful in this setting with the equipment used. The measurements were time-consuming and could not be performed frequently enough. This rendered it impossible to draw any conclusions as to whether any changes were caused by a gas embolus or by a reaction to the surgical procedure. Continuous measurement of CO might be a better technique, since it could reveal immediate changes, as a decrease in CO after a single CO2 injection of 0.4 ml kg⁻¹ has been recorded.

To avoid intravascular volume depletion before the intervention, a minimum CVP of 5 mm Hg was set. In all GE episodes of grades 1 and 2, the abdominal pressure exceeded CVP and thus the external pressure on the vessels was higher than the intraluminal pressure. Whether increasing CVP or applying a higher PEEP would avoid this problem still remains to be addressed. In some cases, we noted a transient decrease in CVP just before an episode of GE; however, this decrease in CVP was minor and thus hardly could have been the cause of GE.

Repeated severe embolism occurred in ~50% of events. This fact revealed an ongoing surgical problem or the possibility of missing an event that might have clinical implications.

In this study, the preset limits, which were chosen in accordance with results of previous studies when relevant, were used for the more important variables to reduce the risk of analysing normal fluctuations during an operation. The dotted lines in Figure 2A–H, representing preset limits, can easily be moved objectively to select other limits to investigate the effect on the result.

TOE is considered a more sensitive method for the detection of GE than end-tidal CO2, PaCO2, or MPAP. The limits for embolism criteria could be debated, but there is no set value of change that signals danger to the patients if
exceeded; whether it is dangerous for the patient depends on the medical history of the individual patient. A young and healthy person could handle a decrease in $P_{aO_2}$ of 6–8 kPa or more, whereas for an older person with concomitant respiratory or circulatory diseases, even a small decrease in $P_{aO_2}$ could be deleterious. The majority of patients who

Fig 2 (A–H) Changes ($\Delta$) during all embolism episodes of grades 1 and 2. In $P_{aO_2}$, $P_{aCO_2}$, end-tidal CO$_2$, and MPAP, the dotted line represents preset criteria. CVP, central venous pressure; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PIP, peak inspiratory pressure; Vd/Vt, ratio dead ventilation (Vd) to tidal ventilation (Vt).
undergo liver surgery during their lifetime belong to this last group. Perioperative complications are often not satisfactorily investigated and a registry to track all perioperative outcomes and occurrences of complications is proposed. In Bazin and colleagues (p. 573), it is stated that ‘Various multicentre investigations of incidents during laparoscopic surgery show that gas embolism is a prime suspect in most cases of “cardiovascular” collapse occurring during laparoscopy’.

There are several means of restoring a disturbed ventilation-perfusion ratio (VA/Q), and the differences between humans and pigs in terms of both pulmonary structure and reactions that might influence this possibility have been discussed in detail. In our study, we used an IAP of 16 mm Hg, which nowadays may be considered as ‘high’, as there has been a tendency to lower IAP. ‘High’ IAP is proposed as an effective way to reduce bleeding from the parenchyma, and in some centres, an IAP of 18–20 mm Hg has been used. The level of IAP can influence the frequency of GE. Anatomically, the left liver lobe in pigs is comparable with that in humans. The vessels are thinner and therefore easier to damage, reflecting the situation in children rather than in adults. This might have influenced the frequency of GE in the present study. Grading is a subjective process. However, the two independent observers who evaluated the videotapes graded the embolism events identically in accordance with the embolism criteria.

In the operating theatre, during a major operation such as liver resection, the physiological variables vary with the operation course. In order to diagnose an event of GE using today’s standard monitoring equipment, correct interpretation of concurrent reaction of variables is important. Knowledge of the correlations could facilitate this interpretation.

Despite occurrence of only two bubbles, one piglet with grade 0 embolism displayed a strong physiological response with a typical pattern of pulmonary embolism: it is unlikely that this reaction was caused by two gas bubbles alone. We suggest that this was caused by embolization of solid biological material not revealed by the TOE.

Physiological responses to GE depend on several factors, including emboli material, type of gas, size and site of emboli, entrance rate, animal species, and study protocols. This could well explain why three grade 1 GE events exceeded the preset limits. In general, pigs appear to react more markedly in terms of respiratory function, whereas circulatory changes are less pronounced than in humans.

On the basis of our results, we are in agreement with O’Sullivan and colleagues, who state that ‘The rate of detection of emboli is particularly influenced by the method of detection and the complexity of the surgery’. This is further supported in several studies which report vast differences in the occurrence and severity of gas embolization using different methods of monitoring.

Furthermore, Ricciard and colleagues reported that GE had no association with laparoscopic hepatic incision. This model is probably less valid, as only a 2 cm incision into the parenchyma was made. It is not likely that with this method, open lumens of larger veins will be exposed to CO₂ in the same way as during a major liver resection.

Conclusion

GE occurred frequently during laparoscopic liver resection in this study. Although approximately half of the embolic events appeared harmless, the others were serious enough to cause disturbances in respiratory gas exchange and to affect pulmonary haemodynamic variables. A combination of several monitoring techniques, with narrow limits for the alarm settings, would ensure correct interpretation of the complex physiological response to GE and would reveal GE early enough to alert the anaesthesiologist and the surgeon to the ongoing problem. In view of the interspecies differences between humans and pigs in cardiopulmonary functions, further studies in humans are required.

Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.

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Conflict of interest

None declared.

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