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Laparoscopic left hemihepatectomy combined with right lateral hepatic lobectomy in pigs: surgical approach and comparative study of the inflammatory response versus open surgery

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Abstract

This study describes a left hemihepatectomy combined with a right lateral hepatic lobectomy. It compares the inflammatory response associated with laparoscopic hepatectomy (LH group, n = 7) with conventional open hepatectomy (OH group, n = 7). Blood was collected before surgery as well as 1, 2, 3, 5, and 7 days after surgery to determine the white blood cell count and levels of serum cortisol (COR), interleukin-6 (IL-6), and C-reactive protein (CRP). The left hemihepatectomy combined with a right lateral hepatic lobectomy was completed in miniature pigs. The average operative time was 139.00 ± 9.07 min, which was longer than that in the OH group (121.67 ± 3.02 min). The length of surgical incision associated with the OH group was 17.93 ± 1.09 cm, significantly longer than that related to the LH group (5.10 ± 0.17 cm). The estimated mean blood loss in the LH group was 136.43 ± 63.24 mL, which was significantly lower than that in the OH group. No severe complications (e.g., massive bleeding, bile leakage, and air embolism) were reported. The CRP levels, COR, and IL-6, increased significantly in the OH group and then slowly returned to their preoperative levels. A postoperative laparoscopic exploration revealed that the incised portion of the liver adhered to the omentum, but no additional abnormalities were observed. These findings indicate that a 4-trocar method for laparoscopic left hemihepatectomy combined with a right lateral hepatic lobectomy is safe and feasible. The inflammatory response for those receiving LH are lower than that for those receiving OH. This porcine model can be used as a research analog for liver disease and regeneration.

Introduction

Laparoscopic hepatectomy is a standard surgical procedure performed to treat liver cancer[1,2] and retrieve donor liver grafts,[3-5] among other techniques. In medical research and experimental studies, the porcine model of hepatectomy is a crucial research tool for evaluating new surgical methodologies,[6-9] transplantation,[10,11] regeneration,[12,13] and medical instruments.[14-16] The successful establishment of hepatectomy models can promote technological advances and develop new treatment methods for hepatic diseases.

Minimally invasive laparoscopic surgery causes minimal trauma to the abdominal wall, resulting in reduced pain and fewer wound complications, faster recovery times, and a more rapid return to activity than conventional surgery.[17] However, only a few previous studies on laparoscopic hepatectomy performed in veterinary surgery and the experimental animal field have been reported, most of which have involved expensive instruments and procedures of varied complexity.[18]

Studies have also shown that the serum levels of interleukin-6 (IL-6) and C-reactive protein (CRP) are lower after laparoscopic surgery than after open surgery.[19-21] Conversely, some studies have shown no significant differences between two surgical approaches concerning the surgical inflammatory response as measured using cortisol (COR) levels.[22,23] However, the surgical stress induced by the laparoscopic and open surgical approaches for extensive hepatectomy has not been compared to determine whether minimally invasive hepatectomy is beneficial based on animal models.

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This study introduces a laparoscopic technique for a purely laparoscopic left hemihepatectomy combined with a right lateral lobectomy in pigs. Additionally, we compared the outcomes and surgical stress associated with the laparoscopic approach with those related to open surgery.

Materials and Methods

Animals. This study used 14 Bama miniature pigs with an average age of 6 months (4 - 8 months old) and an average bodyweight of 18.50 kg (15.80 - 23.50 kg). The pigs were randomly assigned to two groups, including the laparoscopic hepatectomy (LH) group (n = 7) and open hepatectomy (OH) group (n = 7). The Animal Ethics Committee of Northeast Agricultural University, Harbin, China approved the experimental protocol (BUAEC2019-0902). The experiments described herein comply with the People's Republic of China's existing regulations and the standards of the Institutional Animal Care and Use Committee of Northeast Agricultural University, Harbin, China.

Anesthetic protocol. Before surgery, atropine sulfate (0.05 mg kg^{-1}; Harbin Pharmaceutical Group, Harbin, China) was injected subcutaneously; then, xylazine (1.00 mg kg^{-1}; Bayer Health Care AG, Leverkusen, Germany) and ketamine hydrochloride (10.00 mg kg^{-1}; Hansen Pharma Co. Ltd., Changsha, China) were administered intramuscularly 15 min later. After the experimental pigs were sedated, propofol (5.00 mg kg^{-1}; Libang Pharma Co. Ltd., Xian, China) was slowly injected through the ear margin vein to induce anesthesia. Then, endotracheal intubation was performed with a 6.00-7.50-mm endotracheal tube under laryngoscope guidance, and anesthesia was maintained via the inhalation of 1.50 - 3.00% isoflurane (Jiupai Pharmaceutical, Jinzhou, China) using an anesthesia machine. During surgery, normal saline (3.00 mL kg^{-1} per hr) was infused through the ear margin vein, and various physiological parameters were continuously monitored.

Surgical technique. The miniature pigs were placed in the supine position and secured on the operating table, tilted to 10-30° with the head placed more elevated than the tail. The anterior abdomen was shaved, disinfected, and draped for laparoscopic surgery. A Veress needle was used to create an artificial pneumoperitoneum by filling the abdominal cavity with CO_2 (12.00 mm Hg). Four trocars were used for this procedure. One trocar (portal A) was used to place the laparoscope, and the other three (portals B, C, and D) were used for surgical instrument access (Fig. 1).

First, scissors were used to divide the round ligament, sacral ligament, left and right triangular ligaments, and coronary ligament to fully mobilize the liver. Then, under laparoscopy, the left hepatic duct, hepatic artery, and branches of the portal vein were separated, clipped, and divided with titanium clips.

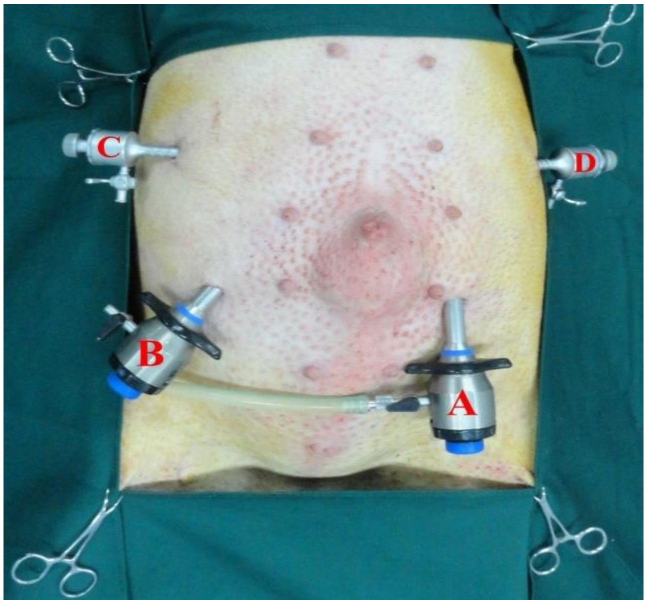

Fig. 1. Locations of portals A, B, C, and D for laparoscopic liver resection. Portal A (laparoscope) was located in the left abdomen below the third nipple from the tail and 3-5 cm from the midline. A 10-mm trocar was placed, and a 30° laparoscope was inserted. Portal B was located approximately 5.00 cm lateral to the third nipple from the tail in the right abdomen, and a 10-mm trocar was placed for laparoscopic surgical instrument access. Portal C was located 3.00 - 5.00 cm below the right costal margin, and a 5.00-mm trocar was placed for laparoscopic surgical instrument access. Portal D was situated on the left side of the abdominal midline at the opposite side of portal C, and a 5.00-mm trocar was placed for laparoscopic surgical instrument access.

A monopole high-frequency electrotome (UES-40; Olympus, Tokyo, Japan) was used to divide the liver parenchyma (Fig. 2) along the middle liver fissure (the boundary between the left and right medial segments) after the double-row transfixing ligation of the left hepatic lobe (the left lateral and medial lobe; Fig. 3) and the base segment of the right lateral hepatic lobe (Fig. 4).

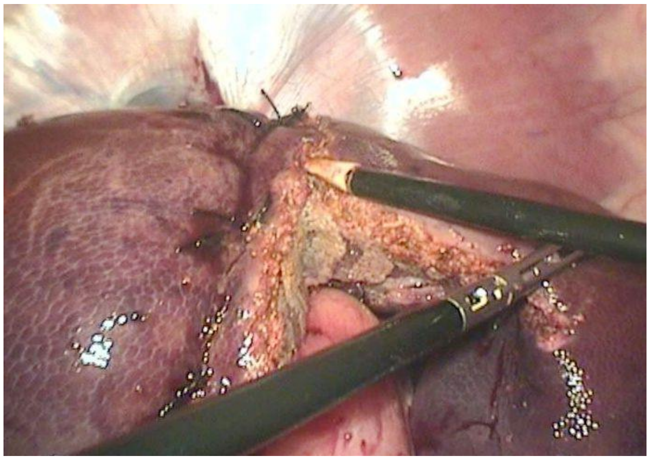

Fig. 2. A high-frequency electric scalpel was used to divide the liver parenchyma.

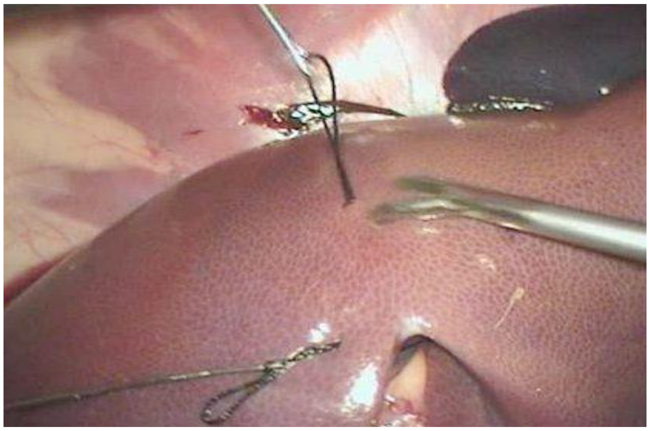

Fig. 3. Two needles threaded with one silk suture were used to penetrate the left hepatic lobe.

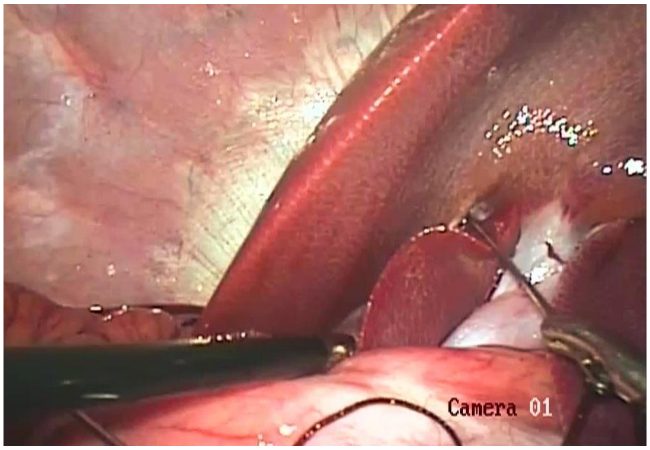

Fig. 4. Double-row transfixing ligation of the right lateral hepatic lobe.

Electrocoagulation and gauze compression was used for hemostasis. Then, the right hepatic parenchyma was divided along the straight double-row ligation line. During the liver parenchyma division, a titanium clip or transfixing suture was used to secure the divided end of the vessels when needed. Before the end of the procedure, medical bioprotein glue was applied to the incised liver section, and hemostatic gauze was used to cover the incised section. The omentum was also sutured to the incised area when it was necessary.

The incised liver section was examined to confirm that no bleeding was present (Fig. 5). A specimen bag was placed into the abdominal cavity through a trocar incision and the resected liver was placed in the bag. The right abdominal trocar incision was extended to remove the resected liver and abdominal drainage tube was placed through a trocar incision into the abdomen and secured. The abdominal wall was closed via a conventional suture.

The seven pigs in the OH group underwent open hepatectomy performed by the same group of surgeons; the double-row transfixing ligation of the hepatic lobe and electrocoagulation was also applied.

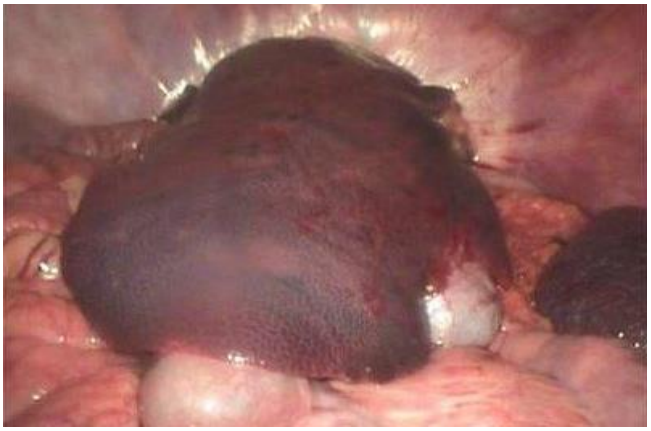

Fig. 5. An intra-abdominal image immediately after surgery.

Postoperative care. After surgery, each miniature pig was individually placed in a warm and dry pig house to recover from anesthesia. The physiological parameters (e.g., body temperature, heart rate, respiratory rate, and blood pressure) were closely monitored until they returned to baseline levels. Intramuscular buprenorphine (0.01 mg kg^{-1}; Hansen Pharma Co. Ltd., Changsha, China) was administered after surgery for analgesia, and ampicillin (20.00 mg kg^{-1}, IM; Lukang Pharma, Jining, China) was administered after surgery every 8 hr for three consecutive days. All animals were clinically examined daily, and white blood cell (WBC) counts were performed. The WBC count was determined using an automatic blood cell analyzer and its corresponding reagents (Mindray Bio-medical Electronics Co. Ltd., Shenzhen, China). The drainage tube was cleaned every day and removed 3 - 5 days after surgery. Laparoscopic exploration was performed in both groups one month after surgery to determine whether abnormalities or adhesions were present throughout the abdominal cavity.

Measurements of CRP, IL-6, and COR concentrations. In the both groups, blood samples were collected from the anterior vena cava before surgery and at 1, 2, 3, 5, and 7 days after surgery, before morning feeding. Serum was separated, and CRP, IL-6, and COR concentrations were measured using enzyme-linked immunosorbent assay kits (Yapp Biological Technology Co. Ltd., Shanghai, China).

Statistical analyses. The operative time, estimated blood loss, incision length, the resected hepatic lobe's weight, and the number of intraoperative and postoperative complications were documented. The operative time was measured as the time from skin incision to skin closure. Blood loss was estimated from the total amount of liquid in the suction container minus the amount of washing liquid. SPSS (version 17.0; IBM Corp., Armonk, USA) was used for the statistical analyses. A one-way ANOVA was used to compare the differences at different time points between and within the groups. The data were expressed as mean ± SEM. The $p < 0.05$ was considered as a significance level.

Results

Surgical and clinical outcomes. In this study, a left hemihepatectomy combined with a right lateral hepatic lobectomy was completed in seven miniature pigs. The average operative time was 139.00 ± 9.07 min, which was longer than that of the OH group (121.67 ± 3.02 min; $0.01 < p < 0.05$). The resected hepatic lobes' weights were similar in the two groups (343.86 ± 69.13 g *versus* 335.33 ± 23.98 g, LH group *versus* OH group, respectively). The incision length was significantly longer in the OH group than in the LH group (17.93 ± 1.09 *versus* 5.10 ± 0.17 cm; $p < 0.01$). The mean blood loss was estimated to be 136.43 ± 63.24 mL in the LH group and 208.67 ± 30.61 mL in the OH group ($0.01 < p < 0.05$). In the LH group, one case of subcutaneous emphysema was observed during surgery, and one pig in the OH group presented with slight oozing of the incised liver section. No serious complications (e.g., massive bleeding, bile leakage, or air embolism) were observed. All experimental pigs showed mild discomfort on the day of surgery, but no painful symptoms (e.g., bowing and trembling) were observed. On day one, after surgery, the pigs' alertness and appetite were nearly restored, a small amount of fluid feeding was initiated, and their body temperatures increased slightly. After surgery, the drainage fluid gradually decreased and became clearer. The abdominal drainage tube was removed after 3 to 5 days. Sutures were removed 7 to 9 days after surgery. Except for a mild incision infection in one pig, the incisions were well healed. Laparoscopic exploration was performed one month after surgery, and adhesions were noted between the incised liver section and omentum or stomach wall. Otherwise, no abnormalities were found in the abdominal cavity.

White blood cell count. At 24 hr after surgery, the WBC count increased from 8.93 ± 0.27 to 15.33 ± 0.56 × 10^9 L^{-1} ($p < 0.01$) and from 9.54 ± 2.12 to 22.14 ± 1.60 × 10^9 L^{-1} ($p < 0.01$) in the LH and OH groups, respectively. The difference between these groups was significant ($0.01 < p < 0.05$). On the third day after surgery, the number of WBCs in the OH group was significantly higher than that in the LH group ($p < 0.01$). The WBC count in the LH group returned to the preoperative level three days after surgery, whereas that in the OH group returned to the preoperative level five days after surgery (i.e., WBC recovery occurred earlier in the LH group than OH group; Table 1).

Serum CRP, IL-6, and COR concentrations. Serum CRP increased initially and then decreased in the two groups. In the LH group, the serum CRP level peaked one day after surgery, and it was significantly higher than that before surgery ($p < 0.01$). The CRP level significantly differed from that before surgery two days after surgery ($0.01 < p < 0.05$), but it was not significantly different three days after surgery ($p > 0.05$). At two days after surgery, the serum CRP level was significantly different between the LH and OH groups ($0.01 < p < 0.05$), and this difference was significant three days after surgery ($p < 0.01$). At five and seven days after surgery, the serum CRP levels did not significantly differ between groups ($p > 0.05$).

The serum IL-6 level in the LH group was significantly higher 1 and 2 days after surgery than before surgery ($p < 0.01$), peaked one day after surgery, and returned to its preoperative level on the 3rd postoperative day. The changing trend of the serum IL-6 level in the OH group was similar to that in the LH group, which was significantly increased 1, 2, and 3 days after surgery compared to before surgery ($p < 0.01$) and returned to its preoperative level on the 5th postoperative day. The serum IL-6 concentration at 1, 2, and 3 days after surgery significantly differed between the LH and OH groups ($p < 0.01$). The differences in IL-6 at other time points were not significant ($p > 0.05$).

The COR concentrations in the LH group significantly differed from those before surgery 1 and 2 days afterward ($p < 0.01$) but returned to their preoperative level 3 days after surgery ($p > 0.05$). The COR level significantly differed between the LH and OH groups 1, 2, and 3 days after surgery ($0.01 < p < 0.05$). The differences in the COR level at other time points were not significant ($p > 0.05$).

Discussion

Successful partial hepatectomy procedures using porcine models have been previously reported. However, most of these procedures require expensive equipment such as LigaSure, an ultrasonic scalpel, and an Endo-GIA Stapler.[24-26] In this study, liver parenchyma was laparoscopically

Table 1. White blood cell (WBC) count and serum levels of cortisol (COR), interleukin-6 (IL-6), and C-reactive protein (CRP) at different time points after surgery.

Time points	**WBC (× 10^9 L^{-1})**		**CRP (mg L^{-1})**		**IL-6 (pg mL^{-1})**		**COR (ng mL^{-1})**	
	LH	**OH**	**LH**	**OH**	**LH**	**OH**	**LH**	**OH**
Pre-Op	8.93 ± 0.27	9.54 ± 2.12	1.19 ± 0.05	1.28 ± 0.19	32.39 ± 1.79	33.25 ± 2.30	21.03 ± 2.30	20.88 ± 1.07
POD-1day	15.33 ± 0.56**	22.14 ± 1.60$^{**\blacktriangle}$	2.35 ± 0.03**	2.74 ± 0.24**	55.31 ± 1.57**	69.23 ± 2.81$^{**\blacktriangle\blacktriangle}$	32.64 ± 1.38**	39.03 ± 1.27$^{**\blacktriangle}$
POD-2day	12.14 ± 1.03*	16.48 ± 2.14$^{**\blacktriangle}$	1.46 ± 0.12*	1.89 ± 0.08$^{**\blacktriangle}$	46.69 ± 2.65**	61.57 ± 1.44$^{**\blacktriangle\blacktriangle}$	30.53 ± 1.66**	38.68 ± 2.31$^{**\blacktriangle}$
POD-3day	9.38 ± 1.57	12.56 ± 0.89$^{*\blacktriangle\blacktriangle}$	1.21 ± 0.10	1.48 ± 0.05$^{**\blacktriangle}$	37.03 ± 2.30	51.80 ± 1.89$^{**\blacktriangle\blacktriangle}$	25.87 ± 2.48	34.30 ± 1.36$^{**\blacktriangle}$
POD-5day	8.68 ± 1.43	9.85 ± 0.66	1.10 ± 0.08	1.07 ± 0.11	33.88 ± 1.73	36.54 ± 2.57	23.77 ± 3.65	22.80 ± 2.15
POD-7day	9.15 ± 0.63	10.05 ± 0.46	1.25 ± 0.07	1.40 ± 0.09	34.02 ± 1.87	34.56 ± 1.72	22.47 ± 2.58	19.86 ± 1.65

Pre-Op: Pre-operative; POD: Postoperative day; LH: Laparoscopic hepatectomy; OH: Open hepatectomy.

* $0.01 < p < 0.05$, ** $p < 0.01$ compared with preoperative values and $^{\blacktriangle}0.01 < p < 0.05$, $^{\blacktriangle\blacktriangle}p < 0.01$ compared with the OH group.

ligated with double-row transfixing sutures. A left hemihepatectomy was successfully combined with a right lateral hepatic lobectomy using titanium clips and a high-frequency electrosurgical scalpel. This simplified method for creating animal models of partial hepatectomy does not require additional specialized instruments or equipment, reduces the difficulty of model establishment, facilitates to replicate and apply the model, and facilitates the model's replication application.

During the operation, the ligaments around the liver should first be divided. Care should be taken during dividing of the coronary ligament, which should not be divided entirely to avoid injury to the posterior vena cava. Unlike the human hepatic anatomy, the hepatic vein of a pig near the diaphragm is buried in the liver parenchyma. Dissection of the hepatic vein here can cause massive bleeding, air embolism, and even death.[27] Therefore, the hepatic vein was not dissected in this study; instead, the liver parenchyma was ligated at the base segment of the liver using transfixing ligation along the fissure between the liver lobes; then, the liver parenchyma was directly divided with a unipolar electrocoagulation hook. Based on our experience, after the full mobilization of the liver lobes, resection can be performed in the following order: First, the left hepatic lobe is ligated, but not removed; after the right lateral lobe is ligated, the right lateral hepatic lobe and left hepatic lobe can be removed together. This sequence improves the efficiency of surgery and facilitates the operation. During the liver parenchyma division, the liver lobe should be retracted as far as possible toward the posterior abdominal cavity to prevent the contraction and burning of the diaphragm muscles with the high-frequency electrosurgical current. Burning of the diaphragm muscles can cause pneumothorax. Using a high-frequency electric scalpel to divide the liver parenchyma, the resection line should be 1.00 - 2.00 cm away from the ligation line to avoid damaging the sutures and causing bleeding from the incised section. If bleeding occurs, then electrocoagulation, large titanium clips, and transfixing ligation technique can be used for hemostasis accordingly.

Compared to traditional open surgery, minimally invasive laparoscopic surgery has obvious advantages, such as a small incision in the abdominal cavity and laparoscopic visualization.[28,29] However, the effect of an extensive hepatectomy on inflammatory response in miniature pigs and comparisons with traditional open surgery had not been fully evaluated or reported. The WBCs and CRP are sensitive indicators of various surgical complications (e.g., inflammation, tissue damage and sepsis). The IL-6 is also an indicator used to evaluate the severity of surgical trauma.[30,31] Our study revealed that WBC, CRP and IL-6 concentrations were significantly higher and returned more slowly to preoperative levels after open hepatectomy compared to laparoscopic hepatectomy.

The effects of two surgical approaches on the metabolic response of the body were also significant. The serum COR concentration in two groups of animals increased significantly after surgery and gradually returned to the normal preoperative levels three days later. These findings are consistent with previously reported inflammatory responses between laparoscopic and open cholecystectomy.[22] Therefore, our results showed a lower inflammatory response in the LH group than the OH group. Laparoscopic hepatectomy has clinical advantages over open hepatectomy because of its lower inflammatory response, fewer postoperative complications, and fewer intra-abdominal adhesions.

This study described a laparoscopic left hemihepatectomy combined with a right lateral hepatic lobectomy using a 4-trocar method. It demonstrated that the body's inflammatory response caused by LH is lower than that caused by OH. From technical and physiological perspectives, the LH approach seems feasible. Additional evaluation is needed to assess the the LH approach's long-term effects in porcine models to improve biomedical research models in the future.

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Conflict of interest

The authors have no conflict of interest to declare.

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