Anesthesia Case of the Month

History

A 15-week-old female crossbred Large White pig underwent laparoscopic orthotopic renal autotransplantation by means of a previously described technique.1,2 The surgical procedure was performed as part of a study that was approved by the Animal Ethics Committee of the University of Western Australia, in conformance with the guidelines of the Australian code for the care and use of animals for scientific purposes.3 This animal was the 38th animal undergoing surgery in this project. The pig was 1 of 4 animals that had been sourced commercially4 and acclimatized to the Large Animal Facility at the University of Western Australia for 2 weeks prior to surgery. The health report from the piggery stated that there were no clinical signs of disease and no health concerns in the herd. The pig had been treated for internal parasites at 3 days of age and had been vaccinated against Actinobacillus pleuropneumonia5 at 9 weeks of age. At the facility, the pigs were housed in raised communal pens (4 × 5 m), fed a commercial diet4 supplemented with fresh pumpkin and apples, and allowed free access to tap water. Environmental enrichment was provided with various toys for play, daytime music, and daily human interaction. The room was maintained at 22 ± 2°C with a 12-hour light-dark cycle. Prior to general anesthesia, food was withheld for 12 hours, but free access to water was allowed.

On the morning of surgery, the pig was clinically normal as determined with examination by a veterinarian; and body weight was 44 kg (97 lb). General anesthesia was induced with a combination of zolazepam and tiletamine6 (4 mg/kg [1.8 mg/lb]) and xylazine7 (2 mg/kg [0.9 mg/lb]) administered IM in the neck. With the pig in sternal recumbency, an IV catheter was placed in the right jugular vein with ultrasound guidance, and a venous catheter8 was placed in the left auricular artery for direct arterial blood pressure measurement. A urethral catheter9 was placed for measurement of urine output during anesthesia.4 Direct blood pressure, ECG, heart rate, arterial oxygen saturation (pulse oximetry), respiratory rate, end-tidal carbon dioxide concentration (capnography), central venous pressure (via a central venous catheter10 placed in the right jugular vein with ultrasound guidance), and pharyngeal temperature were monitored continuously with a multiparameter monitor.1 The supervising anesthesiologist (GCM) recorded the measured parameters every 5 minutes on a paper anesthetic record.

General anesthesia was maintained with isoflurane11 in oxygen. Isoflurane concentration was adjusted depending on the needs of the animal, according to the judgment of the anesthesiologist. The initial isoflurane vaporizer setting was 0.5%, with anesthesia initially maintained by means of the residual combined effects of zolazepam, tiletamine, and xylazine. After 30 minutes, the vaporizer setting was increased to 1% for the next hour, then to 1.6%, and eventually 2%. The depth of anesthesia was assessed subjectively throughout the procedure by the supervising anesthesiologist. Pressure-cycled mechanical ventilation12 was commenced immediately after tracheal intubation and adjusted to target normocapnia (end-tidal carbon dioxide concentration, 35 to 45 mm Hg). The peak inspiratory pressure (PIP) was initially set at 14 cm H2O but was increased to a maximum of 17 cm H2O during insufflation of the abdomen with CO2 for laparoscopy. Alterations to the ventilator settings were made to maintain normocapnia by increasing the PIP, the respiratory rate, or both. Positive end-expiratory pressure was not used, and the tidal volume was not measured. Venous blood samples were collected from the central venous catheter within the first hour of anesthesia and just before the end of anesthesia for measurement of serum electrolyte concentrations. Hartmann solution1 was administered at 10 mL/kg/h (4.5 mL/lb/h) IV throughout the anesthetic period, and a convection warm air blanketm was used for active warming. The surgical procedures required 4 small flank incisions for the laparoscopic equipment, a ventral midline laparotomy for nephrectomy, and an open flank laparotomy for the orthotopic renal transplant.

The total anesthesia time was 8 hours 50 minutes. For most of the procedure, the measured PIP was 16 to 20 cm H2O. The measured PIP was always slightly higher than the set PIP (14 to 17 cm H2O), and the respiratory rate was between 11 and 16 breaths/min. The mean arterial blood pressure remained > 65 mm Hg throughout the procedure. The central venous pressure was 3 cm H2O initially, but increased to between 6 and 10 cm H2O during insufflation of the abdomen with CO2. At the end of the surgery, the central venous pressure was 1 cm H2O. Oxygen...
saturation was consistently 99%, with the need for occasional repositioning of the pulse oximeter probe on the pinna. Normocapnia was maintained for the duration of surgery, apart from a 50-minute period during which the end-tidal carbon dioxide concentration increased to 60 mm Hg in response to abdominal insufflation for laparoscopy. Serum electrolyte concentrations were stable and within reference ranges throughout the procedure. At the end of general anesthesia, immediately prior to extubation, the end-tidal carbon dioxide concentration was 44 mm Hg. The pharyngeal temperature was maintained between 36.5° and 37.6°C (97.7° and 99.7°F) for the duration of surgery. The ECG was always regular, and the heart rate was between 80 and 110 beats/min. The total urine output was 2.5 L. The total volume of Hartmann solution administered was 4.5 L.

For analgesia, a constant rate infusion of morphine was administered (0.2 mg/kg/h [0.09 mg/lb/h], IV) commencing at the time of induction of anesthesia. One hour before the end of anesthesia, the morphine infusion rate was decreased to 0.1 mg/kg/h (0.045 mg/lb/h). A bupivacaine and saline (0.9% NaCl) solution mixture (1:1; 2.3 mg/kg [1.05 mg/lb]) was injected SC at each of the incisions at the end of the procedure. Tramadol (2.3 mg/kg, IV) was also administered at the end of surgery.

Neuromuscular blockade was necessary during CO₂ insufflation of the abdomen and laparoscopic retrieval of the kidney; therefore, pancuronium (0.18 mg/kg [0.08 mg/lb], IV) was administered on 5 occasions. The last dose of pancuronium was administered 2 hours 25 minutes before the end of anesthesia. Neuromuscular transmission was monitored with application of train-of-4 stimuli to the buccal branch of the left facial nerve. Following stimulation, twitching of the nose was evident. Observation of 4 twitches of equal magnitude was considered consistent with return of normal neuromuscular transmission. Mannitol (0.5 g/kg [0.23 g/lb], IV, over 20 minutes) and heparin (34 U/kg [15.5 U/lb], IV) were administered prior to nephrectomy to promote diuresis and avoid thrombosis, respectively. Furosemide (0.9 mg/kg [0.4 mg/lb], IV) was administered immediately after the transplanted kidney was reperfused to promote diuresis. Amoxicillin (10 mg/kg [4.5 mg/lb], SC) was administered at the beginning and the end of the procedure for prophylaxis.

The surgical time for laparoscopic nephrectomy (left kidney) was 1 hour 50 minutes, and the kidney was returned to the abdomen for orthotopic autotransplantation 2 hours after removal. An open surgical approach for transplantation by means of flank laparotomy was performed. Finally, the ureter of the right kidney was ligated. The total procedure time was 3 hours. The pig was initially positioned in dorsal recumbency for instrumentation. For nephrectomy and renal transplantation, the pig was positioned in right lateral recumbency; for ligation of the right ureter, the pig was positioned in left lateral recumbency. The surgery table was cushioned with a thick (12-cm) foam mat.

At the completion of surgery, administration of isoflurane and morphine was discontinued. The central venous catheter and the arterial catheter were also removed at this time. The pig was weaned from the ventilator with pressure support ventilation instituted to deliver a breath to a set PIP of 15 cm H₂O when PIP of at least –2 cm H₂O was achieved during spontaneous ventilation. Pressure support ventilation was discontinued once the spontaneous respiratory rate was 14 breaths/min and the end-tidal carbon dioxide concentration was 44 mm Hg. When recovery from anesthesia was apparent (return of palpebral reflex, increased muscle tone, and adequate spontaneous ventilation) and following observation of the pig swallowing, the endotracheal tube cuff was deflated and the tube removed. The pig was lifting its head and trying to reposition itself on the table at this time. There was no apparent excess respiratory effort, and thoracic wall excursions appeared subjectively normal. The venous catheter in the auricular vein was removed at this time. However, approximately 2 minutes after extubation, the pig suddenly became apneic and the mucous membranes were pale and cyanotic. The trachea was reintubated immediately (without the administration of anesthetic drugs), and 100% oxygen was administered. When the larynx was observed during rapid replacement of the endotracheal tube, a plug of colorless viscous mucus obstructing the larynx was noted. The plug of mucus was manually displaced by the tip of the endotracheal tube to facilitate intubation. Manual intermittent positive-pressure ventilation was commenced. An arterial pulse could be palpated digitally in the auricular artery, and heart sounds were evident on thoracic auscultation. Oxygen saturation and end-tidal carbon dioxide concentration were again monitored with pulse oximetry and capnography, respectively. Twenty minutes after the onset of apnea, an arterial blood sample was collected by direct arterial puncture of an auricular artery. Results of arterial blood gas analysis (not corrected for body temperature) indicated respiratory acidosis (pH, 7.1; PaCO₂, 124.6 mm Hg; PaO₂, 307.8 mm Hg; HCO₃⁻, 28.6 mmol/L; base excess, 4.5 mEq/L; and glucose concentration, 6.1 mmol/L). The situation was managed for another 20 minutes until the pig showed signs of recovery, including attempting to move from the table, and resumed breathing spontaneously. The mucous membranes were pink, and the auricular arterial pulse was palpable. No abnormalities were evident on thoracic auscultation at this time. Therefore, the endotracheal tube was again removed.

Postoperatively, the pig was monitored continuously for 4 hours and then every 30 minutes for another 2 hours. For the first 2 weeks after surgery, twice-daily examinations were performed, and for
the second 2 weeks after surgery, once-daily examinations were performed. Blood samples were collected by jugular venipuncture on postoperative days 1, 3, 7, 14, 21, and 28. Hemoglobin concentration decreased from 112 g/L to 101 g/L, and PCV decreased from 0.39 to 0.30 over the 28-day period. There was an increase in the WBC count from the baseline on days 1, 3, and 7. Serum urea and creatinine concentrations were highest on day 1 after surgery (16.9 mmol/L and 450 µmol/L, respectively). Serum electrolyte concentrations remained within reference ranges throughout the postoperative period.

Following the second tracheal extubation, it was apparent that the pig could not see. The first indications were that the pig did not appear focused on any particular object and its eyes did not follow the movements of personnel in close proximity. The pig also held its head very still. These subtle abnormalities prompted testing of the menace response in both eyes. No menace response was elicited. Unfortunately, thorough ophthalmic examination was not possible, because the pig did not tolerate physical restraint. The pig was moved to the recovery pen for close observation (respiratory rate, skin color, gait and posture, hydration status, nasal and ocular secretions, temperament, food and water intake, urination and defecation, and appearance of the surgical wounds). It otherwise was noted to recover similarly to previous pigs in the study, attempting to stand after approximately 2 hours and eating when fed by hand 6 hours after the end of anesthesia. A second dose of tramadol (2.3 mg/kg, IM) was administered 6 hours after completion of anesthesia. At this time, there was still no menace response, and the pig was calm and moving very little.

The morning after surgery, the pig was bright, alert, and interested in food. There was a normal menace response bilaterally. The pupillary light reflex could not be assessed because restraining the animal was too difficult. Tramadol (2.3 mg/kg, IM) and morphine (0.23 mg/kg [0.1 mg/lb], IM) were administered for additional analgesia. The remainder of the recovery period (28 days) was uneventful.

The pig was anesthetized (as previously) and euthanized (pentobarbital sodium, 160 mg/kg [72.5 mg/lb], IV) according to the study protocol 28 days after surgery. Tissues were harvested during anesthesia, (pentobarbital sodium, 160 mg/kg [72.5 mg/lb], IV) according to the study protocol 28 days after surgery. Tissues were harvested during anesthesia, and a necropsy was performed. No gross abnormalities of the heart, lungs, liver, or gastrointestinal tract were observed during the examination. The right kidney was hydronephrotic because of ligation of the right ureter and there was minor subjective dilation of the left ureter proximal to the anastomosis site; the left kidney appeared grossly normal.

**Question**

What are possible causes of the apparent temporary postoperative vision loss observed in this pig?

**Answer**

We were unable to definitely ascertain the cause of vision loss in this animal. However, it may have been the result of temporary cerebral hypoxia or optic nerve ischemia from residual neuromuscular blockade; or a period of prolonged hypercapnia with an associated increase in intracranial pressure; temporary upper respiratory tract obstruction may also have contributed. We suggest that in this pig, the temporary vision loss was likely the result of a combination of these factors.

**Discussion**

The pig described in the present report made an apparent full recovery from anesthesia, surgery, and temporary vision loss. Pigs are a major animal species used in translational research and surgical teaching. However, it is not known what proportion of pigs involved in research and teaching underwent general anesthesia recover from the procedure. Whereas there are sparse data regarding postoperative care of pigs in a biomedical research environment, there are even fewer reports of postoperative complications. The ARRIVE (Animals in Research: Reporting In Vivo Experiments) guidelines were first published in 2010 and consist of a checklist of 20 items describing the minimum information that all scientific publications reporting research using animals should include. This checklist recommends that the results section of a research paper should report adverse events, with details of all adverse events in each experimental group, and a description of any modifications to the experimental protocol in an effort to reduce adverse events.

Postoperative vision loss is a rare but potentially devastating complication of surgery in human patients. The prevalence of this postoperative complication is unknown, but it is reportedly more common in patients undergoing anesthesia for spinal fusion or cardiac procedures. The most common causes of vision loss reported in human patients include ischemic optic neuropathy, retinal vascular occlusion, and cortical blindness. In humans, ischemic optic neuropathy is poorly described and understood but may be associated with a number of contributing factors including prone positioning during anesthesia, lengthy spinal fusion surgery, intraoperative hypotension, the use of vasopressors, and CSF flow in the optic nerve. Retinal vascular occlusion occurs most frequently when patients are positioned in a manner that creates external compression of the eye. Cortical blindness is not considered an important cause of postoperative vision loss in human patients. In animals, the frequency and causes of postoperative vision loss are poorly described; however, Stiles et al recently suggested that postanesthetic cortical blindness in cats was associated with a period of cerebral ischemia. In that case series of 20 cats, 14 (70%) were documented to have recovered vision, and the authors speculated
that the use of spring-held mouth gags might be a risk factor for decreased brain perfusion by means of compromise of the maxillary arteries. Cerebral ischemia can occur if cerebral blood flow is inadequate because of interference with autoregulation of cerebral blood flow, which may result from a period of hypotension, hypocapnia, or hyperoxia. In pigs, the blood supply to the brain is similar to that of cats, as the maxillary artery is a primary supplier of blood to the circle of Willis. Consequently, pressure or tension on the maxillary arteries may compromise perfusion of the brain in pigs in a manner similar to that for cats. Nonetheless, in the pig of the present report, a mouth gag was not used, and the pig was positioned on a padded surgery table throughout.

In the pig described in the present report, the cause and pathophysiology of vision loss were unknown. However, we suggest either a period of cerebral hypoxia or optic nerve ischemia as a result of a brief episode of hypoxemia because of residual neuromuscular blockade, a period (of unknown duration) of hypercapnia and associated increase in intracranial pressure, temporary upper respiratory tract obstruction, or a combination of these factors. First, residual neuromuscular blockade may have contributed to the respiratory arrest and subsequent development of hypoxemia and hypercapnia. Residual neuromuscular blockade is defined as the presence of signs and symptoms of muscle weakness in the postoperative period after intraoperative administration of a neuromuscular blocking drug. Complete recovery from neuromuscular blockade is essential for normal breathing, maintenance of a patent upper airway, preservation of protective airway reflexes, swallowing, and coughing (and smiling and talking in humans). Despite evidence from capnography of adequate spontaneous ventilation and clinical signs of recovery from anesthesia, residual neuromuscular blockade was a potential cause of respiratory arrest in this pig. Efforts to prevent this complication included monitoring of the facial nerve with a peripheral nerve stimulator and application of a train-of-4 stimulus. The magnitude of each twitch was assessed visually; therefore, it is possible that each twitch was not of equal magnitude and that the train-of-4 ratio was <1.0. If the train-of-4 ratio is <0.9, there is a risk of pharyngeal dysfunction in human patients. Pancuronium use has been reported in pigs, and the dose and frequency of administration of the drug in the present case was consistent with that described in prior experimental surgeries. However, the concurrent administration of volatile anesthetic drugs such as isoflurane may enhance neuromuscular blockade and reduce the effective dose because of the effect on plasma clearance and time for elimination of pancuronium. Furthermore, it is possible that upper airway function may be affected by residual blockade. As such, response to peripheral nerve stimulation may suggest adequate recovery from neuromuscular blockade despite residual impairment of swallowing and pharyngeal function. Objective monitoring of neuromuscular blockade (eg, with acceleromyography) may be more appropriate and should be considered for procedures such as that described in the present report. In addition, the routine administration of neuromuscular blockade reversal agents may also be prudent. It is also important to confirm that the return of spontaneous ventilation is adequate. In the pig of this report, the results of capnography implied normoventilation; however, serial arterial blood gas analyses during anesthesia and at this important stage of recovery may be prudent.

Second, the results of arterial blood gas analysis in the present case revealed severe hypercapnia (\(\text{Paco}_2\), 124.6 mm Hg). This sample was collected after the initial treatment of respiratory arrest was initiated, but before the trachea was extubated a second time. During anesthesia, capnography was the sole source of information in this animal regarding adequacy of ventilation, and on the basis of those results, the minute volume was adjusted to maintain normocapnia. The 50-minute period of intraoperative hypercapnia was untreated because the undesirable cardiovascular consequences of increasing minute volume further were considered unjustifiable in the face of permissive hypercapnia and high intra-abdominal pressure. However, this approach relied on the accuracy of capnography, which measures end-tidal carbon dioxide concentration as a surrogate noninvasive method for estimating \(\text{Paco}_2\). This assumes that there is matching of ventilation and perfusion in the lungs, that anatomic and equipment dead space are minimal, that the volume of the sample the machine aspirates does not interfere with ventilation or entrain room air and dilute the sample, and that the fresh gas flow from the anesthetic machine also does not dilute the sample. It is possible that capnography monitoring was inaccurate in this case, and that the \(\text{Paco}_2\) was higher than normal for a prolonged period.

Cerebral blood flow increases when \(\text{Paco}_2\) is > 80 mm Hg, and an increase in cerebral blood flow may increase intracranial pressure. If the \(\text{Paco}_2\) was increased for a prolonged period, perhaps hours, it may have caused CNS depression, respiratory arrest, and apparent blindness. During anesthesia of pigs for this research study, intermittent positive-pressure ventilation was always administered. In previous cases, analysis of intermittent arterial blood gas samples confirmed that capnography was accurate. In the pig of the present report, we applied the same strategy for mechanical ventilation and thus assumed that capnography was an accurate representation of \(\text{Paco}_2\). It is possible, however, that the pig was hypercapnic as a result of iatrogenic hypoventilation for a much longer period than the 20-minute period between respiratory arrest and arterial blood sample collection. It is also feasible the respiratory depressant effects of morphine caused hypoventilation after weaning from the ventilator. Furthermore, inadequate recovery from anesthesia could
also cause hypoventilation and hypercapnia. This respiratory depression was not apparent at the time, as the end-tidal carbon dioxide concentration was within reference limits just prior to tracheal extubation.

Third, following tracheal extubation at the end of anesthesia, the pig stopped breathing and appeared cyanotic. Although the observation of cyanosis is subjective, it is likely that there was a brief period of hypoxemia. The cause of the respiratory arrest could be attributed to upper respiratory tract obstruction from a plug of viscous mucus in the larynx during a period of slow recovery from neuromuscular blockade. The mucus was clearly visible when the trachea was intubated for the second time, and although it was easily dislodged, it may have caused an obstruction of the airway in the context of decreased respiratory effort. A combination of subclinical respiratory disease and intermittent positive-pressure ventilation with dry and cold gases (oxygen and isoflurane) for many hours would likely facilitate the accumulation of mucus into a large globule within the large airways. Humidification of the inspired gases, by the incorporation of a heat and moisture exchanger in the breathing system, may be prudent to decrease the formation of large plugs of viscous mucus. There was no evidence of respiratory disease in the pig of this report prior to anesthesia and surgery, but we acknowledge that it is difficult to rule out subclinical disease, especially given that it is difficult to perform a thorough clinical examination on a conscious pig. Further evaluation of methods to assess the health of a pig prior to entry into a research study is warranted.

In the pig of the present report, the brief period of respiratory arrest apparently caused temporary hypoxemia, because the mucous membranes were cyanotic. Although this observation was subjective, there was an obvious change in the color of the mucous membranes from pink to pale and cyanotic. Analysis of an arterial blood gas sample showed a high PaO\(_2\) (307.8 mm Hg); however, this sample was collected after a period of resuscitation with 100% oxygen and manual ventilation. In the absence of severe ventilation and perfusion mismatch or alveolar disease, we would expect the PaO\(_2\) to rapidly increase in response to the supportive treatment that was provided. With regard to the results of the arterial blood analysis, the high PaCO\(_2\) (124.6 mm Hg) was the cause of the low pH (7.105) because the base excess and HCO\(_3^-\) concentrations were within reference ranges. The PaO\(_2\) (307.8 mm Hg) was lower than would be expected given that the fraction of inspired oxygen was 1.0. According to the alveolar gas equation, we calculated that the partial pressure of oxygen in the alveoli would be 557 mm Hg. The discrepancy between the arterial and alveolar partial pressure of oxygen suggested some amount of ventilation-perfusion mismatch, which supported the notion that capnography may have been inaccurate in this pig. However, in this case, the duration of anesthesia was prolonged (8 hours 50 minutes), positive end-expiratory pressure was not used, and the animal was repositioned 3 times, so it is likely that ventilation-perfusion mismatching did develop. Nevertheless, the pig was not hypoxemic at the time of collection of the arterial blood sample (PaO\(_2\), 307.8 mm Hg). The other arterial blood gas values were within reference limits; thus, the diagnosis from this information was severe respiratory acidosis.

The results of analysis of the venous blood samples that were collected from this pig were consistent with those from previous animals in this project. Despite the negative fluid balance, there was no evidence of hemoconcentration, so we were unsure of the clinical importance of the large difference between urine output and volume of crystalloid IV fluid infused during anesthesia. Absolute or relative hypovolemia is a potential explanation for this discrepancy. This theory is supported by the fact that central venous pressure was lower at the end of the procedure than at the beginning. Intravenous fluid therapy dose was guided primarily by arterial blood pressure measurements during anesthesia, but it is possible that fluid therapy was insufficient. If the pig was hypovolemic, it is possible that this abnormality contributed to delayed metabolism of drugs such as morphine and pancuronium, increasing the risk for respiratory arrest. The urea and creatinine concentrations increased after autotransplantation, with a peak on the first postoperative day, and did not return to the baseline value in the 28-day period of the study. There was no clinical evidence of renal failure (excessive drinking or urination), and the necropsy appearance of the transplanted kidney suggested that the organ was functional. Although the postoperative baseline plasma potassium concentration measured at the end of surgery was high (6.4 mmol/L), this was attributed to overnight storage of the sample prior to analysis at the laboratory.

The present report describes a rare postoperative complication in a Large White pig after prolonged anesthesia and respiratory arrest following extubation. The pig was blind for < 12 hours and made a full recovery from anesthesia, surgery, and vision loss. Comprehensive monitoring throughout anesthesia and the recovery period will inform the anesthesiologist with objective information and enable targeted, prompt, and effective management of any complications that may arise during recovery.

**Acknowledgments**

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**Footnotes**

a. CM Farms Nambeelup, Mandurah, WA, Australia.
b. Pig Grower, West Feeds, West, Tex.
c. Zoetil 100, Virbac (Australia) Pty Ltd, Milperra, NSW, Australia.
d. Illium Xylazil (100 mg/mL), Troy Laboratories Australia Pty Ltd, Glendenning, NSW, Australia.
References