World Journal of Anesthesiology

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DOI: 10.5313/wja.v4.i3.73

World J Anesthesiol 2015 November 27; 4(3): 73-82
ISSN 2218-6182 (online)
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MINIREVIEWS

Swine model in transplant research: Review of anaesthesia and perioperative management

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Conflict-of-interest statement: None.

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Received: June 22, 2015
Peer-review started: June 27, 2015
First decision: July 27, 2015
Revised: September 18, 2015
Accepted: October 16, 2015
Article in press: October 19, 2015
Published online: November 27, 2015

Abstract

Pigs are one of most common animal species to be used in biomedical models due to their many anatomical visceral similarities with humans, particularly with regards to transplantation. Despite this use, in many of the researches in which pigs are selected for transplantation, the anaesthesia used is an adaptation of human anaesthesia and presents some limitations such as a reduced analgesia a limited control in perioperative period. In this review we show some of the most important conditions in the preanaesthetic management and of swine as well as we review of anaesthetic protocols for the most common types of swine model of transplantation.

Key words: Swine; Anesthesia; Transplantation; Animal model; Perioperative management

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Core tip: Swine is a common model in research, especially in transplantation studies. A correct management and anaesthesia as well as knowledge of the different protocols in pigs are useful in performing these researches.

Morgaz J, Navarrete R, Granados MM, Gómez-Villamandos RJ. Swine model in transplant research: Review of anaesthesia and perioperative management. *World J Anesthesiol* 2015; 4(3): 73-82 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i3/73.htm DOI: http://dx.doi.org/10.5313/wja.v4.i3.73

INTRODUCTION

Pigs are one of most common animal species used in biomedical models due to their many anatomical visceral similarities with humans, particularly with regards to metabolic or cardiovascular diseases and for liver, lung or heart transplantation[1-4]. These similarities have meant that pigs have become a potential species in xenotrasplantation in primates species[5-7]. Despite this resemblance, different anatomical and physiological aspects should be considered in order to perform a successful anaesthesia technique in swine, especially considering that in these researches major surgical procedures are usually performed. In

Table 1 Normal cardiorespiratory parameters of adult and healthy pigs during anaesthesia

Parameter	Range	Parameter	Range
Heart rate (beats/min)	50-100	Temperature (℃)	36-38
Respiratory rate (breaths/min)	10-20	Haemoglobin (g/dL)	11-16
Systolic arterial pressure (mmHg)	80-140	Et CO_2 (mmHg)	40-45 (mechanical ventilation)
Diastolic arterial pressure (mmHg)	60-120	Arterial pH	7.38-7.50
Mean arterial pressure (mmHg)	40-70	PaO_2 (mmHg)	> 70-80
Cardiac output (mL/kg per minute)	60-140	$PaCO_2$ (mmHg)	35-50 (mechanical ventilation)

$EtCO_2$: End-tidal of carbon dioxide; PaO_2: Partial pressure of oxygen; $PaCO_2$: Partial pressure of carbon dioxide.

addition, the perioperative care and management of pigs should be considered. In Table 1 are shown normal cardiorespiratory parameters of adult pigs during anaesthesia.

PERIOPERATIVE CARE AND GENERAL CONSIDERATIONS

As with other animals of research, an acclimatization period of 5-7 d prior to anaesthesia is necessary to reduce the depressant effect of transport or stress, which could alter the anaesthetic effects of different drugs or parameters related to the research. Before anaesthesia, a solid fast period of 24-48 h is recommended, but water must be maintained. The nervous and sometimes aggressive behaviour of pigs prevents venous cannulation before anaesthesia, and for this reason preanaesthetics must be administered by intramuscular route in almost all cases, alone or sometimes with anaesthetics such as ketamine. Athough piglets and some swine breeds have thinner skin, adult pigs usually have a wide tissue adipose and their skin is generally hard, and for this reason intramuscular administration is carried out using a large and thick needle (longer than 35-40 mm, over 18-20 G), to ensure that drugs are deposited in muscle. A longer onset and a softer effect of drugs are noted if anaesthetics are administered into adipose tissue. The most used anatomical locations for intramuscular administration are the lateral cervical muscle region (behind the ear), semitendinosus-semimembranosus muscle areas (posterior side of hindlimb), and the lumbar muscle area[8-10].

Preanaesthetic protocol

There are several anaesthetic protocols suitable for pigs, which include the combination of a hypnotic with a sedative and/or an analgesic. This approach provides a degree of anaesthetic suitable for the handling of pigs, although sometimes it is not enough for endotracheal intubation and an inhalation induction by mask is necessary to complete the anaesthetic induction. Oxygen administration *via* face mask is recommended because these combinations induce a variable degree of cardiorespiratory depression. Since the preanaesthetic combination is applied intramuscularly, dissociative agents such as ketamine and tiletamine (in commercial combination with zolazepam) are used[8,10-12]. Alphaxalone has also been evaluated as acting like a hypnotic in swine and when administered intramuscularly together with midazolam provides an excellent sedation, although it is only recommended for small pigs due to the large volume used[13].

Ketamine is the hypnotic habitually used because it can be administered intramuscularly and has a rapid onset, although due to its excitatory effects it must always be combined with a sedative and muscle relaxant[8,10,11]. Alfa-2 agonist sedatives (xylazine, medetomidine, dexmedetomidine) are widely used in both veterinary medicine and biomedicine, providing central sedative effects accompanied with muscle relaxation and analgesia[8,12,14]. Some frequent anaesthetic combinations in transplant researches with pigs are shown in Table 2.

Since the surgical techniques of transplant imply an aggressive approach or major procedures in most cases, at the time of designing an anaesthetic protocol it is important to consider the potential pain of the procedure during the surgery and the post-operative period. Transplantation surgery is major surgery that requires the use of an opioid analgesic in premedication and especially during the surgery, in which constant rate infusions of pure opiods (fentanyl or remifentanil), may be necessary[8,14]. Likewise, a multimodal approach must be used and f NSAIDs must be administered as carprofen[8-10].

Anaesthetic induction and tracheal intubation

Venous catheterization is often performed after the intramuscular premedication and often when tracheal intubation has been accomplished. The auricular veins are the most common access in pigs for the administration of additional intravenous anaesthetic drugs, fluid therapy and for obtaining venous blood samples. However, for transplantation surgery, central venous and arterial catheterizations are recommended (usually external jugular veins and femoral artery), because a major management of electrolyte and acid-base status is required. Moreover, a central venous access allows the monitoring of cardiac output control and pulmonary pressures. This advanced monitoring is especially indicated for research, when pigs must be maintained and controlled under intensive care conditions for several hours or days after surgery[8-10,15].

Table 2 Intramuscular preanaesthetic combinations for transplantation surgery in pigs

Dissociative	Sedative	Analgesic (optional)	Time induction	Duration of anaesthesia
Ketamine (5-15 mg/kg), or Tiletamine-zolazepam (5-10 mg/kg)	Medetomidine (5-20 mcg/kg), or Romifidine (60-100 mcg/kg), or Dexmedetomidine (5-20 mcg/kg)	Morphine (0.3-0.5 mg/kg), or Methadone (0.3-0.5 mg/kg)	5-20 min	40-60 min

Table 3 Intravenous anaesthetic induction in pigs

Anaesthetic	Intravenous doses
Propofol	2-5 mg/kg
Ketamine	2-10 mg/kg
Tiopenthone	5-15 mg/kg

Table 4 Minimal alveolar concentration of inhaled anaesthetics in pigs

Anaesthetic	Minimal alveolar concentration
Isoflurane	1.2-2.0
Sevoflurane	2.2-3.5
Desflurane	8.3-10

Table 5 Mechanical ventilation settings for pigs

Tidal volume	10-15 mL/kg
Respiratory rate	10-15 breaths/min
Maximum airway pressure recommendable	20 cm H_2O
Normocapnia (end-tidal CO_2 concentration)	40-45 mmHg

Table 6 Recommended doses of constant rate infusion of drugs in pigs

Drugs	Bolus intravenous	Constant rate infusion
Fentanyl	3-10 μ/kg	10-30 μg/kg per hour
Remifentanyl	10 μ/kg	10-50 μg/kg per hour
Morphine	0.1-0.3 mg/kg	0.1-0.3 mg/kg per hour
Dexmedetomidine	0.5-1 μ/kg	0.5-1 μg/kg per hour
Medetomidine	1-2 μ/kg	1-2 μg/kg per hour
Ketamine	0.5-2 mg/kg	0.1-2 mg/kg per hour
Lidocaine	2 mg/kg	1-3 mg/kg per hour
Midazolam	0.2-0.4 mg/kg	0.2-0.4 mg/kg per hour

Usually it is not possible to perform the intubation after premedication since the metabolization of dissociatives is quick, so the induction of anaesthesia must be completed after the administration of the preanaesthetic combination in order to obtain an adequate relaxation of the laryngopharyngeal structures to perform a tracheal intubation. Propofol (2-5 mg/kg), can be administered intravenously if the ear vein has been catheterized (Table 3). Isofluorane or sevofluorane administration (3%-5%) in oxygen (2-4 L/min) *via* face mask is the most used technique. The use of neuromuscular blocks is initially inadvisable because tracheal intubation is difficult to perform and requires some experience[8-10,15].

Tracheal intubation can be performed in sternal, ventral or lateral recumbency, being a difficult procedure, especially in large pigs because the mouth cannot be opened sufficiently and laryngeal structures are not easily visible. In large pigs a specific straight laryngoscope (15-30 cm length) with a large blade is needed. The diameter of the endotracheal tube oscillates between 7 and 12 mm, depending of the size of the swine. In pigs above 25 kg, the use of a rigid or semi-rigid guide for tracheal tubes avoids bending and facilitates the intubation in sternal recumbency especially. To prevent laryngospasm during tracheal intubation, laryngeal irrigation with local anaesthetic (lidocaine or mepivacaine) is recommended[8-10,15].

Anaesthetic equipment

Pigs can be anaesthetized with human or veterinary anaesthetic machines. A corrugated and reservoir balloon must be selected according to the weight of the pig. Precision vaporizers of isofluorane, sevofluorane or desfluorane can be used attending to minimum alveolar concentration (Table 4), and several fraction of oxyegen can be set up. Mechanical ventilation settings for pigs are similar to other species and are shown in Table 5. For an adequate constant rate infusion of drugs (Table 6), a perfusor or infusion pump must be used.

PIG AS A MODEL OF TRANSPLANT RESEARCH

Swine is used extensively as a transplant model of different organs, but despite the complexity of these surgical procedures, in many researches of transplantation in pigs, special considerations are not taken into account and normal anaesthetic procedures are performed, but with important limitations.

Renal transplantation

In all the experimental kidney transplantation papers reviewed, even in very recently published papers, a lack in anaesthetic control and monitoring has been found. In most of the pig model studies, anaesthetic protocol is not even mentioned in a number of different

papers[16-19]. Other studies describe the drugs and doses, but no description of the quality of anaesthesia or an evaluation of anaesthesia's influence on patient evolution are mentioned. An intramuscular injectable mixture of a sedative and ketamine[20,21] or tiletamine-zolazepam[22] is the method most described for the induction of anaesthesia in pigs for kidney transplantation. The sedatives used were xylazine[20,22] or diazepam and azaperone[21]. Atropine was also added[20] to the injectable mixture to prevent bradycardia and reduce bronchial secretions. The authors another paper[23] used ketamine IM and thiopental IV directly as anaesthesia inductor agents without the previous use of sedatives. In this case the ketamine dose was increased to 5 mg/kg. Other papers administered propofol as a bolus for the induction of anaesthesia and to achieve an adequate depth of anaesthesia for tracheal intubation, either as a unique drug[22] or combined with fentanyl[21].

Atracurium and cisatracurium are frequently used in human kidney transplantation due to the fact that their duration of action is independent of either liver or kidney function, since other muscle relaxants, such as pancuronium, vecuronium or rocuronium, have a prolonged duration of action in patients with end-stage renal disease[24,25]. This is not a problem in experimental kidney transplantation if the recipient pig is healthy. Few authors describe the use of neuromuscular blockers in pigs. In[21] a bolus of cisatracurium after induction (15 mg/kg IV) was used and pancuronium (0.1 mg/kg IV) was used in[22], an experimental study. Anaesthesia maintenance in pigs is mainly performed using volatile agents, such as halothane 1%-2%[20], isoflurane[22,23] or sevoflurane 2%[21], although some other drugs have been used during anaesthesia maintenance to reduce the volatile agent requirements, such as remifentanil (0.08-0.1 mg/kg per hour)[21]. Among all the reviewed papers, only[22] described that the depth of anaesthesia was assessed by a veterinary anaesthetist throughout the procedure and adjusted accordingly.

Pigs were under controlled ventilation during some experimental kidney transplantations[21-23]. A description was found only when volume-controlled ventilation was applied, such as in[21] (minute volume 8 mL/kg; adapted according to blood gas analysis) or[22] (tidal volume 10-15 mL/kg; a peak inspiratory pressure of 25 cm of water; adjusted to achieve normocapnia, end-tidal carbon dioxide level 35-45 mmHg) studies. Fluids are needed in order to maintain optimum central venous pressure (CVP) and pulmonary arterial pressure. During a review of papers, no description of the type and rate of fluids used was found. Only[22] mentioned the use of Hartmann solution and Gelofusin and the internal jugular vein was used for this purpose.

With regard to perioperative pain control, drugs such as morphine, meperidine or oxycodone should be used with caution in patients with renal failure because these agents or their active metabolites depend on renal excretion and may accumulate[26,27]. Fentanyl, sufentanil, alfentanil and remifentanil are safe for renal function[26,28-30]. Post-operative pain is controlled in different ways in humans, and it has been shown that the choice of intraoperative anaesthetic influences post-operative pain control, since patients receiving propofol had better recovery of psychomotor function and used patient-controlled analgesia more effectively than patients receiving halotane or isoflurane[31]. No proper descriptions regarding perioperative and post-operative pain control have been found in the pig kidney transplantation review.

Hypotension may occur after unclamping the iliac vessels and reperfusion of the graft. Because the renal graft function depends on adequate perfusion, every effort should be made to avoid episodes of marked hypotension. Few studies describe the monitoring performed. CVP was measured using the internal jugular vein[22,23]. The brachial[23] or the auricular artery[22] were cannulated for blood pressure measurement. Oxygen saturation, ECG, temperature and end-tidal carbon dioxide were continuously measured during general anaesthesia[21-23]. In addition, full blood count, glucose, creatinine, urea, sodium, potassium, haemoglobin, alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase were measured in one study[21]. Some authors described that the recipient's haemodynamic and metabolic alterations were treated, but no data were published. One paper[23] mentioned that they obtained effecctive anaesthetic maintenance until the experimental end point, and in the[22] study, that the vital signs of all pigs were stable during surgery and the post-operative observation period.

In animal models it has been shown that vessels in the transplanted organ seem to be more sensitive to sympathomimetics, and are thus more likely to compromise renal blood flow to the transplanted kidney, so strong alpha-adrenergic vasoconstrictors, such as phenylephrine, should be drugs used only as a last resort[32,33]. Drugs such as mannitol and dopamine have been used in human kidney transplantation but no references have been found to its use in pigs. Mannitol is usually administered to donors before recovery and to recipients just before unclamping the arterial blood flow, because it may give protection against ischaemic injury and induce osmotic diuresis. The use of a low-dose dopamine (2-3 mcg/kg per minute) to stimulate DA1 dopaminergic receptors in the kidney vasculature to induce vasodilation and increased urine output has been shown to be effective during kidney transplantation[34], whereas other studies have shown no significant improvement[35].

Liver transplantation

Although the initial liver transplantation studies included dogs, pig is the preferred species due to its physiologic and anatomic similarity with humans[36].

Azaperone is a butyrophenone that has been used as a sedative before general anaesthesia for liver transplantation, either as a sole agent at premedication[36,37] or in combination with other drugs, such as ketamine,

diazepam or atropine[21,38,39]. Another pharmacological group used frequently for sedation at premedication in pigs undergoing liver transplantation is that of α2-adrenoceptor agonists, such as xylazine[40-44] or romifidine[45]. Benzodiazepines are also used at premedication for muscle relaxation, generally combined with ketamine and/or a sedative drug since they are minor tranquillizers[21,38,41,46,47]. There are authors that have used parasympatholytic drugs at premedication in pigs undergoing liver transplantation[39,41,43], the main use being as an excessive salivation inhibitor; it is unusual for bradycardia to be a problem in anaesthetized pigs[48].

The most common method is the use of a combination of drugs with different properties to induce a balanced premedication-sedation, such us the administration of sedatives with opioids[49]. Furthermore, the administration of an analgesic before a painful stimulus optimizes the control of pain during the surgery procedure and reduces the dose of analgesic during the post-operative period. In general, mu agonists produce a more profound analgesia and they are recommended for moderate to severe pain and to reduce the necessity of anaesthetics[50]. Several authors have used an opioid at premedication in pigs prior to a liver transplantation[45,51].

Ketamine has been used at premedication in pigs undergoing a liver transplantation by several authors to immobilize the animal and to make easier its manipulation[21,39,40,42,45-47,51,52]. However, ketamine as a sole agent does not induce a surgical anaesthesia, so it would be necessary to combine it with opioids, benzodiazepines and/or sedatives[48]. Another dissociative anaesthetic used in pigs is tiletamine, commercialized with zolacepam, a benzodiazepine[43,44]. Like ketamine, it would be convenient to combine it with other sedative and/or analgesic agents to improve the quality or surgery anaesthesia[48].

For anaesthetic induction in pigs undergoing liver transplantation, several studies have used propofol[21,40,46,53,54], etomidate[39] or barbiturates[36,37,44,47]. These drugs produce a faster onset of anaesthesia with short duration of action after the administration of a bolus. Other authors have used an inhalatory anaesthetic through a face mask for the induction of anaesthesia, after a satisfactory premedication[45,51].

Most of the authors have used inhalatory anaesthetics during the maintenance of anaesthesia in pigs undergoing a liver transplantation. Changes in the depth of anaesthesia are faster than with intravenous anaesthetics, with a faster recovery after the anaesthesia procedure[55]. Isoflurane[36,39,40,42,51,54] and sevoflurane[21,41,44] are the anaesthetics most used. None of these anaesthetics are good analgesics, so many authors used them together with continuous infusion of fentanyl[21,36,40,44,45,56] or remifentanil[54]. Other authors described the use of propofol in total intravenous anaesthesia during the maintenance of anaesthesia in pigs undergoing liver transplantation[52], even combined with a continuous infusion of fentanyl because propofol does not have analgesic properties[46,56,57]. In addition, the pharmacological combinations for maintaining the anaesthetic in pigs during a liver transplantation has been described, with ketamine at 15 mg/kg per hour, fentanyl at 0.02 mg/kg per hour and midazolam at 0.9 mg/kg being used[38].

At induction and during the anaesthetic maintenance in pigs undergoing a liver transplantation it is common practice to the use of neuromuscular blocking agents such as pancuronium[36,39,41,45,51], atracurium[45,51], vecuronium[41] and cisatracurium[21]. These agents are indicated to facilitate orotracheal intubation, and are administered together with hypnotic agents to avoid larynx spasm and to provide the fast control of the airway. Other indications included the prevention of spontaneous movement during the maintenance of anaesthesia, reducing the resistance to ventilation and easing surgical access during the surgical procedure[58].

During a liver transplantation, metabolic (acidosis) and cardiovascular changes (hypotension and bradycardia) are usual. To finish the experiences correctly, it is neccesary to understand these alterations, when they are produced and how to correct them. In human medicine, a liver transplantation procedure can be divided in three phases: (1) dissection phase, includes the lysis of adhesion and the removal of the damaged liver; (2) anhepatic phase, includes the implantation of donor liver; and (3) reperfusion phase, including the anastomoses, haemostasis and closure[59]. The ionized calcium levels can decrease during a liver transplantation, mostly during the dissection and anhepatic phases[60]. The exogenous citrate from blood transfusion could be responsible for this low level of ionized calcium and calcium infusions may be required, such as calcium chloride and calcium gluconate[61]. After reperfusion and with the beginning of the functionality of the transplanted liver, the haemostasis of calcium may be corrected and calcium supplementation may no longer be required.

During the anhepatic phase, the donor liver is implanted. If the surgery technique is infracaval interposition, there is a complete vascular occlusion by clamping the hepatic artery and porta, infrahepatic cava and suprahepatic cava veins. Because the inferior cava venous is blocked, a severe hypotension can develop. These haemodynamic effects depend on the patient, so it is advisable to place a previous temporary test clamp on the inferior vena cava to know the haemodynamic response of the animal before realizing the permanent vascular clamping during the anhepatic phase. Once the liver is positioned, the anastomosis of suprahepatic, infrahepatic and portal veins is completed in that order. The anastomosis of the hepatic artery is carried out before reperfusion or after the restoration of blood flow. During this phase hypocalcaemia and acidosis could be observed, so it is important to monitor these parameters closely. Avoid the aggressive infusion rate of fluids in this phase to maintain blood pressure, because this could result in overload of fluids resulting in cardiopulmonar

compromise and liver and intestinal swelling. At the end of this phase the vascular clamps are removed and each anastomosis is observed for the detection of leaks[59]. The withdrawal of the clamps from the portal vein allows blood flow from splanchnic circulation into the donor liver and is the beginning of the reperfusion phase. The most critical point in this phase is the immediate period after the vascular clamps are removed from the liver graft, mainly seconds or minutes after unclamping the portal vein, as is called as reperfusion syndrome[59]. A decrease in cardiac contractility[62], arrhythmias, bradycardia, severe hypotension and hyperkalemic arrest may be observed. The anaesthetic management must be directed at maintaining or recovering cardiovascular stability. The use of epinephrine, atropine, calcium or sodium bicarbonate could be neccesary[59]. Also, the use of methylene blue has been described as attenuating the haemodynamic changes during reperfusion syndrome[63]. In this phase it is common for an alteration in the metabolism of glucose, and progressive hyperglycaeemia may ensue, due to the glycogenolysis by the donor liver, a decrease in glucose use and insulin resistence. In this phase it is possible that coagulopathy may develop, with resultant bleeding[59].

Severe coagulopathy and intraoperative loss of blood are significant problems in patients undergoing liver transplantation. This alteration in the homeostasis, mainly after receiving the donor liver, is multifactorial and inludes hyperfibrinolysis, depletion of coagulation factors, trombocytopenia and platelet dysfunction. The administration of fresh frozen plasma, red blood cells, platelets and cryoprecipitate are the main therapies for blood loss and coagulopatthy during liver transplantation. However, in humans, the use of these blood products during the liver transplantation has been significantly reduced in recent years due to an improvement in surgical technique, intraoperative management and in patient selection[59]. Currently, the administration of haemostatic agents, such as aminocaproic acid, tranexamic acid, *etc.*, are being evaluated as adjunctive therapies[64-69]. It is important to restore diuresis during the procedure to facilitate fluid management and to protect the kidneys during the renal ischaemia in the anhepatic phase. Drugs used to maintain the urine output are loop diuretics, dopamine and mannitol[59].

Most of the pigs used in experimental procedures are euthanized at the end of the surgical procedure. However, some authors keep them alive to continue with the investigation. Authors of[41] described the use of buprenorphine during the post-operative period. Authors of[36] described this period in detail, evaluating the ingestion of the animals and the follow-up treatment with immunosuppression, antibiotics and buprenorphine as analgesic.

Heart transplantation

Porcine models have been used to study cardiovascular disease and transplantation, but have been associated with problems, such as friability of certain organs, anaesthesia difficulties, ventricular fibrillation and oedema[70]. Cardiopulmonary bypass (CPB) models have been described only for two to four hours[71-73] or using swine models not of mature age or body weight, which cannot be considered as true adult size[74] and do not have the same responses to stress as do larger or mature swine[71].

Authors of one paper[75] described a swine model for long-term CPB using an adult pig weighing more than 80 kg. The anaesthesia protocol used for this model was very simple since ketamine and atropine sulphate were given intramuscularly followed by sodium pentobarbital intravenously to maintain a proper level of anaesthesia. Anaesthesia was maintained throughout the entire procedure using sodium pentobarbital in the mechanically ventilated pig. It maintained normothermic CPB and did not develop any previously described problems. Priming the CPB circuit with a combination of more adult blood than crystalloid solution possibly prevented the tissue oedema often seen in such procedures. HR, arterial pressures, urine production, hematocrit, electrolytes, glucose and lactate were within normal range throughout the CPB procedure and were not different from each other from the beginning to the end of CPB. Only the activated clotting time was maintained artificially higher than 1000 s. Prior to the initiation of CPB and throughout the entire procedure and pO_2 was also kept high. Modifications to the procedure, including a higher blood-to-crystalloid ratio in the priming solution, a slightly higher oxygen concentration in the circuit and maintaining the acid base status seemed to contribute to the success of this model.

Recently, the use of porcine cardiac xenografts has become more feasible because of the production of transgenic pig organs expressing human complement regulatory proteins on the endothelium, and continued surgical experimentation involving baboons will contribute to the understanding of the immunological basis for xenograft rejection. Orthotopic pig-to-baboon xenogeneic heart transplantation is the only accepted preclinical animal model for cardiac xenotransplantation[7]. Anaesthetic management of the orthotopic pig-to-baboon model is complicated by ischaemia-reperfusion injury, the use of CPB and the additional immunological processes of xenogeneic transplantation.

A variety of animal experiments[76,77] and human studies[78-80] have investigated the benefits of different anaesthetic regimens in cardiac surgery, suggesting a protective effect of halogenated volatile anaesthetics on the myocardium by mimicking ischaemic preconditioning.

Santerre *et al*[81] described in detail a balanced anaesthetic technique for use in baboons undergoing abdominal porcine cardiac xenografting, and discussed intraoperative monitoring and treatment of the haemodynamic consequences related to infrarenal, aortic cross-clamping. The pharmacological techniques employed were found to be safe and reliable.

Others types of transplant

Swine has been used in other models of transplant such as pancreas[82], cornea[83], duodenum[84], uterus[85], vascularized composite allotransplantation[86], ureter-bladder[87] and lung[88], although in general the anaesthetic considerations are similar to most common transplant in pigs.

CONCLUSION

Swine is a common research model and a complete knowledge of the different protocols of anaesthesia and their perioperative care is important to develop transplant researches without complications. Pigs are excellent models of research and allow a more direct translation of results than laboratory animals, so they will continue to be frequently used in transplant research models.

REFERENCES

1 **Bassols A**, Costa C, Eckersall PD, Osada J, Sabrià J, Tibau J. The pig as an animal model for human pathologies: A proteomics perspective. *Proteomics Clin Appl* 2014; **8**: 715-731 [PMID: 25092613 DOI: 10.1002/prca.201300099]

2 **Lelovas PP**, Kostomitsopoulos NG, Xanthos TT. A comparative anatomic and physiologic overview of the porcine heart. *J Am Assoc Lab Anim Sci* 2014; **53**: 432-438 [PMID: 25255064]

3 **Judge EP**, Hughes JM, Egan JJ, Maguire M, Molloy EL, O'Dea S. Anatomy and bronchoscopy of the porcine lung. A model for translational respiratory medicine. *Am J Respir Cell Mol Biol* 2014; **51**: 334-343 [PMID: 24828366 DOI: 10.1165/rcmb.2013-0453TR]

4 **Golriz M**, Fonouni H, Nickkholgh A, Hafezi M, Garoussi C, Mehrabi A. Pig kidney transplantation: an up-to-date guideline. *Eur Surg Res* 2012; **49**: 121-129 [PMID: 23172014 DOI: 10.1159/000343132]

5 **Koulmanda M**, Qipo A, Smith RN, Auchincloss H. Pig islet xenografts are resistant to autoimmune destruction by non-obese diabetic recipients after anti-CD4 treatment. *Xenotransplantation* 2003; **10**: 178-184 [PMID: 12588650 DOI: 10.1034/j.1399-3089.2003.02040.x]

6 **Hering BJ**, Walawalkar N. Pig-to-nonhuman primate islet xenotransplantation. *Transpl Immunol* 2009; **21**: 81-86 [PMID: 19427901 DOI: 10.1016/j.trim.2009.05.001]

7 **Bauer A**, Baschnegger H, Renz V, Brandl U, Brenner P, Thein E, Reichart B, Schmoeckel M, Christ F. Comparison of propofol and isoflurane anesthesia in orthotopic pig-to-baboon cardiac xenotransplantation. *Xenotransplantation* 2007; **14**: 249-254 [PMID: 17489866 DOI: 10.1111/j.1399-3089.2007.00383.x]

8 **Swindle MM**. Swine in the Laboratory: Surgery, Anesthesia, Imaging, and Experimental Techniques. 2nd ed. Florida: CRC Press, 2007 [DOI: 10.1201/9781420009156]

9 **Swindle MM**, Smith AC, Laber-Laird K, Dungan L. Swine in Biomedical Research: Management and Models. *ILAR J* 1994; **36**: 1-5 [DOI: 10.1093/ilar.36.1.1]

10 **Gómez-Villamandos R**, Redondo J, Santisteban J. Anestesia en veterinaria y experimental. In: Tratado de anestesia y reanimación. Torres LM, Ediciones A, editors. Madrid, 2001: 2979-3019

11 **Sakaguchi M**, Nishimura R, Sasaki N, Ishiguro T, Tamura H, Takeuchi A. Anesthesia induced in pigs by use of a combination of medetomidine, butorphanol, and ketamine and its reversal by administration of atipamezole. *Am J Vet Res* 1996; **57**: 529-534 [PMID: 8712520]

12 **Lu DZ**, Fan HG, Wang HB, Hu K, Zhang JT, Yu SM. Effect of the addition of tramadol to a combination of tiletamine-zolazepam and xylazine for anaesthesia of miniature pigs. *Vet Rec* 2010; **167**: 489-492 [PMID: 20871083 DOI: 10.1136/vr.c4458]

13 **Santos González M**, Bertrán de Lis BT, Tendillo Cortijo FJ. Effects of intramuscular alfaxalone alone or in combination with diazepam in swine. *Vet Anaesth Analg* 2013; **40**: 399-402 [PMID: 23495812 DOI: 10.1111/vaa.12033]

14 **Lima-Rodríguez JR**, García-Gil FA, García-García JJ, Rocha-Camarero G, Martín-Cancho MF, Luis-Fernández L, Crisóstomo V, Usón-Gargallo J, Carrasco-Jiménez MS. Effects of premedication with tiletamine/zolazepam/medetomidine during general anesthesia using sevoflurane/fentanyl in swine undergoing pancreas transplantation. *Transplant Proc* 2008; **40**: 3001-3006 [PMID: 19010173 DOI: 10.1016/j.transproceed.2008.09.042]

15 **Pehböck D**, Dietrich H, Klima G, Paal P, Lindner KH, Wenzel V. Anesthesia in swine : optimizing a laboratory model to optimize translational research. *Anaesthesist* 2015; **64**: 65-70 [PMID: 25384955 DOI: 10.1007/s00101-014-2371-2]

16 **Madariaga ML**, Michel SG, La Muraglia GM, Sekijima M, Villani V, Leonard DA, Powell HJ, Kurtz JM, Farkash EA, Colvin RB, Allan JS, Cetrulo CL Jr, Huang CA, Sachs DH, Yamada K, Madsen JC. Kidney-Induced Cardiac Allograft Tolerance in Miniature Swine is Dependent on MHC-Matching of Donor Cardiac and Renal Parenchyma. *Am J Transplant* 2015; **15**: 1580-1590 [PMID:25824550 DOI: 10.1111/ajt.13131]

17 **Portis AJ**, Elbahnasy AM, Shalhav AL, Brewer AV, Olweny E, Humphrey PA, McDougall EM, Clayman RV. Laparoscopic midsagittal hemicystectomy and replacement of bladder wall with small intestinal submucosa and reimplantation of ureter into graft. *J Endourol* 2000; **14**: 203-211 [PMID: 10772516 DOI: 10.1089/end.2000.14.203]

18 **Caban A**, Oczkowicz G, Budziński G, Suszka-Świtek A, Dolińska B, Ostróżka-Cieślik A, Wieczorek J, Ryszka F, Wiaderkiewicz R, Cierpka L. Toll-like receptors 2 and 4 in pigs' kidneys early after autotransplantation procedure. *Transplant Proc* 2014; **46**: 2545-2547 [PMID: 25380861 DOI: 10.1016/j.transproceed.2014.09.035]

19 **Tillet S**, Giraud S, Delpech PO, Thuillier R, Ameteau V, Goujon JM, Renelier B, Macchi L, Hauet T, Mauco G. Kidney graft outcome using an anti-Xa therapeutic strategy in an experimental model of severe ischaemia-reperfusion injury. *Br J Surg* 2015; **102**: 132-142; discussion 142 [PMID: 25402331 DOI: 10.1002/bjs.9662]

20 **Bretan PN**, Lobo E, Chang JA, Dumitrescu O, Miller B, Yen TS. Assessment of preservation induced reperfusion injury via intraoperative renal transplant blood flow and endothelin concentration studies. *J Urol* 1997; **158**: 714-718 [PMID: 9258066 DOI: 10.1016/S0022-5347(01)64299-X]

21 **Stadlbauer V**, Stiegler P, Taeubl P, Sereinigg M, Puntschart A, Bradatsch A, Curcic P, Seifert-Held T, Zmugg G, Stojakovic T, Leopold B, Blattl D, Horki V, Mayrhauser U, Wiederstein-Grasser I, Leber B, Jürgens G, Tscheliessnigg K, Hallström S. Energy status of pig donor organs after ischemia is independent of donor type. *J Surg Res* 2013; **180**: 356-367 [PMID: 22682714 DOI: 10.1016/j.jss.2012.05.025]

22 **He B**, Musk GC, Mou L, Waneck GL, Delriviere L. Laparoscopic surgery for kidney orthotopic transplant in the pig model. *JSLS* 2013; **17**: 126-131 [PMID: 23743384 DOI: 10.4293/108680812X13517013318021]

23 **Galvão FH**, Pompeu E, de Mello ES, da Costa Lino Costa A, Mory E, Dos Santos RM, Santos VR, Machado MC, Bacchella T. Experimental multivisceral xenotransplantation. *Xenotransplantation* 2008; **15**: 184-190 [PMID: 18611226 DOI: 10.1111/j.1399-3089.2008.00470.x]

24 **Sakamoto H**, Takita K, Kemmotsu O, Morimoto Y, Mayumi T. Increased sensitivity to vecuronium and prolonged duration of its action in patients with end-stage renal failure. *J Clin Anesth* 2001; **13**: 193-197 [PMID: 11377157 DOI: 10.1016/S0952-8180(01)00253-7]

25 **Robertson EN**, Driessen JJ, Vogt M, De Boer H, Scheffer GJ. Pharmacodynamics of rocuronium 0.3 mg kg(-1) in adult patients with and without renal failure. *Eur J Anaesthesiol* 2005; **22**: 929-932 [PMID: 16318664 DOI: 10.1017/S0265021505001584]

26 **Sear JW**. Sufentanil disposition in patients undergoing renal transplantation: influence of choice of kinetic model. *Br J Anaesth* 1989; **63**: 60-67 [PMID: 2569886 DOI: 10.1093/bja/63.1.60]

27 **Angst MS**, Bührer M, Lötsch J. Insidious intoxication after morphine treatment in renal failure: delayed onset of morphine-6-glucuronide action. *Anesthesiology* 2000; **92**: 1473-1476 [PMID: 10781294 DOI: 10.1097/00000542-200005000-00038]

28 **Fyman PN**, Reynolds JR, Moser F, Avitable M, Casthely PA, Butt K. Pharmacokinetics of sufentanil in patients undergoing renal transplantation. *Can J Anaesth* 1988; **35**: 312-315 [PMID: 2968186 DOI: 10.1007/BF03010638]

29 **Michelsen LG**, Hug CC. The pharmacokinetics of remifentanil. *J Clin Anesth* 1996; **8**: 679-682 [PMID: 8982900 DOI: 10.1016/S0952-8180(96)00179-1]

30 **Hoke JF**, Cunningham F, James MK, Muir KT, Hoffman WE. Comparative pharmacokinetics and pharmacodynamics of remifentanil, its principle metabolite (GR90291) and alfentanil in dogs. *J Pharmacol Exp Ther* 1997; **281**: 226-232 [PMID: 9103501]

31 **Lazowski T**. The influence of the type of anaesthesia on postoperative pain after kidney transplantation. *Ann Transplant* 2000; **5**: 28-29 [PMID: 10850607]

32 **Morita K**, Seki T, Nonomura K, Koyanagi T, Yoshioka M, Saito H. Changes in renal blood flow in response to sympathomimetics in the rat transplanted and denervated kidney. *Int J Urol* 1999; **6**: 24-32 [PMID: 10221861 DOI: 10.1046/j.1442-2042.1999.06117.x]

33 **Gabriëls G**, August C, Grisk O, Steinmetz M, Kosch M, Rahn KH, Schlatter E. Impact of renal transplantation on small vessel reactivity. *Transplantation* 2003; **75**: 689-697 [PMID: 12640311 DOI: 10.1097/01.TP.0000044111.12370.ED]

34 **Carmellini M**, Romagnoli J, Giulianotti PC, Pietrabissa A, Di Stefano R, Rindi P, Rizzo G, Mosca F. Dopamine lowers the incidence of delayed graft function in transplanted kidney patients treated with cyclosporine A. *Transplant Proc* 1994; **26**: 2626-2629 [PMID: 7940818]

35 **Kadieva VS**, Friedman L, Margolius LP, Jackson SA, Morrell DF. The effect of dopamine on graft function in patients undergoing renal transplantation. *Anesth Analg* 1993; **76**: 362-365 [PMID: 8424517]

36 **Fondevila C**, Hessheimer AJ, Flores E, Vendrell M, Muñoz J, Escobar B, Calatayud D, Taurá P, Fuster J, García-Valdecasas JC. Step-by-step guide for a simplified model of porcine orthotopic liver transplant. *J Surg Res* 2011; **167**: e39-e45 [PMID: 21324490 DOI: 10.1016/j.jss.2011.01.012]

37 **Foltys D**, Kaths M, Strempel M, Weiler N, Heimann A, Knaak JM, Weyer V, Hansen T, Kempski O, Otto G. Comparative analysis of in situ versus ex situ perfusion on micro circulation in liver procurement--an experimental trial in a porcine model. *Transplant Proc* 2013; **45**: 1693-1699 [PMID: 23769026 DOI: 10.1016/j.transproceed.2013.02.048]

38 **Thiel K**, Schenk M, Etspüler A, Schenk T, Morgalla MH, Königsrainer A, Thiel C. A simple dummy liver assist device prolongs anhepatic survival in a porcine model of total hepatectomy by slight hypothermia. *BMC Gastroenterol* 2011; **11**: 79 [PMID: 21756340 DOI: 10.1186/1471-230X-11-79]

39 **Schoening WN**, Feige I, Schubert T, Olschewski P, Buescher N, Helbig M, Schmitz V, Neuhaus P, Pratschke J, Puhl G. Iloprost donor treatment reduces ischemia-reperfusion injury in an isolated extracorporeal pig liver perfusion model. *Exp Clin Transplant* 2015; **13**: 51-61 [PMID: 25654413]

40 **Rangel Moreira Dde A**, Aoun Tannuri AC, Belon AR, Mendonça Coelho MC, Oliveira Gonçalves J, Serafini S, Roberto Lima F, Agostini LO, Guimarães RR, Tannuri U. Large-for-size liver transplantation: a flowmetry study in pigs. *J Surg Res* 2014; **189**: 313-320 [PMID: 24721605 DOI: 10.1016/j.jss.2014.03.018]

41 **Iguchi K**, Hatano E, Yamanaka K, Sato M, Yamamoto G, Kasai Y, Okamoto T, Okuno M, Taura K, Fukumoto K, Ueno K, Uemoto S. Hepatoprotective effect by pretreatment with olprinone in a swine partial hepatectomy model. *Liver Transpl* 2014; **20**: 838-849 [PMID: 24700629 DOI: 10.1002/lt.23884]

42 **LaMattina JC**, Burdorf L, Zhang T, Rybak E, Cheng X, Munivenkatappa R, Salles II, Broos K, Sievert E, McCormick B, Decarlo M, Ayares D, Deckmyn H, Azimzadeh AM, Pierson RN, Barth RN. Pig-to-baboon liver xenoperfusion utilizing GalTKO. hCD46 pigs and glycoprotein Ib blockade. *Xenotransplantation* 2014; **21**: 274-286 [PMID: 24628649 DOI: 10.1111/xen.12093]

43 **Kim K**, Schuetz C, Elias N, Veillette GR, Wamala I, Varma M, Smith RN, Robson SC, Cosimi AB, Sachs DH, Hertl M. Up to 9-day survival and control of thrombocytopenia following alpha1,3-galactosyl transferase knockout swine liver xenotransplantation in baboons. *Xenotransplantation* 2012; **19**: 256-264 [PMID: 22909139 DOI: 10.1111/j.1399-3089.2012.00717.x]

44 **Gringeri E**, Polacco M, D'Amico FE, Scopelliti M, Bassi D, Bonsignore P, Luisetto R, Lodo E, Carraro A, Zanus G, Cillo U. A new liver autotransplantation technique using subnormothermic machine perfusion for organ preservation in a porcine model. *Transplant Proc* 2011; **43**: 997-1000 [PMID: 21620035 DOI: 10.1016/j.transproceed.2011.01.139]

45 **Aguilar-Melero P**, Luque A, Machuca MM, Pérez de Obanos MP, Navarrete R, Rodríguez-García IC, Briceño J, Iñiguez M, Ruiz J, Prieto J, de la Mata M, Gomez-Villamandos RJ, Muntane J, López-Cillero P. Cardiotrophin-1 reduces ischemia/reperfusion injury during liver transplant. *J Surg Res* 2013; **181**: e83-e91 [PMID: 22906559 DOI: 10.1016/j.jss.2012.07.046]

46 **Noormohamed MS**, Kanwar A, Ray C, Wright MC, Cowie DE, Stamp S, Talbot D, Manas D, White SA. Extracorporeal membrane oxygenation for resuscitation of deceased cardiac donor livers for hepatocyte isolation. *J Surg Res* 2013; **183**: e39-e48 [PMID: 23647801 DOI: 10.1016/j.jss.2013.03.026]

47 **Arkadopoulos N**, Kostopanagiotou G, Nastos C, Papalois A, Papoutsidakis N, Kalimeris K, Defterevos G, Kanna T, Polyzois K, Kampouroglou G, Kypriotis D, Costopanagiotou C, Pafiti A, Tzanatos H, Smyrniotis V. Reversal of experimental posthepatectomy liver failure in pigs: a new application of hepatocyte bioreactors. *Artif Organs* 2011; **35**: 29-36 [PMID: 20618230 DOI: 10.1111/j.1525-1594.2010.01016.x]

48 **Thurmon JC**, Smith GW. In: Veterinay Anesthesia and Analgesia. Tranquilli WJ, Thurmon JC, Grimm KA, editors. 4th ed. Oxford, UK: Blackwell Publising, 2007: 747-764

49 **Murrell S**. Premedication and sedation. In: BSAVA Manual of canine and feline anaesthesia and analgesia. 2nd ed. Seymour C, Duke-Novakovski T, editors. Gloucester, UK: BSAVA, 2007: 120-132

50 **Kerr C**. Pain management I. Systemic analgesics. In: BSAVA manual of canine and feline anaesthesia and analgesia. 2nd ed. Seymour C, Duke-Novakovski T, editors. Gloucester, UK: BSAVA, 2007: 89-103

51 **Ye H**, Wang DP, Zhang CZ, Zhang LJ, Wang HC, Li ZH, Chen Z, Zhang T, Cai CJ, Ju WQ, Ma Y, Guo ZY, He XS. Pathological characteristics of liver allografts from donation after brain death followed by cardiac death in pigs. *J Huazhong Univ Sci Technolog Med Sci* 2014; **34**: 687-691 [PMID: 25318878 DOI: 10.1007/s11596-014-1337-6]

52 **Tao L**, Li Q, Ren H, Chen B, Hou X, Mou L, Zhou S, Zhou J, Sun X, Dai J, Ding Y. Repair of extrahepatic bile duct defect using a collagen patch in a Swine model. *Artif Organs* 2015; **39**: 352-360 [PMID: 25345752 DOI: 10.1111/aor.12388]

53 **Burlak C**, Paris LL, Chihara RK, Sidner RA, Reyes LM, Downey SM, Tector AJ. The fate of human platelets perfused through the pig liver: implications for xenotransplantation. *Xenotransplantation* 2010; **17**: 350-361 [PMID: 20955292 DOI: 10.1111/j.1399-3089.2010.00605.x]

54 **Leal AJ**, Tannuri AC, Belon AR, Guimarães RR, Coelho MC, Oliveira Gonçalves Jd, Sokol SS, De Melo ES, Otoch JP, Tannuri U. A simplified experimental model of large-for-size liver transplantation in pigs. *Clinics* (Sao Paulo) 2013; **68**: 1152-1156 [PMID: 24037013 DOI: 10.6061/clinics/2013(08)15]

55 **Matthews NS**. Inhalant anaesthetics. In: BSAVA manual of canine and feline anaesthesia and analgesia. 2nd ed. Seymour C, Duke-Novakovski T, editors. Gloucester, UK: BSAVA, 2007: 150-155

56 **Leal AJ**, Tannuri AC, Belon AR, Guimarães RR, Coelho MC,

Gonçalves Jde O, Serafini S, Melo ES, Tannuri U. Effects of ischemic preconditioning in a pig model of large-for-size liver transplantation. *Clinics* (Sao Paulo) 2015; **70**: 126-135 [PMID: 25789522 DOI: 10.6061/clinics/2015(02)10]

57 **Minor T**, Koetting M, Koetting M, Kaiser G, Efferz P, Lüer B, Paul A. Hypothermic reconditioning by gaseous oxygen improves survival after liver transplantation in the pig. *Am J Transplant* 2011; **11**: 2627-2634 [PMID: 21906256 DOI: 10.1111/j.1600-6143.2011.03731.x]

58 **Martínez EA**, Keegan RD. Muscle relaxant and neuromuscular blockade. In: Veterinay Anesthesia and Analgesia. Tranquilli WJ, Thurmon JC, Grimm KA, editors. 4th ed. Oxford, UK: Blackwell Publising, 2007: 419-438

59 **Yost CS**, Niemann CU. Anesthesia for abdominal organ transplantation. In: Miller´s anesthesia. Miller RD, editor. 7th ed. Philadelphia, USA: Churchill Livingstone, 2010: 2155- 2184 [DOI: 10.1016/b978-0-443-06959-8.00067-4]

60 **Merritt WT**. Metabolism and liver transplantation: review of perioperative issues. *Liver Transpl* 2000; **6**: S76-S84 [PMID: 10915196 DOI: 10.1002/lt.500060515]

61 **Martin TJ**, Kang Y, Robertson KM, Virji MA, Marquez JM. Ionization and hemodynamic effects of calcium chloride and calcium gluconate in the absence of hepatic function. *Anesthesiology* 1990; **73**: 62-65 [PMID: 2360741 DOI: 10.1097/00000542-199007000-00010]

62 **Webster NR**, Bellamy MC, Lodge JP, Sadek SA. Haemodynamics of liver reperfusion: comparison of two anaesthetic techniques. *Br J Anaesth* 1994; **72**: 418-421 [PMID: 8155443 DOI: 10.1093/bja/72.4.418]

63 **Koelzow H**, Gedney JA, Baumann J, Snook NJ, Bellamy MC. The effect of methylene blue on the hemodynamic changes during ischemia reperfusion injury in orthotopic liver transplantation. *Anesth Analg* 2002; **94**: 824-829, table of contents [PMID: 11916779 DOI: 10.1097/00000539-200204000-00009]

64 **Frenette L**, Cox J, McArdle P, Eckhoff D, Bynon S. Conjugated estrogen reduces transfusion and coagulation factor requirements in orthotopic liver transplantation. *Anesth Analg* 1998; **86**: 1183-1186 [PMID: 9620500 DOI: 10.1213/00000539-199806000-00008]

65 **Boylan JF**, Klinck JR, Sandler AN, Arellano R, Greig PD, Nierenberg H, Roger SL, Glynn MF. Tranexamic acid reduces blood loss, transfusion requirements, and coagulation factor use in primary orthotopic liver transplantation. *Anesthesiology* 1996; **85**: 1043-1048; discussion 30A-31A [PMID: 8916821 DOI: 10.1097/00000542-199611000-00012]

66 **Findlay JY**, Rettke SR, Ereth MH, Plevak DJ, Krom RA, Kufner RP. Aprotinin reduces red blood cell transfusion in orthotopic liver transplantation: a prospective, randomized, double-blind study. *Liver Transpl* 2001; **7**: 802-807 [PMID: 11552215 DOI: 10.1053/jlts.2001.27086]

67 **García-Huete L**, Domenech P, Sabaté A, Martínez-Brotons F, Jaurrieta E, Figueras J. The prophylactic effect of aprotinin on intraoperative bleeding in liver transplantation: a randomized clinical study. *Hepatology* 1997; **26**: 1143-1148 [PMID: 9362354 DOI: 10.1002/hep.510260509]

68 **Kaspar M**, Ramsay MA, Nguyen AT, Cogswell M, Hurst G, Ramsay KJ. Continuous small-dose tranexamic acid reduces fibrinolysis but not transfusion requirements during orthotopic liver transplantation. *Anesth Analg* 1997; **85**: 281-285 [PMID: 9249100 DOI: 10.1097/00000539-199708000-00007]

69 **Marcel RJ**, Stegall WC, Suit CT, Arnold JC, Vera RL, Ramsay MA, O'Donnell MB, Swygert TH, Hein HA, Whitten CW. Continuous small-dose aprotinin controls fibrinolysis during orthotopic liver transplantation. *Anesth Analg* 1996; **82**: 1122-1125 [PMID: 8638778 DOI: 10.1097/00000539-199606000-00004]

70 **Cameron DE**, Tam VK, Cheng W, Braxton M. Studies in the physiology of cardiopulmonary bypass using a swine model. In: Swine as models in biomedical research. Swindle MM, Moody D, Philips LD, editors. 1st ed. Iowa, USA: Iowa State University Press, Ames, 1992: 185-196

71 **Wittnich C**, Wallen WJ, Belanger MP, Ikonomidis JS. Extracellular calcium concentration affects susceptibility to global ischemic injury in newborn but not adult hearts. *J Heart Lung Transplant* 1999; **18**: 675-683 [PMID: 10452344 DOI: 10.1016/S1053-2498(99)00026-1]

72 **Ereth MH**, Nuttall GA, Oliver WC, Santrach PJ, Price RD, Schaff HV. Temperature and duration of cardiopulmonary bypass influence transfusion requirements. *J Clin Anesth* 1998; **10**: 588-592 [PMID: 9805700 DOI: 10.1016/S0952-8180(98)00085-3]

73 **Vienten-Johansen J**, Hammon WJ. Myocardial protection during cardiac surgery. In: Cardiopulmonary bypass: principles and practice. Gravlee GP, Davis RF, Utley JR, editors. 1st ed. Philadelphia, USA: Lippincott Williams and Wilkins, 1993: 155-206

74 **Brooks DL**, Tillman PC, Niemi SM. Ungulates as laboratory animals. In: Laboratory animal medicine. Fox JG, Cohen BJ, Loew FM, editors. 1st ed. London, UK: Academic Press, Inc., 1984: 274-295

75 **Belanger M**, Wittnich C, Torrance S, Juhasz S. Model of normothermic long-term cardiopulmonary bypass in swine weighing more than eighty kilograms. *Comp Med* 2002; **52**: 117-121 [PMID: 12022390]

76 **Warltier DC**, al-Wathiqui MH, Kampine JP, Schmeling WT. Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. *Anesthesiology* 1988; **69**: 552-565 [PMID: 3177915 DOI: 10.1097/00000542-198810000-00016]

77 **Novalija E**, Fujita S, Kampine JP, Stowe DF. Sevoflurane mimics ischemic preconditioning effects on coronary flow and nitric oxide release in isolated hearts. *Anesthesiology* 1999; **91**: 701-712 [PMID: 10485782 DOI: 10.1097/00000542-199909000-00023]

78 **Conzen PF**, Fischer S, Detter C, Peter K. Sevoflurane provides greater protection of the myocardium than propofol in patients undergoing off-pump coronary artery bypass surgery. *Anesthesiology* 2003; **99**: 826-833 [PMID: 14508313 DOI: 10.1097/00000542-200310000-00013]

79 **De Hert SG**, ten Broecke PW, Mertens E, Van Sommeren EW, De Blier IG, Stockman BA, Rodrigus IE. Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. *Anesthesiology* 2002; **97**: 42-49 [PMID: 12131102 DOI: 10.1097/00000542-200207000-00007]

80 **De Hert SG**, Van der Linden PJ, Cromheecke S, Meeus R, Nelis A, Van Reeth V, ten Broecke PW, De Blier IG, Stockman BA, Rodrigus IE. Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. *Anesthesiology* 2004; **101**: 299-310 [PMID: 15277911 DOI: 10.1097/00000542-200408000-00009]

81 **Santerre D**, Chen RH, Kadner A, Lee-Parritz D, Adams DH. Anaesthetic management of baboons undergoing heterotopic porcine cardiac xenotransplantation. *Vet Res Commun* 2001; **25**: 251-259 [PMID: 11432427 DOI: 10.1023/A: 1010683907590]

82 **García-Gil FA**, Albendea CD, López-Pingarrón L, Royo-Dachary P, Martínez-Guillén J, Piedrafita E, Martínez-Díez M, Soria J, García JJ. Altered cellular membrane fluidity levels and lipid peroxidation during experimental pancreas transplantation. *J Bioenerg Biomembr* 2012; **44**: 571-577 [PMID: 22986734 DOI: 10.1007/s10863-012-9459-7]

83 **Cohen D**, Miyagawa Y, Mehra R, Lee W, Isse K, Long C, Ayares DL, Cooper DK, Hara H. Distribution of non-gal antigens in pig cornea: relevance to corneal xenotransplantation. *Cornea* 2014; **33**: 390-397 [PMID: 24488129 DOI: 10.1097/ICO.0000000000000069]

84 **Dong GH**, Li XF, Li JZ, Zhang ZD, Hu WM, Luo YH, Li ZD, Tian BL, He MX, Zhu XW. Intercellular adhesion molecular-1, Fas, and Fas ligand as diagnostic biomarkers for acute allograft rejection of pancreaticoduodenal transplantation in pigs. *Dig Dis Sci* 2014; **59**: 778-786 [PMID: 24162270 DOI: 10.1007/s10620-013-2904-6]

85 **Avison DL**, DeFaria W, Tryphonopoulos P, Tekin A, Attia GR, Takahashi H, Jin Y, Palaios E, Pararas N, Carreno MR, Santiago S, Bazer F, Ruiz P, Tzakis A. Heterotopic uterus transplantation in a swine model. *Transplantation* 2009; **88**: 465-469 [PMID: 19696628 DOI: 10.1097/TP.0b013e3181b07666]

86 **Ibrahim Z**, Cooney DS, Shores JT, Sacks JM, Wimmers EG, Bonawitz SC, Gordon C, Ruben D, Schneeberger S, Lee WP, Brandacher G. A modified heterotopic swine hind limb transplant model for translational vascularized composite allotransplantation (VCA) research. *J Vis Exp* 2013; **(80)** [PMID: 24145603 DOI: 10.3791/50475]

87 **Zonta S**, Lovisetto F, Lorenzo C, Abbiati F, Alessiani M, Dionigi P, Zonta A. Uretero-neocystostomy in a swine model of kidney transplantation: a new technique. *J Surg Res* 2005; **124**: 250-255 [PMID: 15820255 DOI: 10.1016/j.jss.2004.11.006]

88 **Nishikawa H**, Oto T, Otani S, Harada M, Iga N, Miyoshi K, Miyoshi S. Unilateral lung transplantation using right and left upper lobes: an experimental study. *J Thorac Cardiovasc Surg* 2013; **146**: 1534-1537 [PMID: 24079876 DOI: 10.1016/j.jtcvs.2013.08.042]

P- Reviewer: Mentes O, Wong KL
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