


Anaesthesia and Analgesia in Ellegaard Göttingen minipigs

Author: Aage Kristian Olsen Alstrup, D.V.M., Ph.D.

PET Centre, Aarhus University Hospital, Nørrebrogade 44, 10G,
DK-8000 Aarhus C, Denmark. aage@pet.auh.dk

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FOREWORD

The Göttingen Minipig was developed by traditional breeding at the University of Göttingen in the 1960s. Since the early 1990s Ellegaard Göttingen Minipigs A/S has had the global rights to breed and distribute this research model. Today the Göttingen Minipig is recognized globally for its outstanding quality (high health status and strict genetic management). It is used primarily in safety assessment of new medicines but it is also used in many other areas of biomedical research, including research which encompasses surgical intervention.

Numerous publications and several books deal with a variety of surgical techniques in swine and offer guidance in terms of anaesthesia, pre- and postoperative care etc. Most often these texts refer to different types of farm pigs and not to the Göttingen Minipig specifically. With the increasing use of the Göttingen Minipig in areas that include surgical intervention, a publication which brings together current practice is much needed.

This book aims at presenting current practices in anaesthesia, analgesia, pre- and postoperative care of Göttingen Minipigs. It is written by Dr. Aage Kristian Olsen Alstrup who has extensive experience with the Göttingen Minipig in this context and I am grateful that he is willing to share his knowledge with minipig users all across the world. I am sure this book will become an indispensable reference for anaesthesia and analgesia in Göttingen Minipigs. Furthermore, I would like to thank Dr. Anthony Webb (Director at Chiron Bioscience Ltd., UK and Scientific Consultant for Ellegaard Göttingen Minipigs A/S), Dr. M. Michael Swindle (Professor of Comparative Medicine at the Medical University of South Carolina, USA) and Dr. Peter Glerup (Chief Veterinary Surgeon, LAB Research (Scantox), Denmark) for providing us with their input and comments to the manuscript.

While this book is targeted specifically at the Ellegaard Göttingen Minipig, the information may be relevant for most types of swine. Protocols given in this book may well be applied to other types of swine, but doing so must be done with caution while ensuring good animal welfare.

May 2010

Niels-Christian Ganderup

Chief Sales Officer

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*PET Centre, Aarhus University Hospital, Nørrebrogade 44, 10G
DK-8000 Aarhus C, Denmark. aage@pet.auh.dk*

Summary

Successful anaesthesia of Ellegaard Göttingen minipigs should provide sufficient analgesia, narcosis and muscle relaxation. Göttingen minipigs are sedated prior to anaesthesia to avoid physical restraint and stress. Thereafter, an ear vein catheter is placed and used to induce anaesthesia. After induction, tracheal intubation is recommended, particularly for prolonged anaesthesia. The anaesthesia can be maintained by either an inhalation (e.g. isoflurane) or an injection (e.g. propofol) anaesthetic. As Göttingen minipigs have a poor thermoregulation system, thermal blankets should be used to prevent hypothermia. Anaesthesia and analgesia are essential for the prevention of pain during surgery. Careful postoperative observation is of importance following anaesthesia and surgery in Göttingen minipigs. It is of utmost importance that the physiologic effects of the anaesthetic protocol are considered in advance in order to avoid complications of the experiment.

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1. INTRODUCTION

Compared with domestic pigs and other laboratory animals, Ellegaard Göttingen minipigs can easily be anaesthetised for several hours without a higher risk of complications. Göttingen minipigs are microbiologically defined according to international guidelines, and the absence of certain pathogens decreases the risk of respiratory arrest and cardiovascular failure. Furthermore, the absence of the halothane gene prevents the development of malignant hyperthermia. However, any anaesthesia procedure should be carefully planned prior to carrying out the anaesthesia. It is of utmost importance that the physiologic effects of the anaesthetic protocol are considered in advance in order to avoid complications of the experiment.



Figure 1: Göttingen minipigs have to be handled without stress prior to anaesthesia.

2. PRE-ANAESTHESIA CONSIDERATIONS

2.1 At least one week of acclimatisation

Göttingen minipigs should be acclimatised in the experimental unit for at least one to three weeks before any anaesthetic is administered. In this acclimatisation period, the minipigs should be kept in conditions that do not cause stress to the minipigs. Stress or an insufficient period of acclimatisation increases the risk of postoperative complications and death during anaesthesia. Therefore, the Göttingen minipigs should stay in the facility until after sedation has been performed.



Figure 2: The Göttingen minipig should be acclimatised for at least one to three weeks.

2.2 Clinical examination prior to anaesthesia

Clinical examination prior to anaesthesia should be done the day before anaesthesia. A brief examination includes observation of the behaviour of the Göttingen minipigs. The respiratory rate should also be noted, as high frequency may indicate lung disease or stress. In the event disease symptoms are present, the clinical examination should be supplemented with

auscultation of the thorax and measurement of body temperature. Systemic acute diseases must always exclude the use of the Göttingen minipigs from any anaesthesia procedure.



Figure 3: In the event disease symptoms are present, the clinical examination should be supplemented with auscultation of the heart and lung.

Table 1: Reference interval for clinically healthy Göttingen minipigs:

Parameters	Units	Göttingen minipig
Respiration rate	[/min]	11–29
Heart rate	[/min]	68–98
Body temperature	[°C]	37–38

2.3 Preoperative fasting for six to twelve hours

Although vomiting rarely occurs when using Göttingen minipigs, they must be deprived of food for six to twelve hours before any anaesthesia procedure. Neonates only have to be deprived of food for three hours. After twelve hours of fasting, the stomach still contains

food, due to the *torus pyloricus*. An overloaded stomach can put pressure on the diaphragm, decrease lung function and complicate abdominal organ surgery. Therefore, when performing elective surgery involving the abdominal organs, Göttingen minipigs must be deprived of food for twelve to twenty-four hours. All edible bedding must be removed from the cage in the fasting period, because they will readily consume it otherwise. Drinking water must be provided up until the time of anaesthesia.

Table 2: Fasting period for Göttingen minipigs prior to anaesthesia:

Neonates	3 hours
Young and adult	6–12 hours
Abdominal surgery	12–24 hours

2.4 Premedication

Göttingen minipigs are pre-medicated to sedate them before anaesthesia procedures. Various drug combinations are useful for premedication. Some, such as the zoletil mix for pigs, provide good analgesic effects during the first four hours of anaesthesia. The zoletil mix for pigs can be used in physiologically normal pig models, but may have prolonged effects, and therefore be contraindicated in some cardiovascular and renal compromise protocols. Salivation and bradycardia can be prevented by adding atropine for its anticholinergic effect. Most drugs for premedication are injected intramuscularly (IM) while the Göttingen minipigs are still in familiar surroundings, and the procedure should be performed without causing any fear or stress. This can be done by offering the minipigs a small amount of food, or – for young minipigs – letting an assistant carry the animal during injection. It is also possible to manually restrain adult Göttingen minipigs. However, rough handling should always be avoided, because this may cause stress, overheating and in rare cases even acute death of the minipig. Syringes, polyethylene tubes and 18–21 G needles are recommended for IM injections. The needle for an adult minipig has to be at least 30 mm in length, because shorter needles may result in injections into fatty tissue, and this may delay drug absorption and the effects of some drugs. The IM injection is performed 1–3 cm

behind the ear into the lateral cervical muscle region. A disadvantage of IM injection is that it can be painful and stressful to the minipig compared with SC injection. A combination of azaperone (4 mg/kg) and midazolam (1 mg/kg) is very powerful for sedating Göttingen minipigs. The two drugs can be mixed in a syringe before the IM injection. The Göttingen minipig should be left for 5–15 minutes in quiet surroundings after injection before taking it to the preparation room. Also, a mixture of climazolam (0.5–1.0 mg/kg) and ketamine (20 mg/kg) IM has been proven effective in Göttingen minipigs, and it produces a thirty-minute anaesthesia period. Some equipment and drugs useful for pre-medicating minipigs are shown in the tables below.



Figure 4: Intramuscular (IM) injection in a Göttingen minipig. The drug is given just behind the ear, as this may prevent fatty tissue injection.

Table 3: Equipment needed for premedication:

Syringes (2 ml, 5 ml, 10 ml or 20 ml)
 Polyethylene tube (approximately 1 metre)
 Hypodermic needle (30–40 mm; 18–21 G)
 Drugs (atropine, sedative, etc.)
 Small amount of food

Table 4: Examples of premedication (IM) for pigs:

Drugs	Doses [mg/kg]	Comments
Atropine	0.05	Anticholinergic effect only
Azaperone	4–8	Moderate sedation
Acepromazine	0.1–0.45	Slow onset of action
Climazolam-ketamine	0.5–1.0 + 20	Anaesthesia for approximately 30 minutes
Diazepam	0.5–1	Effective muscle relaxation
Midazolam-ketamine	1 + 10	Useful for PET studies
Zoletil mix for pigs ¹	1 ml/15 kg	Deep sedation

¹ Zoletil mix for pigs: zoletil (1 bottle) + 6.25 ml xylazine (20 mg/ml) + 1.25 ml ketamine (100 mg/ml) + 2.5 ml butorphanol (10 mg/ml).

2.5 Ear vein catheter

Intravenous (IV) injection is preferred for inducing anaesthesia in Göttingen minipigs. However, compared to Landrace and Yorkshire pigs, Göttingen minipigs have small, delicate ear veins, and this causes unique challenges when they have to be cannulated repeatedly. An over-the-needle plastic catheter (Venflon, 22 G, 25 mm) can be placed in the central or ventrolateral ear vein, while the major artery is located on the dorsolateral area of the ear and must never be used for injecting anaesthetics. Injection of an anaesthetic into the artery could cause tissue slough of the distal end of the ear. The ear veins are distended by placing a rubber band tightly around the base of the ear. The ear can also be warmed up with water or, alternatively, topical alcohol can be applied. After cleaning and disinfection, the catheter is placed in the ear vein, and the rubber band is removed. To be sure that the

catheter is correctly placed and to avoid the formation of blood clots, the catheter is flushed with heparinised saline. Drugs like thiopentone should be administered strictly IV to avoid necrosis. The catheter is affixed with tape. The catheter can at last be flushed with a heparin saline solution, which is recommended if the catheter should be used several hours later. The catheter placement procedure is shown in the figures below.

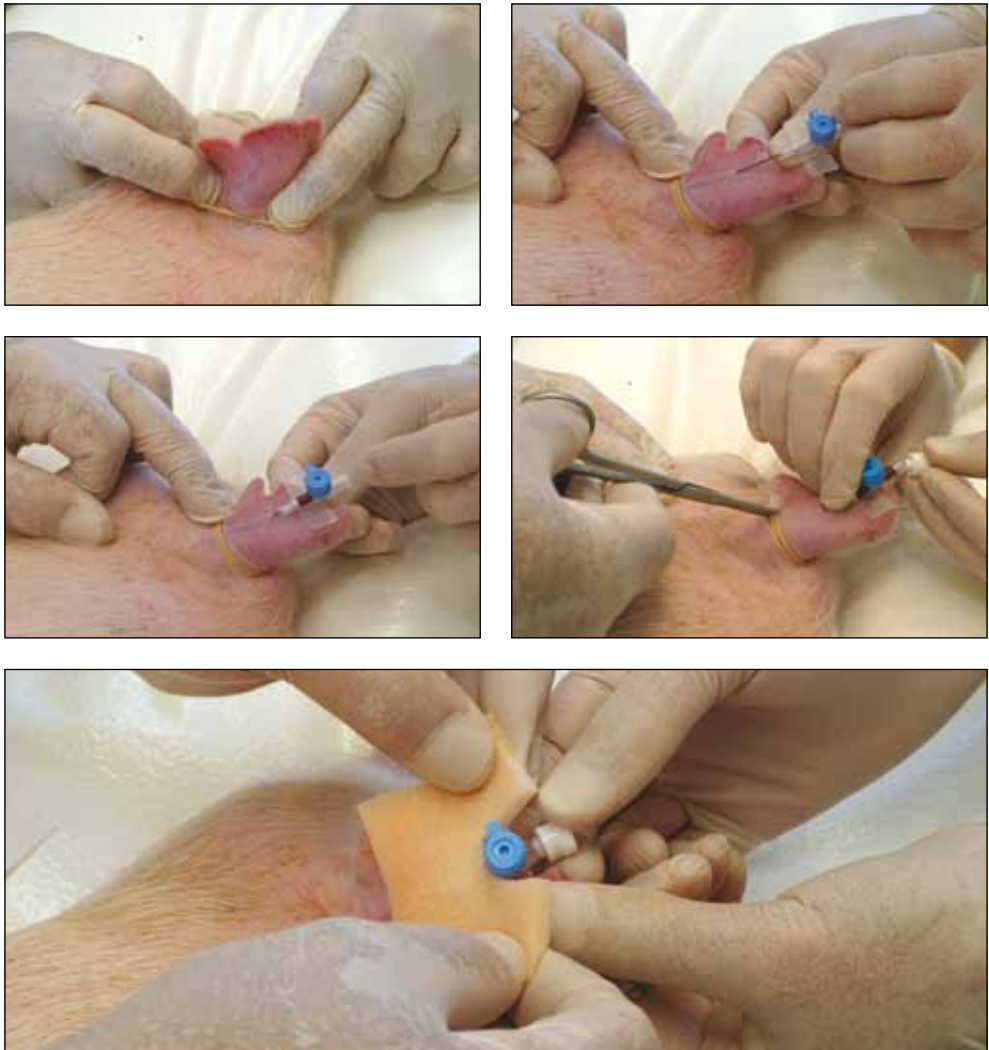


Figure 5: Placing of an ear vein catheter: A rubber band is placed tightly around the base of the ear, and an over-the-needle plastic catheter (Venflon 22G, 25 mm) is placed in the ear vein. The catheter is affixed with tape.

Table 5: Equipment needed for placing an ear vein catheter:

Alcohol
Rubber band
Over-the-needle plastic catheter (Venflon, 22 G, 25 mm)
Tape for securing the catheter
Syringe with saline or a heparin solution to flush the catheter

Table 6: Methods of injection in Göttingen minipigs:

Subcutaneous (SC) injection

The skin of Göttingen minipigs is hardly movable. Two spots for SC injections exist: Small minipigs held in arms or on a table should receive the injection in the knee fold. Large minipigs should receive the injection caudal to the ear base. This can be performed with a butterfly catheter without having to manually restrain the minipig.

Intramuscular (IM) injection

IM injections are administered in the lateral cervical muscle region or in thigh muscles.

Intravenous (IV) injection

Puncture of the ear vein using an over-the-needle plastic catheter.



Figure 6: Subcutaneous (SC) injection in the knee fold of a minipig.

3. ANAESTHESIA

3.1 Induction of anaesthesia

In most cases the anaesthesia must be induced by IV injection of the anaesthetic using the ear vein catheter. However, some premedication has such strong sedative effects that further induction of anaesthesia is unnecessary. This is often the case with the zoletil mix for pigs. However, for most drug combinations, such as the midazolam-ketamine mixture, anaesthesia induction is always needed. Propofol and thiopentone are the drugs of choice for inducing anaesthesia in minipigs, due to their fast-acting effects and the short recovery time. Also midazolam, ketamine and combinations of midazolam and ketamine can be used. To avoid necrosis, thiopentone must be given IV, and the other drugs should also be given IV to obtain fast effects. When using ketamine, a topical anaesthetic should be applied to the larynx prior to tracheal intubation, due to the intact laryngeal reflex. All of these anaesthetics are not given in fixed doses but are administered until effects are observed, which include the absence of corneal reflexes and good muscular relaxation. Instead of injecting anaesthetics, face masks can be used to deliver inhalation anaesthetics. This eliminates the use of IV catheters. It is important that anaesthesia is induced in a quiet environment, because sedated Göttingen minipigs are susceptible to sudden and loud noise.



Figure 7: Anaesthesia induced by IV injection of fast-acting anaesthetics, such as propofol or thiopentone.

Table 7: Drugs useful for inducing anaesthesia in minipigs:

Drugs	Dose ¹ [mg/kg]	Comments
Propofol	1,5-5	Risk of apnoea
Thiopenthone	3–20	Given IV only
Ketamine	20	Poor muscle relaxation
Midazolam–ketamine	1.25 + 6	Useful for PET studies

¹ *The doses are not fixed, but drugs should be given until effects appear (absence of corneal reflexes and good muscular relaxation).*

3.1.1 Zero-stress anaesthesia induction

For animal-welfare and scientific reasons, stress must be minimised before anaesthesia. Therefore, a zero-stress anaesthesia induction method called ZESTRANI has been developed for Göttingen minipigs. The ZESTRANI method is contingent on the minipigs' acceptance of sugar cubes treated with clonidine and fentanyl. The ZESTRANI method decreases heart rate, mean arterial blood pressure and cardiovascular incidents in Göttingen minipigs compared to a standard induction of anaesthesia. When using the ZESTRANI method, the heart rate can be almost as low as that of Göttingen minipigs which have not been anaesthetised. Furthermore, the stress reduction may reduce alterations of the endocrine and hemodynamic profiles. The practical application of the ZESTRANI method in Göttingen minipigs is shown below (halothane was originally used but is now replaced with isoflurane).



Figure 8: Zero-stress anaesthesia induced using a face mask.

Table 8: The ZESTRANI method for stress-free induction of anaesthesia in Göttingen minipigs:

- Fasting for 16 hours
- Clonidine (20 µg/kg) orally on sugar cubes 10 hours before surgery
- Clonidine (10 µg/kg) and fentanyl (100 µg/kg) orally 90 minutes before surgery
- Ketamine (10 mg/kg) + flunitrazepam (150 µg/kg) IM 1 hour before surgery
- Mask ventilation with isoflurane (2 %) and oxygen 50 minutes before surgery
- Ear vein catheter is placed
- Lidocaine (2 mg/kg) and fentanyl (150 µg/kg) IV 40 minutes before surgery
- Endotracheal intubation and ventilation with isoflurane, oxygen and N₂O
- Sulfentanil (10 µg/kg) IV 30 minutes before surgery
- Ringer solution infusion and fentanyl (25 µg/kg/h) IV starting 20 minutes before surgery

Source: Petroianu et al. (1998). NB: Halothane has been replaced with isoflurane.

3.1.2 Endotracheal intubation

Endotracheal intubation maintains clear airways, permits artificial control of respiration and protects the airways from aspiration of foreign material. When anaesthetising Göttingen minipigs for more than one hour, endotracheal intubation is vital. However, endotracheal intubation is also recommended for short anaesthesia. Endotracheal intubation in minipigs is challenging compared to most other large animal species due to the anatomy of the porcine head. With proper training and experience, intubation can be done with little difficulty.

Table 9: Proper training and equipment that are needed:

- a laryngoscope with a long, straight blade (200–250 mm, minimum 170–190 mm),
- endotracheal tubes (tube size, see table 10),
- local anaesthetic spray (Xylocaine™; 2% lidocaine),
- a syringe with air,
- slings for opening the mouth,
- tape for fixation of tube.

Göttingen minipigs can be intubated in dorsal, lateral and sternal recumbency. The method that best serves the staff should be chosen. Sternal recumbency appears to be best for inexperienced staff, and therefore the sternal recumbency will be discussed here.

The jaw has to be held open with suitable slings by an assistant. Alternatively a mouth gag can be used. The head should only be slightly extended. Excessive extension can occlude the airways or make the laryngeal opening more difficult to identify. The position of the epiglottis can be determined after pulling out the tongue slightly. The tip of the laryngoscope is passed into the pharyngeal cavity and used to displace the epiglottis from the soft palate. The laryngeal opening is sprayed with Xylocaine™ (2% lidocaine) to prevent spasms. A muscle relaxant of the depolarising type (such as succinylcholine chloride, 2 mg/kg IV) can be given if necessary. Insufficient anaesthesia, excessive manipulation and repeated, unsuccessful attempts to intubate may lead to laryngospasms. A stylet can be used to keep the endotracheal tube straight except for a slight curve at the tip. The tube is used to press the epiglottis forward onto the base of the tongue, and the tip of the laryngoscope blade is placed to make the vocal cords visible. The tube is then advanced into the trachea during expiration. A slight rotation of the tube will facilitate the introduction without undue

force. Pigs have a bronchus to ventilate the right cranial lobe and therefore endotracheal intubation should not continue as far as the tracheal bifurcation. Resistance should not be felt. A free passage of air should be felt when the minipig is properly intubated. Chest auscultation reveals respiration sounds in both the left and right side of the minipig. Any signs of cyanosis or gasping indicate improper tube placement. Only cuffed tubes should be used for large minipigs, and the cuff must be filled up with air using a 5-ml or 10-ml syringe. Finally, the tube is affixed to the snout using adhesive tape or gauze. Excess inflation of the endotracheal cuff can cause swelling and oedema of the airways, and this may lead to airway obstruction. This becomes apparent when the minipig is extubated. Airway oedema can be treated with NSAIDs (see later) or similar drugs.

3.1.3 Cricothyrotomy as an alternative to intubation

As an alternative to the intubation of Göttingen minipigs, cricothyrotomy can be performed very quickly. However, the method is not recommended for animals that have to survive. Methods of cricothyrotomy have been evaluated in Göttingen minipigs (see Mattinger et al., 2000 or Swindle, 2007).



Figure 9: Endotracheal intubation of a Göttingen minipig in sternal recumbency. The jaws are held open with slings by an assistant. The tip of the laryngoscope is passed into the pharyngeal cavity and used to displace the epiglottis from the soft palate. A slight rotation of the tube will facilitate the introduction. The cuff is filled up with air and the tube is affixed to the snout.

Table 10: Tracheal tube sizes for minipigs:

Body weight	Tube size
Piglets	3–4 mm
10–15 kg	5 mm
Adults	5–7 mm



Figure 10: Some of the equipment needed for intubating Göttingen minipigs.

3.1.4 Artificial ventilation

Göttingen minipigs can breathe spontaneously during anaesthesia. However, for prolonged anaesthesia or when the risk of apnoea is high, it is recommended that artificial ventilation is used. The table below shows ventilation settings for Göttingen minipigs. If partial arterial carbon dioxide (PaCO_2) and partial arterial oxygen (PaO_2) tension are measured, the ventilation settings should be corrected, as seen in another table below.

Table 11: Ventilation settings for Göttingen minipigs:

Parameters	Units	Value
Tidal volume	ml/kg	7–12
Ventilation frequency	/min	10–20
Volume per minute	ml/kg/min	150
Max. pressure	cm H ₂ O	20–25
O ₂ – medical air	ratio	1:2.2
O ₂ – N ₂ O	ratio	1:2

Example of ventilation settings for a 20-kg Göttingen minipig:

- Tidal volume: $20 \times 10 = 200 \text{ ml}$
- Ventilation frequency: $15/\text{min.}$
- Volume per minute: $20 \times 150 = 3000 \text{ ml/min.}$
- O₂: 1 l/min.
- N₂O: 2 l/min.
- Inspiratory pressure: $12\text{--}14 \text{ cm H}_2\text{O}$

Table 12: How to correct insufficient or excessive PaCO₂ and PaO₂ values in Göttingen minipigs:

PaCO₂	PaO₂	
low	low:	decrease volume per minute and increase O ₂ :N ₂ O ratio
low	normal:	decrease volume per minute (and increase O ₂ :N ₂ O ratio)
low	high:	decrease volume per minute
normal	low:	increase O ₂ :N ₂ O ratio
normal	high:	decrease O ₂ :N ₂ O ratio
high	low:	increase volume per minute
high	normal:	increase volume per minute (and decrease O ₂ :N ₂ O ratio)
high	high:	increase volume per minute and decrease O ₂ :N ₂ O ratio

PaCO₂: partial arterial carbon dioxide. PaO₂: partial arterial oxygen.

3.2 Maintenance of anaesthesia

Both inhalation and injection anaesthetics can be used for maintaining anaesthesia. Inhalation anaesthesia is preferred for prolonged anaesthesia, or for studies where the Göttingen minipigs have to recover from anaesthesia. However, expensive equipment is needed for inhalation anaesthesia, and, for staff health reasons, the equipment has to be controlled periodically. In recent decades, new injectable anaesthetics, such as propofol, have been available for anaesthetising Göttingen minipigs. Some of the drugs are very useful for long-term studies and they allow rapid, smooth recovery of minipigs in survival studies.

3.3 Inhalation anaesthetics

Inhalation anaesthetics have the advantage that the anaesthesia can be performed without IV access. Most inhalants, such as sevoflurane and isoflurane, are safe for anaesthetising Göttingen minipigs, and for decades they have been recommended for prolonged anaesthesia. An overdose can easily be controlled by ventilation of the lung with pure gas (oxygen) after turning off the anaesthetic. The mean alveolar concentrations (MAC) in the following table provide guidelines for the percentage of an inhalant required for anaesthesia. MAC is defined as the alveolar concentration of the inhalation anaesthetics that anaesthetised half of the animals. However, as individual variations exist from one minipig to another, the anaesthetics must always be dosed until the absence of reflexes is observed. Furthermore, many factors (such as body temperature, premedication and age) affect MAC values in pigs.

Table 13: Mean alveolar concentrations (MAC) of inhalation anaesthetics in pigs:

Drug	MAC value
Halothane	0.9–1.3%
Isoflurane	1.45–2.0%
Desflurane	10.0 %
Sevoflurane	2.0–2.7%
Enflurane	1.7 %
N ₂ O	162–277%

Table 14: Some factors that increase or decrease the MAC values of inhalation anaesthetics in pigs and other animal species:

Increase	Decrease	Decrease
Hyperthermia	Hypothermia	Other anaesthetics
CNS stimulants	Pre-medications	* N ₂ O
* amphetamine	* acepromazine	* ketamine
* ephedrine	* midazolam	Increased age
* physostigmine	* xylazine	Pregnancy

3.3.1 Nitrous oxide (N₂O)

Nitrous oxide (N₂O) is only used to supplement other anaesthetics. It is not a potent anaesthetic and may therefore be administered in high concentrations, typically 66%. To avoid hypoxia, the maximum concentration of N₂O for safe anaesthesia is 75% N₂O and 25% O₂. Nitrous oxide reduces the dose of more potent anaesthetics (approximately 50% reduction in isoflurane), and in combination with the low toxicity of N₂O and minimal depression of cardiovascular and respiratory system, this increases the safety and keeps the Göttingen minipigs in a more physiologically stable state. Due to the rapid diffusion of N₂O from blood to alveoli, there is a high risk of hypoxia after ending the anaesthesia. Göttingen minipigs should therefore breathe pure O₂ during the first ten minutes after discontinuing N₂O anaesthesia.

3.3.2 Isoflurane

Isoflurane has been extensively used for anaesthetising Göttingen minipigs. Isoflurane is useful and preferable to halothane in Göttingen minipigs due to its broad safety margin, and because it is easy to regulate the depth of the anaesthesia. Compared to halothane, it has a more rapid introduction and recovery due to its lower solubility in blood. Halothane and isoflurane have physical similarities and can therefore be administered using the same vaporisers. Isoflurane may often be combined with a strong analgesic such as fentanyl, because it only offers minimal analgesic effects. Fentanyl reduces the dose of isoflurane required for anaesthetising minipigs.

3.3.3 Combining isoflurane and nitrous oxide in combination

A combination of isoflurane and N₂O has been tested in female Göttingen minipigs. The mean physiological parameters for the combination of 1.75–2.00% isoflurane with an N₂O–oxygen mixture (1:3) are summarised below. Also, other physiological parameters were measured in this study. Blood pressure decreased and the heart rate increased during the first hour of anaesthesia. In general, isoflurane and N₂O seem to be a useful anaesthetic mixture for Göttingen minipigs.

Table 15: Anaesthetising Göttingen minipigs using isoflurane and N₂O:

Time	HR (/min)	BV (ml)	BP (mmHg)
Baseline	104	21	145/105
After atropine	180	13	135/115
30-min. anaesthesia	145	12	90/65
60-min. anaesthesia	140	12	90/60
80-min. anaesthesia	135	13	90/60

HR: heart rate. BP: blood pressure. Source: Becker et al. (1984).

3.3.4 Desflurane, sevoflurane and enflurane

Desflurane, sevoflurane and enflurane are all isomers of isoflurane and they are useful for anaesthetising minipigs. As desflurane has a low solubility in blood, induction and recovery are very fast. Furthermore, the anaesthesia depth can easily be regulated. It is more volatile than halothane and isoflurane, and therefore special vaporisers are needed. The high price of desflurane often limits its use in minipigs. Also sevoflurane is a useful anaesthetic for minipigs. It may be the choice for high-risk cases such as young and sick minipigs. It has a fast recovery. Enflurane can also be used but appropriate premedication is needed. High concentrations of enflurane can cause a seizure-like response in pigs. Enflurane is disappearing in US market, and desflurane requires specialised equipment. In general, isoflurane and sevoflurane – with or without nitrous oxide – are the universal agents for pig anaesthesia in the US today.



Figure 11: Götting minipigs can be anaesthetised for several hours under inhalation anaesthesia.

3.3.5 Enflurane and nitrous oxide in combination

Like isoflurane, enflurane can be combined with N_2O for anaesthetising Götting minipigs. The enflurane- N_2O combination has been evaluated in Götting minipigs. In contradiction to other inhalation anaesthetics, almost no enflurane is metabolised, and this is especially important in cases of repeated anaesthesia of a minipig. The physiological parameters for enflurane and N_2O observed in five-month old Götting minipigs are shown below. Blood pressure decreases and heart rate increases during the first hour of anaesthesia. Other physiological variables were measured too. Spontaneously breathing Götting minipigs develop respiratory acidosis from this enflurane- N_2O mixture, and therefore artificial ventilation is recommended for long-term studies.

Table 16: Anesthetising Göttingen minipigs using enflurane and N₂O

Time	HR/min.	CO (l/min.)	BP (mm/Hg)
Baseline	105	2.7	135/80
After atropine	165	3.2	140/90
30-min. anaesthesia	130	2.2	90/50
60-min. anaesthesia	120	2.1	80/50
80-min. anaesthesia	115	2.0	80/50

HR: heart rate. CO: Cardiac output BP: blood pressure. Source: Becker & Beglinger (1982).

3.4 Injection anaesthetics

We have adopted some useful injectable anaesthetics for minipigs from human medicine. In general, as injectable anaesthetics have to be dosed IV, a vascular catheter is required. In most cases an ear vein catheter or a central vein catheter is used. As central catheters give safer access, they are recommended if anaesthetised Göttingen minipigs have to be transported (see chapters 1, 9 and 12 in Swindle (2007) for insertion technique). However, some injection anaesthetics, such as ketamine, can also be dosed IM. The recovery time of many injection anaesthetics is longer than for most inhalation anaesthetics. Furthermore, it can be difficult to change the anaesthesia stage when using injection anaesthetics. However, one of the preferred injection anaesthetics is propofol, a drug with fast induction and recovery. A few other injection anaesthetics are shown in the table below.

Table 17: Drugs and drug mixtures used for injection and infusion anaesthesia of pigs:

Name	Adm.	Drug(s)	Doses
Propofol	IV	Propofol	4–120 mg/kg/h
AK	IM	Acepromazine	0.5 mg/kg
		Ketamine (after 15 min)	15 mg/kg
DiaKet	IM	Diazepam	1–2 mg/kg
		Ketamine	10–18 mg/kg
KetXyl	IM	Ketamine	15 mg/kg
		Xylazine	2 mg/kg
MBK	IM	Medetomidine	80 µg/kg
		Butorphanol	220 µg/kg
		Ketamine	10 mg/kg
XBK	IM	Xylazine	2 mg/kg
		Butorphanol	220 µg/kg
		Ketamine	5 mg/kg

3.4.1 Adrenoceptor agonists

Xylazine, detomidine and medetomidine are commonly used α_2 -adrenoceptor agonists for anaesthetising minipigs. In ruminants and other species they are potent sedatives, but this is not the case for minipigs. Therefore, adrenoceptor-agonists must be combined with other drugs such as ketamine. The xylazine–ketamine mixtures are used for short (< 30 minutes) anaesthesia of Göttingen minipigs. Yohimbine (0.2 mg/kg, IV) can be used for antagonising overdosing with α_2 -adrenoceptor agonists. Medetomidine is being withdrawn from the US market.

3.4.2 Alpha-chloralose

Alpha-chloralose has been used exclusively in research for many years, and therefore some researchers still use it to induce anaesthesia in some well-established minipig models.

As an example, it is a useful agent in terminal experiments where stable cardiovascular parameters are needed. However, other anaesthetics are preferred today. Alpha-chloralose offers only minimal analgesia, the onset of anaesthesia is slow, and spontaneous leg movements are often observed during anaesthesia. Alpha-chloralose can be combined with either morphine or ketamine and butorphanol. In combination with nitrous oxide it can also be used during surgery. Artificial ventilation is needed to prevent hypercapnia and respiratory acidosis.

3.4.3 Benzodiazepines

Diazepam and midazolam are widely used for sedating and anaesthetising Göttingen minipigs. As mono-drugs they only have a sedative effect and are very safe to use. Benzodiazepines, however, are often combined with ketamine or xylazine for inducing and maintaining anaesthesia. A mixture of ketamine and midazolam is useful for pre-medicating (IM), inducing (IV) and maintaining (IV) anaesthesia in Göttingen minipigs used in scanning studies. As this mixture gives hypothermia in pigs, thermal blankets are needed. Benzodiazepines must be dosed in very high concentrations in Göttingen minipigs and other pigs, compared to the doses required in humans.

3.4.4 Ketamine

Ketamine has been widely used to induce anaesthesia in minipigs, because it can be administered by the IM or SC route. However, the use of ketamine as a mono-anaesthetic in Göttingen minipigs is not acceptable because it does not induce effective anaesthesia. Ketamine does not provide visceral analgesia, even if given in high doses. Therefore, ketamine should be combined with other drugs, such as adrenoceptor agonists, benzodiazepines, opioids, and the combinations can be used for both short and prolonged anaesthesia of minipigs. Also, the dissociative drug combination of tiletamine and zolazepam has been widely used for anaesthetising pigs. However, it may be contraindicated in some cardiovascular and renal

compromised protocols. The mixture provides 20 minutes of immobilisation for minor procedures in pigs.

3.4.5 Medetomidine – butorphanol – ketamine

The drug mixture of medetomidine, butorphanol and ketamine (also known as MBK) is useful for short anaesthesia, and it provides appropriate anaesthesia and analgesia for surgical procedures lasting 30–45 minutes. The pigs should be pre-medicated with atropine. MBK is administered IM and anaesthesia is rapidly induced. Alternatively, xylazine, butorphanol and ketamine (XBK) can be mixed and used (IM) for anaesthetising Göttingen minipigs. First, the minipigs are treated with atropine and after 15 minutes the xylazine is dosed. After another 15 minutes, the butorphanol and ketamine are administered. XBK appears to be relatively safe for at least one hour of anaesthesia in Göttingen minipigs. Administering yohimbine (0.05 mg/kg) can rapidly reverse XBK anaesthesia in minipigs. Medetomidine is currently available in the United States under the name ‘Aquacalm’, and it is less expensive than the equivalent treatment for minipigs.

3.4.6 Propofol

Propofol is not a barbiturate and can only be administered intravenously. It is cleared from plasma rapidly and therefore consciousness returns more rapidly than with most other infusion anaesthetics. As with isoflurane, propofol offers only minimal analgesia. Therefore, it is often combined with a strong analgesic, such as fentanyl. A major disadvantage of using propofol in minipigs is the high price. Also, a bottle of propofol can only be used for a few hours after being opened due to the lack of a bacterial preservative.

3.4.7 Neuroleptanalgesia

As an alternative to general anaesthesia, the Göttingen minipigs can be treated with a mixture of a tranquilliser and a centrally acting opioid. This neuroleptanalgesia can be reversed by narcotic antagonists, such as naloxone. The combination of acetylpromazine and etorphine for neuroleptanalgesia has been tested in Göttingen minipigs. It is an advantage that both drugs can be given IM. The drug combination reduces heart rate, blood pressure,

cardiac output, stroke volume, PaO₂ and pH. Some of the effects of etorphine can be prevented by injecting atropine. At the end of surgery, diprenorphine can be administered as an antagonist for etorphine. Inducing neuroleptanalgesia using acepromazine and etorphine is only recommended for healthy minipigs.

3.4.8 Supplementary operative analgesia opioids

Many commonly used anaesthetics, such as isoflurane and propofol, offer only minimal analgesia, and therefore analgesics are needed for painful procedures. Furthermore, the analgesics can reduce the doses of anaesthetics required. The supplementary analgesic is usually an opioid. Opioids can be used as IV infusions during cardiac surgery, bone surgery, etc. These drugs do not decrease myocardial contractility and coronal blood flow and are therefore useful for cardiac surgery. However, anticholinergics have to be given to prevent the dose-related bradycardic effect of opioids. The opioid dose must be adjusted after effects are observed, though some general doses are shown in the table below.

Table 18: Supplementary analgesia for painful surgery in pigs:

Drug	Infusion [$\mu\text{g}/\text{kg}/\text{min.}$]
Alfentanil	0.1-6
Fentanyl	30-100
Remifentanyl	30-60
Sulfentanyl	15-30

3.5 Monitoring during anaesthesia

Various parameters can be monitored during the anaesthesia of Göttingen minipigs. No single parameter can reflect every aspect of the minipig's condition. The table below shows the reference intervals for monitoring parameters in Göttingen minipigs. In general, the cardiovascular system, the respiratory system and the body temperature should be carefully monitored during anaesthesia and up until the minipig recovers. Furthermore, the interdigital, corneal and palpebral reflexes should be tested.



Figure 12: Testing interdigital (a), corneal (b), and palpebral (c) reflexes in a Götting minipig.

Table 19: Reference values for monitoring anaesthetised minipigs:

Organ system	Parameter	Göttingen minipig
Cardiovascular system	Heart rate	83 ± 15 /min.
	Mean blood pressure	97 ± 14 mmHg
	SatO ₂	95–100%
Pulmonary system	ETCO ₂	40 ± 3 mmHg
	PaCO ₂	40 ± 3 mmHg
	PaO ₂	109 ± 17 mmHg
	Respiration rate	20 ± 9 /min.
Temperature	Body temperature	37–38 °C

3.6 Supportive measures during anaesthesia

3.6.1 Thermal support

Göttingen minipigs are susceptible to hypothermia, due to their relatively hairless skin and the administration of anaesthetics that induce peripheral vasodilation. The body temperature of anaesthetised Göttingen minipigs should always be monitored and thermal insulation or warming blankets should be used. Hot air such as Bair Hugger is also useful. IV infusion of warmed saline and increasing the room temperature can also prevent hypothermia.



Figure 13: Minipigs are susceptible to hypothermia, and thermal insulation or warming blankets should be used during anaesthesia.

3.6.2 Fluid infusion

Due to the fasting period, Göttingen minipigs are often moderately dehydrated during anaesthesia. Therefore, it is strongly recommended to administrate fluid during anaesthesia. First of all, the water loss of dehydrated minipigs must slowly be replenished intravenously, and then homeostasis is maintained by the continuous infusion of saline. As a guideline, 5–10 ml/kg/h of warm (37 °C) saline can be administered IV for maintaining homeostasis. Insufficient urine production, extensive blood loss and hypotension indicate that the saline infusion rate must be higher. However, excessively high flow rates may increase the risk of lung oedema. To maintain the patency of IV catheters, a flow of only 3–5 ml/h is required.

Table 20: Fluid infusion in Göttingen minipigs:

Calculations	Replacement (ml) = body weight (g) x dehydration (%) Maintaining homeostasis: 5–10 ml/kg/h
Example	A 20-kg Göttingen minipig, 5 % dehydrated, anaesthesia for 2 hours: Replacement = 20000 x 5 % = 1000 ml Maintaining = 100–200 ml/h Total = 1000 ml + 2 x (100–200 ml) = 1200–1400 ml of saline

3.7 Neuromuscular blocking agents

Neuromuscular blocking drugs are used to produce paralysis. Therefore, they can be used to facilitate stable mechanical ventilation by blocking spontaneous respiration and to provide suitable conditions for surgery. However, since they prevent all movements in response to pain, they must be used with great care. When using neuromuscular blocking agents, monitoring of anaesthesia depth is crucial. Changes in heart rate or blood pressure may indicate pain. Some commonly used neuromuscular drugs are shown in the table below:

Table 21: Neuromuscular blocking drugs used in pigs:

Alcuronium	0.25 mg/kg IV
Gallamine	2 mg/kg IV
Pancuronium	0.06 mg/kg IV
Suxamethonium	2 mg/kg IV
Vecuronium	0.15 mg/kg IV

3.8 Recovery from anaesthesia

The recovery period after anaesthesia poses high risks for the Göttingen minipig. The recovery should always take place in a room where the animal cannot injure itself. It must never be placed in a pen with other minipigs, as they may attack the unconscious pig. The

room temperature must be 20–25 °C to prevent hypothermia, or alternatively, a thermal blanket or lamp can be used. If N₂O has been used for inhalation anaesthesia, the Göttingen minipig must be ventilated with pure oxygen for at least ten minutes to prevent hypoxia. Until extubation and recovery of the righting reflex, pulse, temperature and respiration rate must be monitored at least every five minutes. At the transition between unconsciousness and consciousness, the minipig may pass through a period of excitation, and it may therefore hurt itself if left unattended. Furthermore, vomiting may occur. Extubation should only be performed when a strong swallowing reflex is apparent. If it is done too early, there is a high risk for hypoxia. In case of postoperative vomiting, the respiration passages should be cleared. Once the Göttingen minipig is fully conscious, but not before, it may be given food and water as it has usually been fasting for several hours prior to the surgery. Following recovery, the Göttingen minipig has to be monitored daily until removal of the sutures. Antibiotics may be applied during recovery from surgery and during the first 1–3 days afterwards. However, animal studies have shown that antibiotics should be administered IV 30 minutes to 1 hour before surgery to maximise their effect. Postoperative treatment with antibiotics has only minor effects.

Table 22: Recovery of Göttingen minipigs after anaesthesia:

Room temperature	20–25° C
Until extubation	Monitoring every 5 minutes
Extubation	When strong swallowing reflex is apparent
Food and water	When the minipig is fully conscious

4. RECOGNITION AND MANAGEMENT OF POSTOPERATIVE PAIN

4.1 Clinical signs of postoperative pain

No objective tool for assessing pain in Göttingen minipigs exists, and therefore the minipigs have to be clinically examined several times during the first 1–3 days after surgery. Additionally, it is strongly recommended to examine the minipigs at least one day after the end of the analgesic treatment. Since the animal staff regularly observes the minipigs, they often identify signs of pain. Behavioural changes include: decreased interest in surroundings, decreased locomotive activity and anorexia. Note that opioids can also induce anorexia in pigs. Finally, unresponsive sternal recumbency indicates pain and distress. Pain-score systems can be helpful in evaluating the need for analgesics.



Figure 14: Göttingen minipigs must be examined during the first days after surgery.

4.2 Postoperative analgesia

Two major classes of drugs are used for postoperative analgesia in Göttingen minipigs: opioids and non-steroidal anti-inflammatory drugs (NSAID). In general, opioids have stronger analgesic effects than NSAIDs, but they have to be administered more often. Surgically-induced pain may very often require the use of opioids for the first 1–2 days or even 3 days after major surgery. NSAIDs can be used in combination with opioids 1–1½ days postoperatively and can be continued for 1–1½ days after opioids are no longer administered. The goal of pain control is to interrupt the nociceptive process between the peripheral nociceptor and the cerebral cortex, and this is done by using balanced analgesia.

4.2.1 Opioids

Opioids are potent analgesics with short half-lives. However, both butorphanol and buprenorphine are long-acting in minipigs and may be the opioids of choice for postoperative analgesia. Buprenorphine is a partial mu-agonist with very long half-life. Butorphanol has a greater potency than morphine and has only a weak or no sedative effect. It is a potent agonist–antagonist. As an antagonist, it can be used to reverse the action of fentanyl while maintaining some analgesic effects by its action at kappa receptors. Transdermal fentanyl patches have been tried in pigs, but titration of the dosage is difficult, and overdosing has been observed if pigs ingested the patches. In general, pigs need a much higher dose of opioids as compared to humans to achieve comparable effect.

4.2.2 NSAIDs

Most NSAIDs have to be dosed on a daily basis only, which makes them popular for postoperative analgesia. Compared with opioids, NSAIDs are only effective against weaker pain. They are useful against inflammatory pain but may be combined with opioids for the treatment of acute pain. Due to the anti-inflammatory effect of NSAIDs, they very often affect porcine models. Flunixin has a prolonged effect, but should not be administered for more than three days. Ketoprofen can be used for postoperative and chronic pain. Carprofen has good analgesic effects for soft-tissue and orthopaedic pain. Furthermore, gastrointestinal bleeding and nephrotoxicity is minimal. Side effects are only observed after several

days of treatment with NSAIDs. As an alternative to opioids and NSAIDs, local anaesthetics (e.g. bupivacaine) infiltrated at the site of incision will provide prolonged analgesia without side effects or anorexia, but administering them is more difficult. Bupivacaine has to be infiltrated every 10–12 hours.

4.2.3 Preemptive analgesia

Opioids and/or NSAIDs can be given already before making the first cutaneous incision. This is called preemptive analgesia and may greatly shorten the postoperative pain period. It has been shown that NSAIDs alone may prevent moderate pain without the confounding effects of opioids. Pain can also be blocked using local anaesthetics prior to surgery (for more information on this topic, see chapter 2 in Swindle (2007)).

Table 23: Postoperative analgesia for pigs:

Drug class	Drug	Dose	Frequency
Opioids	Buprenorphine	5–20 µg/kg	every 6 to 12 hours
	Butorphanol	0.1–0.4 mg/kg	every 4 to 6 hours
	Morphine	0.2-1 mg/kg	every 4 hours
	Pethidin	2 mg/kg	every 2 to 4 hours
NSAID	Acetylsalicylic acid	10–20 mg/kg	every 4 hours
	Carprofen	1–4 mg/kg	daily
	Flunixin	1-2 mg/kg	daily
	Ketoprofen	3 mg/kg	daily
	Meloxicam	0.4 mg/kg	daily

5. ANAESTHETIC EMERGENCIES

Respiratory arrest and cardiovascular failure may lead to the death of the anaesthetised Göttingen minipig and must therefore be prevented or treated rapidly. As the porcine heart shows a lower stress tolerance when compared with other species, pigs are more prone to cardiovascular failure. However, Göttingen minipigs have a greater stress capacity compared with other pig breeds due to their greater relative heart weight, thinner myocardial muscle fibres and a more favourable diastolic/systolic ratio. Malignant hyperthermia is a well-known condition in different kinds of laboratory pigs, and symptoms such as tachycardia, muscle stiffness, hyperthermia and hyperventilation develop with dramatic speed after the induction of halothane anaesthesia. However, malignant hyperthermia, which is a hereditary condition treatable using Dantrolene (3.5–5 mg/kg IV), occurs rarely in the Göttingen minipigs. Another hyperthermia condition has been described in pigs, and it occurs during the recovery period. Symptoms are similar to malignant hyperthermia, but the condition is treated with methylprednisolone (1–5 mg/kg IV) and diazepam (0.5–1 mg/kg IV). The pathogenesis is unknown, but anecdotal information suggests a genetic predisposition.

5.1 Respiratory arrest

Insufficient ventilation of Göttingen minipigs can lead to acidosis, respiratory arrest and death. If there are signs of respiratory arrest, any administering of anaesthetics must be stopped and the oxygen supply should be checked. Furthermore, the Göttingen minipig should be mechanically ventilated with pure oxygen. If the Göttingen minipig is not intubated, airways must be checked to see if the tongue is obstructing the larynx. The respiratory tract should be aspirated to remove blood, vomit and bronchial secretions. Doxapram (5–10 mg/kg IV), administered intravenously, can be used to stimulate spontaneous respiration in pigs.

5.2 Cardiovascular failure

In case of cardiovascular failure, the administering of anaesthetics should be stopped and ventilation assisted with pure oxygen. Rapid IV infusion of saline or plasma expanders

is given. In case of cardiac arrest, external cardiac massage (80–100 compressions/min.) should be given. Adrenaline can be administered intracardiacally, IV or into the endotracheal tube. The symptoms of cardiovascular failure are paleness of the skin and mucous membranes, weak and rapid pulse and falling blood pressure.

Table 24: Some emergency drugs used for minipigs:

Drug	Dose (IV)	[Unit]	Indication
Adrenaline	0.02	mg/kg	Cardiac arrest
Atropine	0.05	mg/kg	Bradycardia
Dantrolene	3.5–5	mg/kg	Malignant hyperthermia
Digoxin	0.01–0.04	mg/kg	Supraventricular arrhythmias
Dopamine	2–20	µg/kg/min.	Hypotension
Doxapram	5–10	mg/kg	Hypoventilation
Lidocaine	2–4	mg/kg	Arrhythmias
	+50	µg/kg/min.	
Neostigmine+atropin	0.15+0.5	mg/kg	Reverse alcuronium
Pentobarbitone	100-150	mg/kg	Euthanasia
Propranolol	0.04-0.06	mg/kg	Tachycardia

6. EUTHANASIA

At the end of the experiment, Göttingen minipigs are euthanised. This can be done humanely by administering an overdose of a 20% solution of sodium pentobarbitone (100 mg/kg IV). After sedation, the pentobarbitone can be administered directly into a central vein or into an ear vein catheter, and neonatal minipigs can be euthanised IP with pentobarbitone. However, this pentobarbitone may enlarge the size of the spleen and other organs. When this excludes the use of pentobarbitone, 2 mmol/kg KCl can be injected IV or a captive bolt can be used. However, KCl may only be used in deeply anaesthetised minipigs, and the use of a captive bolt must always be followed by exsanguination, and a cerebral hemisphere and the brainstem must be sufficiently disrupted. With any method for euthanasia, cessation of respiration and heartbeat as well as loss of reflexes are good indicators of death.



Figure 15: Euthanasia of minipigs can be performed using a captive bolt pistol.

Table 25: Euthanasia of Göttingen minipigs:

Pentobarbitone	100 mg/kg	IV, IP	May enlarge the size of different organs
KCl	2 mmol/kg	IV	Used only in deeply anaesthetised pigs
Captive bolt			Exsanguination required

7. KNOWLEDGE ABOUT GÖTTINGEN MINIPIGS

The knowledge about anaesthesia and analgesia of Göttingen minipigs is growing year by year. However, much of the information is still based on practical experience only. Published investigations of how anaesthetics and analgesics affect Göttingen minipigs are rare. Therefore, much of the information in this manuscript is based on practical experience and published studies involving other breeds of domestic pigs and minipigs. More studies about anaesthesia and analgesia in Göttingen minipigs are needed.

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9. ABOUT THE AUTHOR

Aage Kristian Olsen Alstrup earned his veterinary education in 1997 from the Royal Veterinary and Agricultural University (R.V.A.U.) in Copenhagen, Denmark. In 2002, he earned his Ph.D. degree from the R.V.A.U. with a thesis about pig and rat models in thrombosis research. Since then he has worked with animal models of human diseases at the Aarhus PET Centre at Aarhus University Hospital in Denmark. Since 1999, he has published more than 35 peer-reviewed papers, 109 other papers, 13 books and book chapters and 94 abstracts. Many of these publications concern laboratory pigs.



Aage Kristian Olsen Alstrup.

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