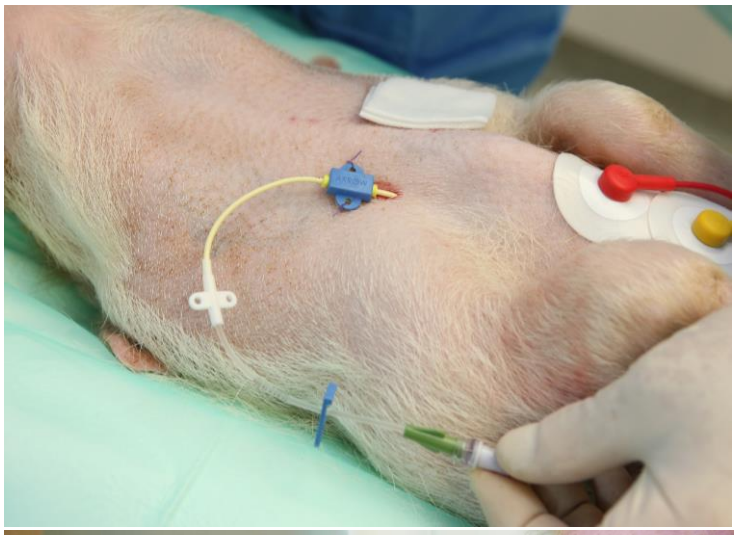
Technical Guide

Catheters and VAP in the Göttingen Minipig



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ELLEGAARD
GÖTTINGEN MINIPIGS

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Introduction

The main reason for using catheters in a minipig is to facilitate repeated serial blood sampling or intravenous dosing. It reduces the stress on the animal, improves the welfare and decreases the number of employees required for the procedure.
Although the surgical procedure and the maintenance of the catheter entail some risks and challenges, if properly managed they can be successfully executed after some training.
There are a lot of possibilities for catheterisation, careful consideration regarding study design and animal welfare has to be given when choosing the appropriate approach.

The purpose of this paper is to provide information on the material and methods tested at Ellegaard Göttingen Minipigs and other Minipig users. The details are based on our in-house experience and by no means exhaustive.

Summary

There are several types of catheters that could potentially be used with a Göttingen Minipig. A central venous catheter (CVC) is, by definition, a catheter whose tip resides in the central circulatory system. It is often inserted in close proximity to the heart. A PICC is a **p**eripherally **i**nserted **c**entral **c**atheter and a Midline catheter is peripherally inserted without ending up in the central circulatory system. As a short-term option, an over-the-needle catheter can also be very useful.

There are various manufacturers of catheters that can be implanted using the Seldinger Technique, each of which offers a multitude of models in different lengths, calibre, coatings, etc. They have single, double or multi lumen and almost all of them are made of polyurethane. Common to all is that they are designed for humans and not for pigs, so it can be a bit tricky to find the model that suits a particular study best. These types of catheters are intended for short-term use; the patency of the catheter can be anything between 3 and 28 days, depending on multiple factors. The use of a dual lumen catheter, one lumen for dosing and the other for sampling, bears the risk of contaminating the blood sample with a compound as the two distal ports are close to each other. On the other hand, using two lumens for sampling could provide an alternative if one lumen becomes occluded.

Cut down technique is a bit more invasive but gives better certainty in regard to insertion site and position. At the same time a general increase of patency is observed when using this method. A Limited supply of material specifically designed for lab animals is available, but systems with intended human use are also fine.
These catheters can be tunnelled to a preferred exit site or attached to a Vascular Access Port that is placed subcutaneously. A fully integrated system with VAP has the advantage that there are no exterior parts and the Minipigs can be group housed.

Catheterisation should be executed using aseptic procedures and under general anaesthesia. Using the Seldinger technique, or a modified Seldinger technique, sampling can already take place the day after.

At least 7 days recovery is recommended after cut down surgery, preferably longer.

Infections and a loss of patency are the main delayed complications whereas arterial puncture and impossibility to advance the guide wire are possible complications during Seldinger insertion.

Ellegaard Göttingen Minipigs can deliver Minipigs with indwelling catheters to your facility. These will be surgically implanted with VAP, VAB or externalized. Seldinger catheters should be implanted at the respective institution short before use. All the techniques described in this paper can be learned at our training centre.

Please contact us to discuss your need.

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Comparison of Methods

Seldinger Short term 1- 21 Days		Cut-down Long term up to 12 Months	
Percutaneous implantation		Surgical implantation	
Easy to remove		Surgical removal	
Minimal invasive		Invasive	
Risk of displacement		Tied with ligatures to vessel	
CVC	Midline	Externalized	With VAP
Bandage necessary		Bandage	No Bandage
Patency of vessel maintained	Patency of vessel (partially) maintained	Patency of vessel lost	
Risk of infection		Risk of infection	Low risk of infection
Painless access		Painless access	Painful access
Single housing		Single housing	Group housing
Re-implanting possible	Re-implanting not always possible	No re-Implantation in the same vessel	

Anaesthesia

The Minipigs must be anesthetised for catheter placement. There are numerous protocols published for swine anaesthesia. Use the protocol you are most familiar with. The procedures for catheter implantation, from preparation to application of the bandage, can take from 20 to 45 minutes depending on experience and the challenges encountered. Placement of an over-the-needle catheter is considerably faster.

Our preferred protocol is:

1 bottle of Zoletil 50 dry matter	
(125 mg tiletamine + 125 mg zolazepam)	*(conc. in mix: 12.5 mg/ml)*
+ 6.25 ml Narcoxyl (xylazin 20 mg/ml)	*(conc. in mix: 12.5 mg/ml)*
+ 1.25 ml Ketaminol (ketamine 100 mg/ml)	*(conc. in mix: 12.5 mg/ml)*
+ 2.50 ml Torbugesic (butorphanol 10 mg/ml)	*(conc. in mix: 2.5 mg/ml)*

Dose: 1ml per 10–15kg IM

This will give about one hour of deep narcosis and is sufficient for the implantation of a CVC. For the cut down method, anaesthesia by volatile gas or Total Intravenous Anaesthesia (TIVA) is recommended. This allows easier management and prolongation of the aesthetic stage.

Isofluran/Sevofluran administered by facemask can be used as induction or for the short procedure of placing an IV cannula in the V. auricularis or V. saphena.

Remember analgesia. Volatile gases and Propofol (used for TIVA) have no analgesic properties. Give analgesia separately per institutional protocol.

Analgesia

Seldinger implantation are minimal invasive, however some analgesia is required. Please check your preferred anaesthesia protocol to make sure adequate pain control is provided for the procedure and the hours after recovery.

For the tunnelled Seldinger Insertion, NSAID (Meloxicam) should be given until post op day 3, but depending on tunnelling procedure, opioids can be considered as well.

For the cut down method a longer analgesia regime is essential. We suggest prescribing opiates (Butorphanol or Buprenorphine) until post op day 1 and NSAID until post op day 3.

For more information regarding anaesthesia and analgesia please consult the booklet:

Anesthesia and Analgesia in Ellegaard Göttingen Minipigs by Aage Kristian Olsen Alstrup, D.V.M., Ph.D.

(available from Ellegaard Göttingen Minipigs)

Flushing, Locking and Lock Solutions

During catheter access, it is important to minimise the contact time of blood with catheter to reduce the tendency of biofilm or thrombi to accumulate. After collecting the blood samples, the catheter lumen should be flushed immediately with 0.9% saline. Do this by brisk injection to flush all traces of blood back into the circulation. Pulsating flushing might help to displace blood from the lumen of the catheter. Between the sessions of accessing a catheter, the lumen must be filled with a suitable solution to exclude blood and prevent the formation of thrombi. This process is called “locking”. The locking technique and solutions are also important to preventing infection. If the interval between experimental accesses of the catheter is prolonged, flushing might be necessary. Frequency of maintenance flushing is a balance between risk and benefit. When catheters are accessed, there is always a risk of pyrogenic or microbial contamination entering the bloodstream. With longer intervals between flushing, the risk of thrombi forming at the catheter tip increases but if properly flushed and locked catheters can be left undisturbed for up to a week or longer.

Regardless of the amount and frequency of flushing, it is important to use a positive-pressure flushing technique. A proper positive-pressure flushing technique creates positive pressure within the lumen of the catheter and is believed to minimise the reflux of blood into the tip of the catheter, and thus prevent clotting. This flushing can best be performed by closing the catheter or extension clamp while flushing before the syringe empties completely. Another way to accomplish this is by maintaining pressure on the syringe plunger while withdrawing the syringe from the injection cap or port.

If there are any lateral openings in the catheter, it is also important to maintain firm pressure while flushing/locking to make sure the flushing also reaches the distal opening. However, make sure not to exceed the maximum pressure for which the catheter is designed. Use a large syringe: this will reduce the pressure in the catheter.

The most commonly used lock solution is saline containing heparin. The concentration of heparin in saline is rather empirical. References found in various scientific publications are in the range of 20–1000 IU/ml.

We have very good experiences with a product, containing Taurolidine citrate and Heparin, called Tauro-Lock Hep500.

Overview of Catheter lock solutions

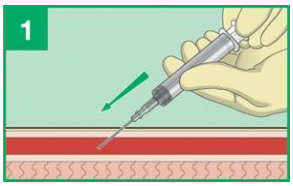
Lock solution	Advantages	Disadvantages	Notes
0.9% saline	• Enables filling of the catheter without exogenous chemical matter • Cheap and easy to obtain	• Does not prevent thrombosis • No antibacterial activity	• Continuous low rate of infusion is effective in maintaining catheter patency
0.9% saline with heparin (20–1000 IU/ml)	• The most widely used material, with heparin providing the thrombosis prevention	• Provides no antibacterial action	• Low concentrations for frequent flushing • Higher concentration for less frequent flushing
40% dextrose (glucose)	• The high osmolarity prevents bacterial colonisation and multiplication • The high osmolarity contributes non-specifically to clot prevention/disruption • Dextrose occurs naturally in the blood and is rapidly metabolised • Available cheaply as a pharmaceutical formulation	• Risk of crystallisation • The viscosity of the solution helps to prevent blood accessing the catheter lumen (but makes the lock solution slightly more difficult to withdraw)	• Adding heparin (100–500 IU/m) will increase the prevention of thrombosis
46% sodium citrate	• A cheap antithrombotic which can be used where heparin is contraindicated	• Heat labile, therefore cannot be sterilised by autoclave • No antibacterial action	• Commercially available under the name DuraLlock-C®
6.7% taurolidine citrate solution	• Taurolidine is an effective and convenient antibiotic • Citrate salt provides specific antithrombotic action	• Expensive	• Supplied commercially for catheter locking in preclinical research
TauroLock®	• Commercial Product used in clinical settings • Different varieties • Contains Taurolidine, citrate and heparin.	• Expensive	• One variety contains Urokinase; very useful when there are clotting issues.

Seldinger Method

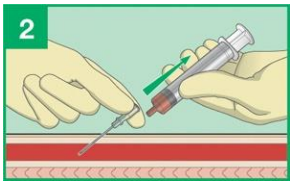
Seldinger Technique

This important technique for catheter placement was devised by Dr Seldinger and is described in his paper of 1953 (Catheter replacement of the needle in percutaneous angiography: a new technique, Acta Radiol (Stockholm) 1953. His apparently simple idea represented a big step forward and his technique facilitates straightforward catheterisation of blood vessels.
There are three key steps to the technique - a hollow needle is first inserted into the vessel or organ to be catheterised. A guidewire is then threaded through it and the needle removed. The final catheter is then threaded over this wire and the guidewire removed to complete catheterisation.

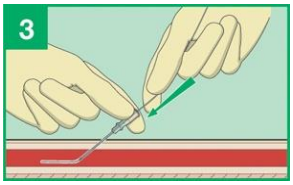
Placement of a catheter in jugular vein:



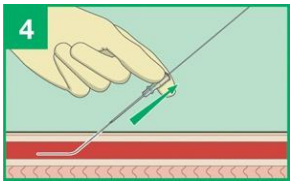
Prepare and drape site, then insert introducer needle using an aseptic gloved technique.



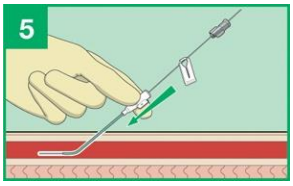
Remove syringe.



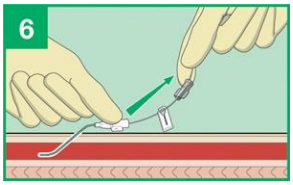
Advance the "J" tip guidewire to desired position in vessel,
using the distance markings provided. Use the straight end for narrow vessels.



Withdraw needle, keeping guidewire position fixed.



Advance vessel dilator over guidewire, then remove.



Place the catheter to correct depth, using markings,
then withdraw guidewire.

Catheters

Commonly available catheters are designed for use in humans and are mainly used for fluid administration. Blood sampling is secondary. Due to different indications and anatomy, it has not been possible to find an ideal catheter for minipigs; compromises have to be made.

Different types of coatings (anti-thrombotic, anti-microbial) are also available, but the benefits are not conclusive in the scientific literature. All manufacturers claim that their particular coating works and is the best.

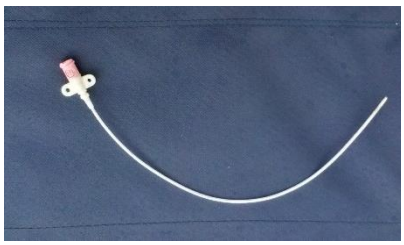
Polyurethane (PU) is a commonly used material; different styles and makes are offered, with or without integrated extension, 1 to 3 openings and different flow rates. PU can be a bit stiff at room temperature but will soften at body temperature.

Catheters from several manufacturers have been tested, but as there are a multitude of different products not all were considered. Preferences are always subjective and are not based on extensive scientific studies.

Traditionally larger Göttingen Minipigs have been catheterised because lifting and handling becomes more challenging as age and thus weight increase. Therefore large-calibre catheters were used, but, as the procedure was applied in a broad spectrum of animal sizes and intentions, many different products were used.

The following list itemises the catheters successfully used in Göttingen Minipigs. It is based on user feedback, but is by no means complete. Most are single lumen; some have an integrated extension and others do not. You will probably have to try out a few to find the one that suits your taste and purpose.

For larger Minipigs > 15kg a 7 Fr catheter works fine in the jugular vein, but for smaller pigs and other vessels, the size should be adjusted accordingly.



Catheter without extension.

Extension with valve.

Catheter with integrated extension.

Manufacturer	Calibre Ga/Fr	Length cm	Site used	Reference
Cook Medical	20/3	8	Jugularis/Saphena	C-PUM-301J
Edwards Lifesience	20/3	13	Jugularis/Saphena	M1 20130 HS
Teleflex	14/7	16	Jugularis	ES 04706
	18/4	20	Saphena	ES 04218
	16/5	30	Jugularis tunnelled	ES 04400
	20/3	12	Jugularis/Saphena	ES 04150
Braun	14/7	15	Jugularis	Certofix mono S415
	18/4	15	Jugularis	Certofix mono S215
	18/4	20	Saphena	Certofix mono S220
	16/5	30	Jugularis	Certofix mono V330
	16/5	32	Jugularis	Cavafix certo 335
	13/7 (Dual lumen 16/16g)	30	Jugularis	Certofix duo V730
Argon	20/3	15/20	Saphena/auricularis	Careflow 681639

General preferences:

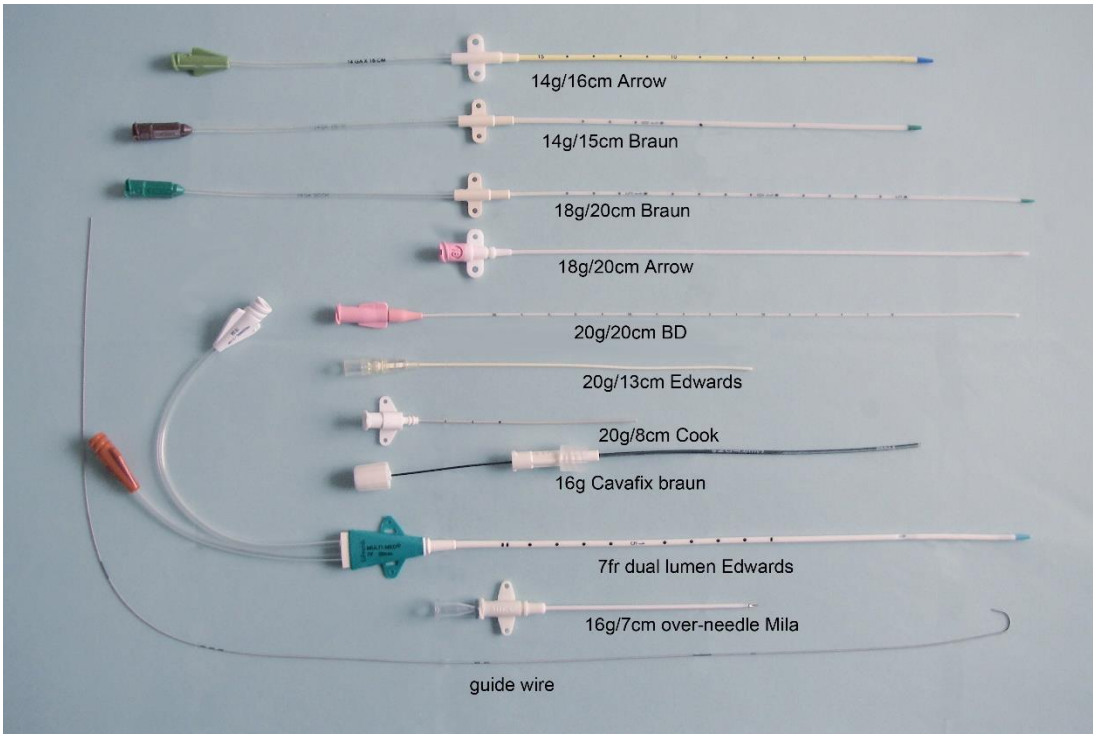
Integrated extension tube is preferable for the neck, as no extra extension is required. At other sites it is unwanted.

The absence of lateral openings reduces the risk of clotting and washout of lock solution.

Soft bevelled/rounded tip/softness.

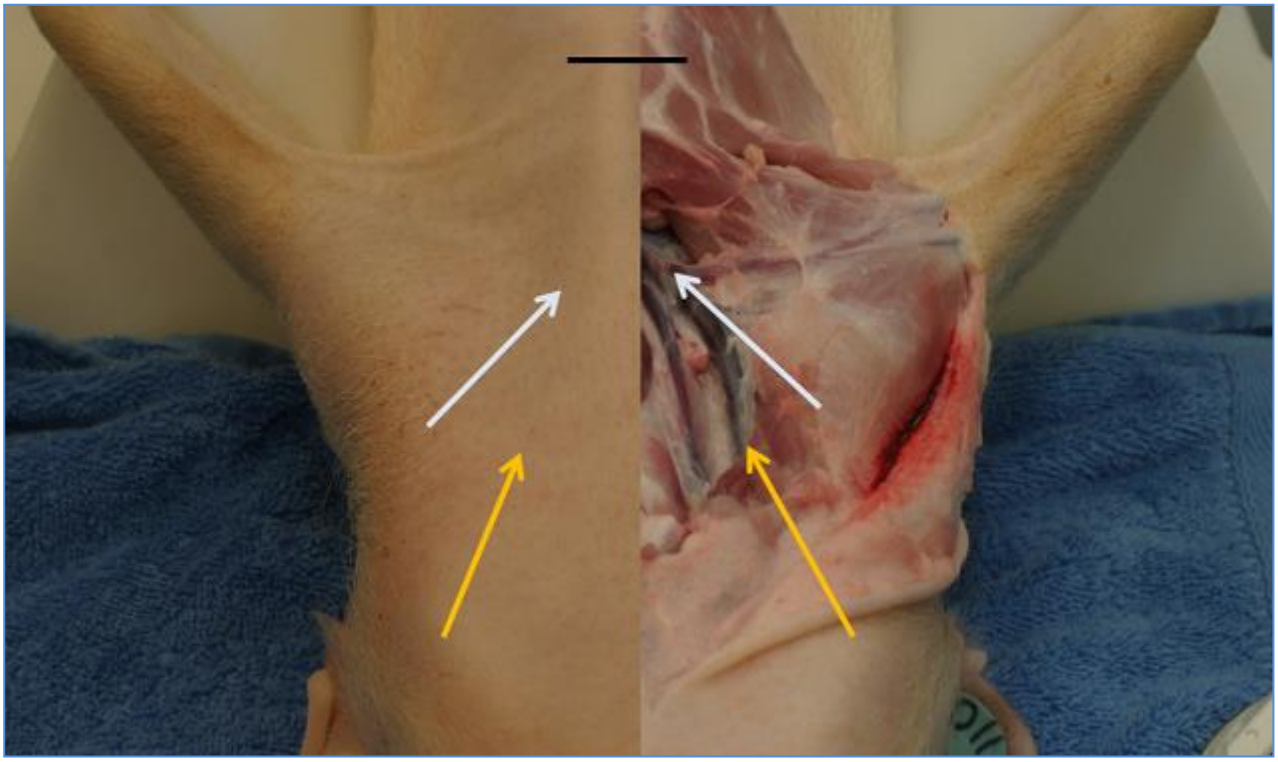
Small dead volume reduces waste and rinsing volume.

Mila International (http://www.milainternational.com/) has a range of catheters and extensions designed for animals and are worth looking at.



Sites

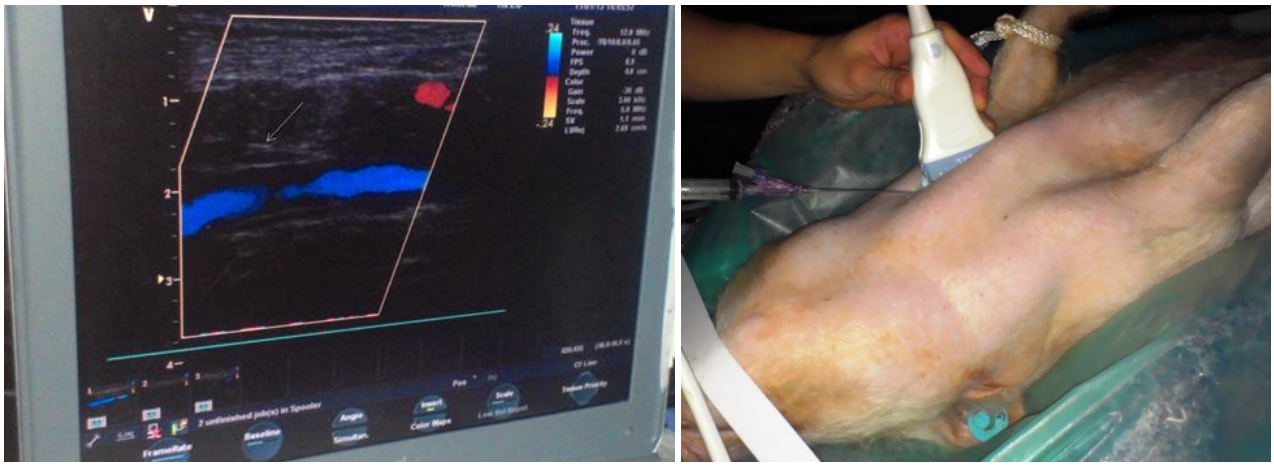
Neck, V. Jugularis, Central Venous Catheters



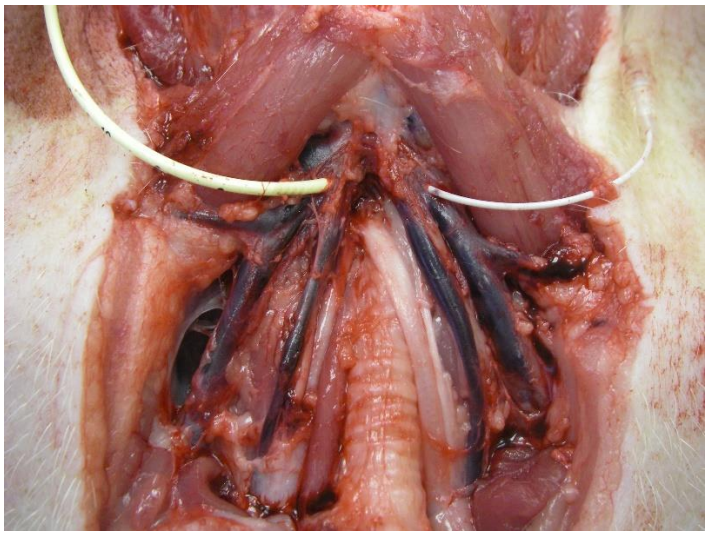
The preferred insertion site is the jugular groove, entering the external jugular vein at a shallow angle (yellow arrows). This gives a penetration site where fixation is easy and the extension can be smoothly led away dorsally for effortless access later on. As the site is located between the legs and the mandible, where the neck has its lowest circumference, it is also the simplest site to bandage. This site also reduces the risk of puncturing the carotid artery.

In practice, successfully penetrating the vein proves to be quite difficult as only landmarks are available for guidance in many cases. Ultrasound-guided access is possible and will help a great deal in identifying the vein and cannulating it. Unfortunately, the respective equipment is rather expensive and often unavailable. It also requires a fair bit of training to use ultrasound guidance for this procedure.

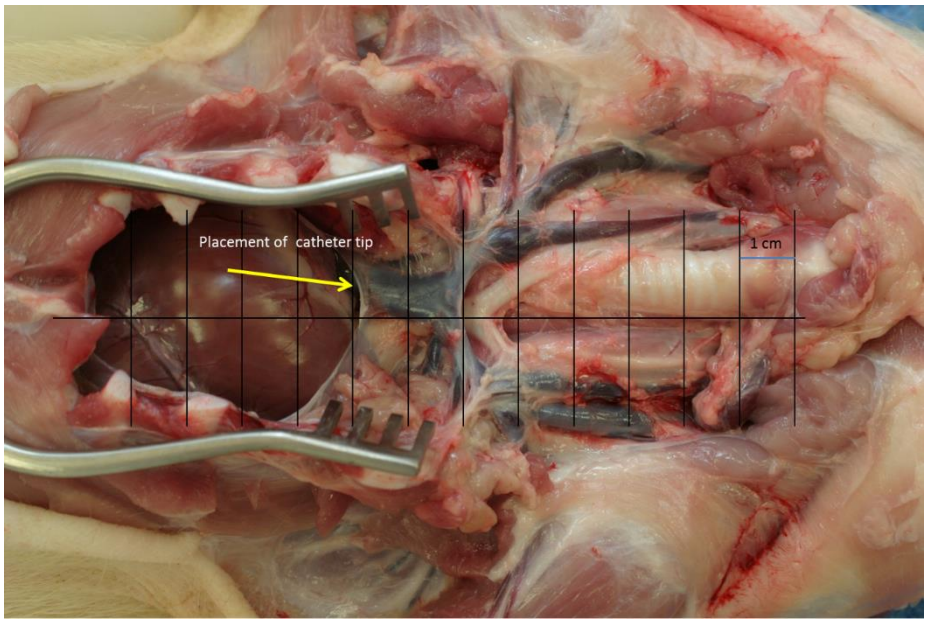
The second penetration site (white arrows) is usually used for drawing blood samples. It is more difficult to bandage, there is a greater risk of finding an artery, and the inserted section of the catheter inserted is rather short (tip of catheter at the black line on the photo). On the other hand, venous access is easy, often by entering the vena cava. It is important to keep the angle of penetration shallow to avoid a kink in the catheter.



Ultrasound picture of external jugular vein with penetrating needle (arrow). Position of transponder and needle during penetration.



Typical entry site: Two different catheters entering vein.



Site for tip placement; Vascular anatomy of the neck, male minipig, 4 months old, 8kg
One concern about catheters with side holes is the necessity of advancing the catheter far enough inwards to ensure that the proximal opening is within the central vein. For example, the distance from tip to last proximal opening on a Teleflex® ES 04706 catheter is 2.5cm.

Catheter Tip Placement

The catheter tip should be placed in the vena cava cranialis, just before the right atrium. The vessel diameter is large there, which reduces the risk of irritating the vessel wall, and blood flow is high. The catheter should not penetrate the right atrium to avoid complications. The following is a recommendation from the human sector:

"Probably the most important factor in the prevention of complications is the location of the catheter tip. The pericardium extends for some distance cephalad along the ascending aorta and superior vena cava. In order to guarantee an extra pericardial location, the catheter's tip should not be advanced beyond the innominate vein or the initial segment of the superior vena cava. (It is important to note that a portion of the superior vena cava lies within the pericardium.) Some practitioners may prefer a deep SVC placement (within the lower third of the SVC), but nearly half the length of the SVC is covered by pericardial reflection that slopes downward toward its lateral edge. To avoid the risk of arrhythmias and tamponade, the tip of a CVC should lie above this reflection and not in the right atrium."

(Source: QUICK GUIDE TO Central Venous Access, Edwards Lifesciences LLC)

There are three possibilities for checking the position of the tip:

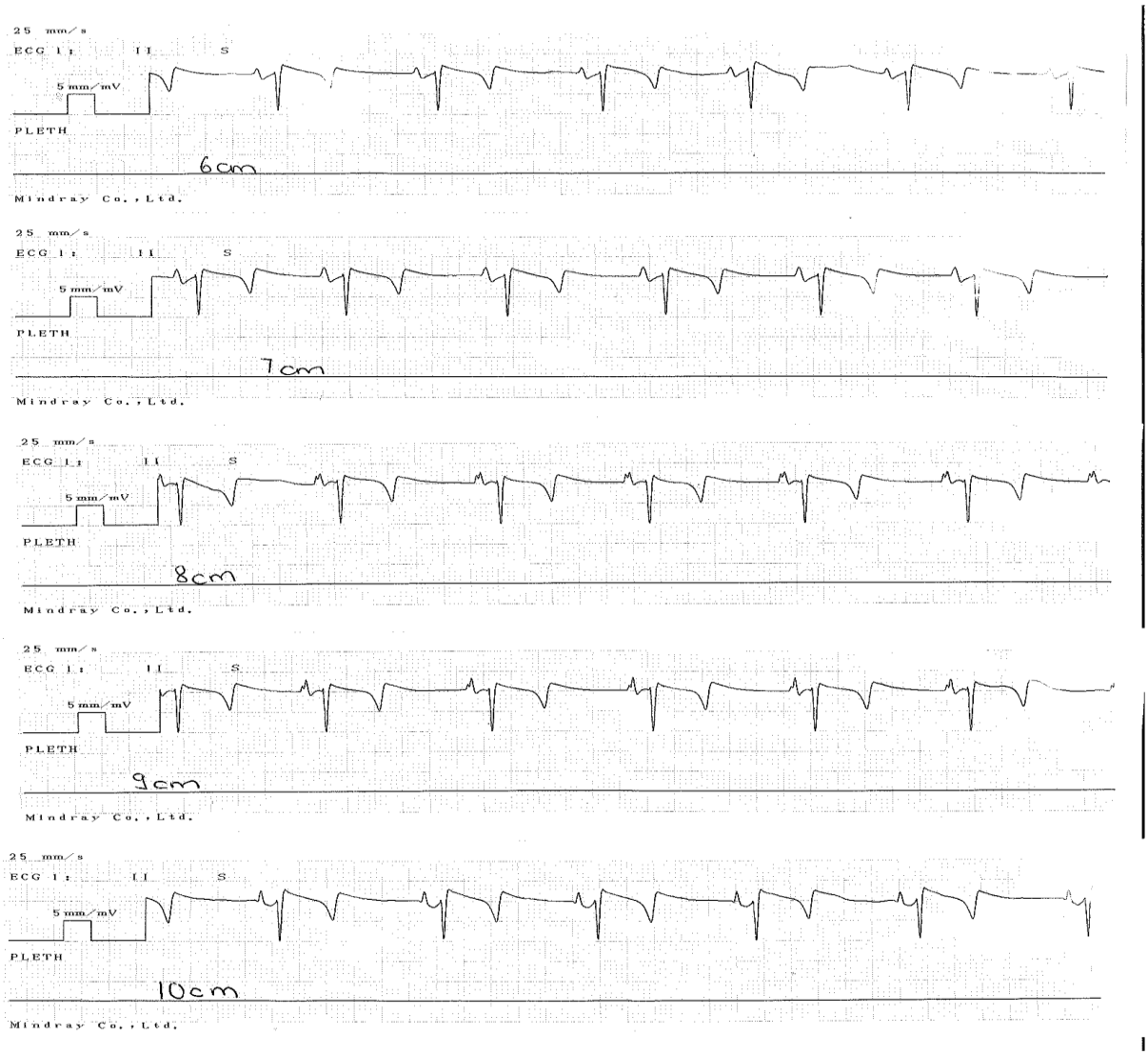
- X-ray/fluoroscopy
  Catheters are radiopaque and show up on x-rays. This is the most secure method as it verifies the position in situ but this equipment is not always available.

- ECG
  When inserting the catheter, pull back the guide wire so that the end aligns with the tip, connect the guide wire to the RA lead (red in Europe, white in the US) and monitor lead II. When the central venous catheter is advanced from the jugular vein into the superior vena cava, the intra-atrial lead produces a normal P wave. As soon as the catheter tip reaches the sinoatrial node, there is an abrupt increase in the height of the P wave. When the tip enters

the right atrium, the height of the P wave potential is reached. If the tip is advanced further into the atrium, the P wave declines again and becomes slightly negative. A negative P wave will be noticeable if the catheter tip is inadvertently advanced into the inferior vena cava.
Slightly retract the catheter after you have seen an increase in the P wave to obtain the tip position desired.

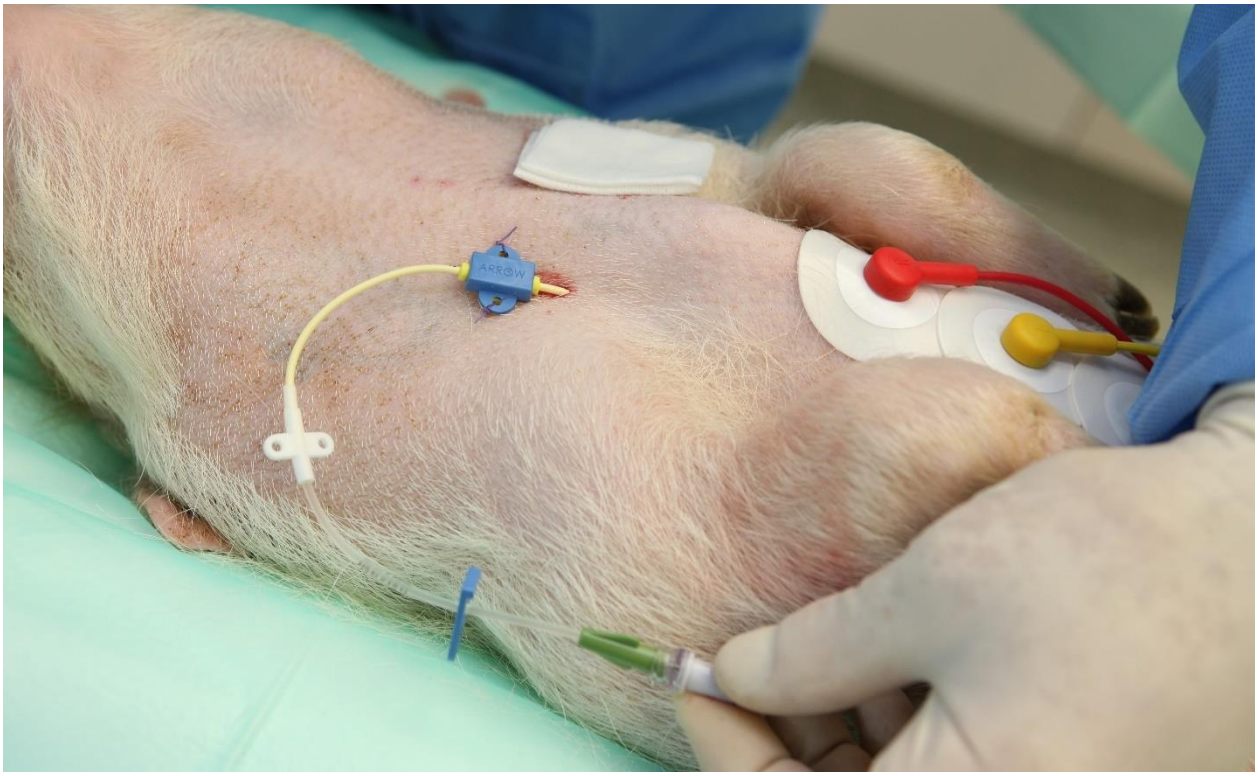
- Landmark

  The required placement of the tip can easily be established with this method. Put the pig in dorsal recumbency, hold a foreleg straight up and pull it slightly in a lateral direction. You will clearly see a tendon protruding. Draw a line on the sternum just caudal to the tendon. This landmark has been proven accurate by numerous necropsies. However, it is only a landmark and does not take account of anatomical differences.



ECC of a minipig using the Nehb-Spoerri lead-placement measuring lead II. There is a clear change at the 8cm length of insertion. Necropsy showed that the desired insertion would have been between 7 and 7.5cm.

Landmark for positioning the catheter tip.

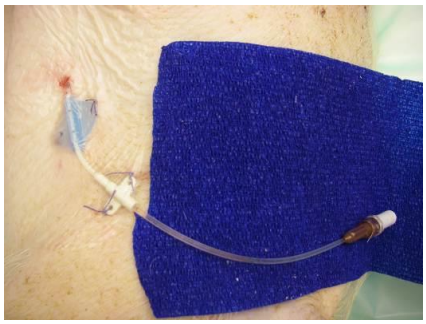


CVC implanted in the jugular vein.

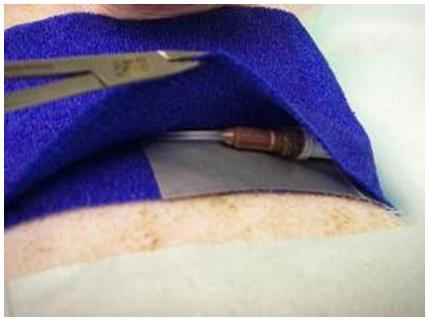
Dressing and Bandaging

Attach the extra clamp close to the penetration site, making sure kinks are avoided. If no extra fixation device is available, you can make your own using two pieces of tape, with the adhesive sandwiching the catheter. Cover the whole area with Opraflex® or another membrane with a high moisture-vapour transmission rate.
The conical shape of the pig's neck makes it slightly difficult to bandage. Depending on the catheter entrance site, it is not always possible to cover it well. A flexible material like Vetrap® is advised, and there is no need to wrap it too tightly as it is only meant as protection. It helps to create a pocket of sorts where the catheter hub can be placed when not in use and easily taken out for access.
The application of duct tape has been very successful in preventing bandage edges from curling.
Check patency again at the end of bandaging to make sure the catheter and the extension are properly positioned within the bandage.
After a few days, the covering can shift or loosen, so check regularly to see if it needs to be replaced.
Depending on the pig's temperament, anaesthesia might be necessary for re-bandaging. As there is vascular access, the use of Propofol is an option.







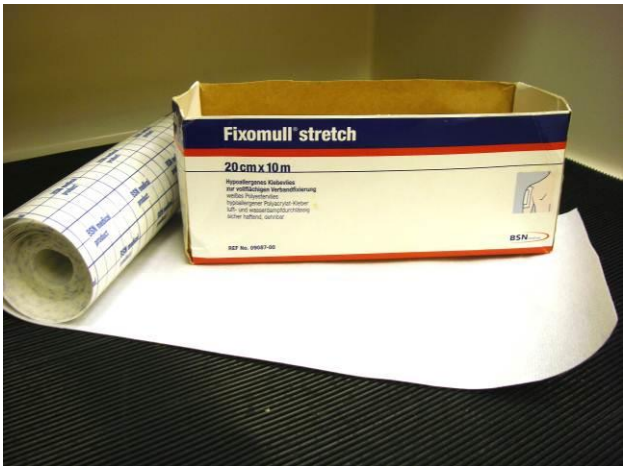


Alternative Dressing and Bandaging Material

The following combination of bandaging material has also been used successfully.

Instead of	Opsite®	use	Fixomull® stretch	cut to size and edges rounded
	Vetrap®	use	Mollelast® haft	
	Duct tape	use	Optiplaste®-C	

The actual bandaging is done in a similar fashion.

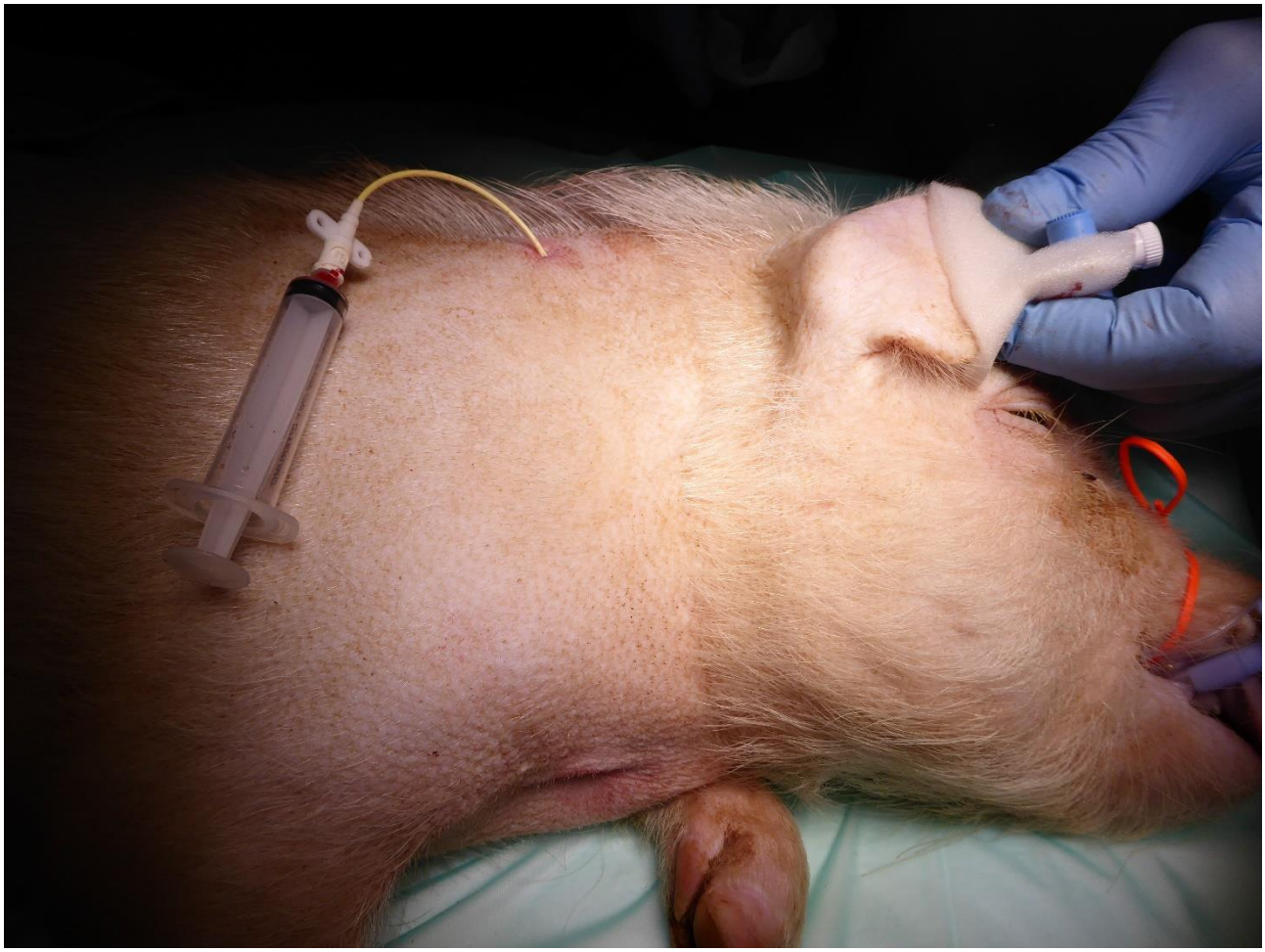


Neck, V. Jugularis, Central Venous Catheters, tunnelled

Rather than fixing the external part of the CVC laterally and lead it to the dorsal part, a long enough catheter can be tunnelled to a dorsal exit. This makes bandaging easier and the system more secure in regard to interference. On the downside, this method is a bit more invasive.

Access to the vessel is established by Seldinger technique through a small incision in the skin. Another incision is placed dorsally, and a small trocar is from this site advanced subcutaneously to the caudal incision where the guide wire exits. The catheter is treaded trough the trocar and the trocar removed. Now the catheter is fed over the guidewire into the vessel to the required length. After removal of the guidewire the caudal incision is sutured.

For detailed description refer to chapter: Procedure for Jugular Vein Placement



Göttingen Minipig with a tunneled CVC.

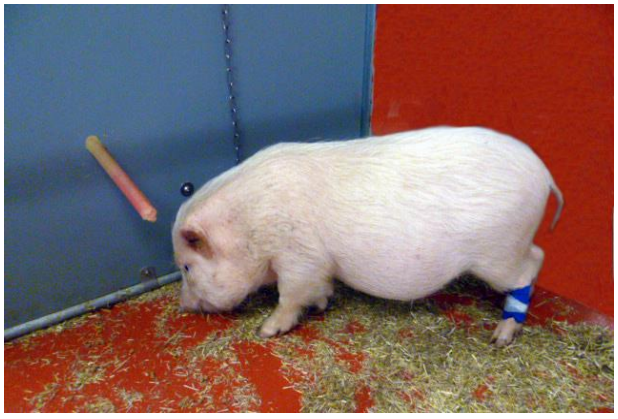
Leg, V. Saphena, midline catheter

The saphenous vein is usually prominent and visible in the Göttingen Minipig. The leg can easily be bandaged and as pigs are not very athletic it is impossible for them to interfere with their own bandage.

The disadvantage of this site is that there is some movement of the catheter along the vein as the minipig moves its leg (when walking or lying down). Whether this has a negative effect, like irritation or inflammation of the tissue concerned has not been tested.

A midline catheter can easily be placed at that site. The preferred technique is to gain venous access by placing an over-the-needle catheter first and then feeding the guide wire through this temporary catheter. If the guide wire has a J-tip, turn it around and use the straight end for this purpose. In an initial study, 18g 20 cm catheters were successfully used; the position of the tip was found to be in the area of the hip joint in a 12 kg minipig. Re-implantation at the same site proved to be challenging or impossible, due to changes in the tissue around the site of insertion. Further studies using smaller calibre catheters showed less of this effect on the vein and surrounding tissue. The use of longer and thinner catheters, so the tip rests in the caudal vena cava, would be preferable but are not so easy to source.

A 20g over-the-needle catheter can be placed at this site for vascular access and multiple blood sampling. It can be left in place for a 24h period.



Pig in pen with bandaged catheter.

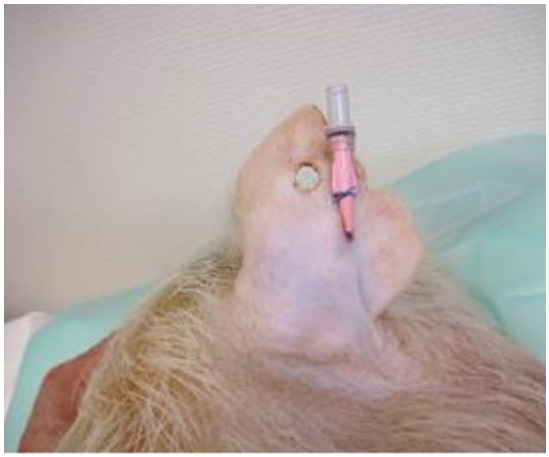
Catheter hub after 3 days.

Saphenous vein with puncture site.

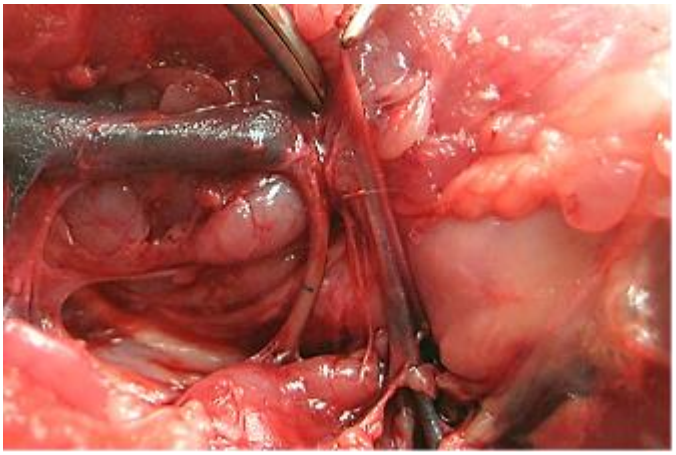
Over-the needle catheter in place

Ear, V.Auricularis, midline catheter

A 20 g or smaller catheter can be implanted into the auricular vein. To be successful, the minipig needs to be above 14 kg, the vein well developed and straight. A large part of the vein lumen is occupied by the catheter, severely reducing circulation through the vessel. This can cause tissue changes, and re-implantation will be difficult if not impossible. The small size of the vein makes it a difficult technique as well, compared to the other sites, as narrow corners have to be navigated during insertion. In a 15-kg minipig, the tip of a 15-cm catheter rests in the middle of the external jugular vein and with a 20-cm catheter, the tip rests just before the right atrium.



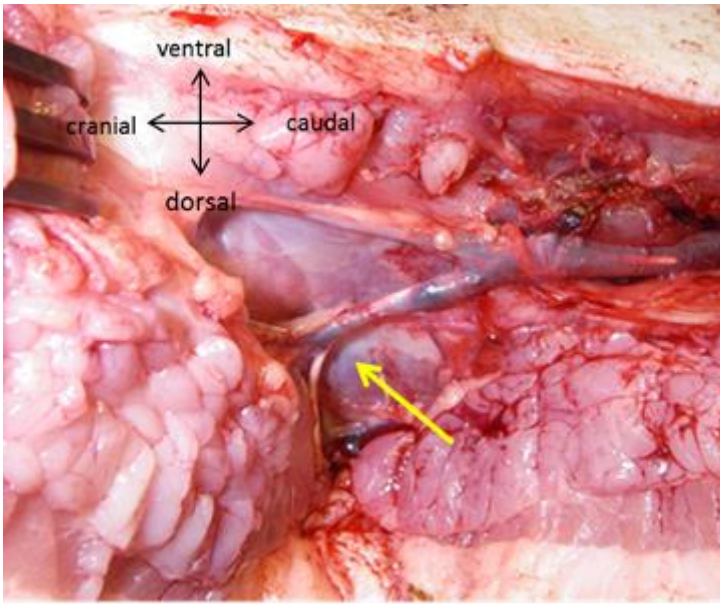
Catheter with Bionector valve sutured to the ear.



The auricular vein is filled out by the catheter and this vascular occlusion may be associated with significant alteration of the blood flow. Necrosis or other histopathological changes of vessel tissue are possible side effects.

Path of the catheter from v. auricularis to v. maxilaris and v. jugularis with the yellow arrow indicating the bend where navigation of the catheter during insertion is difficult.

The tip of the 15cm catheter rests in the V. jugularis externa about 7 cm from the right atrium.



Materials Required

Catheter sets usually come in trays with all the items required for the procedure included.

- Anaesthetic

  According to your preferred anaesthesia protocol* or:
  Zoletil 50
  Xylazin
  Ketamin
  Butorphanol

  *please make sure it includes analgesia

  21 g butterfly, syringe for IM injection

- Preparation

  Ointment for eye protection
  Ez-scrub – Iodine – Alcohol
  Table with beanbag or V-bench
  Hair clipper

- Insertion

  Sterile gloves
  Incise drape, or other draping
  Catheter set (Extension)
  Scalpel 11
  Syringes
  Saline for flushing (20 IU/ml Heparin as an option)
  Heparin/saline 100–500 IU/ml or other lock solution
  Cap or Bionector® (Vygon) for catheter hub
  Over-the-needle catheters
  Trocar for the tunnelled version

- Fixation

  Suture (Prolene 2-0 Ethicon or similar)
  (Bio Patch)
  Wound cover (Opraflex® or similar)
  Bandage (Vetrap® or similar)
  Tape (Tesa extra power universal or similar).
  Polsterplast®
  Surgical tape

Notes to Material

Extensions

Depending on type of catheter, insertion site and size of the minipig, an extension to the catheter might be advisable to enable comfortable dorsal access. Some people choose a longer catheter to avoid using extensions. Extensions with integrated filters are not encouraged as they can block when aspiring.

Needleless access valves

Closed, needle-free IV access systems which minimise the risk of infection and eliminate the risk of needle-stick injury during IV access. Once is in place, you can infuse, inject and sample blood and change your IV tubing without opening the IV system, thereby enhancing safety and sterility. The system is ideal for use in animals and allows easy, repeated IV connection and disconnection, regardless of how uncooperative the patient is.
Several suppliers have them for sale; some small and therefore convenient ones are: Bionector® from www.Vigon.com or SWAN-LOCK® from www.codan.de

BioPatch

BIOPATCH® Protective Disk with CHG is a hydrophilic polyurethane absorptive foam with Chlorhexidine Gluconate (CHG). The foam material absorbs up to eight times its own weight in fluid, while the CHG incorporated into the dressing inhibits bacterial growth under the dressing. Manufactured for ETHICON.

Applied around the catheter at the exit site it can prevent infections.

Trocar

Use a trocar with the smallest possible diameter, that can still accommodate the catheter. Stainless steel is preferred.

Polsterplast®

Plosterplast is a foam with an adhesive side. It is marketed by: www.snogg.no It has excellent adhesive properties on pig skin, is very versatile and can therefore be used for various applications.

Duct tape

Vet-wrap tend to roll up at the edges. The application of duct tape prevents that from happening and adds a waterproof layer at the same time.

Procedure for CVC Placement in the Jugular Vein

Prepare the pig for surgery

- Anaesthetise according to chosen protocol
- Provide analgesia according to the chosen protocol
- Apply eye ointment
- Shave around the neck
- Wash the pig thoroughly
- Mark the position of the right atrium with a pen (length of catheter)
- Disinfect the skin

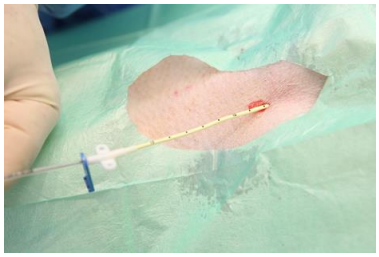
Aseptic procedure

- Drape
- Penetrate the skin and find thee vein, easy flow of blood into syringe
- Insert guide wire to required length, compare to landmark
- Remove needle (with syringe), leave wire in place
- Use dilator to extend opening, use of No. 11 scalpel is an option
- Remove dilator
- Measure depth of catheter insertion (scale on catheter)
- (prime catheter with 20 IU/ml of heparin in saline)
- Thread catheter over guide wire, making sure the end is protruding at hub
- Insert catheter with a twisting motion to required length
- Remove guide wire
- Check patency and flush with saline
- Attach extension if necessary
- Fit cap or valve to the hub
- Suture wings to skin

Bandage

- Apply wound dressing
- Bandage pig with Vetrap®
- Secure with duct tape
- Check patency and flush with saline
- Lock catheter with lock solution (Heparin, Taurolock™, DuraLock™, etc.).



Procedure for a tunnelled CVC in the Jugular Vein

Prepare the pig for surgery

- Anaesthetise according to chosen protocol
- Provide analgesia according to the chosen protocol
- Apply eye ointment
- Shave around the neck dorsal and ventral
- Wash the pig thoroughly
- Mark the position of the right atrium with a pen (length of catheter)
- Disinfect the skin.

Aseptic procedure

- Drape
- Make a small incision with a No 11 scalpel in jugular fossa
- Insert needle and find thee vein, easy flow of blood into syringe
- Insert guide wire to required length, compare to landmark
- Remove needle (with syringe), leave wire in place
- Use dilator to extend opening
- Remove dilator
- Measure depth of catheter insertion (mark on catheter)
- Make a small incision with a No 11 scalpel dorsally
- Push trocar from one incision to the other
- Feed catheter trough trocar; dorsal to ventral
- Remove trocar
- Feed guide wire into catheter forming a loop
- Make sure the end of the guide wire is protruding at hub
- Insert catheter into the vein with a twisting motion to required length
- Remove guide wire
- Check patency and flush with saline
- Pull catheter hub so the loop disappears but tip is not pulled back
- Check patency and flush with saline again
- Attach extension if necessary
- Fit cap or valve to the hub
- Suture ventral incision (including ligature around catheter)
- Suture dorsal exit site if necessary

Bandage

- Apply BioPatch and wound dressing
- Bandage pig with Vetrap® or collar
- Pocket for excess catheter
- Check patency and flush with saline
- Lock catheter with lock solution (Heparin, Taurolock™, DuraLock™, etc.).

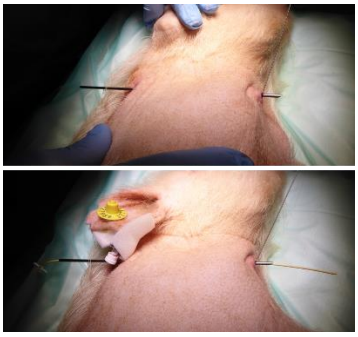
Sequence of tunnelling procedure

Incision to access vein.

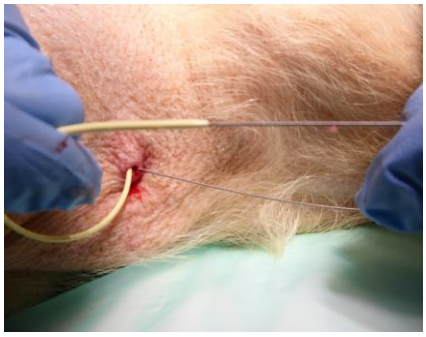
Access confirmed.

Guide wire in place.

Inserting the trocar

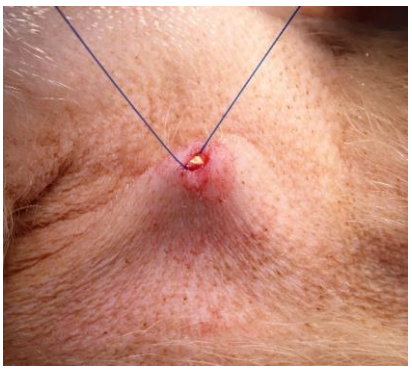


Trocar in place

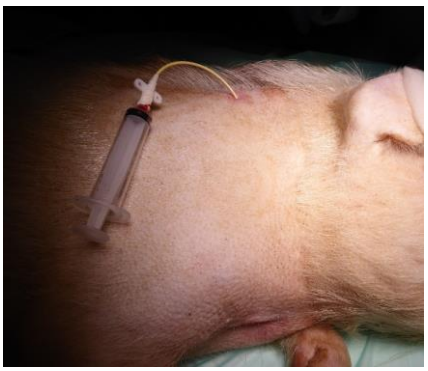


Threading catheter and guide wire

Catheter loop



Suture



Catheter in place

Procedure for Saphenous Vein Placement

The modified Seldinger technique is applied in this procedure. Please make sure over-the-needle catheter and guide wire fit in dimension.

Prepare the pig for surgery

- Anaesthetise per chosen protocol
- Apply eye ointment
- Shave the leg
- Wash the leg thoroughly
- Disinfect the skin

Aseptic procedure

- Drape
- Make a small incision in the skin over the vein
- Place an over-the-needle catheter in the vein; good flush back essential
- Mark the length of the catheter on the guide wire (tip at straight end)
- Insert guide wire with the straight end through temporary catheter, ca. 5–7 cm
- Remove temporary catheter, leave wire in place
- Use dilator to extend opening
- Remove dilator
- (prime catheter with 20 IU/ml of heparin in saline)
- Thread catheter over guide wire, making sure the end is protruding at hub
- Insert catheter with a twisting motion into the vein
- Advance catheter so the tip protrudes from the guide wire by a few mm
- Advance catheter and guide wire together carefully the whole length
- Remove guide wire
- Check patency and flush with saline
- Attach Bionector®

Bandage

- Apply wound dressing
- Put padding under the hub
- Tape hub
- Bandage pig with Vetrap®
- Secure with tape
- Check patency and flush with saline
- Lock catheter with lock solution (Heparin, Taurolock™, DuraLock™, etc.)

Wound dressing, padding and tape in place

Wrapping with Vetwrap

Procedure for Ear Vein Placement

The modified Seldinger technique is applied in this procedure. Please make sure over-the-needle catheter and guide wire fit in dimension.

Prepare the pig for surgery

- Anaesthetise per chosen protocol
- Apply eye ointment
- Shave the ear if necessary
- Wash the ear thoroughly
- Disinfect the skin
  It is difficult to disinfect the inside of the ear. A sterile tape can be attached to the tip of the ear so it can be handled aseptically

Aseptic procedure

- Drape
- Place an over-the-needle catheter in the vein; rinse to confirm placement
- Mark the length of the catheter on the guide wire (tip at straight end)
- Insert guide wire with the straight end through temporary catheter, ca. 3–7 cm
- Remove temporary catheter, leave wire in place
- Use dilator to extend opening
- Remove dilator
- (prime catheter with 20 IU/ml of heparin in saline)
- Thread catheter over guide wire, making sure the end is protruding at hub
- Insert catheter with a twisting motion into the vein
- Advance catheter so the tip protrudes from the guide wire by a few mm
- Advance catheter and guide wire together carefully the whole length.
- Remove guide wire
- Check patency and flush with saline
- Attach Bionector®

Bandage

- Suture hub to ear
- Apply wound dressing
- Tape hub, secure with tape
- Check patency and flush with saline
- Lock catheter with lock solution (Heparin, Taurolock™, DuraLock™, etc.)
- Put tape flap over valve

Bandaging an ear vein catheter with tape

Cut down Method

Technique

The Minipigs are surgically prepared, a skin incision made, and the desired vessel is dissected. After a distal ligature access to the lumen is established with a cut or needle. The catheter is then inserted to the required length and fixed with a ligature. The catheter is then tunnelled to the site of the port or the desired exit site.

If a port is used, a subcutaneous pocket is created at the desires site and with the help of a trocar, a tunnel is established to site where the catheter enters the vessel. The port, after connection to the catheter is placed in the pocket and all wounds sutured.

In case the catheter is externalized, a trocar is subcutaneously tunnelled from a small incision at the desired exit site to the cannulated vessel. After feeding the catheter trough, the trocar is removed, and all wounds closed.

Catheters

Catheters, ports and accessories are available from Access Technologies, www.norfolkaccess.com or SAI Infusion Technologies www.sai-infusion.com . They come in a variety of designs and sizes to fit different types projects.

All catheter materials available have both advantages and disadvantages. Polyurethane and Silicone are materials in the most common catheters. They have good biocompatibility, but compound compatibility needs to be considered as well. Silicon is generally a bit softer and flexible but have thicker walls and therefore a smaller lumen at the same outside diameter, compared to PU catheters. The companies mentioned above have tables comparing different materials on their websites or catalogues.

There are also different shapes of tips available, rounded tips are preferred for long time catheter implantations.

Catheters can also have suture beads for securing them to the vessel and/or flanges or cuffs to secure them at the exit through the skin.

Design, length and diameter all depend on which vessel they are intended for and what type of study they will be applied in. Careful consideration needs to be given to all available parameters to have success with the intended use. Most certainly some compromises will have to be made.

Ports

A vascular access port (VAP) permits intermittent access to a catheter using a chamber connected to the catheter lumen. The chamber consists of a metal or plastic casing with a connecting stem for the catheter and a thick, self-sealing septum, which can be punctured with a needle.

The port is implanted at a subcutaneous site so that a suitable needle inserted through the skin and septum accesses the lumen of the port-catheter system. Once healing of the surgical incision is complete, the port and catheter are surrounded by intact skin and connective tissue so the likelihood of an implant infection arising from the animal's skin is unlikely.

As mentioned, the above companies have also a variety of ports available. Materials are typically Titanium or plastic. Titanium is more durable, but plastic ports are often cheaper and are compatible when MRI scans are required.

At Ellegard we have successfully used a Port system called Power Port from Bard Medical. www.crbard.com for implantation in the jugular vein. It is designed for humans, comes as a kit that includes all you need for the implantation: Port, 6 Fr catheter, vein pick (introducer), hubs, connectors and Huber needles.

We have also pioneered the use of rat vascular access buttons (VAB) in Minipigs. This is a port that sits percutaneously and allows painless access at the time of sampling and dosing. There is the option to connect 1-4 catheters to the same port, but only catheters with a diameter of 3 fr are available.

The buttons are available from www.instechlabs.com

Sites

Jugular vein

The preferred vessel for insertion is the external jugular vein. It has a relatively large diameter and can be accessed by an incision in the jugular fossa. Even though it is placed quite deep it can be easily desiccated by blunt dissection of the overlying tissue.

For catheter tip placement please refer to the Seldinger chapter.

From insertion site the catheter can, without difficulties, be tunnelled to the place of exit or port. The percutaneous exit will typically be on the dorsal part of the Minipig.

Port location has to be given some consideration. It is important to have easy access when sampling/dosing is required. The skin should not be too thick for ease of palpating the septum and forceless penetration with the Huber needle. Penetration is facilitated if the port rests on a relative hard backing like the rib cage or scapula, but it increased the risk of interference by the Minipig rubbing against a wall.

Our chosen site for the port is behind the ear. The main advantage of this position is the thin skin and ease of access when the minipig is in a sling.

Other sites

Other options are:

- Catheter in the femoral vein with port/exit near sacrum
- Catheter in saphenous vein and port caudally of tibia

This options are not further discussed in this paper as we currently do not have enough practical experience with these sites.

Material required

- Anaesthesia

  According to your preferred anaesthesia protocol

- Analgesia

  According to your preferred analgesia protocol

- Preparation

  Ointment for eye protection
  Ez-scrub – Iodine – Alcohol
  Operating table
  Hair clipper
  Syringes, needles
  Over-the-needle catheters
  Adhesive surgical tapes

- Surgery

  Surgeon's clothing
  Sterile gloves
  Incise drape, or other draping
  Catheter set (VAP)
  Surgical instrument set Syringes
  Gauze swabs
  Saline for flushing (20 IU/ml Heparin as an option)
  Sutures non-resorbing (4-0 Polyamid)
  Huber needles
  Heparin/saline 500 IU/ml or other lock solution
  Cap or Bionector® (Vygon) for catheter hub
  Trocar for the tunnelling

- Wound closure

  Sutures resorbing for soft tissue (3/4-0 PDS II, Monocryl or Vicryl)
  Sutures resorbing for skin closure (2/3-0 Monocryl, PDSII or Vicryl)
  (Bio Patch) for percutaneous exit
  Pocket for percutaneous catheter
  Bandage (Vetrap® or similar)
  Polsterplast®

Procedure for catheter placement in the Jugular Vein

- Prepare pig for surgery
  - Anesthetise per chosen protocol
  - Analgesia per chosen protocol
  - Apply eye ointment
  - Shave ventral neck and intended position of the port/exit
  - Administer prophylactic antibiotic and analgesic by appropriate route
  - Wash pig thoroughly
  - Mark position of right atrium with pen (length of catheter)
  - Mark incision site in jugular fosse and at position of port/exit
  - Disinfect skin

- Sterile procedure
  - Drape
  - Skin incision jugular furrow
  - Blunt dissection and exposure of external jugular vein;
  - Dissect adventitia
  - Place two non-resorbable sutures around vessel
  - Apply tension to sutures creating a bobble of blood
  - Tie a ligature with distal (cranial) suture
    - do not release tension on proximal suture!
    - do not cut ligature tails
  - Make a cut in vessel 1/3 of diameter with sharp scissors
  - Leakage of blood confirms lumen penetrated
  - Measure insertion length of catheter
  - (Place beads accordingly)
  - With help of introducer, insert catheter in vessel to required length
  - Test patency/withdraw blood (Syringe with saline/heparin 20 IU/ml)
  - Tie ligature with proximal suture around vessel and catheter
  - Tie ligature around catheter with remaining distal suture
  - Test patency and cut ligature tails when catheter function is confirmed

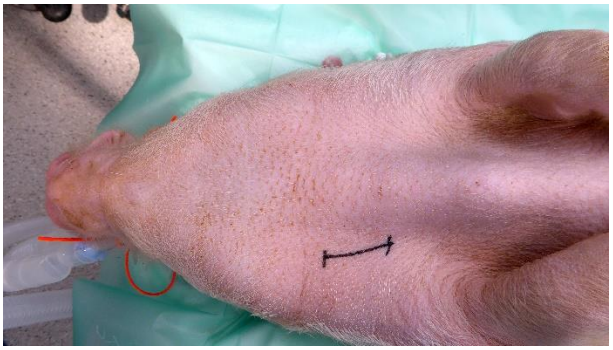
FOR VAP

  - Make a skin incision around 2cm from intended port position
  - Create subcutaneous pocket for port by blunt dissection
  - Tunnel trocar subcutaneously from pocket to neck incision
  - Occlude catheter by folding and remove syringe and adaptor
  - Feed catheter trough trocar and remove trocar
  - Place reinforcing sleeve over catheter at pocket end
  - Fold catheter on pocket side and release other kink
  - Cut catheter to length allow for growth
  - Record length of catheter for computing dead volume of system
  - Attach port and reinforcing sleeve
  - Release kink and test for patency
  - Place port in pocket and make sure catheter is not kinked anywhere
  - Close wounds
    - VAP pocket: two-layer closure
    - Ventral neck: three-layer closure
  - Puncture VAP with Huber needle for final test
  - Lock System with lock solution (Heparin, Taurolock™, DuraLock™, etc.)

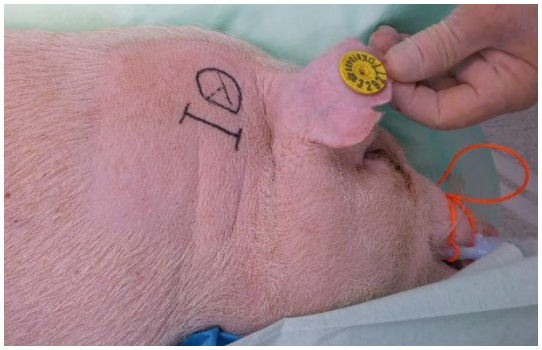
FOR EXTERNALIZED CATHETER

- Make a fine skin incision around at intended exit position
- Tunnel trocar subcutaneously from there to neck incision
- Occlude catheter by folding and remove syringe and adaptor
- Feed catheter trough trocar and remove trocar
- Kink catheter on pocket side and release other kink
- Cut catheter to length
- Record length of catheter for computing dead volume of system
- Attach hub and valve (Bionector)
- Release kink and test for patency
- Close wounds
    - Ventral neck: three-layer closure
    - Exit: place a suture if nessesary
- Final test: draw blood and rinse with Saline
- Lock System with lock solution (Heparin, Taurolock™, DuraLock™, etc.)

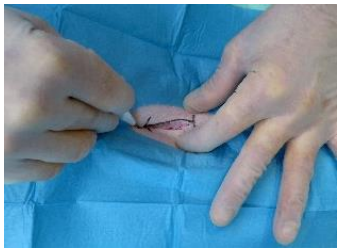
Note: if you use a catheter with integrated hub, the order of the steps above is different:
First you need to feed the catheter trough the tunnelled trocar and after its removal the catheter tip will be implanted to the required length as described above.



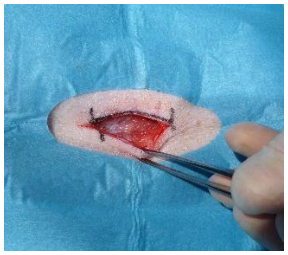
Site of neck incision



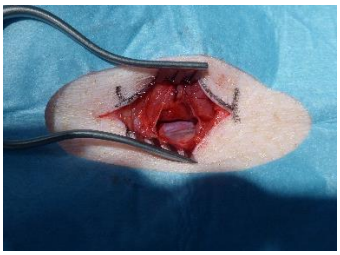
Site of port



Incision



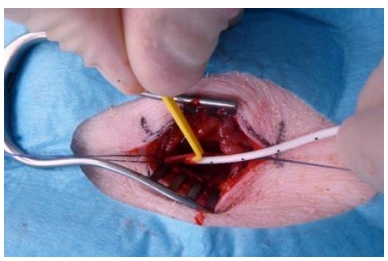
blunt dissection of the vein



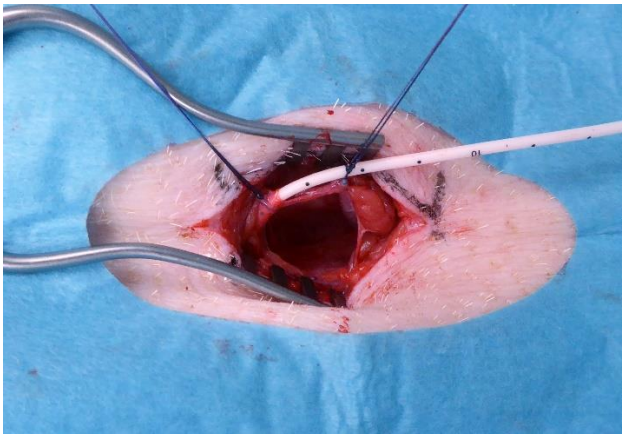
loops around the vein

Cutting the vein

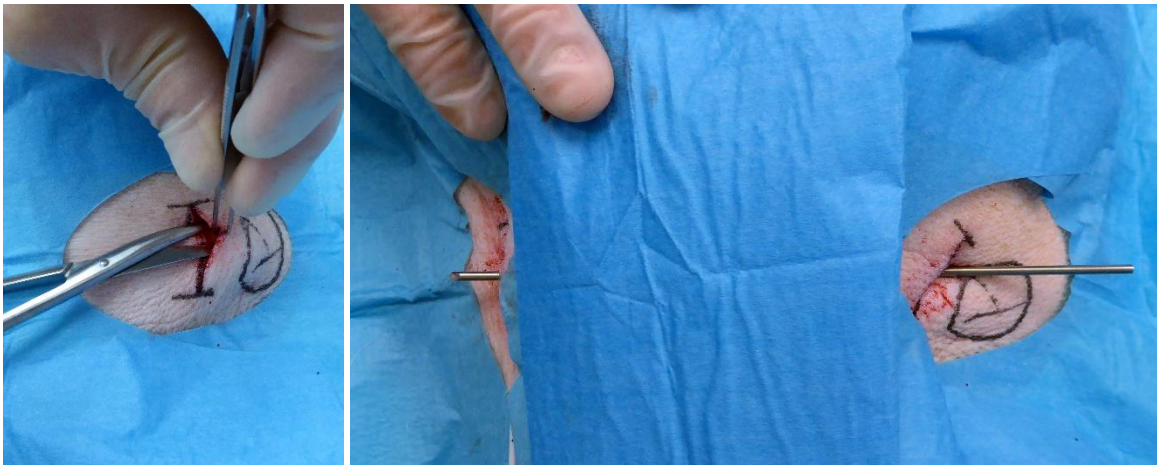
introducer inserted



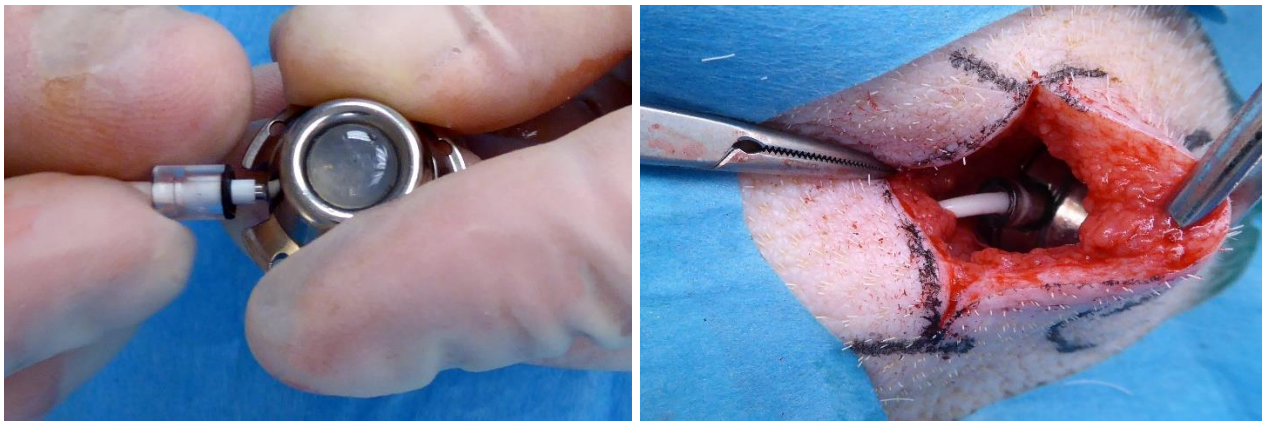
feeding the catheter



Catheter secured to the vessel



Creating the pocket for the port, blunt dissection, and tunnelled trocar



Connecting the catheter to the port and placing it in the pocket.

Sampling and Catheter Maintenance

Use sterile gloves and wear a mask for all catheter handling and disinfect the hub before and after every access to avoid infection. Use aseptic technique.

Discard a certain amount of blood prior to blood sampling (the discard volume) to avoid contamination of laboratory samples with heparin or saline. The amount of blood drawn to clear the line depends on several factors, including:

- tubing size and length,
- amount of heparin in the line,
- the type of study to be performed.

This volume is often expressed as multiples of the dead space within the catheter. This is a function of the volume contained in the catheter from the tip of the catheter to the port from which the sample is to be drawn. Anywhere from two to ten times the dead space has been advised. To reduce waste, if the total amount of blood to be drawn is high, it is possible for the rinsing to be done by moving blood back and forth in the catheter, after the initial discard of blood, but bear in mind that there is a contamination risk with regard to the lock solution.

Flush immediately with saline after drawing blood to avoid prolonged contact with blood on the inside of catheter. Do this by brisk and pulsating pushing of the syringe plunger. This will create turbulences in the catheter and results in a higher quality flush. The flushing volume should be two to four times the dead volume.

Always use a positive-pressure technique for flushing and locking.

If the intervals between sampling are short, it is sufficient to flush with saline, whereas longer periods and overnight demand a lock solution. Idle catheters should be attended to as follows:

- disinfect hub/Bionector®,
- draw a small amount (at least twice the dead volume) of blood and discard,
- flush with saline,
- lock with slightly more than the dead volume. If you have a catheter with lateral openings make sure you have enough pressure to fill it all the way to the proximal opening,
- disinfect the hub/Bionector®.

Check for infection on a daily basis and check to see whether the bandage is causing discomfort. To palpate the insertion site, use sterile gloves.

Possible complications

Complications at Insertion, Seldinger Technique

Arterial puncture while trying to puncture jugular vein

Arterial Puncture can easily occur due to arterial and venous proximity, as well as variable venous anatomy and a lack of visual guidance. If bright red, pulsatile blood appears, applying local pressure may be enough to stop the bleeding.

Use the other side for the second attempt.

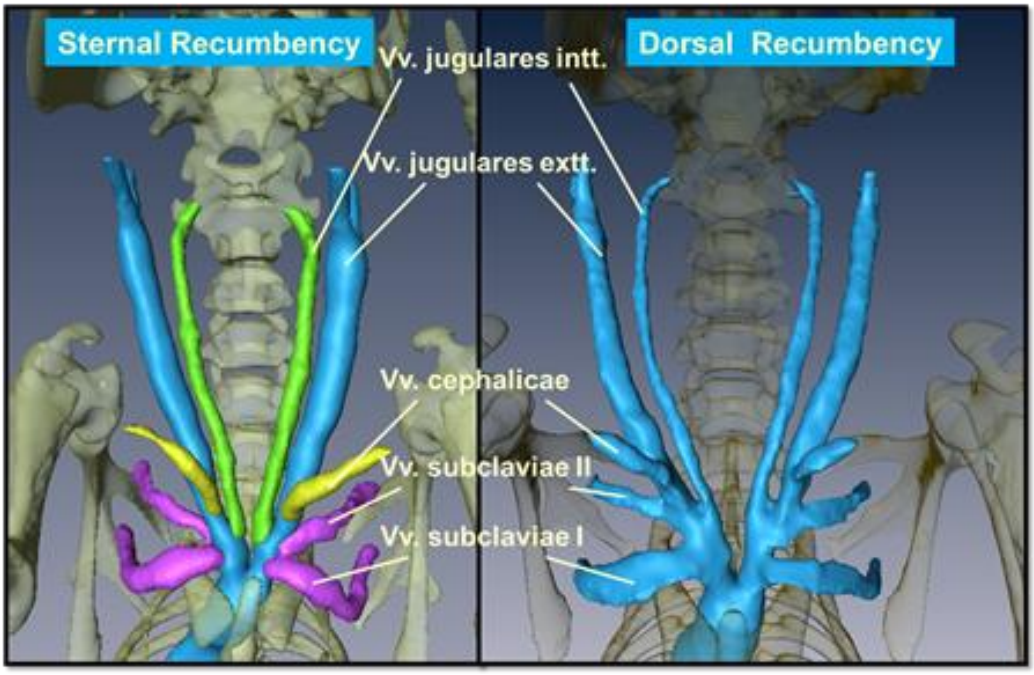
Tracheal puncture and **air embolism** may also occur in rare instances.

Difficulties in advancing the guide wire

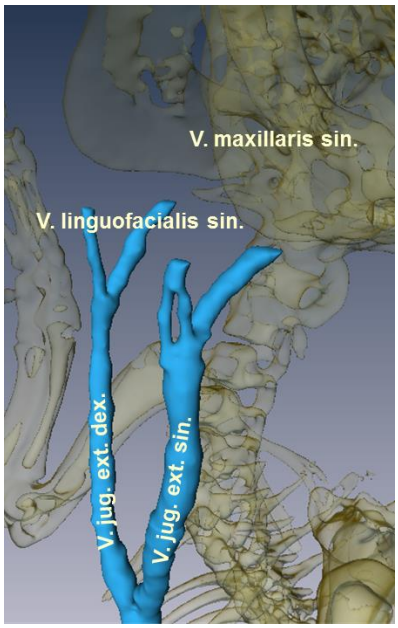
Impossibility to advance the guide wire can occur (there should be no resistance whatsoever inserting the wire). This can have several causes depending on the depth of insertion. If the insertion is as far as the needle, then the needle is probably not in the vessel any more. (Remove the guide wire, attach the syringe and relocate the vessel.) Or it could be a mechanical problem (check the equipment).

If the wire has advanced beyond the needle, then the J-tip might be stuck in a small branch. (Carefully retract the wire slightly and turn it before advancing again. Retracting the wire can cause it to be damaged by the sharp edges of the needle. Never use force to advance and, if no progress is made, withdraw the wire together with the needle to avoid damage.)

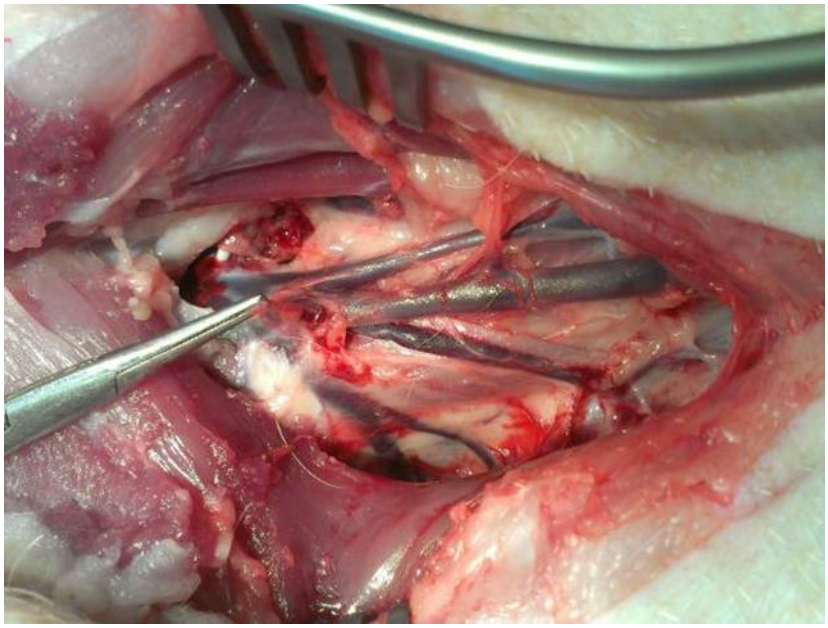
Sometimes, repositioning the head leads to success. Remember that the anatomy and paths of the veins are subject to variation. In older pigs, veins can form islands, exemplified by the observance of three jugular veins in one location.



CT Scan of the veins in the Neck.
Images courtesy of Christine Müller Charité Universitätsmedizin Berlin



CT Scan of vein – islands.



Three major veins in the neck.

Systemic changes

Arrhythmias are usually related to over-insertion of guide wire or catheter, with impingement of the tips of these devices in the region of the right bundle branch.

Cardiac tamponade: fluid in the pericardial cavity can be caused by the perforation of structures by a catheter or guide wire – the most serious condition (euthanasia).

Delayed Complications

The most common delayed complications of vascular-access device insertion are thrombosis and infection. These two complications are somewhat related, as thrombotic complications are common in catheterised veins and are often associated with sepsis.

Thrombosis

All catheters are thrombogenic. Within seconds after insertion, much of the catheter body is coated with body fluids and proteins. Platelets adhere and thrombi form. Catheters can become encased within 5–7 days, forming a fibrin sheath. Mural (wall) thrombi may form on the catheter and/or on the wall of the vessel.

Thrombolysis of vascular catheters

Where a thrombus or fibrin flap is confirmed or suspected at or around a catheter tip, the use of thrombolytic therapy may be considered. A variety of agents are available: historically, urokinase was used and more recently streptokinase and tPA are an option as well.
One problem of introducing a thrombolytic solution into a catheter lumen is inability to infuse due to obstruction. In this event, intermittent positive and negative pressure can be applied either by using a three-way tap connected to the port puncture needle. Quite strong negative pressure is applied deliberately to collapse the catheter and withdraw content, before adjusting the tap position to allow injection of the enzyme solution. Repeating the process will gradually allow flow of the solution to the catheter tip.

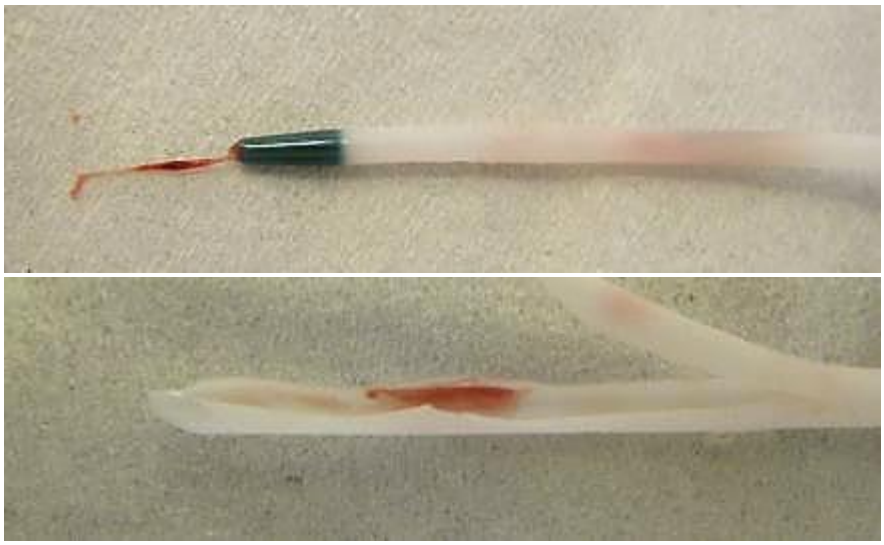
Alternatively, the port can be punctured with two needles - one for the suction syringe, the other for the infusion solution.
Catheter thrombolysis is most likely to be effective for recent or freshly formed thrombus. It is less effective or ineffective as thrombus ages.
Use of thrombolytic solutions within the catheter lumen will not, of course, influence fibrin flap or cuff arising in the vessel wall around the catheter tip. In these cases, system thrombolysis could be considered but is likely to be limited in effect.

Catheter occlusion

Catheter occlusion can result from the formation of a fibrin sheath and/or thrombi at the tip of the catheter, but has also been associated with blood clotting, lipid deposits or precipitates within the catheter lumen. Fibrin sheath formation is significant in that the sheath may eventually encase the catheter completely and affect the functional ability of the catheter. Withdrawal occlusion may occur if the fibrin sheath acts as a flap blocking the tip of the catheter when the drawing of blood is attempted, and then opens up with injection.

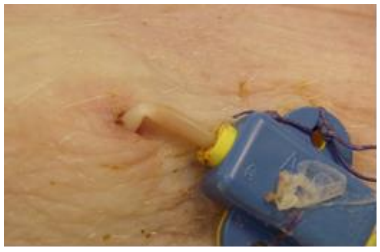
Venous valves can also interfere with sampling. The first step with a blocked catheter is always to reposition the animal and manipulate the catheter trying to move the tip to another location.

Often blockage is due to a slight or severe kink in the catheter or extension. Try to reposition the animal or remove the bandage to check. Attempts to clear catheter occlusions include the use of fibrinolytic agents or gentle pulsating suction.



Clogged lateral port

Fibrin sheath/thrombi formation at the tip and inside after being in place for eight days.



Kink in the catheter due to combination of a steep angle of entrance and movement of the head on day two after implantation.

Infection

We recommend that a strictly aseptic insertion technique is used. At times, suboptimal conditions can prevail, in which case the use of antibiotics is indicated. A broad-spectrum antibiotic like Curamox could be used. This prophylactic course of antibiotics should be administered according to the institutes protocol at surgical prep time.

Catheter related sepsis (CRS)

CRS is an ever-present hazard of implanted vascular catheters. The catheter forms a direct portal to the blood stream through its lumen and the potential space around the outside of the catheter wall (the catheter track) is a second (and often overlooked) portal of infection.

Direct exteriorization of a catheter through the skin poses additional risks of infection over totally implanted devices (vascular access ports, VAPs). Once bacterial colonization has occurred on the catheter, the complex reaction between bacteria and the biofilm provides an environment, which is highly resistant to attempts to eliminate the contaminants.

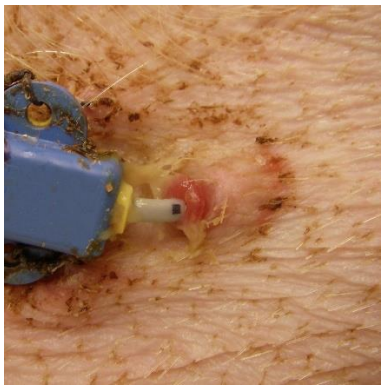
Provided that catheters are inserted and maintained with suitable aseptic technique, the most likely source of infection is from the animal's own flora - either the skin surrounding the catheter exit site, or a distant focus of infection within the body. Use of Dacron™ velour cuffs deep to the dermis has proved an effective barrier to the ingress of bacteria.

Once CRS is established, it is effectively impossible to eliminate using antibiotic and other therapy. Experience in some laboratories of removing infected catheters and then delivering a course of appropriate systemic antibiotic is that the original infection will recur at the site of implantation of a fresh catheter. Prevention is therefore of the utmost importance and the value of adherence to strict aseptic technique cannot be over emphasized

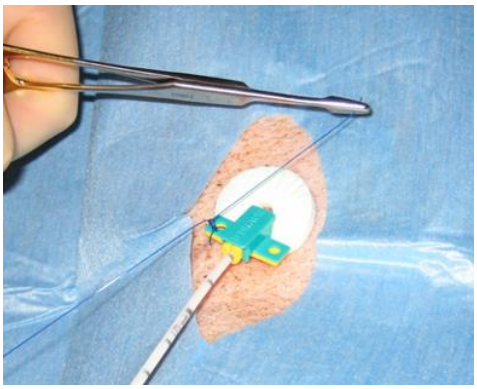
Catheter-related bloodstream infection can be due to hub contamination and is the most likely mechanism for infection occurring in long-term catheters with repeated manipulation. Skin contamination and the migration of dermal organisms through the cutaneous catheter tract is the most likely cause of infection in the short term.

Aseptic techniques and hub disinfection are imperative. The use of a Biopatch® (Ethicon) may prevent infection around the exit site.

Clean site.



Infected site.



BioPatch placed at insertion site.

Catheter Replacement

There can be many reasons for replacing a catheter, including infection or occlusion.

Replacement over wire is a fast and easy method for a Seldinger catheter. However, it is contraindicated when infection is detected or suspected. With this technique, the guide wire is inserted through the line in place, followed by the removal of the old catheter and its replacement with a new one.
Extreme care should be taken as there is the possibility of loosening a thrombus or pushing it into the bloodstream, especially if a catheter is occluded.

Surgically implanted (cut-down) catheters can rarely be replaced to the same vessel and if so only surgically.

Catheter Removal

It is straightforward to remove a Seldinger catheter. Depending on the temperament of the animal, anaesthesia is not required for removal. Clip the sutures and pull out the catheter with a smooth steady motion. Apply pressure for two minutes. Observe for after bleeding.

Catheter that have been surgically implanted are sutured to the vessel and can therefore only be removed surgically.

Conclusion

The use of Seldinger catheters is a valid option for short term, repeated serial blood sampling, even though it poses some risks and challenges. The most frequent ground for failure at implantation time is the unsuccessful penetration of the jugular vein, or arterial puncture. Surveys from the human medicine sector show that even with the best equipment and well-trained personnel, the success rate is only 90%.

The greatest variety we found is in the duration of patency: this depends on many factors and is not easy to control. This led us to conclude that replacing a catheter is better than having to maintain an idle catheter over a long period and risk losing patency.

Completely implanted systems with VAP is a good option for long time vascular access with reduced infection risk. However, as the skin still must be perpetrated it is painful and the fact, that Huber needles are generally not as sharp as high quality ordinary hypodermic needles, does not help. Local topical anaesthetic should be considered.

For frequent, medium term access an externalized catheter provides a painless dosing and sampling possibility.

Of course, there are numerous factors to consider, as well as weighing the risk, cost, benefit and animal welfare issues, before reaching a decision as to which of these methods is most appropriate.

This guide is meant to help you with this process. We welcome any input you have if you wish to share your catheter experiences, as this will improve our guide for the benefit of others.

Courses

Ellegaard Göttingen Minipigs A/S regularly holds catheter courses at the facility in Dalmose, Denmark. These Catheter Workshops are held at the best convenience for the parties involved and scheduled by mutual agreement. All the above techniques can be trained in practice, theoretical lectures are at a minimum. The typical number of participants is two, so there is plenty of hands-on training. The course has a standard programme, but the contents can be adjusted to your particular needs.

We hope that this educational package will be useful when you work with Minipigs.

More copies of this educational package are available.

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