

INVITED REVIEW

Vascular access animal models used in research

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ABSTRACT

Purpose: To provide a systematic literature review on effectiveness of arteriovenous fistula (AVF) and Shunt (AVS) research animal models.

Background: Due to advancing human population age, there is increased incidence of patients suffering from vascular and renal diseases leading to dialysis access using AVF and/or AVS. During those interventions native venous or synthetic grafts are arterialized. Despite temporary good patency, complications are a consequence of neointimal hyperplasia (NIH) development that contributes to patients' morbidity and mortality. Basic research attempts to elucidate the pathomechanisms, therefore the small and large animal models are becoming attractive.

Methods: Medline search (within 1966–2018) was performed on AVF/AVS animal models. Studies fulfilled following criteria: (1) reported complete material-methods-results section, (2) included statistically significant number of animals, (3) provided statistically significant results. 55 articles were identified encompassing six animal species used.

Results: Large animal models include creation of AVF and AVS in pig, sheep and dog. Porcine animal models use pelvic or femoral vessels, ovine use the common carotid artery (CCA) and jugular vein (JV). Canine animal models use the femoral vessels. Small animal models use rabbit (CCA/JV), rat (JV/CCA, abdominal aorta /Vena cava inferior and femoral artery/femoral vein) and mouse (aortocaval and supraortic AVF models).

Conclusions: Large animal models are best for haemodynamic shear stress studies and in vivo evaluation of new synthetic vascular grafts. Small animal models, especially the genetically manipulated ones, are ideal for analysis of molecular and cellular pathomechanisms. The selection of animal species to be used depends on the addressed research question.

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Contents

1. Introduction.....	66
2. Experimental requirements	66
3. Methods	67
4. Existing animal models	67
4.1. Large animal models	67
4.1.1. Porcine vascular access model	67
4.1.2. Sheep vascular access model	67
4.1.3. Canine vascular access model	68
4.2. Small animal models	68

Abbreviations: ACE, angiotensin converting enzyme; AVF, arteriovenous fistula; AVS, arteriovenous shunt; CCA, common carotid artery; CKD, chronic renal disease; CRF, chronic renal failure; EJV, external jugular vein; ESRD, end-stage renal disease; FA, fistula artery; FV, fistula vein; JV, jugular vein; NIH, neointimal hyperplasia; ePTFE, expanded polytetrafluorethylen.

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4.2.1.	Rabbit vascular access model	68
4.2.2.	Rat vascular access model	68
4.2.3.	Mouse vascular access model	69
5.	Experiment complexity factor	69
6.	Overview (Table 1)	69
	Funding	73
	References	73

1. Introduction

Chronic kidney disease (CKD) was at position 25 in 1990 in regards to years of life loss (YLL) and has gradually moved to position 17 in 2015 ([Mortality and Causes of Death, 2016](#)). The global estimation for CKD prevalence is 10–16 % in adults worldwide ([Hill et al., 2016](#)). According to the quality assurance annual report on maintenance therapy for end-stage renal disease (ESRD) (QuaSi Niere gGmbH, Modellprojekt des Bundesministeriums für Gesundheit) of the year 2006, the recorded number of patients requiring dialysis in Germany was 66,508, 808 ESRD patients per million of population. That reflects an increase of 60.84% in comparison to the year 1995. There is a total of 17,548 (49.59% more) new ESRD patients in the year 2006 in comparison to 1995. That corresponds to a rate of 213 new patients/million population in comparison to 1995. In the same year, 12,124 deaths of ESRD adult patients and six minor patients treated with different means of maintenance therapy were recorded. The continual increase of the prevalence and age of ESRD patients reveals underlying prerequisite conditions of a constant rising mortality ([Frei and Schober-Halstenberg, 2006](#); [Thomas et al., 2017](#)). Respectively high are also the hemodialysis costs that ranged between 3,424 Int\$ to 42,758 Int\$ ([Keller et al., 2007](#); [Mushi et al., 2015](#)).

Dialysis vascular access in chronic haemodialysis patients is established via the connection of an artery and a vein usually in the upper or lower arm, through which puncture for the performance of dialysis takes place. The classic AVF used in patients is the Brescia-Cimino fistula an end-to-side vein-to-artery anastomosis ([Vascular Access Work, G., 2006](#)). It uses the cephalic vein and the radial artery (brachiocephalic fistula), proximal to the carpal joint, and after sufficient maturation it can be successfully used for years ([Brescia et al., 1966](#); [Reinhold et al., 2011](#); [Widmer et al., 2008](#)). The first choice is always the native arteriovenous fistula (AVF) ([Jennings, 2006](#)) and secondarily the synthetic, mainly expanded polytetrafluoroethylene (ePTFE) vascular grafts or arteriovenous shunts (AVS) ([Roy-Chaudhury et al., 2001](#)). Another possibility is the usage of the basilic vein to construct the brachio-basilic fistula ([Hossny, 2003](#)). In the case of AVS, prosthetic ePTFE grafts with a diameter 4–8 mm are used to create the so called interposition grafts between a vein and an artery ([Schuman et al., 1997](#)). Those grafts can be straight or looped. The primary first- to second-year patency of arteriovenous fistulas is 85–90% ([Leitlinien der Deutschen Gesellschaft für Gefäßchirurgie, 2019](#)). The primary first year patency rates of vascular grafts (AVS) are between 70–90% while that of the second year are 50–70% ([Barron et al., 1993](#); [Garcia-Pajares et al., 2003](#); [Kaufman et al., 1997](#); [Lenz et al., 1998](#); [Tordoir et al., 1995](#)). Along with that, the interventions necessary for native AVFs are 0.2/patient/year while it is 1/patient/year for the vascular grafts ([Hollenbeck et al., 2009](#)). That makes the native AVF the preferred method of choice for vascular access. In Germany 85% of the dialysis access is done via native AVF and 25% via vascular grafts, while in the USA 70% of the haemodialysis patients are using synthetic graft material for vascular access ([Barron et al., 1993](#); [Leitlinien der Deutschen Gesellschaft für Gefäßchirurgie, 2019](#); [Garcia-Pajares et al., 2003](#); [Hollenbeck et al., 2009](#); [Kaufman et al., 1997](#); [Lenz et al., 1998](#); [Pisoni et al., 2002](#); [Roy-Chaudhury et al., 2001](#); [Tordoir et al.,](#)

[2007, 1995](#)). Nevertheless, seen globally, during the “Dialysis Outcomes and Practice Patterns Study” (DOPPS) 1–5, from 1996 until 2014 the use of AVFs in Europe remained stable while in the US it declined from 70% to 32% implying a lack of biological material for the creation of AVF. At the same time the successful use of AVF and AVS have been similar in the study conducted for the time from 2012 to 2014 ([Pisoni et al., 2018](#)).

The main cause of graft failure is the development of neointimal hyperplasia (NIH) in the graft lumen mainly because of reduced haemocompatibility of the graft material and foreign body reaction with accompanying myofibroblast migration to the NIH-sites, with further progress of cellular death and calcification ([Roy-Chaudhury et al., 2009](#)). Additionally, a biomechanical compliance mismatching between the native vessel and the bypass graft induces haemodynamic changes such as turbulent flow and shear stress, especially near the anastomosis-site leading to thrombus formation and excessive NIH formation ([Mehta et al., 2011](#)).

ESRD patients are patients with a complicated medical history background including several chronic diseases involved in their clinical pathology ([Dierkes et al., 2018](#); [Foster et al., 2013](#); [You et al., 2018](#)). This fact makes the need for more research on the pathophysiology of arterialized veins even more urgent. Extracting information on the behavior of the arterialized veins under different background conditions is necessary for the development of perioperative therapies, but also for the optimisation of alloplastic vascular implants with luminal coatings that will increase the life span of the chosen vascular access method.

Therefore, suitable AVF and AVS animal models are required to understand the pathophysiological events leading to vascular access complications as a basis to develop novel vasculoprotective therapeutical strategies. The animal AVF or AVS model that will be selected should reflect the human pathophysiology to the greatest degree possible and should be able to guarantee the highest transferability of results possible.

2. Experimental requirements

In vitro experimentation and testing is supplying valuable results but their outcome has to be tested and validated in a complete organism and in its complex context. Animals have been used to model diseases since Antiquity and during many important scientific experiments. The important question of tissue regeneration has been addressed early enough in animal models ([Klug et al., 1996](#)). The next issue that needs to be taken into account in the use of animals for scientific purposes is the issue of animal protection and welfare. For this reason the European Union has set a regulatory framework under the European Directive 2010/63/EU. The latter is based on the “three Rs principles” for replacement, reduction and refinement of animal experiments ([Russel and Burch, 1959](#); [Tannenbaum and Bennett, 2015](#)). There are remarkable anatomical and physiological similarities between humans and animals, especially mammals, and animal models that resemble the clinical human condition are instrumental for the extraction of pathophysiological information on the arterialized vein and for the selection of information concerning preclinical therapies trial.

In this case there are requirements that need to be fulfilled depending on the use of the model, so that both experimental and regulatory issues are addressed with carefully designed, relevant and well-characterized animal models.

- They have to be non-primate.
- Humane endpoints of animal experimentation should not be reached or exhausted.
- They should mimic the human lesions and hemodynamic stress of the human condition.
- They need to be readily translatable to humans.
- They need to allow preclinical evaluation of therapeutic devices or methods.
- They should develop lesions in a short period of time (between 3 to 16 weeks).
- They should be easy to implement.
- They should be sufficient to produce statistically significant results.
- They should be inexpensive.
- They need to allow a good correlation between cost effectiveness and sample size.

3. Methods

Medline search (within the time span 1966–2018, limited to original publications in English language) on animal models with an AVF or AVS.

4. Existing animal models

4.1. Large animal models

Large animal models are often preferred by researchers since the size and the anatomy of the model is closer to the clinical condition that is being addressed.

4.1.1. Porcine vascular access model

Porcine models are used most often to assess new techniques or new grafting materials.

Wang et al., successfully used the femoral vessels to create AV fistula conduits in pigs that showed a high clinical relevance (Wang et al., 2008). The authors identified possible mechanisms involved in fistula failure which was characterized by stenosis due to intima-media thickening and the presence of myofibroblasts after 28 days (Chan et al., 2014). The histopathology was very similar to the ones in the developed NIH in dialysis patients. The femoral vessels were used by Rajabi-Jaqahrgah et al. to optimize a new technique of documenting the intima-media thickening via a radiopaque marker that was sutured to the AVF and was detected via CT-scan, micro-MRI and common histology 28 days postoperatively (Rajabi-Jagahrgah et al., 2014). Another model that showed 100% patency after 28 days in minipigs used side-common carotid artery (CCA) to end-external jugular vein (EJV) AVFs and was created with a tunnelled central catheter (Loveland-Jones et al., 2014). Nevertheless, there are potential drawbacks concerning both above mentioned models in regard to their application in (i) clarification of pathobiological facts involved in AVF failure, and (ii) testing medicinal products that could reduce/inhibit AVF failure. That is due to the lack of a uremic version of this model since only healthy animals were used for the experiments. There are practical difficulties if one would choose the $\frac{3}{4}$ nephrectomy to produce uraemia, a method that is expected to also produce hypertensive individuals that would have to be excluded from the study; or to use feed with adenine, a method that has till now been applied only in rats.

The AVS porcine models are often used to test different synthetic graft materials or different material coatings (Baek et al., 2012; Kelly et al., 2002; Terry et al., 2009). ePTFE is the material that is

most often used in AVS, therefore any coating that will prevent the formation of NIH and calcification is of great clinical interest. Baek et al. have created an AVS with sirolimus-eluting ePTFE between the CCA and the EJV and compared it with paclitaxel-coated vascular grafts. They used 14 female Landrace pigs with significant reduction of NIH to the favor of the sirolimus-eluting grafts. In the developing NIH in both the control and the sirolimus-eluting grafts, the dominant cell type were the myofibroblasts and the contractile smooth muscle cells (Baek et al., 2012).

Recently, new porcine models show up to assess biocompatibility of biomedical interface materials, where bilateral femoral artery-to-vein shunts are created and scientists operated two tubes per shunt and the one side was coated while the other remained uncoated. It was not a model that evaluated the formation of lesions in the vasculature but it was a model that effectively evaluated material biocompatibility with a maximum experimental animal reduction (3Rs Principle) (Takaseya et al., 2018).

4.1.2. Sheep vascular access model

Sheep AVF and AVS models are used in a similar way to the porcine ones. Very often it is rather up to the researcher's preference and the housing opportunities available by the relevant animal experimentation institute. Especially in the cases of graft testing, when longer grafts should be tested, sheep become mostly the model of choice due to the long vessels of the neck that are available.

Florescu et al. (2015) introduced a very interesting AVF model in sheep using the basilic vein in an end-to-site anastomosis, termino-laterally to the brachial artery. The experiment duration was five weeks, four out of six animals completed the study and three out of four AVFs remained patent to the 5th week (Florescu et al., 2015). This fistula including a superficial vein is almost identical to the Cimino fistula performed in human patients and therefore can be used in both graft material testing and perioperative drug studies.

A successful sheep AVS model was developed by Kohler and Kirkman (1999) by using a PTFE graft between the right EJV and the left CCA (Kohler and Kirkman, 1999). The graft was placed low in the neck in a gentle S course to minimize failure caused from kinking. The lesions stably developed within the first four weeks, thus producing stenosis (Kohler and Kirkman, 1999). The next model evolved from a uremic sheep model created with subtotal nephrectomy allowing only 8–10% of the blood supply to the intact kidney (Eschbach et al., 1980). The authors cannulated the carotid and jugular vessels as described by Dennis et al. (1974). Dennis et al. (1974) used an AVF in the neck (CA-JV) and the foreleg (radial artery-cephalic vein). The AVFs remained patent up to 775 days. Eschbach et al. (1980) compared A-V cannula and Coumadin treatment (active substance: warfarin) on the foreleg; A-V fistula in the neck or leg and arterial catheters in the right atrium or neck. They all proved to be very complicated for the expected outcome since the median survival of the cannulas was 142 days in the 9 uremic sheep not receiving Coumadin, but only one with Coumadin survived for 208 days.

Schleimer et al. (2018) evaluated vascular prosthesis material by using three different procedures in the vessels of the animals' neck. They used the material as a patch in the CCA, as a graft interposition with a cranial and a caudal end-to-end anastomosis in the CCA and as an arteriovenous shunt in an end-to-side anastomosis between the CCA and the EJV. Most animals (23/24) survived the observation periods of 2–8 weeks with patent operated vessels (Schleimer et al., 2018). The approach used by the researchers offers the possibility to test different materials in different vascular application techniques including perioperative drug studies.

Sheep has a good potential to be used as a model, pertaining an immunological system that has quite some similarities with the human system and being a species one could easily monitor

while in the field. Nevertheless, there is a remarkable difficulty to perform detailed analysis of any experiment in this model at the protein level since very little reagents are commercially available (e.g. antibodies).

4.1.3. Canine vascular access model

There is an older work of Hatzibaloglou et al. describing the operation of a side-to-side AVF femoral artery and vein, an external “shunt” that simultaneously connected the distal and the proximal femoral vein (Hatzibaloglou et al., 1989). Although the authors present haemodynamic data, there are no data conferring to the long-term patency of this fistula, along with the fact that it does not necessarily correlate to the Cimino fistula applied in humans. Another canine model studying shear stress in AVF creating an end-to-side connection between the right femoral artery and vein revealed 28 days’ post operatively that NIH was detectable in the venous segment and there was a strong inverse correlation with wall shear stress levels and it was influenced by flow patterns (Jia et al., 2015).

Nakagawa et al. (1991) interposed the graft between the right CA and the left JV via anastomosis (Nakagawa et al., 1991). Most canine haemodialysis graft models seem to be non-sufficient for research purposes because there is an inconsistent NIH development since it progresses at a slower rate, in some cases in 10–12 months (Trerotola et al., 1999). Therefore, the model is not predictive enough of the pathology developing in humans. Additionally, the NIH developed in these models occurs within the AVS graft rather than within the outflow vein (Trerotola et al., 1999).

The main disadvantage of canine models is the enormous genetic diversity of the canine breeds. Due to this fact, different breeds present different results especially concerning pharmacodynamics and kinetics. That results in severe pathophysiological differences and leads to chaotic complications when interpreting the results (Fleischer et al., 2008).

Nevertheless, due to the fact that dogs are known as domestic animals and they have their place in society as beloved pets, they are not prioritised any more as experimental models.

4.2. Small animal models

4.2.1. Rabbit vascular access model

An end-to-side distal right EJV/CCA anastomosis was made in rabbits by Baldwin et al. (2006). The study presented two different exposure models; one with immediate and one with delayed exposure to ultralow ($<1 \text{ dyn/cm}^2$) shear stress (τ_w). As expected the histological examination revealed statistically significant less NIH development in the delayed exposure group (Baldwin et al., 2006). Simultaneously another research group (Sho et al., 2004) used the same anastomosis on the left side and studied the influence of sequential and prolonged exposure to high and low shear stress. The outcome of this study was that the development of NIH along the arterial segments of the AVF was absolutely related to the local levels of τ_w and the 5 dyn/cm^2 was the pivotal point that NIH starts occurring (Sho et al., 2004). Another research group used the same model and induced chronic renal failure (CRF) with the administration of adenine to study the effects of hyperbaric oxygen in prevention of AVF failure. The development of venous NIH was effectively reduced by hyperbaric oxygen and the blood flow was promoted (Li et al., 2017). That has been a successful variation to induce chronic renal failure via adenine since that is mainly used in the rat models.

4.2.2. Rat vascular access model

There are four main vascular access models in the rat: (i) the anastomosis of the CCA to the EJV (ii) the aortocaval fistula, (iii) the femoral arteriovenous fistulae and (iv) the rat tail AVF model.

The first model is mostly reported as an end-to-side anastomosis between the EJV and the CCA and the arteriovenous malformations caused are similar to the human ones (Yassari et al., 2004). The authors using it recommended it as an appropriate model to study the effects of radiosurgery on arteriovenous malformations (Karunanyaka et al., 2008; Storer et al., 2007; Yassari et al., 2004). This model has been successfully used by several researchers, by some in its uremic variation via 5/6 nephrectomy (Zheng et al., 2015).

The aortocaval fistula model was first reported by Hatt et al. (1980) but remained mainly in the surgical point of it focussing on heart pathology but very little information on basic histopathology of the fistula was provided. Later on, the model was radiologically and histologically evaluated and complete maturation of the fistula was documented histologically between one day and six months (Quisling et al., 1983). Garcia and Diebold (1990), simplified the method by puncturing the aorta and causing a perforation point in the adjacent wall between the aorta and the vena cava sealed with glue. The patency of the fistula reached 100% but the histopathology of the fistula was not addressed in the study. Nevertheless, NIH induced by this model was described in detail by Nath et al. (2003). It was detectable at varying degrees between five weeks or 16 weeks post-operatively (Nath et al., 2003). Researchers used the same model in ovariectomized female and castrated male rats later to study the effect of sex hormones on the aortic wall remodelling. They demonstrated an increase in aorta wall thickness by testosterone and a decrease induced by estrogen (Dorsett-Martin and Hester, 2007). Others successfully proved that by the use of this model MMP inhibition reduces the myocardial remodelling taking place “physiologically” due to chronic blood volume overload (Brower et al., 2007; Chancey et al., 2002). In general, due to the fact that it is a maximally invasive procedure, it is a high-risk surgical operation compared to the CCA-EJV and the models using the femoral vessels, concerning both the actual operation time needed and the postoperative complication risk for the animals. In addition, it is accompanied by a substantial pathology and hence used as a typical heart failure model (Abassi et al., 2011; Brower et al., 2007; Francis et al., 2004).

The AVF model in the femoral vessels of rats is first described as a side to side anastomosis of the femoral artery (FA) to the femoral vein (FV) (Tasbas et al., 2003). Further studies used the same model and reported venous hypertension limb oedema, increased valvular reflux and morphological changes of the vein wall with increase of the MMP-2 and MMP-9 (Pascarella et al., 2005). A femoral AVF rat model is published by Langer et al. (2009), presenting an end-to-side anastomosis of the FV to the FA (Fig. 1), very similar to the Cimino fistula applied in human patients with similar NIH and calcification patterns developed in both the healthy and its chronic kidney disease version. In this case CKD was induced with the feed of adenine (Langer et al., 2010). All rats survived surgery and the patency rate was 93%. The fistula vein diameter increased to double and the mean flow velocity up to 4-fold increase in the intima-media thickness without significant luminal loss. There was no change in the intima-media thickness and minimal adaptive diameter and flow velocity increases in the fistula vein were observed (Fig. 2). Ultrasound was successfully used to detect all those changes and in total, this model presented maturation effects in the fistula veins that are very similar to the typical clinical findings in haemodialysis patients. The model has been successfully used to explore the antagonism between the vitamin K and vitamin K antagonists in uraemia context (Zaragatski et al., 2016).

A last model was demonstrated by Lin et al. (2008). In this model the fistula was an anastomosis of the end of the lateral vein to the side of the ventral artery of the rat tail. The authors mention that there was NIH in four out of five fistulae after 28 days but there are no measurable details or functional data demonstrated. A letter to

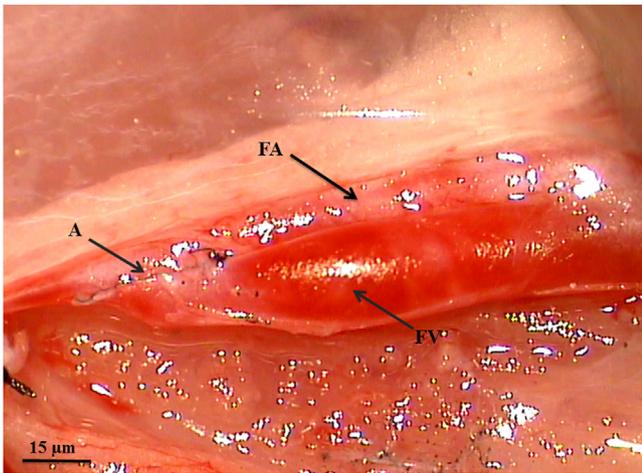


Fig. 1. Native intraoperative image immediately after fistula creation in the femoral vessels of a rat, shows a distinct fistula vein dilatation (25-fold magnification). FA = femoral artery, FV = femoral vein, A = anastomosis of the AVF.

the Editor in the following year reported of encountering technical problems such as scar tissue adhesions, thrombosis in spite of heparinisation, desiccation and the need to compromise the wound closure in order to avoid anastomotic compression of the fistula (Beatty et al., 2009).

4.2.3. Mouse vascular access model

The mouse AVF models are likewise to the rat models either between the CCA and the JV or aortocaval. The CCA/JV models are mostly end-to-side anastomoses of the CA to the JV (Castier et al., 2006; Kang et al., 2011; Wong et al., 2016). Since the human model used is in the opposite direction (end-to-side vein to artery) and has different haemodynamics, the results of this model have to be

considered with caution. Nevertheless, it is an excellent model to study diseases in a genetically modified background in a significant group size (Kang et al., 2016; Misra et al., 2010; Nath et al., 2018) and after extracting the necessary results, move, if necessary, with a filtered experimental plan to another animal model. Similar it is with the aortocaval model; that has been successfully used to explore the effects of intraluminal drug delivery on the AVF endothelium (Hashimoto et al., 2016). As already described for the rat it represents a valuable cardiac hypertrophy model (Karram et al., 2005) and hence, it was used e.g. to prove the fact that an impaired ACE expression does not protect from cardiac hypertrophy (Perry et al., 2001) or the involvement of MMP-9 in myocardial contractile performance (Moshal et al., 2008).

5. Experiment complexity factor

Any of the above mentioned procedures for AVF or AVS creation require surgical skills above the average. The different anatomical relationships in the different species require training to acquire familiarity. Most authors describe very little complications and very low mortality (less than 3%) on their experiments except for the rat tail fistula (Lin et al., 2008) that a follow up publication expresses the authors' distress due to the very low efficiency of this model (Beatty et al., 2009). Concerning the cost effectiveness, such experiments are joint to high costs, especially large animal studies and studies in mice that carry a genetically modified background. Therefore, careful planning is required. If the main prerequisites are provided, namely good surgical skills, good animal surgical practice and appropriate planning, such experiments are expected to have a positive cost effectiveness balance.

6. Overview (Table 1)

Large animals are an ideal model for the configuration of different anatomical relationships to haemodynamic shear stress profiles

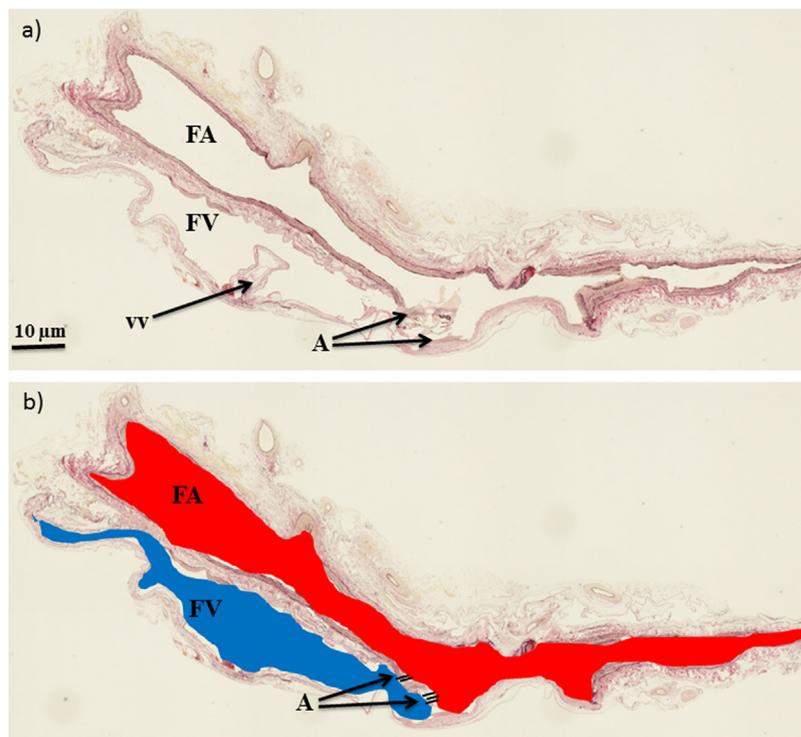


Fig. 2. (a) Longitudinal histological section stained with Elastica von Giesson (X20-fold magnification) of the entire AVF in the femoral vessels of a rat on day 42 postoperatively. The intima–media thickness is most pronounced at the opposite site of the anastomosis (arrow), and the femoral vein dilatation is obvious. (b) graphical reconstruction of image a. FA = femoral artery, FV = femoral vein, A = anastomosis of the AVF, vv = venous valve.

Table 1

Overview of the large and small animal AVF and AVS models described in this review FV = femoral vein, d = days, w = weeks.

Model	Surgical method	Major findings	Patency rates	Methods used to assess findings	Limitations of the model	References
Porcine AVF	End to side FV-to-FA.	Significant early, aggressive luminal stenosis, NIH in the FV at 28- and 42-days (d) post-operatively. Histological pattern similar to the dysfunctioning human AVF (Wang et al., 2008). Adventitial proliferation at 2 days that declined at day 7, 28 and 42 suggesting that perivascular anti-proliferative therapies during surgery might reduce AVF maturation failure. Active myofibroblasts within the “neointimal buds” (Chan et al., 2014). Adequate model for mapping haemodynamic changes (Rajabi-Jagahrgh et al., 2014).	Over 90% at all tested time points.	Histology, immunohistochemistry, micro-MRI.	(i) Use of healthy animals, no uremic version (ii) no AVF cannulation was attempted.	(Chan et al., 2014; Rajabi-Jagahrgh et al., 2014; Wang et al., 2008)
	Side-CCA to end-EJV.	28 days postoperatively 65.2% luminal stenosis & 430.4 μm intima-media thickening. Rapid NIH development.	100% at 28 days	Angiogram, histology, immunohistochemistry.	Use of healthy animals, no uremic version.	(Loveland-Jones et al., 2014)
Porcine AVS	Serolimus coated grafts between the CCA and the EJV.	Serolimus dose dependent, significantly suppressed the NIH development on the venous anastomosis site after 6 weeks (w).	100% at 6 weeks	Histology, immunohistochemistry.	Use of healthy animals, no uremic version.	(Baek et al., 2012)
	PTFE loop grafts between the FA and the FV.	Grafts were removed by day 2, 4, 7, 17 and 28. Minimal NIH was at the arterial anastomosis site. Smooth muscle cells Please delete, myofibroblasts and macrophages in the venous site. Lesions similar to the human.	100% at all time points	Histology, immunohistochemistry.	Use of healthy animals, no uremic version.	(Kelly et al., 2002)
	PTFE grafts between the CCA and the ipsilateral EJV bilaterally.	Good NIH correlation between MRI and histology.	100%	MRI, histology.	Use of healthy animals, no uremic version.	(Terry et al., 2009)
Sheep AVF	Bilateral femoral artery-to-vein shunts. Two tubes per shunt were placed, the left were coated and the right uncoated.	Good model for biocompatibility evaluation of device coatings at early investigation time points.	100%	Arterial gas and flow measurements.	Use of healthy animals, no uremic version.	(Takaseya et al., 2018)
	End-to-site anastomosis, basilica vein to the brachial artery.	Similar to Cimino fistula, adequate model for perioperative drug studies.	60%	Angiogram, histology.	Use of healthy animals, no uremic version.	(Florescu et al., 2015)

Table 1 (Continued)

Model	Surgical method	Major findings	Patency rates	Methods used to assess findings	Limitations of the model	References
Sheep AVS	PTFE graft between the right EJV and the left CCA.	Stable lesion's development within 4 weeks, lesions in the venous end of the graft very similar to the human ones.	72%	Ultrasound, histology.	Use of healthy animals, no uremic version.	(Kohler and Kirkman, 1999)
	AVFs between the CA and the JV, the radial artery and the cephalic vein.	Venipuncture easily performed in a herd environment.	100% to the time of sacrifice		Venipuncture may elicit aversion responses from the animals.	(Dennis et al., 1974)
	AVS via CA-JV cannulas in uremic sheep (via two-stage subtotal nephrectomy). AVS end-side CCA-EJV.	Median survival while uremic 145 days, median survival on dialysis 70 days. 2–8 weeks observation period.	AVS remained patent during the whole survival time of the animals. almost 95% at all time points.		Blood and urine values and chemistries, haemodialysis. Bidirectional Doppler measurement, color-coded duplex ultrasonography, histology, immunohistochemistry.	Uremic animals could survive longer without dialysis. Hypercoagulability (heparin administration).
Canine AVF	Side-to-side femoral artery and vein. End-to-side right femoral artery and vein.	7 and 28 days' observation period. NIH in inverse correlation with the wall shear stress and related to flow patterns.	100% at all time points	Blood pressure and blood flow measurements. Computational flow dynamics, histology.	Does not correlate to the Cimino fistula in humans.	(Hatzibaloglou et al., 1989) (Jia et al., 2015)
Canine AVS	Poly(ether-urethane) graft interposition (loop) between the right CA and left JV.	Graft wall thicknesses of 0.8 mm, 0.9 mm and 1.0 mm.	70% at 2 weeks and 9 months after implantation	Tensile strength tests, burst test, scanning electron microscopy.		(Nakagawa et al., 1991)
	Arteriovenous grafts between the femoral artery and vein.	6 mm PTFE grafts.	All 6 animals had variable stenosis	Contrast material fistulography with iodinated contrast material, histology	Not predictive enough for the human pathology, the NIH develops within the graft and not within the outflow vein.	(Trerotola et al., 1999)
Rabbit vascular access models	End-to-side anastomosis of the right EJV-CCA.	Two groups one with immediate and one with delayed exposure to ultralow shear stress. Less NIH in the delayed exposure.	90%	Blood pressure and flow measurements, histology, western blotting		(Baldwin et al., 2006)
	End-to-side anastomosis of the left EJV-CCA.	NIH due to low shear stress is maximal in the distal CA and related to the levels of local shear stress.		Blood flow measurements, histology, histomorphometry.		(Sho et al., 2004)

Table 1 (Continued)

Model	Surgical method	Major findings	Patency rates	Methods used to assess findings	Limitations of the model	References
Rat vascular access models	Side-to-side anastomosis of the left EJV-CJA while the distal side of the CJV was permanently ligated.	Renal failure model after adenine administration.	All fistulas remained patent at time points of 1, 7, 14 and 28 days.	High-frequency ultrasonography, histology, immunohistochemistry, western blot.		(Li et al., 2017)
	End-to-side anastomosis of the EJV to the CCA.	Arteriovenous lesions similar to human. Appropriate model for radiosurgery effects on malformations. There is a successful uremic variation via 5/6 nephrectomy. Typical heart failure model. Appropriate model hormonal influence studies in the vessels wall. NIH appears between 5 and 16 weeks post-operatively.	High patency levels in not treated control groups at all time points.	Flow measurements, angiography, histology, immunohistochemistry.	Not adequate for graft material testing.	(Karunanyaka et al., 2008; Storer et al., 2007; Yassari et al., 2004; Zheng et al., 2015)
	Aortocaval fistula: side-to-side anastomosis of the abdominal aorta and Vena cava inferior.	Typical heart failure model. Appropriate model hormonal influence studies in the vessels wall. NIH appears between 5 and 16 weeks post-operatively.	Very high in non-treated animals at all time points.	Angiography, histology, immunohistochemistry.	Not adequate for graft material testing.	(Abassi et al., 2011; Brower et al., 2007; Chancey et al., 2002; Dorsett-Martin and Hester, 2007; Francis et al., 2004; Garcia and Diebold, 1990; Hatt et al., 1980; Nath et al., 2003; Quisling et al., 1983)
	Femoral fistula: side-to-side anastomosis of the femoral artery to the femoral vein. Femoral fistula: end-to-side anastomosis of the femoral vein to the femoral artery.	Very similar to the Cimino fistula, similar lesion development to human condition, good model for perioperative drug testing and antagonising studies, uremic variant with adenine.	98–100% at all time points.	98–100% at all time points.	Ultrasound sonography, histology, immunohistochemistry.	Not adequate for graft material testing.
Mouse vascular access models	Tail fistula model: end-to-side anastomosis of the lateral tail vein to the ventral tail artery.	No measurable data.	Almost 80% at all time points.	Histology, immunohistochemistry.	Scar tissue adhesions, thrombosis in spite of heparinisation, desiccation.	(Beatty et al., 2009; Lin et al., 2008)
	End-to-side anastomosis of the CCA to the JV.	Very good model to study disease in a genetically modified background.	100% at all time points.	Angiography, echocardiography, hemodynamics, histology, immunohistochemistry, western blotting.	Opposite direction to the human fistulae used in the clinic.	(Castier et al., 2006; Kang et al., 2016; Kang et al., 2011; Misra et al., 2006; Nath et al., 2018; Wong et al., 2016)
	Aortocaval fistula: side-to-side anastomosis of the abdominal aorta and Vena cava inferior.	Very good model to study disease and vessel wall changes in a genetically modified background, cardiac hypertrophy model, model for intraluminal drug delivery testing.	100% at all time points.	Intraluminal delivery via Adenovirus-GFP, real time PCR, Western and Northern blotting, histology, immunohistochemistry etc.		(Hashimoto et al., 2016; Karram et al., 2005; Moshal et al., 2008; Perry et al., 2001)

and the corresponding AV fistula maturation and stenosis circumstances. Pigs develop stenotic lesions in a consistent manner at the centre of the anastomosis in the outflow vein, rather than within the graft, dissimilar to dogs, sheep and goats. If one for any reason would prefer to eliminate the factor “growth” from the experiment the use of “minipigs” or “micropigs” would almost eliminate it allowing more consistent measurements. Sheep is easier to handle as a model during the monitoring time since pigs have to be trained before experimentation or even anaesthetised in order to perform ultrasound follow-up examinations etc. Additionally to that, pigs respond to follow up examination–stress with the development of hypertension that can end up in bleeding and development of haematomas (Martinez-Miro et al., 2016). The neck and the femoral vasculature of the sheep is similar in size to the human’s equivalent and readily available under the skin in contrary to the porcine ones. All large animal models are very appropriate for clinical animal testing of medical and medicinal products and innovative implants. Nevertheless, the small sample size due to the necessary reduction can be a limiting parameter. Concerning the uremic variation of the models there are very few, and most of them are created with subtotal nephrectomy. That is a limiting parameter because individuals that shall develop hypertension have to be excluded from the vascular studies (Becker and Hewitson, 2013). That is reducing the sample size even more and the significance of the results can be endangered.

Canines are not a species that is used in such experimental setups. Their domestic relationship to humans makes them a non-desirable model, especially when it can be substituted by other species of large or even small animals, depending on the experimental goals. The use of dogs for the creation of AVF and AVS is scarce due to the very slow development of the fistula pathology (Trerotola et al., 1999).

Rodents and rabbits are excellent models for detailed molecular analysis and study of gene expression in the background of genetic modification of the animals. They can be useful up to a point in haemodynamic shear stress studies but not sufficient for intravascular flow studies due to their small vascular diameter and the technical difficulty to develop equipment that can support experimentation on this size level. The development of this technology makes the value-for-money principal relatively difficult to apply. They can definitely be used in animal trials of perioperative medicinal products and in that case they offer the great advantage of the significant sample size number in contrast to the large animal models. Especially rats have a size that permits easier handling, performing of procedures and sampling. The ability of the rat to learn, remember and interact gives the opportunity to train them to cooperate during follow-up monitoring like sampling and ultrasound performance.

Nevertheless, it is worth to mention that apart from one ovine model (Eschbach et al., 1980) no large animal model neither native fistula nor shunt has been tested under uremic conditions. That is an issue in any case of peri- or endovascular therapy testing in large animal studies since there is till now no report in the literature on a respective model. Nevertheless, the pig models seem to be the most appropriate for mechanistic and interventional studies (Krishnamoorthy et al., 2008) and testing of new graft materials (Baek et al., 2012; Misra et al., 2006).

A very good example is the fact that much of the understanding about the pathophysiological responses to chronic cardiac overload has been gained by the use of rat and mouse models of aortocaval fistula. Global understanding of a clinical issue always includes a combination of experimental approaches, even more so when therapeutic agents and approaches are getting involved. Therefore, it is important to combine multidisciplinary expertise that shall be able to address the problem successfully in its different facets.

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