Scand. J. Lab. Anim. Sci. No. 4. 1999. Vol. 26

The pig as a model in blood coagulation and fibrinolysis research

by *Aage Kristian Olsen*[1,2,3], *Axel Kornerup Hansen*[2], *Jørgen Jespersen*[1], *Peter Marckmann*[3] *and Else Marie Bladbjerg*[1].
[1] Department of Thrombosis Research, The University of Southern Denmark, and Department of Clinical Biochemistry, Ribe County Hospital, Esbjerg;
[2] Department of Pharmacology and Pathobiology and
[3] Research Department of Human Nutrition, The Royal Veterinary and Agricultural University, Frederiksberg, Denmark.
Correspondence: Aage Kristian Olsen, Department of Clinical Biochemistry, Ribe County Hospital, Østergade 80, DK-6700 Esbjerg, Denmark
Phone +45 79182415. Fax: +45 79182430. E-mail: aako@ribeamt.dk

Abstract

Animal models are widely used in research on blood coagulation and fibrinolysis, and the choice of a relevant species is crucial. This review focuses on farm and mini-pigs, which have several advantages as animal models in the field of coagulation. The porcine cardiovascular system is rather similar to that found in human beings. Like man, the pig is an omnivore, and in spite of anatomical differences the physiology of the porcine digestive system is also very similar to that of the human system. The pig is sensitive to the development of both spontaneous and diet-induced atherosclerosis, but cerebral and myocardial infarction are uncommon. The porcine coagulation and fibrinolytic systems are in many aspects comparable to those of humans. However, porcine blood is in a hypercoagulable state. The intrinsic coagulation system, in particular, seems to be hyperactive. Sufficient quantities of blood can be obtained but, especially in mini-pigs, good sampling methods are lacking. Generally, the human functional laboratory assays are useful for examination of porcine blood, while only a minority of immunological methods can be used. Ketamin and halothan/nitrous oxide anaesthesia do not seem to have any impact on blood coagulation and fibrinolysis. It is concluded that in comparison with other species both the farm and the mini-pig are good options in coagulation research.

Introduction

Ischemic heart disease (IHD) is the most prevalent cause of death in the Western world (*Møller, 1998*), and blood coagulation and fibrinolysis have a key role in its pathogenesis. Animal models may be of great value in the investigation of this multifactorial disease provided relevant animal species are chosen.

An animal model may be defined *as a living organism in which normative biology or behaviour can be studied, or in which a spontaneous or induced pathological process can be investigated, and in which the phenomenon in one or more respects resembles the same phenomenon in humans or other species of animal (Wessler, 1976).* For models to be attractive, they must be practically applicable. It is essential that samples of sufficient amount and quality can be obtained, and that samples can be analysed in reproducible laboratory assays. Last but not least, welfare aspects of the model have to be considered.

Pigs are widely used in medical research on thrombosis (*Unterberg et al., 1995*), atherosclerosis (*Jacobsson, 1989*), and cardiovascular surgery (*Robotin-Johnson et al., 1998*).

The Subcommittee on Standardisation and Calibration (SSC) has established the *Animal, Cellular, and Molecular Models of Thrombosis and Haemostasis*-workgroup, as a part of the

International Society on Thrombosis and Haemostasis (ISTH) work on standardisation and calibration (*Johnson et al., 1999*).
This review has its special emphasis on the biology, pathology, and practical advantages and disadvantages of the farm as well as the mini-pig as a model in coagulation and fibrinolysis research.

Breeds of pigs
The farm pig (Sus Scrofa Domesticus) belongs to the non-ruminants in the order of cloven-footed animals (*Haarløv, 1986*). Farm pigs grow very rapidly, e.g. Danish land-race pigs grow approximately 800 grams per day, reaching an adultweight of 200 - 400 kg. Several breeds of mini-pigs raised specifically for research purposes have been developed over the last 30 years. Most of them, e.g. Göttingen or Sinclair mini-pigs, derive from the Minnesota mini-pig. The Yucatan mini-pig is originally a Mexican feral pig, which has later been developed into the Yucatan micro-pig. Mini-pig breeds grow far less than farm pigs, e.g. Göttingen mini-pigs and Yucatan micro-pigs have an adultweight of 30 - 50 kg, while the Yucatan mini-pig reaches 70 - 90 kg (*Bollen et al., 1999*). The smaller weight makes transport and handling easier, and feeding costs are lower. The latter may compensate for the higher price of mini-pigs (*Muller et al., 1992*). Genetically, mini-pigs are more homogenous than farm pigs.

Anatomy and physiology
The cardiovascular system. The pig heart is anatomically and physiologically rather similar to the human heart. The presence of a left vena azygous draining the intercostal system into the coronary sinus represents an important exception. Porcine haemodynamics are also largely similar to humans. In mini-pigs of 40 - 50 kg, the porcine heart is of approximately the same size as an adult human heart, and the coronary system is anatomically and physiologically similar to that of the human (*Swindle and Smith, 1998*). The diameter of the coronary arteries is 1.0 - 2.5 mm in both farm and mini-pigs, which is comparable to those of humans (*Muller et al., 1992*). The right coronary artery and the left anterior descending artery each supply 40% of the myocardium, while the left circumflex artery plays a relatively minor role, fairly similar to the situation in man (*Gross, 1994*).
The digestive system. The anatomy and physiology of the porcine digestive system have previously been described in detail (*Nicel et al., 1984; Herdt, 1992*). The stomach of the pig is typical of a monogastric species (such as humans) with the exception of a pouch designated *torus pyloricus* near the pyloric sphincter, which has the consequence that a fasting pig stomach contains more food than a human stomach (*Nickel et al., 1984; Swindle & Smith, 1998*). Like man, the pig is a true omnivore, and it normally accepts consuming a diet similar to the human diet (*Muller et al., 1992; Gross, 1994*). This has led to the pig being used extensively as a gastrointestinal model. Only minor differences are found between man and pig in the manner in which dietary lipids are absorbed, transported, and metabolized. Pigs fed a diet containing 2 - 3% cholesterol easily develop plasma cholesterol levels of 25 mmol/l, while plasma cholesterol levels in pigs fed a cholesterol free diet are lower than 2.5 mmol/l (*Gross, 1994*), similar to the level of newborn human babies (*Bellú et al., 1992*).
The interrelationship between diet, blood coagulation, and fibrinolysis in humans is of great importance (*Marckmann, 1995*), and it is reasonable to believe that the pig is a good model for dietary studies.

Atherosclerosis and thrombosis in pigs
Pigs may develop spontaneous atherosclerosis at the age of 2 to 4 years (*Moreland, 1993*), and they are also susceptible to diet-induced atherosclerosis. Atherosclerotic lesions are observed in pigs maintained on a normal pig diet, but are more common in pigs fed cooked garbage (*Gross, 1994*). The location and morphology of the atherosclerotic lesions are similar to those in humans, but ulceration, thrombosis, and plaque haemorrhage are uncommon (*Gross, 1994*). Severe atherosclerosis in pigs is accompanied by increased blood clotting activity (*Rowsell et al.,1958*). Cerebral and myocardial infarctions in

pigs are, however, only rarely observed (*Muller et al., 1992*).

Blood coagulation and fibrinolysis

The components of the porcine and the human coagulation and fibrinolytic systems are assumed to be identical (Figure 1). Several investigators have measured the concentration of single factors and/or global coagulation tests, such as prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT), in pigs (*Earl et al., 1971*; *Kase, 1972*; *Bowie et al., 1973*; *Kostering et al., 1983*; *Lutze et al., 1992*; *Karges et al., 1994*; *Reverdiau-Moalic et al., 1996*; *Hahn et al., 1996*; *Roussi et al., 1996*). PT is used to screen the extrinsic coagulation cascade, APTT is used to screen the intrinsic coagulation cascade, and TT expresses the concentration of fibrinogen (*Jespersen et al., 1999*). These data are summarized in Tables 1-4. Differences in calibrators, kits, pre-analytical handling, breeds, and ages are major contributors to the variation in published data.

Some differences between pigs and humans can be observed. The PT values are approximately equal, but the APTT is shorter in porcine than in human plasma (Table 1). This is in accordance with the fact that the levels of several coagulation factors, e.g. factor IX (FIX), factor XI (FXI), factor XII (FXII), and high-molecular-weight-kininogen (HMWK) are all higher in porcine plasma (Table 2). This might indicate accelerated intrinsic cascade activity in pigs. Concentrations of thrombin-antithrombin complexes (TAT) are dispersed in porcine plasma (Table 3) (*Roussi et al., 1996*), whereas the concentration of soluble fibrin is nearly identical in humans and pigs (Table 3 and 4) (*Spannagl et al., 1993*). The concentration of the coagulation inhibitor antitrombin is nearly identical in humans and pigs, whereas the activity of protein C is lower in porcine plasma (Table 4) (*Roussi et al., 1996*). These observations suggest that porcine plasma is hypercoagulable compared with human plasma, and which probably explains why it is easy to induce disseminated intravascular coagulation (DIC) in the pig. A pre-thrombotic state associated with an increase in the concentration of TAT has previously been induced in pigs by infusion of thromboplastin through the ear vein (*Ravanat et al., 1995*). Infusion of lipopolysaccharide (LPS) or dextran sulphate through the jugular vein of mini-pigs induced increased concentrations of soluble fibrin and TAT over the following few hours (*Spannagl et al., 1993*).

When comparing the blood coagulation system of farm pigs with that of mini-pigs, only minor differences were found. Both breeds showed a tendency to hypercoagulability (*Kostering et al., 1983*).

Only a few studies have measured variables of the fibrinolytic system in pigs. Plasminogen concentrations are only 3.6% of human levels, while antiplasmin concentrations are 80% of human levels (Table 4). The low plasminogen level may be an artifact - due to insufficient activation of plasminogen (*Karges et al., 1994*). The porcine plasma concentration of tissue plasminogen activator (t-PA) antigen is similar to human concentrations (Table 3 and 4) (*Roussi et al., 1996*). The porcine platelet system has been described elsewhere and is also in many aspects similar to that of man (*Søfteland et al., 1992*).

Blood sampling techniques

In haemostasis research, it is essential to have access to blood samples in sufficient quantities. The porcine blood volume is 75 ml/kg. Although 25% of the volume may be sampled without causing the death of the pig, it is not advisable to sample more than 10%, i.e. 7.5 ml/kg (*Bollen et al., 1999*). The ear veins are the only visible veins in the pig, and in farm pigs they are large and catheterization is easy. In mini-pigs, however, the ear veins are small and fragile, and catheterization is difficult. In both farm and mini-pigs, blood can be drawn using a long silicone catheter intruded into the ear vein and reaching the vena jugularis or the vena cava cranialis, if more than 5 ml of blood are needed. Such a catheter may prove to be difficult to insert in the mini-pig.

The easiest non-visible vein to access in the farm pig is the external vena jugularis, which can be punctured in the supraclavicular fossa. In the mini-pig it is easier to access the cranial vena cava just cranial to the sternum (jugulum) (*Svendsen &*

Figure 1. Blood coagulation and the extrinsic or tissue-type dependent fibrinolytic system.

activation: ——, inhibition:-----. HMWK: high-molecular-weight-kininogen, FXII: factor XII, FXI: factor XI, FIX: factor IX, TF: tissue factor, FVII: factor VII, FX: factor X, FV: factor V, FXIII: factor XIII, F1+2: prothrombin fragment 1+2, AT: antithrombin, TAT: thrombin-antithrombin complexes, FPA: fibrinopeptide A, SF: soluble fibrin, PAI: plasminogen activator inhibitor, t-PA: tissue-type plasminogen activator, AP: antiplasmin, PAP: plasmin-antiplasmin complexes, Pho: phospholipids. *a*: activated coagulation factors.

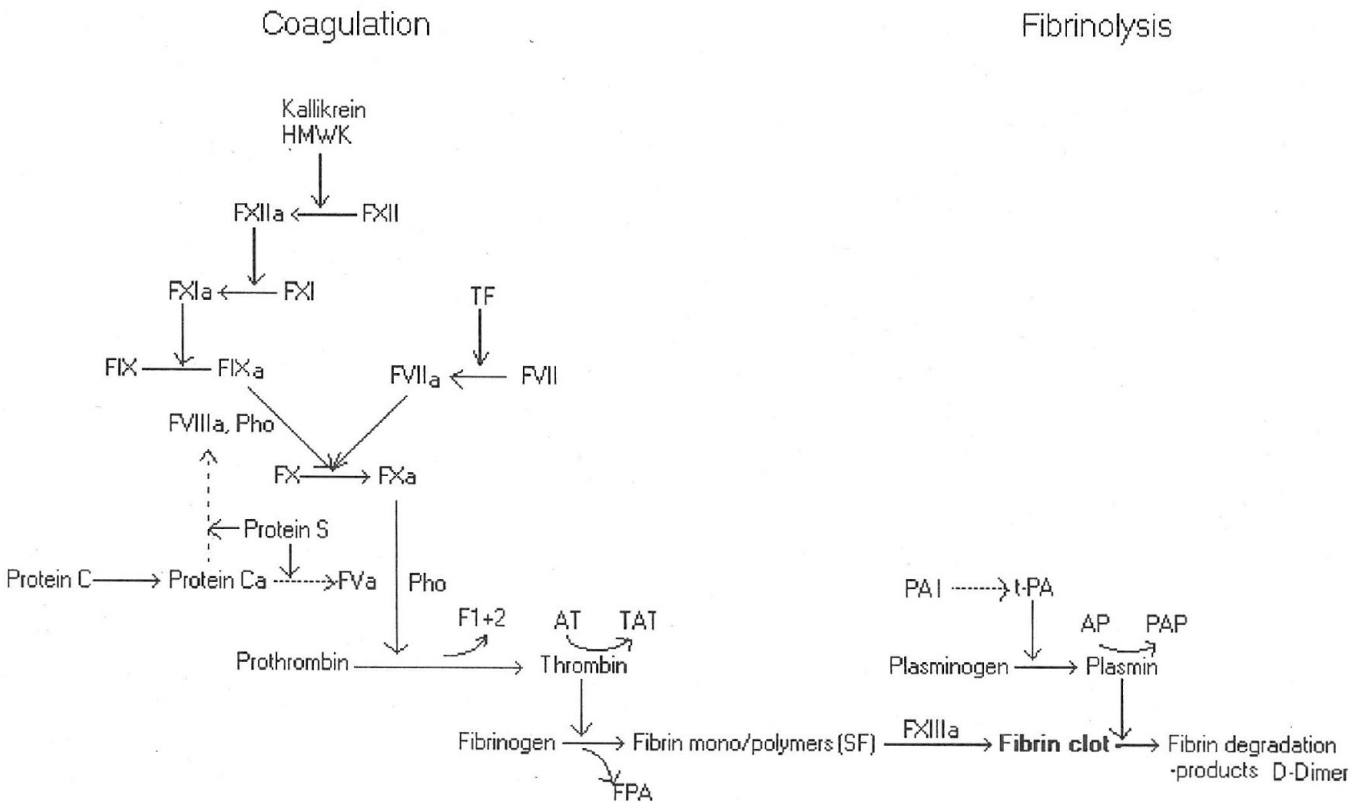

Table 1. Global coagulation tests in pigs and humans

Variable	Pig	Human
PT (s)	11-13 [1,2,3]	10-14 [2]
APTT (s)	15-21 [1,2,3]	28-40 [2]
TT (s)	23-35 [1,2,3]	14-21 [2]

PT: prothrombin time, APTT: activated partial thromboplastin time, TT: thrombin time.
[1] Lutze et al., 1992, [2] Karges et al., 1994, [3] Reverdiau-Moalic et al., 1996.

Table 2. Plasma concentrations of coagulation variables in pigs measured with clot assays.

Variable	Concentrations (% of normal human plasma)
Fibrinogen	60-133% [1,5-7]
Prothrombin	60-90% [2-5]
Factor V	1100% [2-5]
Factor VII	30-196% [2-5]
Factor VIII	555-782% [2-5]
Factor IX	300-450% [2,3,5]
Factor X	50-289% [2,3,5]
Factor XI	200-275% [3,5]
Factor XII	747-1275% [3,5]
Factor XIII	220% [3]
HMWK	847% [3]

HMWK: high-molecular-weight-kininogen, [1] Bowie et al., 1973, [2] Lutze et al., 1992, [3] Karges et al., 1994, [4] Hahn et al., 1996, [5] Reverdiau-Moalic, 1996, [6] Roussi et al., 1996, [7] Dickneite & Leithäuser, 1999.

Table 3. Plasma concentrations of coagulation and fibrinolysis variables in pigs measured with immunological methods.

Variable	Commercial kit	Concentrations
F1+2	Enzygnost F1+2 Behring (Marburg, Germany)	n.d.[2-4]
	Dade Prothrombin F1+2 Baxter Diagnostics (Deerfield, IL)	n.d.[2]
	Thrombonostika F1.2 Organon Teknika (Durham, NC)	n.d.[2]
TAT	Enzygnost TAT Behring (Marburg, Germany)	9-20 ng/ml[3-6]
FPA	Asserachrom FPA Stago (Asnières, France)	n.d.[3]
Soluble fibrin	Enzymun-Test Boehringer (Mannheim, Germany)	1 µg/ml[1]
t-PA	Asserachrom tPA Stago (Asnières, France)	24 ng/ml[4]
	TintElize t-PA Biopool (Umeå, Sweden)	1.5 ng/ml[5]
PAI	Asserachrom PAI Stago (Asnières, France)	n.d.[4]
D-Dimer	Asserachrom D-Di Stago (Asnières, France)	n.d.[3,4]

n.d.: not detectable with the reagent used, F1+2: prothrombin fragment 1+2, TAT: thrombin-antithrombin complex, FPA: fibrinopeptide A, t-PA: tissue-type plasminogen activator, PAI: plasminogen activator inhibitor, [1] Spannagl et al., 1993, [2] Valdes-Camin & Ebert, 1994, [3] Ravanat et al., 1995, [4] Roussi et al., 1996, [5] Jourdain et al., 1997, [6] Dickneite & Leithäuser, 1999. Note: Plasma was recalcified in reference number 3 before analysis.

Table 4. Plasma concentrations of coagulation and fibrinolysis variables in pigs measured with chromogenic substrates.

Variable	Commercial kit or reagent	Concentrations (Units or % of normal human plasma)
Protein C	Staclot Protein C Stago (Asnières, France)	3.2U/ml[4]
Protein S	Staclot Protein S Stago (Asnières, France)	n.d.[4]
Antithrombin	Stachrom ATIII Stago (Asnières, France)	155%[3]
	Berichrome ATIII Behring (Marburg, Germany)	101%[1]
Soluble fibrin	For details see reference	20 nmol/l[2]
Plasminogen	Berichrome Plasminogen Behring (Marburg, Germany)	3.6%[1]
Antiplasmin	Berichrome α_2-antiplasmin Behring (Marburg, Germany)	80%[1]
t-PA	Coa-Set t-PA/PAI Diagnostica (Mölndal, Sweden)	4 IU/ml[2]
PAI	Coa-Set t-PA/PAI Diagnostica (Mölndal, Sweden)	30-45 AU/ml[2,5]

n.d.: not detectable with the reagent used, t-PA: tissue-type plasminogen activator, PAI: plasminogen activator inhibitor, AU: arbitrary unit, [1] Karges et al., 1994, [2] Villeda et al., 1995, [3] Reverdiau-Moalic et al., 1996, [4] Roussi et al., 1996, [5] Jourdain et al., 1997.

Rasmussen, 1998). Since punctures of the two veins are performed blindly, there is always a risk of damage to the vein. If repeated sampling of arterial and venous blood are required, a permanent catheter is therefore preferred. Under general anaesthesia, a permanent catheter can be placed in the jugular vein, the femoral vein and artery, the carotid artery, the cephalic vein, and (in females) the epigastric vein (*Svendsen & Rasmussen, 1998*). Investigations of the coagulation system often exclude the use of heparin in the catheter, and therefore, the period during which blood catheters can be used, is short. The use of Vascular Access Ports®, which for other studies have proved useful in pigs (*Svendsen et al., 1989*), is difficult without heparin. It is also a disadvantage that pigs with permanent catheters have to be isolated from one another. Recently, a new rapid and non-surgical method for jugular catheterization was developed (*Matte, 1999*). Especially in mini-pigs, a validated method for continuous sampling of blood is lacking.

The use of anaesthesia

Ethical, legal, and practical circumstances often necessitate the use of general anaesthesia, and it is important to know the physiological impact of the anaesthetic drugs. Several anaesthetics have been reported to modify coagulation and fibrinolytic variables (*Gross, 1994*). Measurements of haemostasis in farm pigs, pre-anaesthetized with ketamine chloride and ventilated with a mixture of halothane, nitrous oxide and oxygen, showed no modifications of bleeding time, platelet aggregation, coagulation factors, coagulation inhibitors, and fibrinolytic variables, and, therefore, this procedure should be preferred for experimental studies on thrombosis in pigs (*Roussi et al., 1996*).

Blood analyses

Tables 2-4 show concentrations of blood coagulation and fibrinolysis variables in pigs measured by clot assays (Table 2), immunological assays (Table 3), or by use of chromogenic substrates (Table 4). As a general rule, functional human methods can be applied on pig plasma as well, whereas immunological methods cannot and they have to be modified.

Comparison with other species

The choice of the pig for animal models depends on its usefulness compared with alternative species. Advantages and disadvantages of other species are briefly presented in Table 5. In the species examined, the PT is shorter than the APTT, which is similar to the situation in humans (*Karges et al., 1994*). Both primates and pigs have a cardiac system similar to that of man. Rats, mice, pigs, and primates are all omnivores like humans. There is no doubt that, from a comparative point of view, primates are valuable models and, in general, human analytical methods work better with primates. Primates are, however, expensive and difficult to maintain, in contrast to rabbits, mice, and rats, and to some extent also pigs. Dogs are also expensive, although not that difficult to maintain. All species but mice are in most cases large enough to deliver off blood samples, but blood sampling from pigs and monkeys is more troublesome for other reasons. Pigs, rats, mice, and rabbits defined free of a long range of microorganisms may be obtained (*Hansen, 1998*), while breeds of primates and dogs are normally only defined free of a limited number of microorganisms.

Final remarks

The biology and pathology of the pig are very similar to those of humans, and the practical problems with blood sampling are surmountable. Whether the pig is a good model in research on coagulation and fibrinolysis depends on the actual subject of investigation. The phenomenon studied in the animal model must resemble the same phenomenon observed in humans. Generally, the pig is a good model in research of atherosclerosis. Furthermore, due to the fact that porcine blood apparently is in a hypercoagulable state DIC is easy to induce.

We conclude that the pig is a good animal model in research on blood coagulation and fibrinolysis, but the hypercoagulable state, the accelerated intrinsic cascade, and the rarely occurring

Table 5. Selected variables and characteristics of relevance when choosing a species as a model in coagulation research.

	Rat	Mouse	Rabbit	Dog	Pig	Primate	Human
The coagulation system PT (s):	12,1[3]	7,3[1]	9,9[3]	7.4[3]	11.4[3]	12.0[3,a]	10-14[3]
APTT (s):	64.9[3]	22.0[1]	21.4[3]	17.7[3]	16.6[3]	36.8[3,a]	28-40[3]
TT (s):	48.2[3]		15.7[3]	15.3[3]	22.6[3]	20.3[3,a]	14-21[3]
Susceptibility to atherosclerosis	resistant[2]	dietary	dietary[2,b]	resistant[2]	spontaneous[2]	variable[2]	spontaneous[2]
Digestive system	omnivore	omnivore	herbivore	carnivore	omnivore	omnivore	omnivore
Acquiring and maintaining[c]	cheap/easy	cheap/easy	cheap/easy	expens./easy		exps./diffic.	
Volume of blood sampling[d]	2.4 ml	0.35 ml	34 ml	160 ml	240 ml[e]	56 ml[f]	500 ml[g]
Methods of blood sampling	easy	easy	easy	easy	difficult	difficult	easy

[1]Tsang et al., 1979, [2]Muller et al., 1992, [3] Karges et al., 1994, [a] Maccacca fascicularis, [b] Watanabe-heritable-hyperlipidemic (WHHL) rabbits developed spontaneous atherosclerosis, [c] Compared with pig, [d] Max. 10% of the blood, [e] Mini-pig, [f]Rhesus monkey, [g] The normal quantum drawn from blood donors.

spontaneous thromboses must be taken into consideration.

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