Scand. J. Lab. Anim. Sci. No. 1. 1997. Vol. 24

Blood coagulation, platelets and haematocrit in male, female, and pregnant Göttingen minipigs

by *G. Petroianu, W. Maleck, S. Altmannsberger, A. Jatzko & R. Rüfer.*
Institute of Pharmacology, University of Heidelberg at Mannheim
Maybachstr. 14-16, D-68169 Mannheim, Germany.

Introduction

Pigs are commonly used animals for research in resuscitation and experimental anaesthesia. Reasons for this are their "human-like" size and physiology, which allows use of most equipment for human medicine without modification and the fact that use of "pet-animals" (i.e. dogs) is unpopular. Although juvenile domestic pigs can be used for research, adult minipigs (e.g. Göttingen breed) are a better approximation of adult human physiology. For some types of research (e.g. obstetrical) they are almost essential, because adult pregnant domestic pigs are too big to be convenient lab animals.

Information on the coagulation system of an experimental animal is essential for scholars to select an appropriate model (*Karges et al.* 1994, *Ellegaard et al.* 1995).

Comparatively few reports exist on coagulation and haematological parameters in Göttingen breed minipigs. None of them mentions single factor activities.

Even more sparse is information on such parameters in *pregnant* Göttingen sows (*Grote et al.* 1977).

In this report, we present normal coagulation and haematological parameters in Göttingen breed minipigs (male, female, and pregnant) as measured in our laboratory and compare these to the literature.

Material & Methods

Animals, housing, and health status

39 Göttingen breed minipigs were used. 15 were gravid (gestation day 105 out of 110, age 30 ± 11 months, weight 49 ± 12 kg), 16 were female non-pregnant (age 11 ± 8 months, weight 24 ± 10 kg) and 8 were male (non-castrated, age 8 ± 2 months, weight 21±3 kg). They were not specifically used for obtaining baseline values of coagulation, rather belonged to two experimental series on amniotic fluid embolism and organophosphate poisoning. These animal experiments were performed with consent of state authority according to federal law. The animals were obtained from the former breeder (Versuchsgut Relliehausen, Universität Göttingen, Waldstrasse 5, 37586 Dassel) about 2 weeks before the experiments. They were kept in individual cages in a room kept at 21°C, 60% relative humidity and 12 hours of light per day. The minipigs were fed 500-700 g dry food (Sauenmehl Provit Uni, Raiffeisen Kraftfutterwerke Süd GmbH) and tap water ad libitum. All animals were in apparently good health at the time of the experiments.

Blood Sampling

For induction a ZESTRANI-(zero-stress-anaesthesia-induction)-method (*Petroianu & Rüfer* 1994) was employed. Animals fasted for 12 h were premedicated with Fentanyl applied on sugar cubes p.o. ad libitum (mean intake 2.5 ± 1.6 mg). After adequate sedation (as assessed by clinical impression) was achieved (mean time 24 ±11 min) Ketamine 400 mg + Flunitrazepam 2 mg were given i.m. The animals were weighed and the left ear vein was cannulated (1 mm I.D.). After preoxygenation by mask, muscle relaxation was achieved with Alcuronium 0.2 mg*kgBW^{-1} i.v. and additional drugs given Lidocaine 2 mg*kgBW^{-1} and Fentanyl 0.005 mg*kgBW^{-1}. The animals were orotracheally intubated (7 mm I.D.) and mechanically ventilated (F_iO_2 = 0.5, 0.2 % Halothane and balance N_2O; tidal volume 10 ml*kgBW^{-1}; 15 cycles min^{-1}).

The left external jugular vein was surgically exposed and a catheter introduced. As soon as venous access was established, 5 ml of 10% citrated blood for coagulation analyses and 5 ml of EDTA (1.6 mg/ml) blood for microhaematocrit and platelets

was obtained. After this the main procedures (on amniotic fluid embolism or organophosphates) were performed.

Analytical methods

Haematocrit was determined using a microhaematocrit centrifuge Z 230 HA (Hermle Labortechnik GmbH, D-78564 Welingen, Germany). Platelets were measured on a Coulter Counter ZM (Coulter Electronics, D-47803 Krefeld, Germany). Coagulation analyses were done on a Behring Chromotimer System (Behringwerke, D-35037 Marburg, Germany) using Behring reagentia as follows:

PTT:	CTS-Neothrombin
PTI (Quick):	Chromoquick
AT III:	Berichrom-Antithrombin III
Protein C:	Berichrom Protein C
Fibrinogen:	CTS-Fibrinogen-Reagenz
Factors V,VII,VIII:	Specific factor-deficient plasma

Factor activities are expressed in a system where the normal human standard is assumed to be 100 %.

Statistical methods

The three groups of animals were compared using the Whitney-Mann rank-order test. A Bonferroni-correction (factor 30) was applied (*Bland & Altmann* 1995). All values are rounded to significant decimals. We did *not* exclude outliers.

Table 1. Reference values of our laboratory for Göttingen minipigs.

Parameter	Unit	Males (n=8)	Females (n=16)	Pregnant (n=15)
Haematocrit	%	34 ± 4 (30-42)	33 ± 5 (18-42)	30 ± 4 (26-41)
Platelets	10^9/l	490 ± 90 (349-630)	420 ± 120 (166-651)	310 ± 80 (155-494)
Fibrinogen	g/l	9.0 ± 2.6 (4.0-13.2)	7.5 ± 3.3 (2.4-15.6)	5.8 ± 1.1 (3.6-8.7)
PTT	sec	26 ± 7 (19.3-47.3)	30 ± 4 (22.1-39.5)	29 ± 5 (21.2-49.9)
PTI (Quick)	% human	170 ± 30 (128-227)	180 ± 30 (108-267)	190 ± 40 (130-254)
AT III	% human	110 ± 20 (67-150)	110 ± 10 (81-146)	100 ± 20 (59-138)
Factor V	% human	360 ± 80 (270-830)	450 ± 150 (230-860)	420 ± 120 (240-630)
Factor VII	% human	110 ± 40 (50-174)	140 ± 40 (43-200)	110 ± 40 (42-170)
Factor VIII	% human	260 ± 100 (126-498)	340 ± 90 (219-511)	350 ± 160 (122-857)
Protein C	% human	52 ± 19 (28-70)	76 ± 18 (43-132)	83 ± 18 (31-109)

All values are given as Mean ± SD (Minimum – Maximum).

Data analysis

A Medline Search from 1966 to 1996 was done with the items (blood coagulation or blood clotting) and (pig or swine).

Additionally, secondary literature and literature otherwise known to us was included. Because the body of literature specifically dealing with normal values of coagulation in the pig is small, we included baseline values from studies dealing with other issues.

- We tried to extract number, age, weight and sex of the pigs used. Ill or pretreated pigs were excluded.
- For each parameter, we tried to extract the way the blood was collected, the method of measurement, the mean and the standard deviation. In some cases missing standard deviations were estimated from the range (*Lentner* 1980).
- Omissions in the methods of most studies make this data incomplete. Parameters for which the number of animals or the mean of the value were unknown are not included.
- Parameters that could not be converted into the system of units used in our laboratory are not included. This applies to coagulation factors given as percent of pig standard because we used percent of human standard and to prothrombin time (Quick) given in seconds instead of percent.
- If for a parameter reference values in Göttingen minipigs were found, all others were omitted (table 2-6). For the factor activities however no comparison values in Göttingen minipigs were found, so studies in other races are given for comparison (table 7-10).

Results

Our reference values for 2 haematological and 8 coagulation parameters for male, female, and pregnant Göttingen minipigs are shown in table 1. For each parameter mean values, standard deviations

Table 2. HK (%)

Reference	Race	Age	Sex	#	Mean±SD	Blood	Method
Becker 1976	Gött.	15w	?	20	32 ± 3	ac	Micro
	Gött.	15w	?	60	39 ± 4	vp	Micro
	Gött.	>7m	?	20	40 ± 4	vp	Micro
Brechbühler 1984	Gött.	5-10w	b	54	33 ± 4	ac	Micro
Ellegaard 1995	Gött.	3m	m	15	37 ± 2	vp	Cobas
	Gött.	3m	f	15	37 ± 2	vp	Cobas
	Gött.	6m	m	15	38 ± 2	vp	Cobas
	Gött.	6m	f	15	38 ± 2	vp	Cobas
Grote 1977	Gött.	adult	p	6	55	hp	?
Oldigs 1984	Gött.	?	?	16	31 ± 1	c	Coulter
	Gött.	?	?	16	36 ± 1	vp	Coulter
Pering 1975	Gött.	?	m	10	45	vp	?
Taupitz 1977	Gött.	5-6m	c	8	39 ± 1	vp	Micro
Wrogemann 1977	Gött.	1-1$^1/_2$y	m	4	34 ± 3	vc	Coulter
	Gött.	1-1$^1/_2$y	f	4	32 ± 3	vc	Coulter

Abbreviations:
Race: Gött. = Göttingen Minipig
Sex: f = female, p = pregnant, m = male, c = castrated, b = both
Sample: ac = arterial catheter, c = catheter, vc = venous catheter, vp = venipuncture, hp = heart puncture

Table 3. Platelets (10^9/l)

Reference	Race	Age	Sex	#	Mean ± SD	Blood	Method
Ellegaard 1995	Gött.	3m	m	15	510 ± 90	vp	Cobas
	Gött.	3m	f	15	490 ± 110	vp	Cobas
	Gött.	6m	m	15	350 ± 80	vp	Cobas
	Gött.	6m	f	15	360 ± 50	vp	Cobas
Heitz 1990	Gött.	?	?	19	450	?	Coulter
Köstering 1983	Gött.	?	?	84	330 ± 60	vp	Coulter
Pering 1975	Gött.	?	m	10	767	vp	Fonio
Schmidt 1980	Gött.	?	?	15	330	?	?
Stokke 1986	Gött.	?	?	9	325 ± 120	vc	Fonio
Wolter 1978	Gött.	?	?	4	364 ± 74	vc	Coulter

Abbreviations:
Race: Gött. = Göttingen Minipig Sex: f = female, m = male
Sample: vc = venous catheter, vp = venipuncture

Table 4. Fibrinogen (g/l)

Reference	Race	Age	Sex	#	Mean ± SD	Blood	Method
Ellegaard 1995	Gött.	3m	m	15	6.5 ± 1.3	vp	IL Test
	Gött.	3m	f	15	5.4 ± 0.7	vp	IL Test
	Gött.	6m	m	15	6.8 ± 1.2	vp	IL Test
	Gött.	6m	f	15	4.8 ± 0.6	vp	IL Test
Köstering 1983	Gött.	?	?	84	3.6 ± 1.0	vp	Schulz
	Gött.	?	?	84	1.4 ± 0.3	vp	Clauss
Schmidt 1980	Gött.	?	?	15	1.6	?	?
Stokke 1986	Gött.	?	?	9	1.1 ± 0.2	vc	Clauss
Wrogemann 1977	Gött.	1-1½y	f	3	3.7 ± 1.1	vc	?

Abbreviations:
Race: Gött. = Göttingen Minipig Sex: f = female, m = male
Sample: vc = venous catheter, vp = venipuncture

and lowest and highest values are shown.
Significant differences were noted between male and pregnant animals for the following parameters:

- Protein C is higher in pregnant compared to male pigs ($p<0.03$)
- Fibrinogen is lower in pregnant compared to male pigs ($p<0.03$)
- Platelets are lower in pregnant compared to male pigs ($p<0.03$).

Neither between male and non-pregnant female

Table 5. aPTT (s)

Reference	Race	Age	Sex	#	Mean ± SD	Blood	Method
Ellegaard 1995	Gött.	3m	m	15	46±6	vp	IL Test
	Gött.	3m	f	15	44±10	vp	IL Test
	Gött.	6m	m	15	43±8	vp	IL Test
	Gött.	6m	f	15	43±10	vp	IL Test
Köstering 1983	Gött.	?	?	84	21±2	vp	Behring
Schulz 1995	Gött.	?	f	18	17	vc	?
Stokke 1986	Gött.	?	?	9	17±2	vc	?
Wrogemann 1977	Gött.	1-1$^1/_2$y	f	3	24±1	vc	?

Abbreviations:
Race: Gött. = Göttingen Minipig Sex: f = female, m = male
Sample: vc = venous catheter, vp = venipuncture

Table 6. PTI (Quick) (human%)

Reference	Race	Age	Sex	#	Mean ± SD	Blood	Method
Heitz 1990	Gött.	?	?	19	85	?	Behring
Köstering 1983	Gött.	?	?	84	90±15	vp	Behring
Stokke 1986	Gött.	?	?	9	99±3	vc	?

Abbreviations:
Race: Gött. = Göttingen Minipig Sample: vc = venous catheter, vp = venipuncture

Table 7. AT III (human%)

Reference	Race	Age	Sex	#	Mean ± SD	Blood	Method
Karges 1994	Germ.	10m	?	14	101±6	ap	Behring
Lutze 1992	Germ.	10m	b	12	113±12	vp	?
Massicotte 1986	?	0-1d	?	12	35	vp	?
	?	7d	?	12	70	vp	?
	?	adult	b	20	76	vp	?
Porte 1991	York.	?	f	23	115	ac	?
Reverdiau 1996	White	fetus	?	20	54±11	up	Stago
	White	0d	?	20	76±12	vp	Stago
	White	adult	?	20	155±15	vp	Stago

Abbreviations:
Race: Germ. = German Land, York. = Yorkshire Sex: f = female, b = both
Sample: ac = arterial catheter, vp = venipuncture, ap = arterial puncture, up = umbilical cord

Table 8. Factor V (human%)

Reference	Race	Age	Sex	#	Mean ± SD	Blood	Method
Bengmark 1972	Swed.	?	?	5	510 ± 240	ac	Aas
Bowie 1973	York.	3-5m	?	7	480	vp	?
Hafström 1974	Swed.	?	?	14	790 ± 350	ac	Aas
Hahn 1996	Germ.	2-4m	b	23	367 ± 50	vc	Biggs
Harrison 1985	?	4m	?	1	250	vc	?
Hathaway 1964	?	0-1d	?	5	200 ± 30	vp	Borchg.
	?	7d	?	5	280 ± 30	vp	Borchg.
	?	adult	?	5	800	vp	Borchg.
Karges 1994	Germ.	10m	?	14	790 ± 140	ap	Behring
Lutze 1992	Germ.	10m	b	12	1200 ± 200	vp	?
Massicotte 1986	?	0-1d	?	12	100	vp	?
	?	7d	?	12	400	vp	?
	?	adult	b	20	200	vp	?
McLoughlin 1996	York.	?	f	29	588 ± 77	c	?
Reverdiau 1996	White	fetus	?	20	133 ± 23	up	Stago
	White	0d	?	20	188 ± 38	vp	Stago
	White	adult	?	20	444 ± 95	vp	Stago

Abbreviations:
Race: Germ. = German Land, Swed. = Swedish Land, York. = Yorkshire
Sex: f = female, b = both
Sample: ac = arterial catheter, c = catheter, vc = venous catheter, vp = venipuncture, ap = arterial puncture, up = umbilical cord

pigs nor between non-pregnant female and pregnant pigs were significant differences found.

Discussion / Blood sampling
As we obtained blood samples after induction of anaesthesia, our values should be compared with caution to values obtained either by puncture in awake animals or from chronically catheterized animals as an influence of anaesthesia cannot be excluded. However, the drugs used are approved for use in human surgical anaesthesia and intensive care, have an excellent record of safety and to our knowledge no short term effect on the coagulation. Blood sampling in minipigs without sedation is ethically questionable and would probably not receive regulatory approval. Furthermore, the sympathetic activation associated with immobilisation may lead to alterations in haematological and coagulation parameters, too. Differences between values obtained by puncture and catheter techniques were shown by two groups (*Becker et al.* 1976, *Oldigs et al.* 1984).

System of units
As absolute values for single coagulation factors are rarely used, we used for the single factor activities a system where the normal human factor activities are assumed to be 100 %human to allow for interspecies and interracial (i.e. Göttingen mini-pig vs. other pig races) comparison (*Lutze et al.* 1992, *Karges et al.* 1994).
The alternative would have been a system where

Table 9. Factor VII (human%)

Reference	Race	Age	Sex	#	Mean ± SD	Blood	Method
Bowie 1973	York.	3-5m	?	7	130	vp	?
Hahn 1996	Germ.	2-4m	b	23	195 ± 34	vc	Koller
Harrison 1985	?	4m	?	1	83	vc	?
Karges 1994	Germ.	10m	?	14	58 ± 10	ap	Behring
Lutze 1992	Germ.	10m	b	12	33 ± 5	vp	?
Massicotte 1986	?	0-1d	?	12	60	vp	?
	?	7d	?	12	200	vp	?
	?	adult	b	20	139	vp	?
McLoughlin 1996	York.	?	f	29	83 ± 8	c	?
Reverdiau 1996	White	fetus	?	20	53 ± 8	up	Immuno
	White	0d	?	20	86 ± 7	vp	Immuno
	White	adult	?	20	127 ± 12	vp	Immuno

Abbreviations:
Race: Germ. = German Land, York. = Yorkshire Sex: f = female, b = both
Sample: c = catheter, vc = venous catheter, vp = venipuncture, ap = arterial puncture, up = umbilical cord

normal Göttingen minipig plasma would have been assumed to be 100%, which would have allowed only comparisons between the three groups of Göttingen minipigs used.

Sex differences
It should be noted that the differences found between male and pregnant animals could possibly be explained by the different age of the male (8 ± 2 months) and pregnant animals (30 ± 11 months). We will discuss this problem below for each of the parameters concerned separately.

Haematocrit
Our mean values (male 34, female 33, pregnant 30%) fit well within the mean values of other groups obtained by catheter (31-34%; see table 2). Values obtained by venous puncture are higher (36-45%; see table 2), which is highlighted by the two groups which compared catheter and puncture techniques (*Becker et al.* 1976, *Oldigs et al.* 1984).

The only values previously reported in *pregnant* Göttingen minipigs (*Grote et al.* 1977) are exceptionally high (55%). This might be caused by the unusual and probably extremly stressful sampling technique (heart puncture).

Except for two reports (*Pering et al.* 1975, *Grote et al.* 1977), all haematocrit values reported for Göttingen minipigs are lower than the normal human range.

Differences between male and female pigs were small and insignificant both in our study and in the two other studies comparing sexes (*Ellegaard et al.* 1995, *Wrogemann & Holtz* 1977).

Platelets
Our mean values (male 490, female 420, pregnant 310*10^9/l) fit well within the range of mean values reported by others (320-767*10^9/l; see table 3). They are also in the normal human range.
As mentioned before, we noted significantly lower platelets in pregnant as compared to male pigs. Because pregnant pigs were older than male pigs and a decline of platelets between age 3 and 6 months with minimal sex differences was shown by an-

Table 10. Factor VIII (human%)

Reference	Race	Age	Sex	#	Mean ± SD	Blood	Method
Bengmark 1972	Swed.	?	?	5	590±400	ac	Aas
Bowie 1973	York.	3-5m	?	56	700	vp	?
Hafström 1974	Swed.	?	?	14	910±290	ac	Cellos.
Hahn 1996	Germ.	2-4m	b	23	782±196	vc	Egli
Harrison 1985	?	4m	?	1	390	vc	?
Karges 1994	Germ.	10m	?	13	550±110	ap	Behring
Lutze 1992	Germ.	10m	b	12	570±110	vp	?
Massicotte 1986	?	0-1d	?	12	500	vp	?
	?	7d	?	12	800	vp	?
	?	adult	b	20	380	vp	?
McLoughlin 1996	York.	?	f	29	760±192	c	?
Perkins 1970	?	?	?	8	470	?	?
Reverdiau 1996	White	fetus	?	20	191±40	up	Immuno
	White	0d	?	20	524±75	vp	Immuno
	White	adult	?	20	701±67	vp	Immuno

Abbreviations:
Race: Germ. = German Land, Swed. = Swedish Land, York. = Yorkshire
Sex: f = female, b = both
Sample: ac = arterial catheter, c = catheter, vc = venous catheter, vp = venipuncture, ap = arterial puncture, up = umbilical cord

other group (*Ellegaard et al.* 1995), an explanation of this difference by age cannot be excluded.

Fibrinogen
Our mean values (male 9.0 ± 2.6, female 7.5 ± 3.3, pregnant 5.8 ± 1.1 g/l) are higher than either normal values in man and most mean values previously reported in Göttingen minipigs (1.1-6.5 g/l; see table 4).
If values obtained by the Clauss method, which was shown to be unreliable in pigs (*Lutze & Kutschmann* 1989), are excluded, our agreement with the values reported in the literature is better (3.6-6.5 g/l; see table 4).
As mentioned before, we noted significantly lower fibrinogen in pregnant as compared to male pigs. Another group showed a minimal influence of age, but like us higher values in male pigs (*Ellegaard et al.* 1995). Therefore it seems likely that our significantly higher values of fibrinogen in male compared to pregnant pigs (with non-pregnant pigs in between) are caused by a true sex difference rather than an age difference.

PTT
Our mean values (male 26 ± 7, female 30 ± 4, pregnant 29 ± 6 sec.) fit well within the mean values reported for Göttingen minipigs in the literature (17-46 sec.; see table 5). It seems that the values obtained by the IL Test (*Ellegaard et al.* 1995) are higher than values obtained with the Behring reagentia used by us or unspecified tests.

Prothrombin index (Quick)
As noted before, we give the prothrombin index as percent activity for the human prothrombin com-

plex, not as prothrombin time in seconds. Our mean values (male 170 ± 30, female 180 ± 30, pregnant 190 ± 40% human) are higher than normal values in man and also higher than the mean values reported in Göttingen minipigs by others (85-99% human; see table 6).
It should be noted, however, that these differences might be in part a cut-off artefact as many laboratories report prothrombin indices over 100% as 100%.

Antithrombin III
Our mean values (male 110 ± 20, female 110 ± 10, pregnant 100 ± 20% human) fit well within the normal human range as well as in the range reported in the literature for pigs of other races (76-155% human, excluding pigs under 2 weeks; see table 7). No values in Göttingen minipigs are published so far.

Factor V
Our mean values (male 360 ± 80, female 450 ± 150, pregnant 420 ± 120% human) are higher than normal values in humans, but in agreement with mean values reported in the literature for pigs of other races (200-1200% human, excluding pigs under 2 weeks; see table 8). No values in Göttingen minipigs are published so far.

Factor VII
Our mean values (male 110 ± 40, female 140 ± 40, pregnant 110 ± 40% human) are in the normal human range and in agreement with mean values reported in the literature for pigs of other races (33-195% human, excluding pigs under 2 weeks; see table 9). No values in Göttingen minipigs are published so far.

Factor VIII
Our mean values (male 260 ± 100, female 340 ± 90, pregnant 350 ± 160% human) are higher than normal values in humans, but in agreement with mean values reported in the literature for pigs of other races (380-910% human, excluding pigs under 2 weeks; see table 10). No values in Göttingen minipigs are published so far.

Protein C
Our mean values (male 52 ± 19, female 76 ± 18, pregnant 83 ± 18%) are lower than normal human values. No values in pigs of whatever race are published so far. The significant difference noted between male and pregnant pigs might be either explained by sex or age.

Conclusion
The Göttingen minipig is an animal suited for studies involving coagulation measurements. It should be noted, however, that the activities of Factor V and Factor VIII are higher in pigs (including Göttingen minipigs) than in man and that haematocrit is lower.
Highly significant ($p < 0.03$ with Bonferroni-correction applied) sex or age differences exist in Göttingen minipigs concerning platelets, fibrinogen and Protein C. Studies reporting coagulation parameters should mention sex and age of the animals used.

Summary
Pigs are commonly used animals for research. Information on the coagulation system of an experimental animal is essential for scholars to select an appropriate model. We present information on coagulation and haematological parameters in Göttingen breed minipigs (male, female, and pregnant). Factor activities are expressed as percentage of human activity to facilitate interspecies comparison.
Protein C was significantly higher, fibrinogen and platelets were significantly lower in pregnant compared to male pigs ($p < 0.001$ without Bonferroni-correction, $p < 0.03$ with Bonferroni-correction applied). As pregnant sows were older (30 ± 11 months) than female non-pregnant animals (age 11 ± 8 months) and boars (8 ± 2 months) an influence of age on the observed differences can't be excluded.
The Göttingen minipig is an animal suited for studies involving coagulation measurements. It should be noted, however, that compared to normal human values factor V (about 400% human) and Factor VIII (about 300% human) are higher in Göttingen breed minipigs and that haematocrit (33% absolute) is lower.

References:

Becker M, R Beglinger & UG Stauffer: Das Göttinger Miniaturschwein als Versuchstier. 2. Mitteilung: Blutbild, Serumelektrolyte, Wasserstoffionenkonzentration und Blutgase. Res. Exp. Med. 1976, *167,* 185-192.

Bengmark S, L Hafström & K Korsan-Bengtsen: Early changes in blood coagulation after short time hepatic inflow occlusion in pigs. Europ. Surg. Res. 1972, *4,* 429-437.

Bland JM & DG Altman: Multiple significance tests: the Bonferroni method. BMJ 1995, *310,* 170.

Bowie EJW, CA Owen, PE Zollman, JH Thompson & DN Fass: Tests of hemostatis in swine: normal values and values in pigs affected with von Willebrand's disease. Am. J. Vet. Res. 1973, *34,* 1405-1407.

Brechbühler T, M Kaeslin & F Wyler: Reference values of various blood constituents in young minipigs. J. Clin. Chem. Clin. Biochem. 1984, *22,* 301-304.

Ellegaard L, K Damm-Jorgensen, S Klastrup, A Kornerup-Hansen & O Svendsen: Haematologic and clinical chemical values in 3 and 6 months old Göttingen minipigs. Scand. J. Lab. Anim. Sci. 1995, *22,* 239-248.

Grote W, LC Schulz, W Drommer, S Überschär & EA Schäfer: Überprüfung einer Kombination der Wirkstoffe Cumarin und Troxerutin auf embryotoxische und teratogene Nebenwirkungen an Göttinger Miniaturschweinen. Arzneim. Forsch./Drug Res. 1977, *27,* 613-617.

Hafström L, K Korsan-Bengtsen & S Bengmark: Changes in blood clotting and fibrinolysis after liver ischemia in pigs. Am. J. Surg. 1974, *127,* 300-305.

Hahn N, S Popov-Cenic & A Dorer: Basiswerte von Blutgerinnungsparametern des Hausschweins (sus scrofa domesticus). Berl. Münch. Tierärztl. Wschr. 1996, *109,* 23-27.

Harrison J, C Abildgaard, J Lazerson, R Culbertson & G Anderson: Assessment of thrombogenicity of prothrombin complex concentrates in a porcine model. Thromb. Res. 1985, *38,* 173-188.

Hathaway WE, HS Hathaway & LP Belhasen: Coagulation factors in newborn animals. J. Lab. Clin. Med. 1964, *63,* 784-790.

Heitz J, B Semsch, C Emde, U Jansen & JH Schäfer: Proteaseninhibitor Gabexatmesilat bei der experimentell induzierten akuten Pankreatitis mit früher gram-negativer Infektion am Göttinger Zwergschwein. Z. Gastroenterol. 1990, *28,* 192-197.

Karges HE, KA Funk & H Ronneberger: Activity of Coagulation and Fibrinolysis Parameters in Animals. Arzneim.-Forsch./Drug Res. 1994, *44,* 793-797.

Köstering H, WP Mast, T Kaethner, K Nebendahl & WH Holtz: Blood coagulation studies in domestic pigs (Hanover breed) and minipigs (Göttingen breed). Lab. Anim. 1983, *17,* 346-349.

Lentner C: Wissenschaftliche Tabellen Geigy, Teilband Statistik. 8th Edition, Ciba-Geigy, Basel 1980, p. 54-55.

Lutze G & K Kutschmann: Zur Problematik der Fibrinogenbestimmung bei Rind, Schwein und Hund. Mh. Vet.-Med. 1989, *44,* 28-30.

Lutze G, KJ Hartung & K Kutschmann: Aktivitätsbestimmungen von Einzelfaktoren der Gerinnung bei klinisch gesunden Schweinen und Rindern. Berl. Münch. Tierärztl. Wschr. 1992, *105,* 411-414.

Massicotte P, L Mitchell & M Andrew: A comparative study of coagulation systems in newborn animals. Pediatr. Res. 1986, *20,* 961-965.

McLoughlin TM, JL Fontana, B Alving, PD Mongan & R Bünger: Profound Normovolemic Hemodilution: Hemostatic Effects in Patients and in a Porcine Model. Anesth. Analg. 1996, *83,* 459-465.

Oldigs B, FW Schmidt & F Douwes: Blut- und Serumwerte des Göttinger Miniaturschweines 4. Mitteilung: Der Einfluß endogener und exogener Faktoren auf das kleine Blutbild. Zbl. Vet. Med. A. 1984, *31,* 46-58.

Perings E, C Hauswaldt, E Schumann, HG Seidenkranz, Smidt D, Holtz W & JN Meyer: Untersuchungen zum Einfluß von Azathioprin auf das periphere Blutbild und blutbildende Organe bei Göttinger Miniaturschweinen. Dtsch. Tierärztl. Wschr. 1975, *82,* 281-285.

Perkins HA, RE May & FO Belzer: Cause of abnormal bleeding after transplantation of pig liver stored by a perfusion technique. Arch. Surg. 1970, *101,* 62-68.

Petroianu G, R Rüfer: Zero-Stress-Anaesthesia-Induction (ZESTRANI) in mini-pigs: A five year experience in 200 (plus) pigs. Proceedings of the 5th International Congress of Veterinary. Anesthesia, Guelph 1994, p. 97.

Porte RJ, JD Blankensteijn, EAR Knot, MPM de Maat, THN Groenland & OT Terpstra: A comparative study on changes in hemostatis in orthotopic and auxiliary liver transplantation in pigs. Transplant. Int. 1991, *4,* 12-17.

Reverdiau-Moalic P, H Watier, I Vallée, Y Lebranchu, P Bardos & Y Gruel: Comparative Study of Porcine and Human Blood Coagulation Systems: Possible Relevance in Xenotransplantation. Transplant. Proc. 1996, *28,* 643-644.

Schmidt EH, C Ebert, H Stellpflug & FK Beller: Gerinnungsphyiologische Untersuchungen beim Göttinger Miniaturschwein nach Infusion von Endotoxin. In: Deutsch E Fibrinolyse, Thrombose, Hämostase Schattauer, Stuttgart 1980, p.183-187.

Schulz E, F Ruschitzka, S Lueders, R Heydenbluth, J Schrader & GA Müller: Effects of endothelin on hemodynamics, prostaglandins, blood coagulation and renal function. Kidney International 1995, *47,* 795-801.

Stokke T, H Burchardi, I Hensel, H Köstering, T Käthner & G Rahlf: Continuous intravenuous infusion of elastase in normal and agranulocytic minipigs – effects on the lungs and the blood coagulation system. Resuscitation 1986, *14,* 61-79.

Taupitz-Stahn E: Untersuchungen über den Einfluß von Äthanol-Gaben auf den Harnsäurestoffwechsel von Minipigs. Res. Exp. Med. 1977, *170,* 57-69.

Wolter J, H Liehr & M Grün: Hepatic Clearance of Endotoxins: Differences in Arterial and Portal Venous Infusion. J. Reticuloendothelial Soc. 1978, *23,* 145-152.

Wrogemann J & W Holtz: Blutuntersuchungen am Göttinger Miniaturschwein. Z. Versuchstierk. 1977, *19,* 276-289.