Chapter 4

Comparative Fibrinolysis

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1. Introduction

Haemostasis prevents leaks or obstructions within the blood vessels following three interrelated sequences: formation of the haemostatic plug, platelet consolidation and dissolution of fibrin clot by the fibrinolytic system (Juhan-Vague and Hans 2003; Van Cott and Laposata 2001; Vasse 2008). Coagulation factors circulate in the blood as proenzymes until they are activated by vascular damage (Lane et al. 2005; Owens and Mackman 2010). These enzymes amplified and disseminated the sequence and then are stopped by natural inhibitors (Mulder et al. 2010; Middeldorp 2011) and the fibrinolytic system (Greenberg and Orthner 1999; Levi et al. 2012). Cellular phospholipids make the process much more efficient (Hoffman 2003; Gentry 2004; Rivera et al. 2009).Activated Factor XIIIa stabilizes the polymer (Sidelmann et al. 2000; Greenberg and Lai 2003; Muszbek et al. 2011). Plasminogen (Plg) is the key in thrombus lysis; and is synthesized in mammals principally by the liver (Stafford 1964; Degen 2001; Zhang et al. 2002; Zorio et al. 2008). Natural Plg activators are: tissue plasminogen activator (tPA) and urokinase (uPA) (Fleming and Melzig 2012); streptokinase (SK) acts as in an exogenous path (Sazonova et al. 2009). Free Plm is very active and degrades other proteins, such as complement, fibrinogen (Fbg), factors II, V and VIII or activates metallo-proteases involved in tissue remodeling by degradation of cellular matrix (Collen 2001; Parfyonova et al. 2002; Dewyer et al. 2007).The main inhibitors of Plm are the alpha2 plasmin inhibitor (α2PI) (Menoud et al. 1996; Fraser et al. 2011) and Plasminogen activator inhibitor type 1 (PAI-1) (Declerk et al. 1998; Vaughan 2005). Thrombin activatable fibrinolysis inhibitor (TAFI) is a link between the two systems, it is activated by thrombin generated during coagulation, and suppresses fibrinolysis (Marx 2004; Hilmayer et al. 2006; Milijic et al. 2010).

2. Selection of animal model in fibrinolysis, a challenge

There is a growing homology in the components of the fibrinolytic system along zoological evolution. Fibrinolysis is present in all vertebrates but invertebrates generally only have clumping of blood corpuscles (Withers 1992). Vertebrates factors involved in coagulation and fibrinolysis have evolved from common ancestral proteins and fibrinolytic ones seem to be related to digestive proteolytic enzymes used by rudimentary microorganisms to be released and disseminated, avoiding the host´s nonspecific defense and immunity response (Patthy 1990; Gladysheva et al, 2003; Opal and Esmon 2003; Levi et al. 2012).

Insects have rich sources of pharmacological active substances that may have medical value: The venom of *Lonomia oblique* caterpillar may induce a hemorrhagic syndrome in humans, and blood incoagulability in laboratory animals (Prezoto et al. 2002). Bee venom of *Bombus ignites* contains a Kunitz type serine protease inhibitor (Bi-KTI) that acts as an antifibrinolytic agent inhibiting plasmin (Choo et al 2012). In nature, there are many animals adapted to a diet of fresh blood, and they had to evolve mechanisms to control their host coagulation processes, to maintain the blood in a fluid state during intake and subsequent digestion (Tanaka-Azevedo et al 2010). A variety of coagulation inhibitors have been isolated from blood sucking animals such as ticks (Jacobs et al 1990; Waxman et al 1990), leeches (Sawyer 1986, 1991), hookworms (Cappello et al 1995) and bats (Gardell et al 1991).

Very little is known about the fibrinolytic system and its component concentrations in animals and the relevance of these models for human health is questioned due to many reasons: interspecies differences (Siller-Matula et al. 2008; Ralph and Brainard 2012), lack of reliable results (Vap et al. 2012), use of diagnostic equipment designed only for human care, inadequate relationship of test reagent to clotting factor concentration (Ravanat et al. 1995; Jagadeeswaran and Sheehan 1999; Kubalek et al. 2002, Münster et al. 2002; Gentry 2004; Weir-M et al. 2004). Also, anatomical features of the animal chosen can make it really difficult to obtain good quality blood samples (Saito et al. 1976; Meinkoth and Allison 2007). For example, vessel size and blood flow are important determinants of vascular function when mouse model is used for human research of aorta (Fay et al 2007).

3. Objective of this chapter

In this chapter we summarize the actual knowledge about fibrinolytic assays among different animal species and we compare these findings with healthy adult human beings.

4. Fibrinolytic parameters

A review of laboratory tests was conducted in a phylogenetic order: fish, amphibians, reptiles, birds and mammals. It was designed to assess the fibrinolytic system in its various stages: global (whole blood lysis time WBLT, whole blood diluted lysis time WDLT,

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euglobulin lysis time ELT), specific (Plg, PAI-1, tPA, α2PI and the thrombin-activatable fibrinolysis inhibitor TAFI) and degradation products generated from the degradation of fibrinogen / fibrin FDP, D Dimer DD, and Plm-α2PI, tPA-PAI-1, uPA-PAI-1 complexes (Blanco 2003; Urano and Suzuki 2011).

The results of these assays are summarized in Tables 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 (Tentoni et al, 2010).

In fishes the information is insufficient (Tables 1 and 2). WBLT is undetectable in lamprey and black fish, while lysis is fast in dog fish. The genes encoded for Plg and tPA were identified in the blowfish *Fugu rubripes* (Jiang and Doolittle 2003). Rats with diets based on fish oil decrease the fibrinolytic activity due to an increase of PAI-1 (Sano et al. 2003), whereas dietary supplementation with fish protein increases fibrinolysis by increasing tPA in blood (Murata et al. 2004).

In amphibians (Tables 1 to 3), the marine toad *Bufo marinus* and the tree frog *Hyla caerula* show spontaneous WBLT (Hackett and Lapage 1961, Hackett and Hann 1964), while it does not occur in the common frog *Rana temporaria*, leopard frog *Rana pipiens* or the clawed toad *Xenopuslaevis*(Table 2),but can be induced if possible inhibitors are removed, which suggests a large concentration of antifibrinolytic agents. The existence of a protein similar to Plg in *Rana tigrina* and *Xenopus laevis* is explained by the fibrinolysis produced after the addition of uPA (Srivastava et al. 1981).

There is no evidence of a fibrinolytic system in reptiles, lizards (Trachydosaurus rugosus rugosus, Tiliqua scincoides, Amphibolorus barbatus, Varanus acanthrus, Iguana iguana), turtles (Chelodina longicollis), crocodiles (Crocodylus porosus) or pitons (Liasis spp, Morelia spp) (Tables 1 and 10). A strong circulating antithrombin protects these vertebrates from intravascular thrombosis (Hackett and Hann 1964; Kubalek et al. 2002), however low concentrations of α2PI were detected in the circulation of the snake Bitis arietans using a chromogenic method (Table 10).

Snake venoms are mixtures of many peptides which affect the blood coagulation and fibrinolysis pathways such as Plg activators (Kini 2005; Miller et al 2009) and fibrinogen degradators (Meyer 2000). Recently a non hemorrhagic metalloproteinase (BleucMP) was purified from *Bothrops leucurus* snake venom by two chromatographic steps procedure on DEAE-Sephadex A-25, which has an efficient proteolytic action over fibrinogen (Sérgio et al 2011).

Birds are deficient in Factors XI and XII so the clotting times exceeding 70 minutes (Wartelle 1957; Soulier et al. 1959, Bigland 1964). Fibrinolysis can be activated with the saliva of the vampire *Diaemus youngui* (Cartwright and Hawkye 1969), but not with SK (Cliffton and Cannamela 1951). Plg concentration in quails is indetectable due the chromogenic assay is activated with SK instead of uPA. Vultures have the highest reported value DD concentration among the animals with reduced levels of Fbg and clotting factors, remaining a disseminated intravascular coagulation in man, with the advantage of being easily reversible (Weir-M et al. 2004).

The WDLT in the *Halichoerus grypus* is lower than in humans (Table 3), suggesting the existence of an active fibrinolytic system.The Plg activity in *Balaenoptera borealis*is cannot be activated by SK but reacts against rabbit antibody antiPlg (Robinson et al. 1969).

FDP was undetectable in the *Mirounga angustirostris* elephant seal (Table 1 and 6).

Plg activators similar to tPA were discovered in the South American vampire bat´s *Desmodus rotundus* saliva (Verstraete 1995) and they all need fibrin as a cofactor (Schleuning et al. 1992).These activators do not degrade Fbg, or cause neuronal damage such as tPA does (Grandjean et al. 2004) and also have a prolonged plasma half-life (Zavalova et al. 2002).

In dogs (Tables 1, 3, 4, 5, 6, 7 and 10), except for the Plg when it is measured by activation with SK, the values of all the fibrinolytic assays are quite similar to the values in humans, as reported by Wohl et al. (1983).

In cats (Tables 1, 3, 5, 9 and 10) there is a marked difference in functional PAI-1 activity when compared to man, and its Plg cannot be activated with tPA but with uPA (Welles 1996).

In studied rodents, the fibrinolytic system is quite similar to that in humans, but Plg is poorly activated with SK; Plg, tPA, uPA and PAI-1 have been described in *Mus musculus* mouse (Tables 1, 7 and 8), the first two having high sequence homology with their human counterpart (Poplis and Castellino 2002). Interesting enough, PAI-1 deficient mice present a mild hyperfibrinolytic state in adulthood, whereas Plg deficiency predisposes to severe thrombosis (Eitzman et al. 2000; Mackman 2005). The main inhibitors of fibrinolysis in mice are α2PI and TAFI (Marx et al. 2000). In rodent capybara *Hydrochaeris hydrochaeris* (Tables 1 and 5), Plg cannot be activated even with 500 U/mL of SK (Leitao et al, 2000).

Rat (Tables 1, 3, 4, 5, 7, 8, 9 and 10), guinea pigs (Tables 4, 5 and 10) and rabbits (Tables 1, 3, 4, 5, 7, 9 y 10) are the most employed animal models in fibrinolytic research.

Plg cannot be activated with SK in cattle (Tables 1, 5, 6 and 10), pigs (Tables 1, 5, 7 and 10) and sheep (Tables 5, 7 and 10), (Cliffton and Cannamella 1953; Korninger and Colleen 1981; Wohl et al 1983; Zhang et al 2012). Horses (Tables 1, 5, 6, 7, 9 and 10) have higher levels of functional PAI-1 and α2PI when compared to humans (Barton et al. 1998). The fibrinolytic activity in llama is similar to that of horses and other domestic species (Morin et al 1995).

In armadillos *Chaetophractus villosus* our research group found prolonged WBLT and WDLT with PAI-1 functional activity four times greater than in man; this high concentration of inhibitor can be successfully removed with the ELT technique, despite the anticoagulant used (citrate/oxalate). The α2PI concentration is similar to that measured in humans. DD was undetectable in the immunological test (Tentoni et al., 2008). Nevertheless we found FXIII activity in this mammal, with a range from 32 to 78 percent (%) in relation to the calibration curve obtained with a pool of healthy humans platelets poor plasma using Berichrom chromogenix assay (Dade Behring). The fibrin plug was resistant to urea 5M for more than 36 hours; its coagulation factors depend on the vitamin K cycle because the oral administration of 0.28 mg/kg/day of acenocumarol increased baseline values of Prothrombin time PT ($p<0.01$) and activated Partial Thromboplastin time aPTT ($p<0.05$). When PTT-LA reagent is used in aPTT assays in armadillos, the typical shortened values of this specie (20 seconds) increases (26-30 seconds) (Tentoni et al., unpublished), as observed in pigs by Velik-Salchner et al. (2006).

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Species	Fbg (mg/dL)	Author
human	188 - 381	Williams *et al*, 2005
armadillo[a]	211 - 333	Casanave *et al*, 2006
armadillo[a´]	258 - 380	Tentoni *et al*, 2008
whale[b]	147	Saito *et al*, 1976
iguana[c]	420 - 440	Kubalek *et al*, 2002
cat[d]	50 - 165	O´Rourke *et al*, 1982
cat	150 - 400	Herring and McMichael, 2012
eagle[e]	80 - 160	García-Montijano *et al,* 2002
frog[f]	590 - 990	Coppo *et al*, 2005
dolphin[g]	269 - 417	Tibbs *et al*, 2005
mouse[h]	200 - 260	Tsakiris *et al*, 1999
dog	141 - 227	Mischke *et al*, 2000
dog	179. - 329	Machida *et al*, 2010
dog	150 - 400	Herring and McMichael, 2012
rat	168 - 192	Honda *et al*, 2008
japanese quail[i]	140 - 260	Belleville *et al*, 1982
pig[j]	181 - 534	Velik-Salchner *et al*, 2006
pig	130 - 170	Schöchl *et al*, 2011
rabbit[k]	257 - 286	Marval *et al*, 1992
cow[l]	125 - 697	Heuwieser *et al*, 1989
sheep	178 - 215	Wilhelmi *et al*, 2012
horse[m]	78 - 156	Barton *et al,* 1998
monkey[n]	119 - 239	Suzuki *et al*, 1977
elephant seal[o]	50 - 162	Gulland *et al*, 1996
capybara[p]	124	Leitâo *et al*, 1999
ostrich[q]	172 - 356	Frost *et al*, 1999
caiman[r]	430 - 1500	Arocha-Piñango *et al*, 1982.
marine fish[s]	220 - 280	Pavlidis *et al*, 1999
asian elephant[t]	412 - 510	Gentry *et al*, 1996
vulture[u]	< 20	Weir-M *et al*, 2004
llama[v]	140 - 300	Morin *et al*, 1995

A Chaetophractus villosus (n:20); a´ (n:24); b Balaenoptera borealis (n:1); c Iguana iguana (n:26); d (n:21); e Aquila adalberti (n:12); f Rana catesbeiana (n:302); g Tursiops truncatus (n:17); h Mus musculus; i Coturnix coturnix japonica ; j(n: 80); k New Zealand rabbits (n:102); l (n:90); m foals (n:53); n Macaca fuscata (n:52); o Mirounga angustirostris (n:19); p Hydrochaeris hydrochaeris (n:2); q Struthio camelus (n:30); r Caiman crocodilus; s Dentex dentex; t Elephas maximus; u Coragyps atratus (n:2); v (n: 46 adult females); < less than.

Table 1. Fibrinogen (Fbg) concentration values in different vertebrates

Species	WBLT (hours)	Author
human	"/> 24	Conard, 1976
lamprey[a]	nd	Hawkey, 1971
black fish[b]	nd	Hawkey, 1971
common frog[c]	nd	Blofield, 1965
leopard frog[d]	nd	
clawed toad[e]	nd	
domestic birds	nd	Niewiarowski & Latallo, 1959
dogfish[f]	2 – 4	Hawkey, 1971 Doolittle & Surgernor, 1962
japanese quail[g]	"/> 72	Belleville *et al*, 1982
armadillo	"/> 72	Tentoni *et al*, 2008

a Petromyzon marinus; b Tautoga onitis; c Rana temporaria; d Rana pipiens; e Xenopus lavéis; f Mustelus canis; g Coturnix coturnix japonica (n:10 adult males); nd: not detectable; > more than.

Table 2. Whole blood lysis time (WBLT) values in different vertebrates

Species	WDLT (hours)	Author
human	> 20	Fearnley *et al*, 1957
tiger frog[a]	> 48	Srivastava *et al*, 1981
seal[b]	5.9 – 8.5	Lohman *et al*, 1998
dog[c]	> 20	Hedlin *et al*, 1972
rat[d]	> 20	
rabbit[e]	> 20	
rabbit[f]	> 30	Hassett *et al*, 1986
cat[g]	nd	Welles *et al*, 1994
armadillo	> 72	Tentoni *et al*, 2008

nd: not detectable; a *Rana tigrina* (n:6) measured at 4 and 37ºC; at 22ºC WDLT range was 31.5-45.3 hours; b *Halichoerus grypus* (n:2, both females), before immersion; c (n:3); d (n:6); e (n:4); f New Zealand male rabbits (n:4); g (n:15); > more than.

Table 3. Whole blood diluted lysis time (WDLT) values in different vertebrates

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Species	ELT (minutes)	Author
human	"/> 120	Kowalski *et al*, 1959
armadillo[a]	15.4 – 45.6	Bermúdez, 2003
armadillo [a´]	24.5 - 93	Tentoni *et al*, 2008
tiger frog[b]	nd	Srivastava *et al*, 1981
japanese quail[c]	nd	Belleville *et al*, 1982
dog	21 - 109	Hedlin *et al*, 1972
guinea pig[d]	< 90	Kaspareit *et al*, 1988
rabbit	270 - 450	Hassett *et al*, 1986
monkey[e]	240	Suzuki et al, 1977
vulture[f]	nd	Weir-M *et al*, 2004
rat	105 - 145	Groza *et al*, 1988

a *Chaetophractus villosus* using citrated plasma (n:20, 10 females and 10 males); a´ using oxalated plasma; b *Rana tigrina* (n:6); c *Coturnix coturnix japonica* (n:10 young males); d *Cavia porcellus* (n:45); e *Macaca fuscata*; f *Coragyps atratus* (n:2); nd: not detectable; > more than; < less than.

Table 4. Euglobulin lysis time (ELT) values in different vertebrates

Species	Plg (%)	Author
human	80 - 120	Perkins, 1999
japanese quail[a]	0	Belleville *et al*, 1982
dog	102 - 115 #	Lanevschi *et al*, 1996b
dog	3,2 - 4,4	Karges *et al*, 1994
cat	50 - 200	O´Rourke *et al*, 1982
cat	94 - 122	Karges *et al*, 1994
rat	6 - 14	
guinea pig[b]	0.4 – 6.1	
rabbit	2	
rabbit	147 - 217 #	Marval *et al*, 1992
rabbit	84 - 108 #	Hassett *et al*, 1986
sheep	0.7 – 1.5	Karges *et al*, 1994
cow	0	

Species	Plg (%)	Author
monkey[c]	24 - 39	
monkey[d]	164 #	Suzuki *et al*, 1977
capybara[e]	0	Leitâo *et al*, 2000
pig	2.1 – 5.2	Karges *et al*, 1994
pig	0	Hahn *et al*, 1996
horse[f]	66.5 – 98.1	Barton *et al*, 1998
whale[g]	112 #	Saito *et al*, 1976
armadillo	28 - 40	Tentoni *et al*, 2008

Results are expressed as percent for Plg activity in relation to the calibration curve obtained with a pool of healthy humans platelets poor plasma, using a chromogenix assay after activation with SK.

a *Coturnix coturnix japonica* (n:10 young males); b *Cavia porcellus*; c *Macaca fascicularis*; d *Macaca fuscata*; e *Hydrochaeris hydrochaeris*, it was impossible to activate its Plg with 500 U/mL of SK; f neonatal foals, Plg calibration curve was performed using equine pooled plasma; g *Balaenoptera borealis* (n:1); # Plg measured using uPAas activator.

Table 5. Plasminogen (Plg) activity values in different vertebrates

Species	FDP (µg/mL)	Author
human	< 10	Amiral *et al*, 1990
dog	< 5	Boisvert *et al*, 2001
dog	< 5	Stokol, 2003
dog	< 5	Griffin *et al*, 2003
dog	0 – 1.18	Machida *et al*, 2010
dog	< 10	Herring & McMichael, 2012
cat	< 10	Herring & McMichael, 2012
horse	5.5 – 10.9	Barton *et al,* 1998
horse	< 10	Stokol *et al*, 2005
elephant seal[a]	0	Gulland *et al*, 1996
dolphin[b]	< 10	Tibbs *et al*, 2005
cow	< 5	Irmak & Turgut, 2005
armadillo	0 - 10	Tentoni *et al*, 2008

A *Mirounga angustirostris*; b *Tursiops truncatus* (n: 12); < less than.

Table 6. Fibrin fibrinogen degradation products (FDP) concentration values in different mamals

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Species	DD (µg/mL)	Author
human	< 0.50	Estève *et al*, 1996
dog	0.08 – 0.39	Stokol *et al*, 2000b
dog	0.02 – 0.28	Caldin *et al*, 2000
dog	< 0.25	Nelson, 2005
dog	< 0.25	Herring & McMichael, 2012
cat	< 0.25	Herring & McMichael, 2012
rat	0.18	Asakura *et al*, 2002
rat	< 0.02	Ravanant *et al*, 1995
hen	< 0.02	
rabbit	< 0.02	
sheep	< 0.02	
monkey[a]	< 0.05	
mouse	< 0.02	
mouse	0	Tsakiris *et al*, 1999
pig	0	Roussi *et al*, 1996
pig	< 0.01	Schöchl *et al*, 2011
horse[b]	0.46 – 0.92	Monreal *et al*, 2000
horse	0 – 0.91	Machida *et al*, 2010
horse	< 0.50	Stokol *et al*, 2005
ostrich	0.25	Frost *et al*, 1999
vulture	"/> 1	Weir-M *et al*, 2004
armadillo	nd	Tentoni *et al*, 2008
dolphin	< 0.50	Tibbs *et al*, 2005

A *Papio papio*; b (n: 30); nd: not detectable; < less than; > more than.

Table 7. D Dimer (DD) concentration values in different vertebrates.

Species	PAI-1 immunologic (ng/mL)	Author
human	4 – 43	Declerck *et al*, 1988
mouse[a]	1.3 – 2.5	Tsakiris *et al*, 1999
mouse	1 – 2	Matsuo *et al*, 2007
pig	0	Roussi *et al*, 1996

Species	PAI-1 immunologic (ng/mL)	Author
pig[b]	5.6 – 9.0	Schöchl *et al*, 2011
armadillo	1.0 – 2.2	Tentoni *et al*, 2008
rat	3.9	Nieuwenhuys *et al*, 1998

A *Mus musculus* (n: 160); b measured with Porcine PAI-1 Activity Assay

Table 8. Immunological Plasminogen activator inhibitor type 1 (PAI-1) concentration in different mammals

Species	PAI-1 functional (U/mL)	Author
human	< 10	Van Cott & Laposata, 2001
cat	0	Welles, 1996
rabbit	0.06 – 0.16	Hassett *et al*, 1986
horse	19.6 – 42.2	Barton *et al*, 1998
armadillo	24.8 – 37.7	Tentoni *et al*, 2008
rat	1.0	Nobukata *et al*, 2000
rat	4.9 – 7.4	Emeis *et al*, 1992

Results are expressed as units of PAI-1 present in plasma in relation to the calibration curve obtained with a commercial standard when using immunological test; < less than

Table 9. Functional Plasminogen activator inhibitor type 1 (PAI-1) concentration in different mammals

Species	α_2PI (%)	Author
Human	70 - 130	Teger-Nilsson *et al*, 1977
japanese quail[a]	65 - 85	Belleville *et al*, 1982
ostrich[b]	115.6	Frost *et al*, 1999
hen	109.4	
snake[c]	10	
Sheep	68.8	
whale[d]	50	Saito *et al*, 1976
dog	96 - 103	Lanevschi *et al*, 1996b
dog	92 - 94	Karges *et al*, 1994
cat	70 - 86	
rat	118 - 138	

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Species	α_2PI (%)	Author
guinea pig[e]	91 - 101	
sheep	90 - 109	
pig	63 - 104	
monkey[f]	82 - 99	
rabbit	91 - 108	
rabbit	66 - 92	Hassett *et al*, 1986
pig	87 - 127	Hahn *et al*, 1996
rat	120	Nobukata *et al*, 2000
horse	154 - 240	Barton *et al*, 1998
cow	80 - 94	Daugschies *et al*, 1998
armadillo	72 - 101	Tentoni *et al*, 2008

Results are expressed as percent for α_2PI activity in relation to the calibration curve obtained with a pool of healthy humans platelets poor plasma, using a chromogenix assay after activation with an excess of Plm.

a Coturnix coturnix japonica; b Struthio camelus; c Bitis arietans; d Balaenoptera borealis (n:1); e Cavia porcellus; f Macaca fascicularis.

Table 10. alpha2 plasmin inhibitor activity (α_2PI) in different vertebrates

5. Conclusions

The information summarized in this chapter helps the choice of appropriate animal experimental models for studying fibrinolysis and the correct extrapolation of animal results toward humans. Previous work from our laboratory, has identified the choice of the armadillo as an animal model because it adapts well to captivity conditions, endures repeated blood sampling, shows excellent tolerance to cardiac puncture and recovers quickly from anaesthesia (Bermúdez et al. 2004; Casanave et al. 2005; 2006). *Chaetophractus villosus* has a hypercoagulable and hypofibrinolytic profile (Tentoni et al., 2008) as pigs, which are frequently used as an animal model in human research. Finally, the study of animals' haemostatic mechanisms is important in the field of zoology, for the advancement of scientific knowledge and in biomedicine, helping to select a suitable experimental animal model.

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