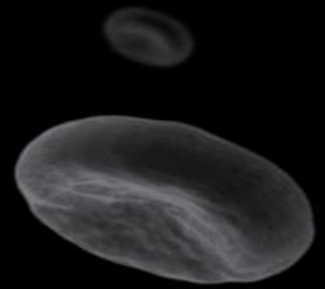
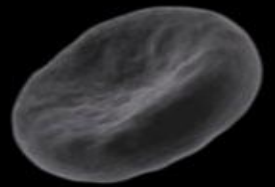
Coagulation Testing

Erik Zager
Cornell University

Outline

- Brief Coagulation Review
- Platelet Testing
  - Platelet Counts
  - Platelet Abnormalities
  - BMBT
- In Vitro Plasma Based Testing
  - PT
  - aPTT
- Indirect Testing
  - Fibrin Split Products
  - D-Dimers
  - Fibrinogen Concentration
  - Antithrombin
- In Vivo Whole Blood Based Testing
  - TEG and PlateletMapping





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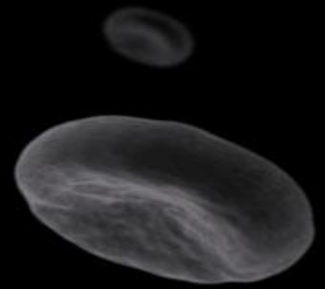
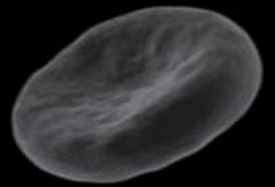
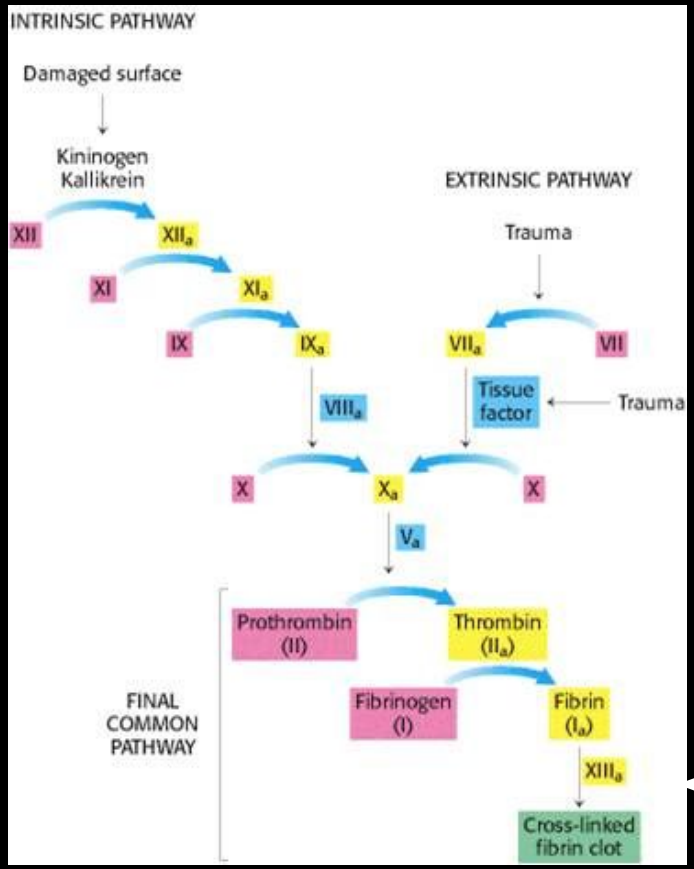
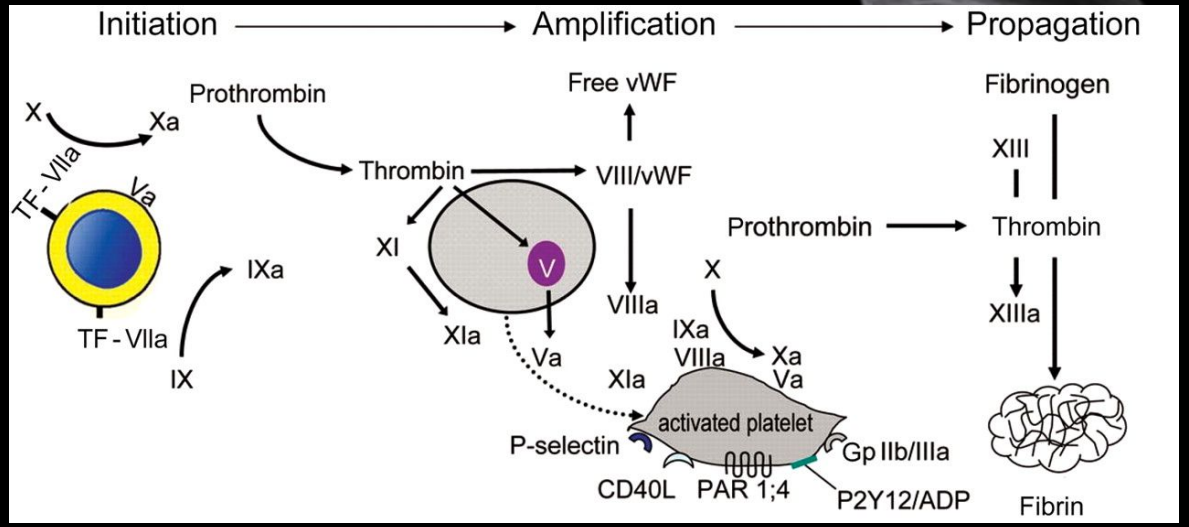




Coagulation Review



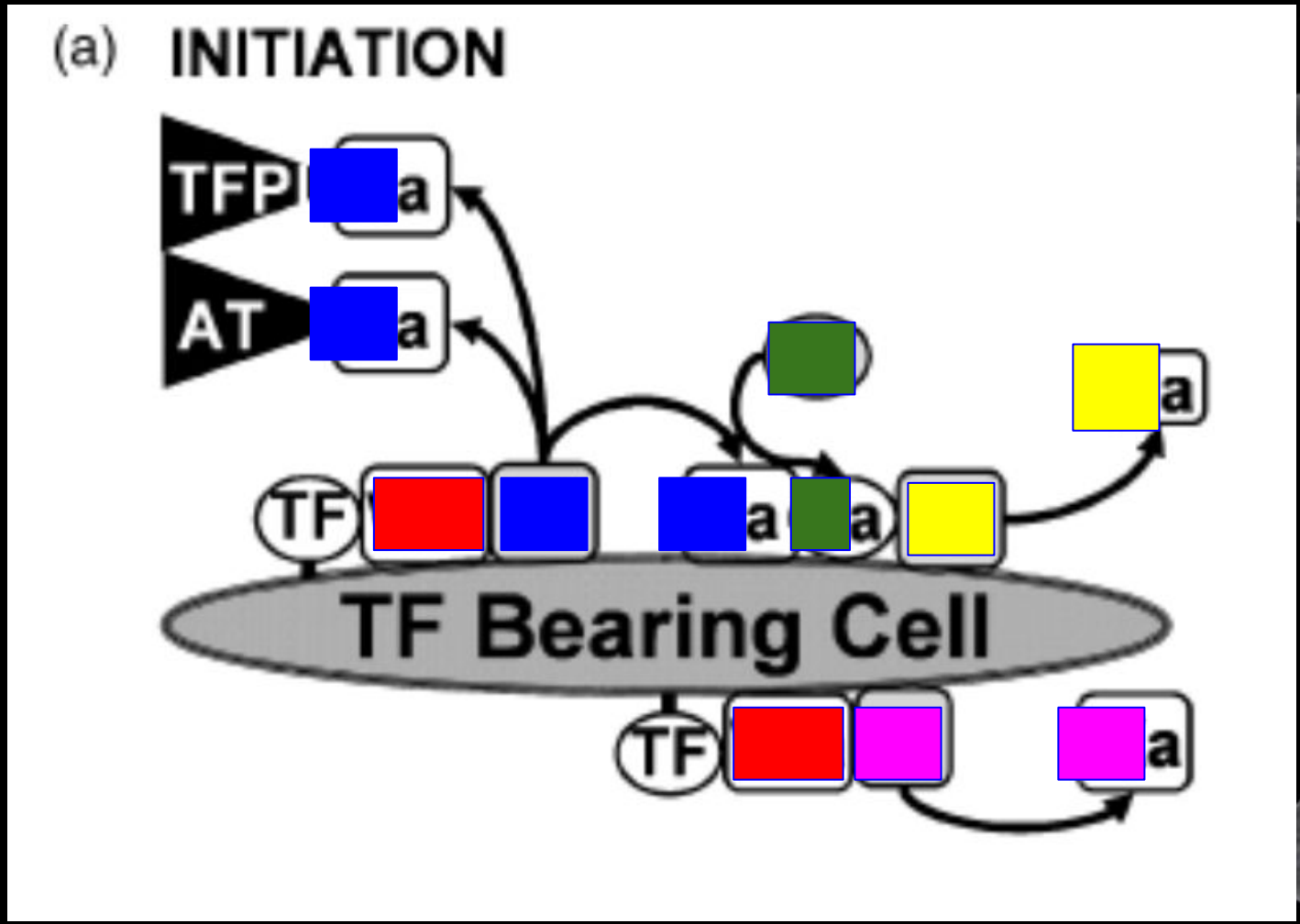


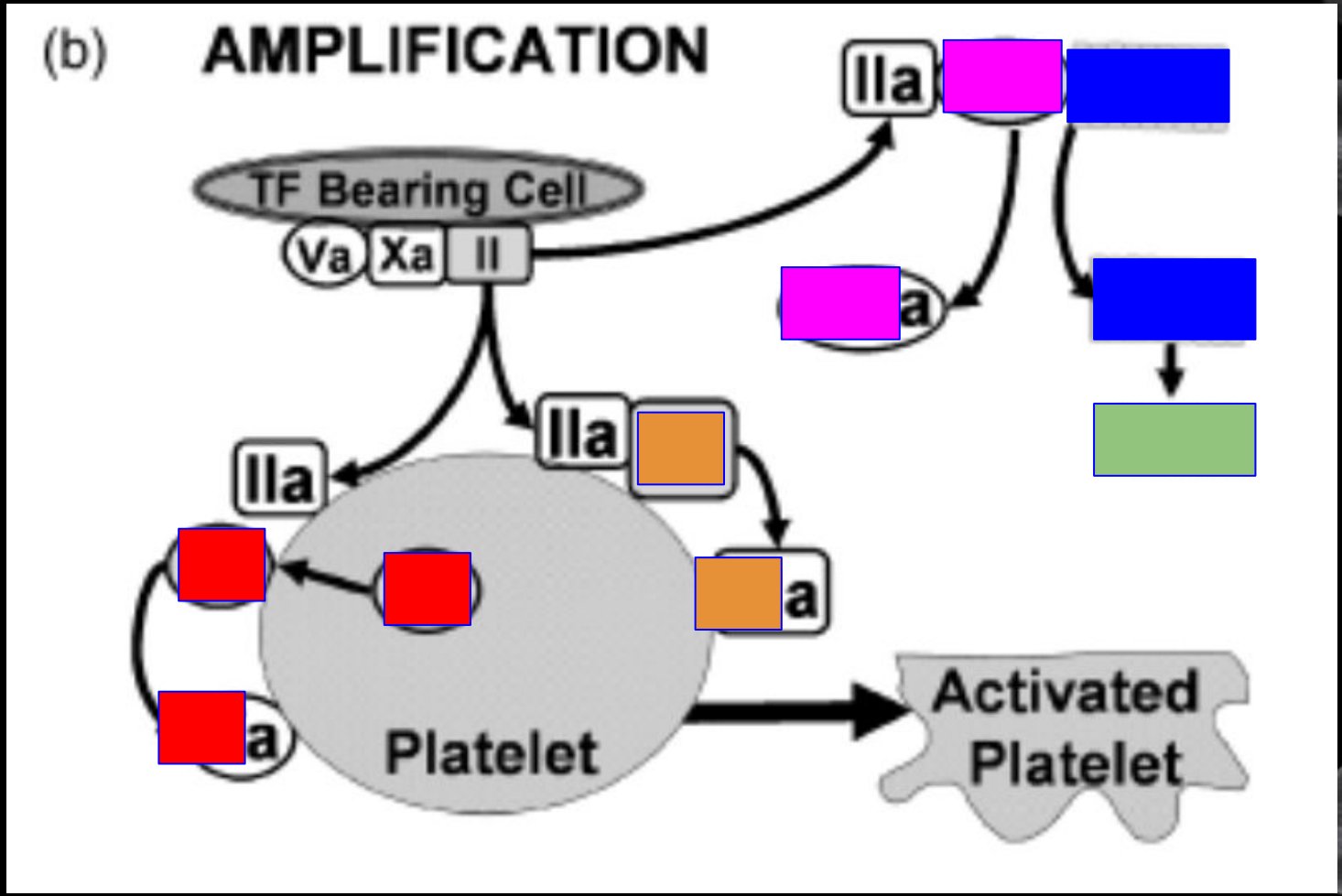
http://d1vzuwdl7rxiz0.cloudfront.net/content/ehj/28/7/880/F1.large.jpg

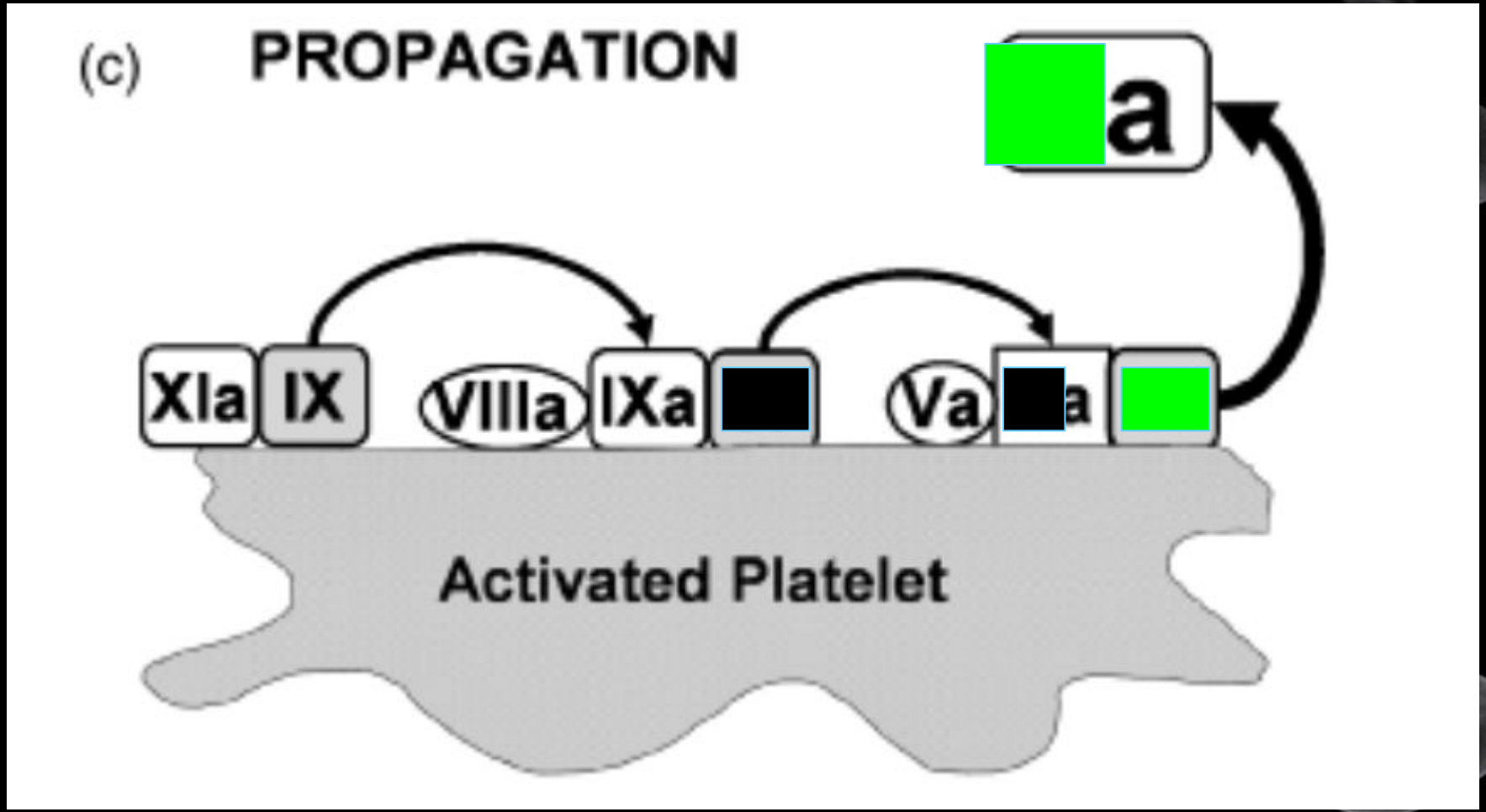
In Vivo

In Vitro

http://cancergrace.org/cancer-101/files/2009/12/clotting-cascade.jpg


(a) INITIATION
TFP
a
AT
a
a
TF
a
a
TF Bearing Cell
TF
a


(b)
AMPLIFICATION
IIa
TF Bearing Cell
Va
Xa
II
a
IIa
IIa
a
a
Platelet
Activated
Platelet


(c)
PROPAGATION
a
XIa
IX
VIIIa
IXa
Va
Activated Platelet

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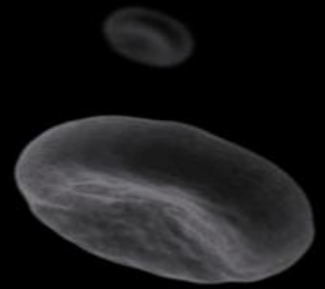
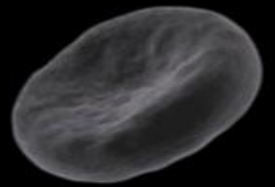




Platelet Testing

- Manual platelet count
  - Each platelet per high power field = ~20k platelet/uL

Estimation of Platelet Counts on Feline Blood Smears

Séverine Tasker, BSc, BVSc,[1] Peter J. Cripps, BSc, BVSc, MSc, PhD,[2] Andrew J. Mackin, BSc, BVMS, MVS, DVSc[1]

Page 42 **Veterinary Clinical Pathology** Vol. 28 / No. 2 / 1999

BRIEF COMMUNICATION

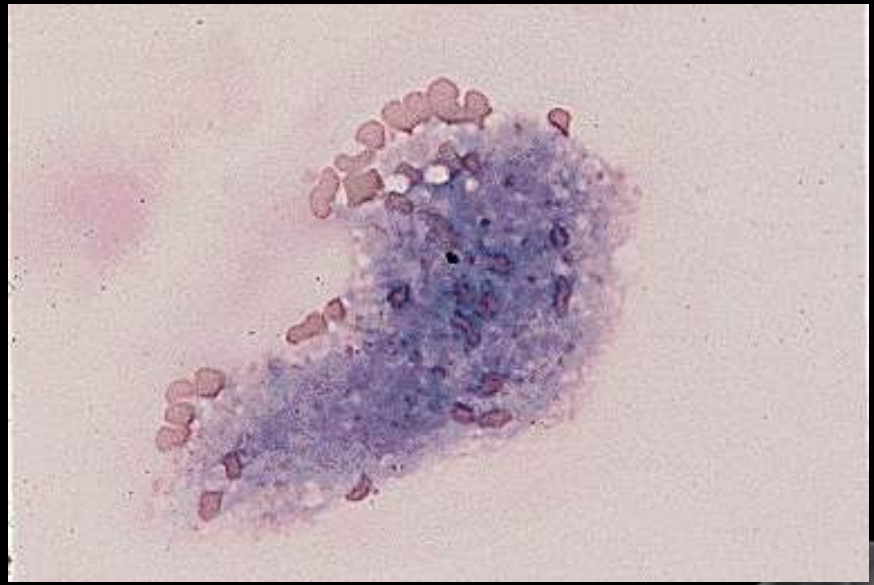
Estimating Platelets and Leukocytes on Canine Blood Smears

PAGE 4 • Vol. 17, No. 1 • VETERINARY CLINICAL PATHOLOGY

Harold Tvedten
Sharon Grabski
Linda Frame

Platelet Testing

- Cats with platelet clumps likely have adequate platelets
  - 260-587k based on 9 cats in study

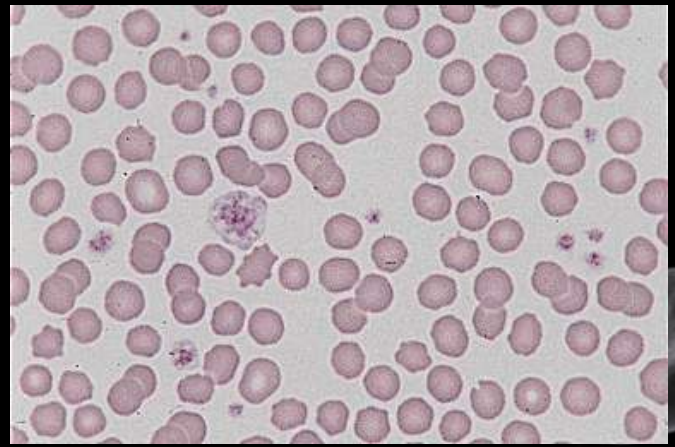


http://vetbook.org/wiki/cat/images/1/16/Thrombo03.jpg

Platelet Testing

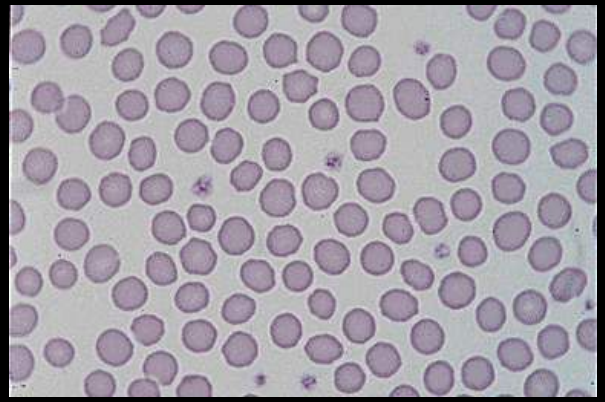
- Automated counts flawed
  - Pseudothrombocytopenia in cats due to overlap of erythrocyte and platelet volumes

http://img.medicalexpo.com/images_me/photo-m2/automatic-hematology-analyzer-bench-top-26-parameter-veterinary-79218-2862341.jpg



http://vetbook.org/wiki/cat/images/f/f2/Thrombo02.jpg

Platelet Testing



http://vetbook.org/wiki/cat/images/e/ed/Thrombo01.jpg

Prevalence of Low Automated Platelet Counts in Cats: Comparison with Prevalence of Thrombocytopenia Based on Blood Smear Estimation

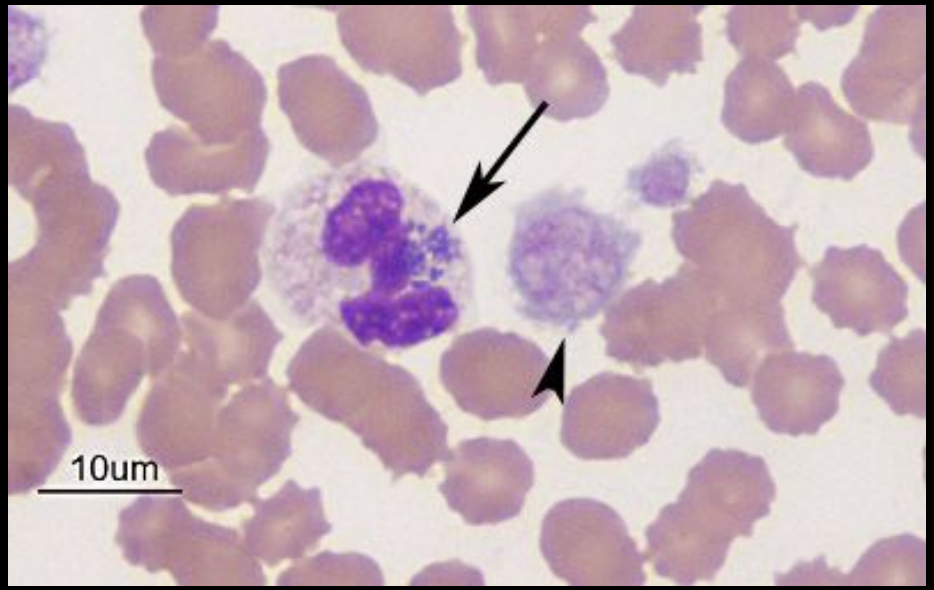
Elizabeth J. Norman, BVSc; Ronnie C. J. Barron, HNC (MLS); Andrew S. Nash, BVMS, PhD, MRCVS; Roger B. Clampitt, BSc, PhD, MPhil

Vol. 30 / No. 3 / 2001 Veterinary Clinical Pathology Page 137

- Thrombocytopenia likely greatly overestimated in cats using automated counts
  - 71% of samples in 1 year <200k in auto vs 3.1% of manual counts (similar split for <50k)

Platelet Testing

- Macrothrombocytopenia



http://www.eclinpath.com/wp-content/uploads/Figure-4.jpg

Platelet Testing

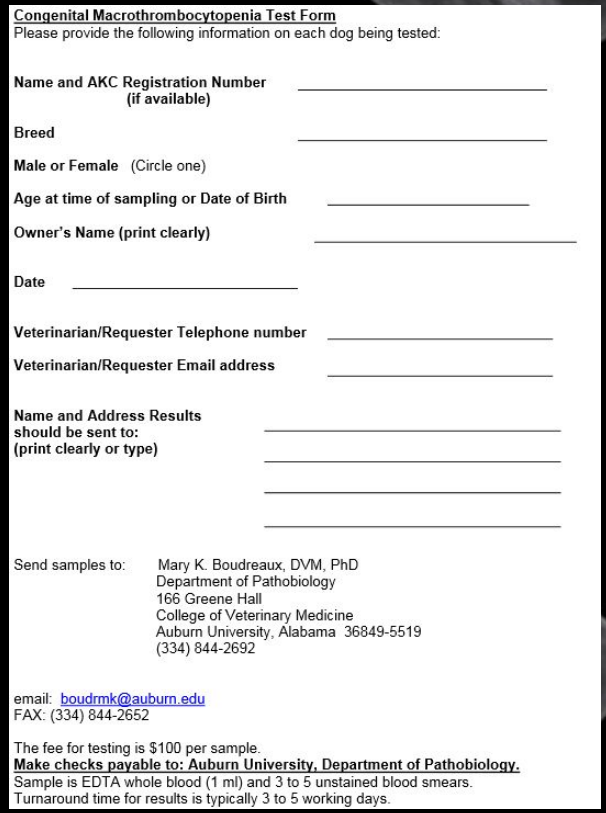
- Macrothrombocytopenia
  - Cavalier King Charles Spaniels, Cairn and Norfolk Terrier

Idiopathic thrombocytopenia in Cavalier King Charles Spaniels MK SINGH and WA LAMB

Australian Veterinary Journal Volume 83, No 11, November 2005

Platelet Testing

- Macrothrombocytopenia
  - Has been described in:
    - Chihuahua, Labrador retriever, Poodle, English Toy Spaniel, Labradoodle, Shih Tzu, Maltese, Jack Russell, Havanese, Boxer, Cocker Spaniel, and Bichon Frise
  - DNA Test available through Auburn University



Congenital Macrothrombocytopenia Test Form
Please provide the following information on each dog being tested:

Name and AKC Registration Number (if available) _____

Breed _____

Male or Female (Circle one)

Age at time of sampling or Date of Birth _____

Owner's Name (print clearly) _____

Date _____

Veterinarian/Requester Telephone number _____

Veterinarian/Requester Email address _____

Name and Address Results should be sent to: (print clearly or type) _____

Send samples to: Mary K. Boudreaux, DVM, PhD
Department of Pathobiology
166 Greene Hall
College of Veterinary Medicine
Auburn University, Alabama 36849-5519
(334) 844-2692

email: boudrmk@auburn.edu
FAX: (334) 844-2652

The fee for testing is $100 per sample.
Make checks payable to: Auburn University, Department of Pathobiology.
Sample is EDTA whole blood (1 ml) and 3 to 5 unstained blood smears.
Turnaround time for results is typically 3 to 5 working days.

Platelet Testing

- Macrothrombocytopenia
  - CKCS have autosomal dominant version
    - 30-50% of CKCS in USA

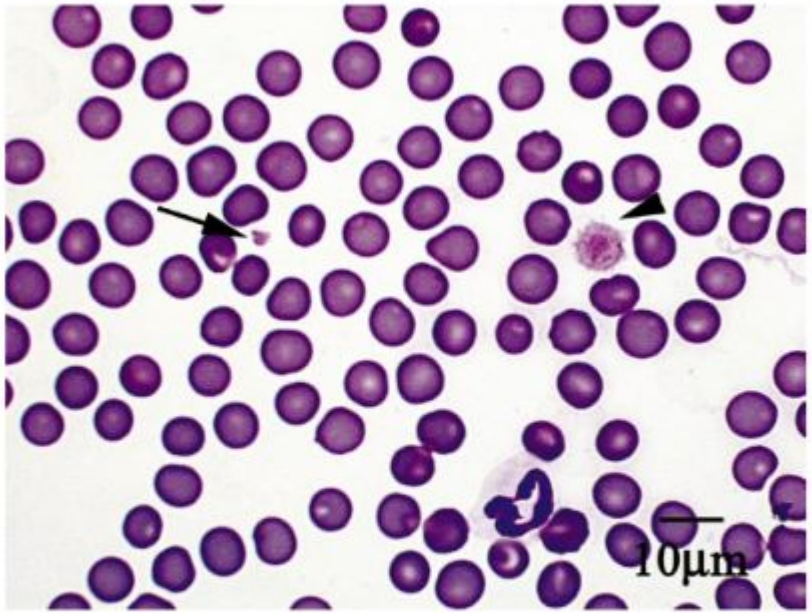


Figure 1. Blood smear from a CKCS with macrothrombocytopenia. An enlarged platelet (arrowhead), as large as a red blood cell; a platelet of normal size (arrow); and a neutrophil granulocyte are seen (1,000×; Hemacolor stain, Merck).

J Vet Diagn Invest 16:167–170 (2004)

Comparison of manual and automated methods for determining platelet counts in dogs with macrothrombocytopenia

Lisbeth H. Olsen, Annemarie T. Kristensen, Karen Qvortrup, Henrik D. Pedersen

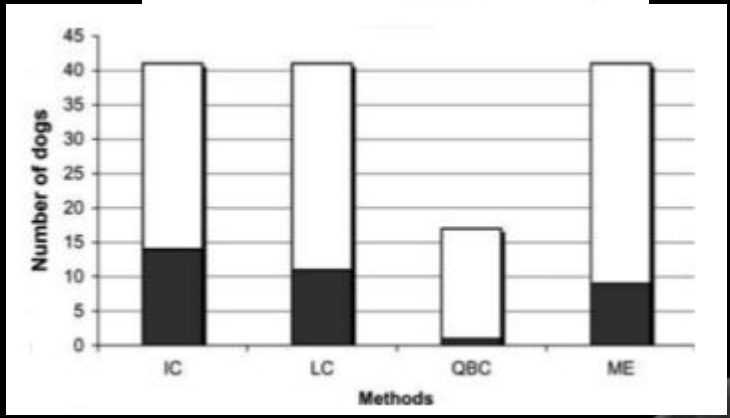
Platelet Testing

- Quantitative buffy coat analysis may be superior for Cavaliers
- Cavaliers can have counts as low as 25k/uL and be ‘normal’

Comparison of methods for determining platelet numbers and volume in cavalier King Charles spaniels

Journal of Small Animal Practice (2007) **48**, 556–561
DOI:10.1111/j.1748-5827.2007.00319.x

W. Bertazzolo, S. Comazzi,* L. Sesso,* P. Scarpa,† G. Ru‡ and S. Paltrinieri†



IC = impedence cell counter, LC = laser cell counter, QBC = quantitative buffy coat analyser, ME = microscopic estimation

Platelet Testing

- Buccal Mucosal Bleeding Time
- Measurement of formation of clot after established cut size/depth made
- Normal is <4min for dog
- Cats less established range: ~ <2.5min

https://www.atdove.org/videos/Procedure/Buccal-Mucosal-Bleeding-Time-BMBT

Platelet Testing

- Significant interobserver and intraobserver differences
  - On average 2 minute!!
    - Normal is under 4 minutes
- “The current study indicated that on 95 per cent of occasions, any two readings within a dog may differ by up to ± 2 minutes within an observer and between two observers. A single reading was accurate to within ± 80 seconds.”

An interobserver and intraobserver study of buccal mucosal bleeding time in Greyhounds

I. SATO*, G. A. ANDERSON, B. W. PARRY

*Research in Veterinary Science 2000, **68**, 41–45*

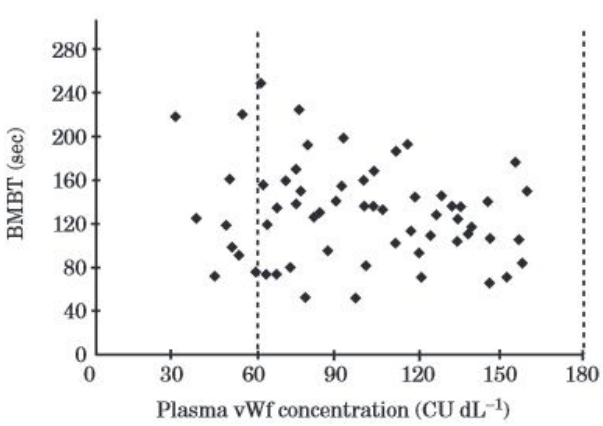


FIG 1: Relationship of buccal mucosal bleeding time and vWf in 61 Greyhounds
The dotted lines represent limits of the laboratory's reference interval for plasma vWf concentration for conventional dogs

Platelet Testing

- Review article of human data
  - Significant overlap between normals bleeding times and abnormal patients and vice versa

The Bleeding Time Does Not Predict Surgical Bleeding

JUNE 15, 1991 By Stuart E. Lind REVIEW ARTICLE

BLOOD

VOL 77, NO 12

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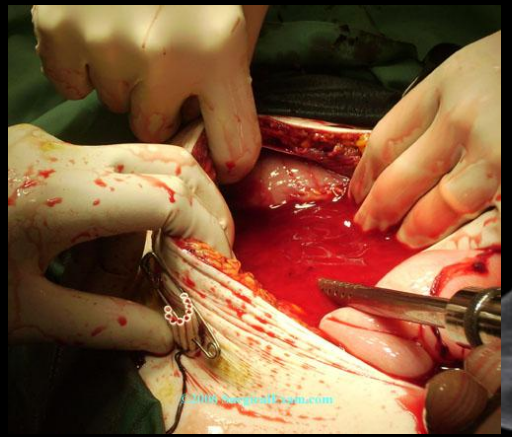

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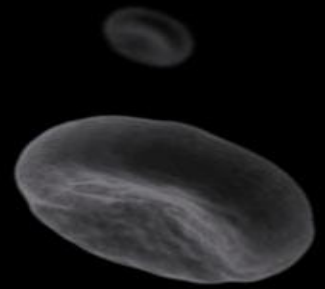
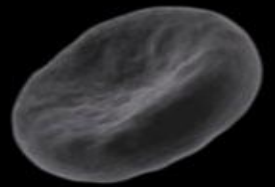
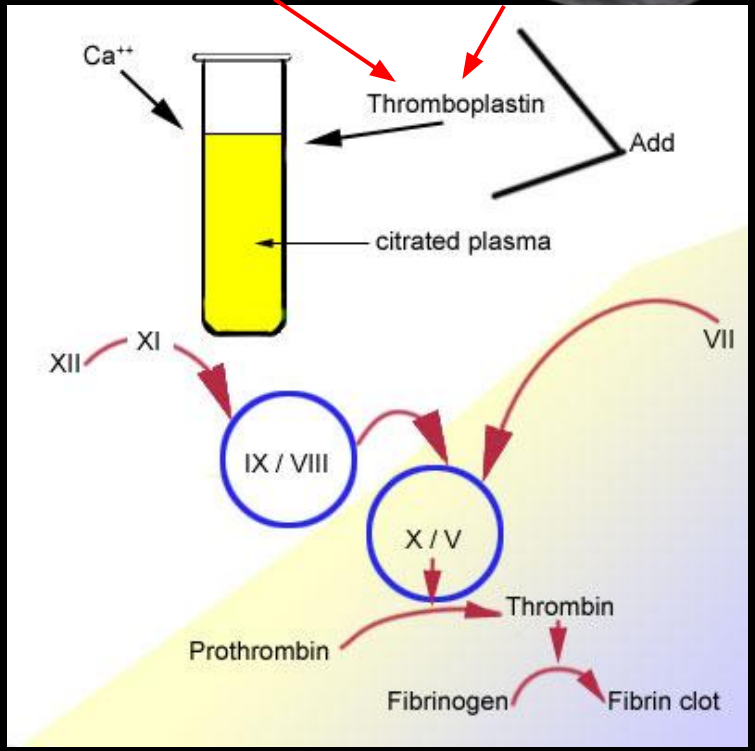




Prothrombin Time

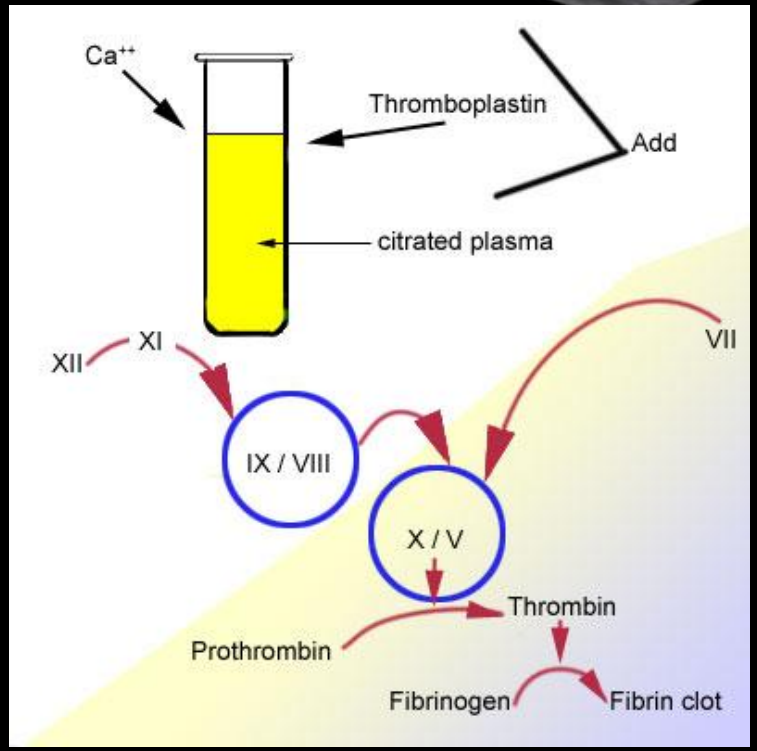
- Citrated blood
- Ca++ and thromboplastin (often made from rabbit brains) added
- The thromboplastin activates factor VII to VIIa
- Measures extrinsic and common pathways



http://www.medicine.mcgill.ca/physio/vlab/bloodlab/pt_ptt.htm

Prothrombin Time

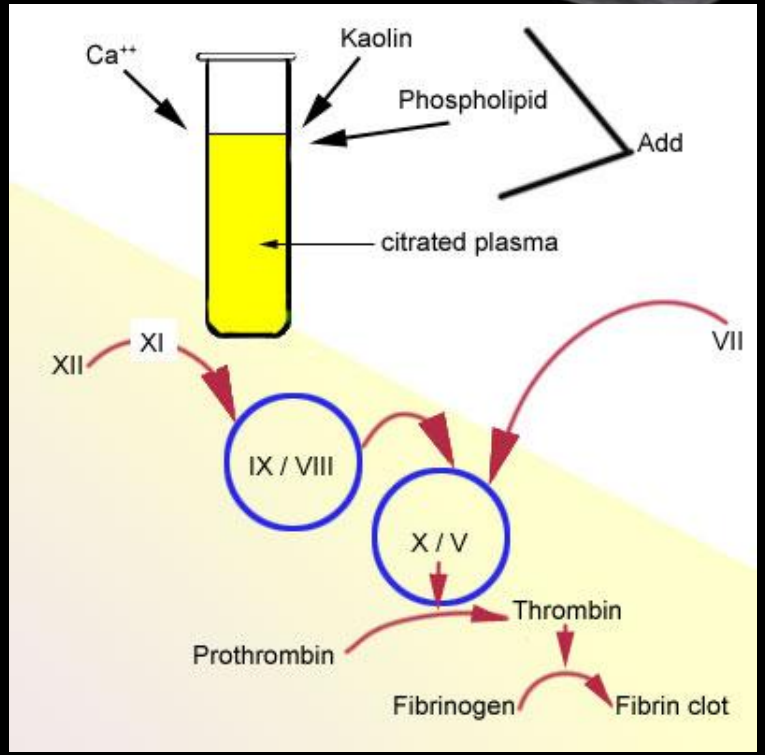
- After mixing, blood is moved through tube within spectral analyzer
- Once blood's mobility reduced to certain point, wavelength of light changed and reading given



http://www.medicine.mcgill.ca/physio/vlab/bloodlab/pt_ptt.htm

Activated Partial Thromboplastin Time

- aPTT uses kaolin to activate
- Spectral analyzer the same
- Measures intrinsic and common pathway



Does PT or aPTT predict anything?

Hemostasis in Massively Transfused Trauma Patients

Ann. Surg. • July 1979

R. B. COUNTS, C. HAISCH, T. L. SIMON, N. G. MAXWELL, D. M. HEIMBACH, C. J. CARRICO

TABLE 4. *Number of Patients Having Prolonged PT or PTT*

Patient Category	Prothrombin Time				PTT			
	<1.3 × Control	>1.3 × Control	>1.5 × Control	Total No. Pts.	<1.3 × Control	>1.3 × Control	>1.5 × Control	Total No. Pts.
Generalized bleeding	1	7	4	8	3	5	4	8
No generalized bleeding	11	8	2	19	15	4	2	19
Total	12	15	6	27	18	9	6	27

For patients with bleeding, the results of tests at time of bleeding are tabulated; for non-bleeding patients, the longest PT and PTT.

Does PT or aPTT predict anything?

How Well Does the Activated Partial Thromboplastin Time Predict Postoperative Hemorrhage?

Anthony L. Suchman, MD, Alvin I. Mushlin, MD, ScM

JAMA, Aug 8, 1986—Vol 256, No. 6

Table 4.—Operating Characteristics of the APTT* Test in the Clinically Defined Subgroups†

Test Characteristic	Clinically Defined Subgroup: Low Risk	Combined High Risk	Known Coagulopathy	Potential Deficiency	Trauma/ Hemorrhage
Sensitivity, %					
Narrow	7.7	57	100‡	67§	44
Broad	11.9	60	84	76	41
Specificity, %					
Narrow	86.7	67	18	56	78
Broad	86.3	78	20	70	83
Positive likelihood ratio					
Narrow	0.58	1.74	1.22	1.52	1.99
Broad	0.87	2.75	1.05	2.50	2.41
Negative likelihood ratio					
Narrow	1.07	0.64	0	0.59	0.72
Broad	1.02	0.52	0.80	0.34	0.71

*APTT indicates activated partial thromboplastin time.
†See text for definitions of subgroups and descriptions of "narrow" and "broad" definitions of hemorrhage.
‡Estimate based on two cases.
§Estimate based on three cases.

	Narrow		Broad	
	Hemorrhage			
	Present	Absent	Present	Absent
APTT Elevated	9	338	102	245
APTT Not Elevated	18	1769	359	1428
Sensitivity	33.3%		22.1%	
Specificity	83.9%		85.4%	
Positive Likelihood Ratio	2.08		1.51	
Negative Likelihood Ratio	0.79		0.91	

Outcome Group	Criteria
Definite hemorrhage	Discharge diagnosis code for postoperative hemorrhage, or secondary procedure code for control of postoperative bleeding
Statistically defined hemorrhage	In top 2% of distribution (for a given procedure) of blood transfused during five-day interval beginning on day of surgery
Procoagulant administered	Fresh-frozen plasma or other procoagulant administered during five-day interval beginning on day of surgery
No hemorrhage	Does not meet any of the above criteria

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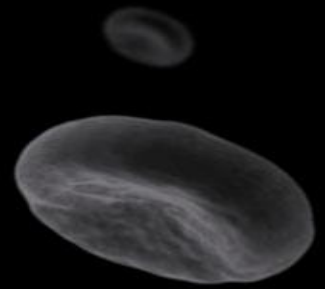
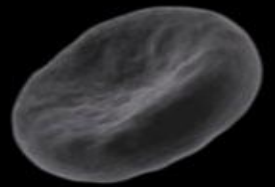
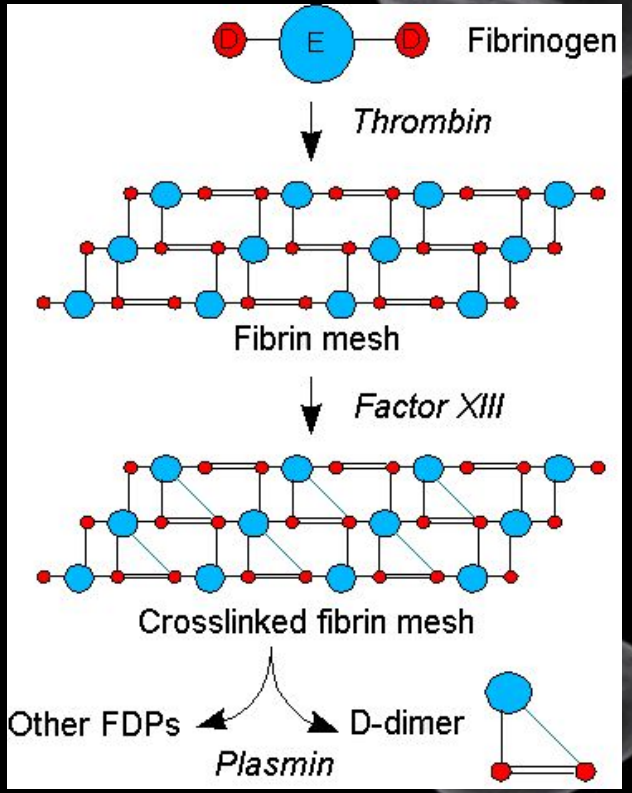




D-Dimers

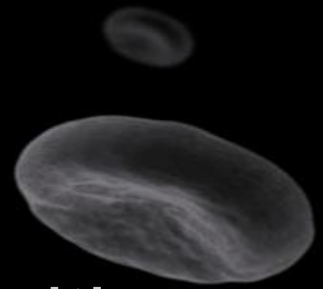
- Breakdown product of *crosslinked* fibrin meshwork
  - FDPs don't need crosslinking
- Half-life is 5 hours
  - Indicates active or ongoing fibrinolysis

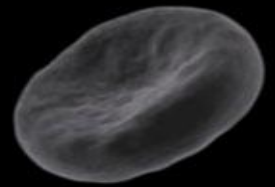


http://www.pathologystudent.com/wp-content/uploads/2013/03/D-dimer.jpg

D-Dimers vs FDPs

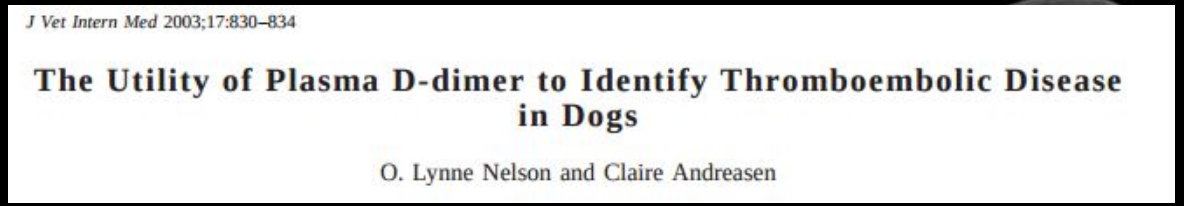
- D-Dimers are more specific and sensitive than fibrin degradation products for DIC
  - Abstract from ACVIM 1998
  - Specificity and sensitivity of D-Dimers in DIC compared to FDPs
    - 94.7% and 76.5% for D-Dimers
    - 84.2% and 73.5% for FDPs





D-Dimers

- 3 groups of dogs
  - Normal dogs
  - Sick dogs (hepatic, cardiac, renal, neoplastic, postoperative)
  - Dogs with thromboembolic disease
- Dogs with PTE had significantly elevated D-Dimers, as did liver disease. Neoplasia trended towards elevated (had influence from hemoabdomens), others were not significantly different.



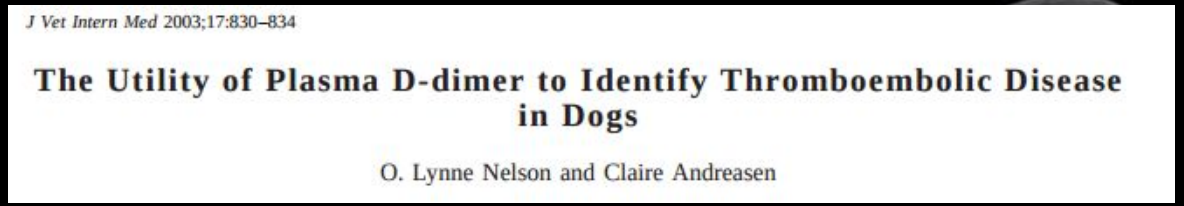
J Vet Intern Med 2003;17:830–834

The Utility of Plasma D-dimer to Identify Thromboembolic Disease in Dogs

O. Lynne Nelson and Claire Andreasen

D-Dimers

- Sensitivity of D-dimer concentrations >500 ng/mL for predicting TE was 100%
  - Specificity was 70%
- Sensitivity at >1,000 ng/mL was 80%
  - Specificity of D-dimer to predict TE was 94%
- Sensitivity at >2,000 ng/mL was 35%
  - Specificity of D-dimer was 98.5%
- No dog in the TE group had abnormal FDPs


J Vet Intern Med 2003;17:830–834

The Utility of Plasma D-dimer to Identify Thromboembolic Disease in Dogs

O. Lynne Nelson and Claire Andreasen

D-Dimers in Cats

D-Dimers neither sensitive nor specific for cats with DIC or cardiomyopathy

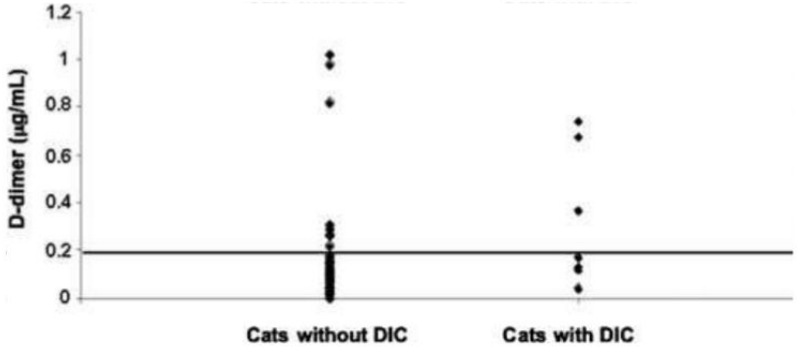


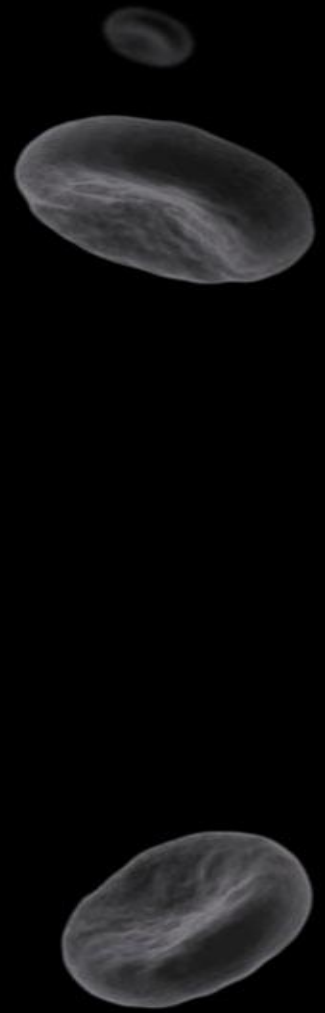
Figure 3. Concentration of D-dimer in ill cats and cats with cardiomyopathy with and without disseminated intravascular coagulation. Black horizontal line represents the lower limit of detection and the upper limit of the reference interval of the immunoturbidimetric D-dimer assay.

Evaluation of plasma antithrombin activity and D-dimer concentration in populations of healthy cats, clinically ill cats, and cats with cardiomyopathy

Jennifer L. Brazzell, Dori L. Borjesson Vol. 36 / No. 1 / 2007 Veterinary Clinical Pathology

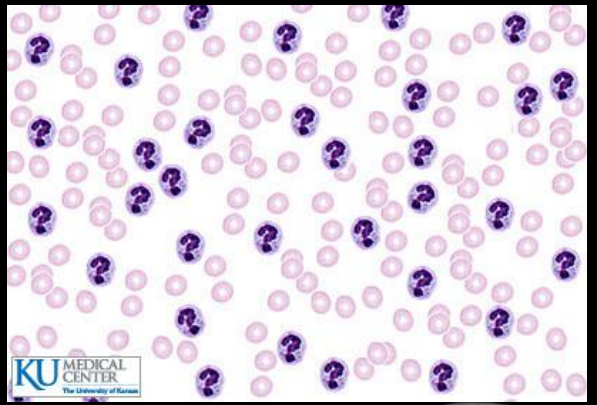
Fibrinogen

- Positive acute phase protein
- In humans, relationship between fibrinogen levels and coronary disease and thromboembolic disease have been described



Fibrinogen

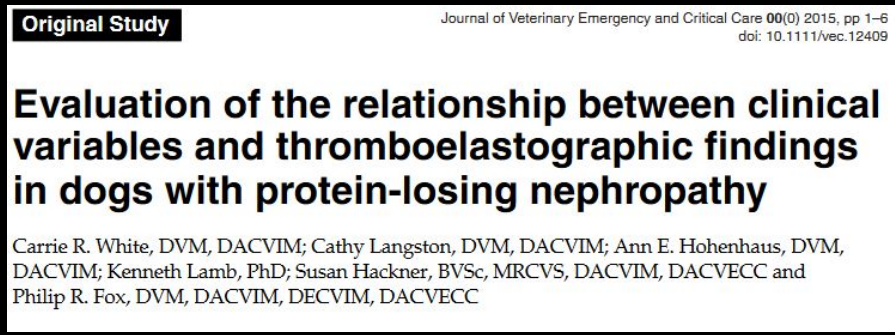
- SAECC: “Acquired disorders are described with hemodilution, massive transfusion, hepatic dysfunction, DIC and sepsis”
  - Difficult to find supporting evidence in animals



http://www.kumc.edu/instruction/medicine/anatomy/histoweb/blood/small/Blood00s.JPG

Antithrombin

- Protein that plays in a role in hemostatic regulation
  - Loss can occur with disease such as PLN
  - Recent study showed that hypercoagulability in PLN is not associated with AT levels



Original Study

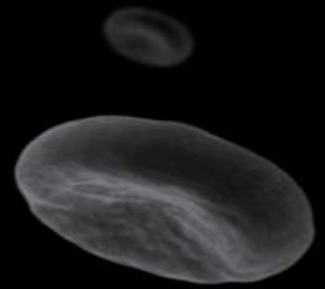
Journal of Veterinary Emergency and Critical Care **00**(0) 2015, pp 1–6
doi: 10.1111/vec.12409

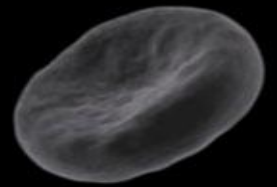
Evaluation of the relationship between clinical variables and thromboelastographic findings in dogs with protein-losing nephropathy

Carrie R. White, DVM, DACVIM; Cathy Langston, DVM, DACVIM; Ann E. Hohenhaus, DVM, DACVIM; Kenneth Lamb, PhD; Susan Hackner, BVSc, MRCVS, DACVIM, DACVECC and Philip R. Fox, DVM, DACVIM, DECVIM, DACVECC

Outline

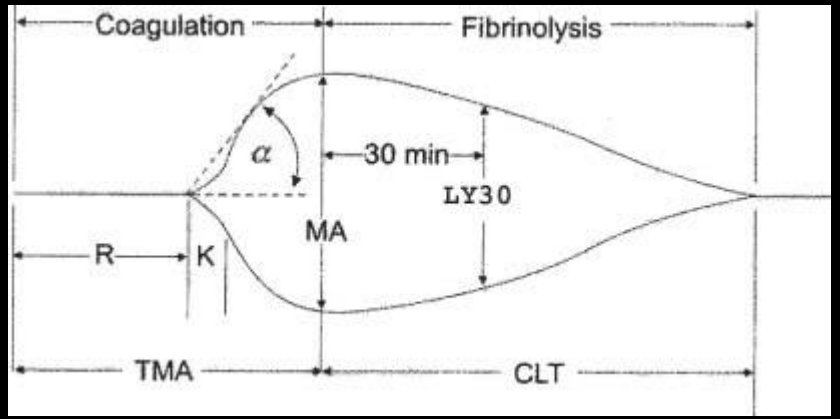
- Brief Coagulation Review
- Platelet Testing
  - Platelet Counts
  - Platelet Abnormalities
  - BMBT
- In Vitro Plasma Based Testing
  - PT
  - aPTT
- Indirect Testing
  - Fibrin Split Products
  - D-Dimers
  - Fibrinogen Concentration
  - Antithrombin
- In Vivo Whole Blood Based Testing
  - TEG and PlateletMapping





Thromboelastography (TEG)

- Better representation of in vivo hemostasis
  - Run on blood with platelets and clotting factor



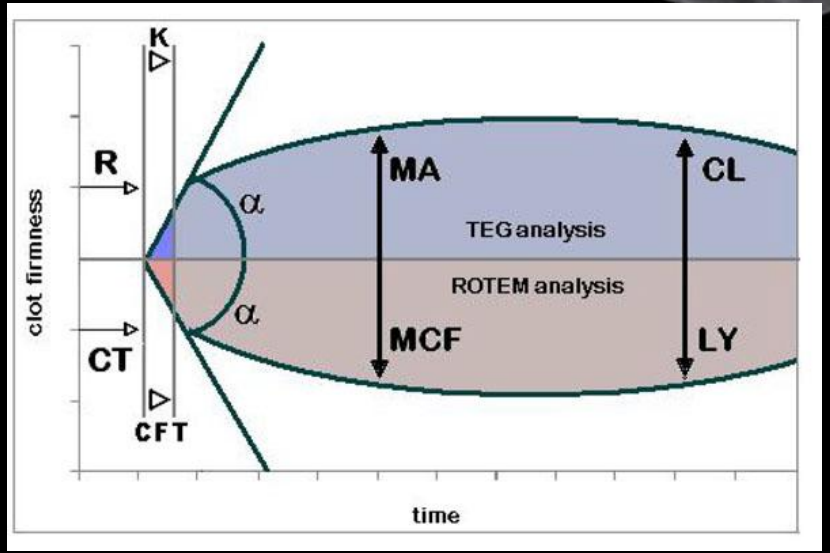
Explicative TEG tracing (modified from TEG 5000 User's Manual,Haemoscope, Niles, IL)

Thromboelastography (TEG)

- Consists of heated cup (37C)
- Citrated whole blood
- Pin connected to torsion wire
- Spinning of cup (or pin) is translated to electric signal and tracing

TEG vs ROTEM

- TEG
  - Cup spins
  - Torsion wire converted to electric signal
- ROTEM
  - Pin spins
  - Optical monitor
- Most companion animal studies performed with TEG



TEG vs ROTEM

- TEG
  - Cup spins
  - Torsion wire converted to electric signal
- ROTEM
  - Pin spins
  - Optical monitor
- Most companion animal studies performed with TEG

Thromboelastography (TEG)

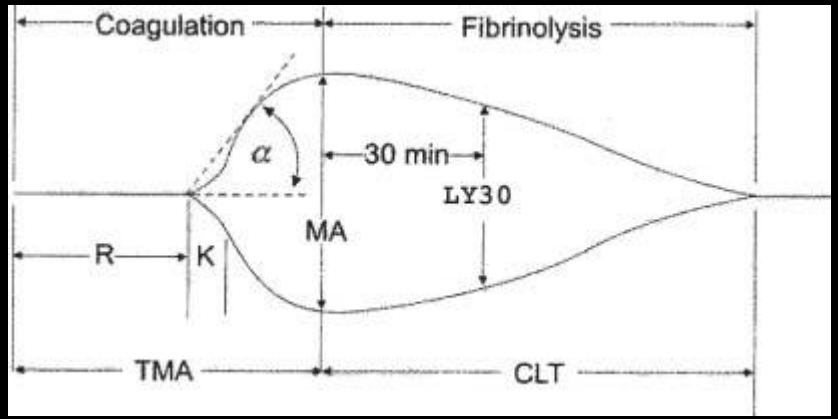
- Coagulation activated by
  - Kaolin
    - Intrinsic pathway
  - Tissue factor
    - Extrinsic
  - Both kaolin and tissue factor
    - (r-Teg)

Thromboelastography (TEG)

- Kaolin cups are commercially available, as are r-TEG with kaolin and TF
- rhTF (recombinant human TF) used for experimental studies
  - Not available commercially
  - TF activated TEG showing narrower standard deviations of normals and lower interoperator differences

Thromboelastography (TEG)

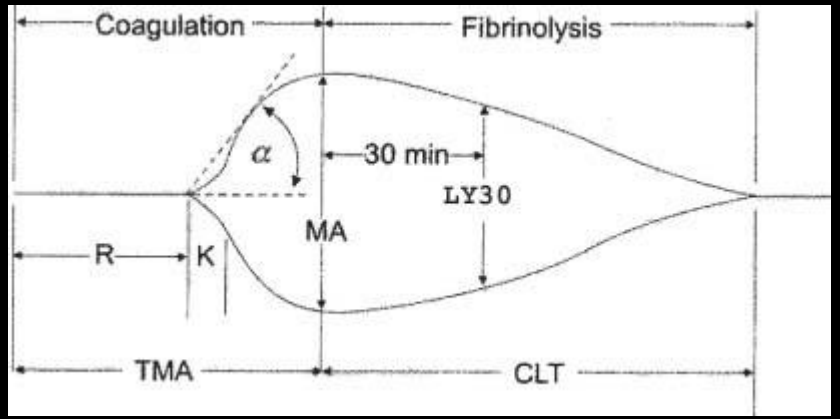
- R time = reaction time
  - Time to formation of initial fibrin
- K time = kinetic time
  - Time for fibrin cross linkage to reach 20mm (from 2mm)
- α Angle =
  - Angle from baseline to the slope of tracing represents clot formation



Explicative TEG tracing (modified from TEG 5000 User's Manual,Haemoscope, Niles, IL)

Thromboelastography (TEG)

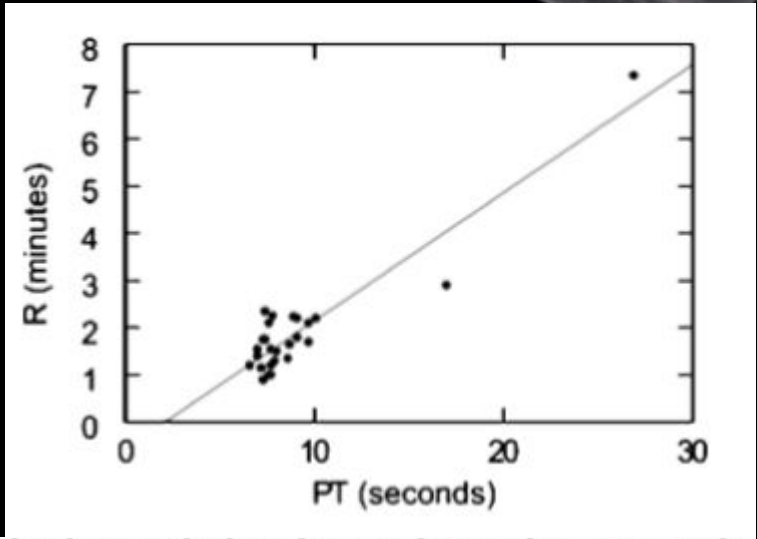
- MA
  - Maximum amplitude of tracing
- G
  - Calculated value of clot strength (5000xMA)/(100-MA)
- LY 30
  - Clot lysis at 30 min following MA



Explicative TEG tracing (modified from TEG 5000 User's Manual,Haemoscope, Niles, IL)

TEG Interpretation

- R time
  - Correlation to PT
  - Not reproducible in many studies



Thrombelastography in dogs admitted to an intensive care unit

Catherine R. Wagg[1], Søren R. Boysen[2], Christian Bédard[1] Veterinary Clinical Pathology ISSN 0275-6382

TEG Interpretation

- K time and α Angle
  - Platelet concentration and function
  - Fibrinogen concentration and function
  - Clotting factor activity

TEG Interpretation

- K and MA both affected by platelet count
- Logarithmic relationship
- May not be true at higher platelet counts

Influence of platelet count and activity on thromboelastography parameters

Platelets (June 2003) **14(4)**, 219–224

Virginia A. Bowbrick, Dimitri P. Mikhailidis, Gerard Stansby

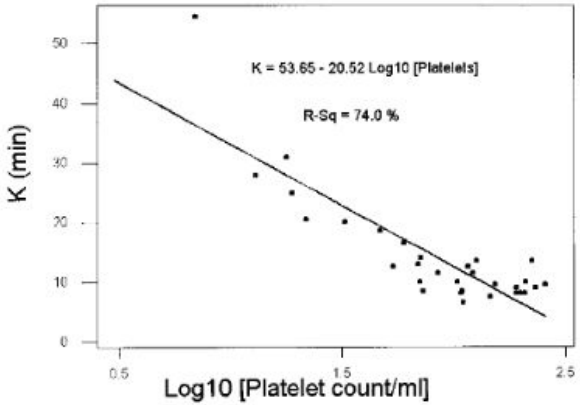


Figure 2. Control subjects. Plot of K time (min) against Log_{10} [platelet count/ml].

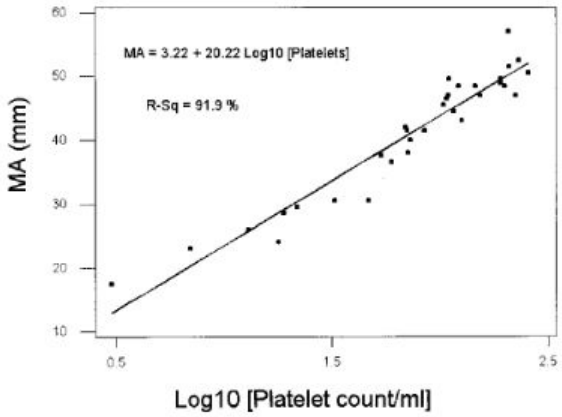


Figure 1. Control subjects. Plot of MA (mm) against Log_{10} [platelet count/ml].

TEG Interpretation

- Hypercoagulability may cause reduced R and K values and increased angle and increased MA

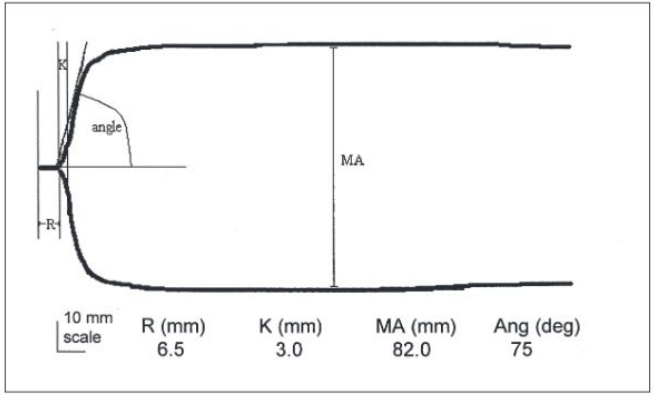


Figure 2—Thromboelastographic tracing obtained from analysis of a blood sample from a 4-month-old puppy with canine parvoviral enteritis. *See* Figure 1 for key.

TEG Interpretation

- Multiple hypercoagulable states have had increased MA, including parvovirus, IMHA, and hyperadrenocorticism

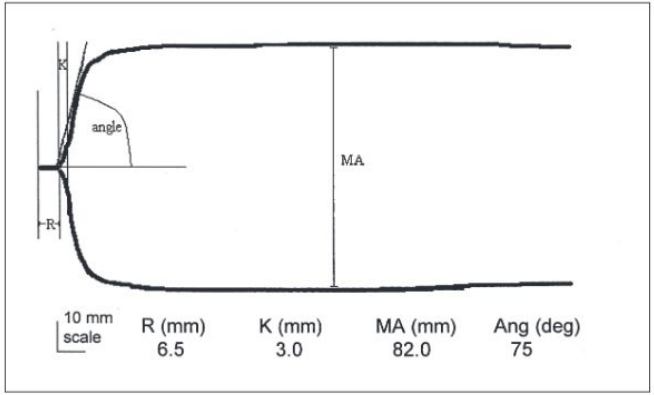


Figure 2—Thromboelastographic tracing obtained from analysis of a blood sample from a 4-month-old puppy with canine parvoviral enteritis. *See* Figure 1 for key.

TEG Interpretation

- In human study of post-surgical patients, the use of G of r-TEG showed 100% sensitivity and 45% specificity for thromboembolic event

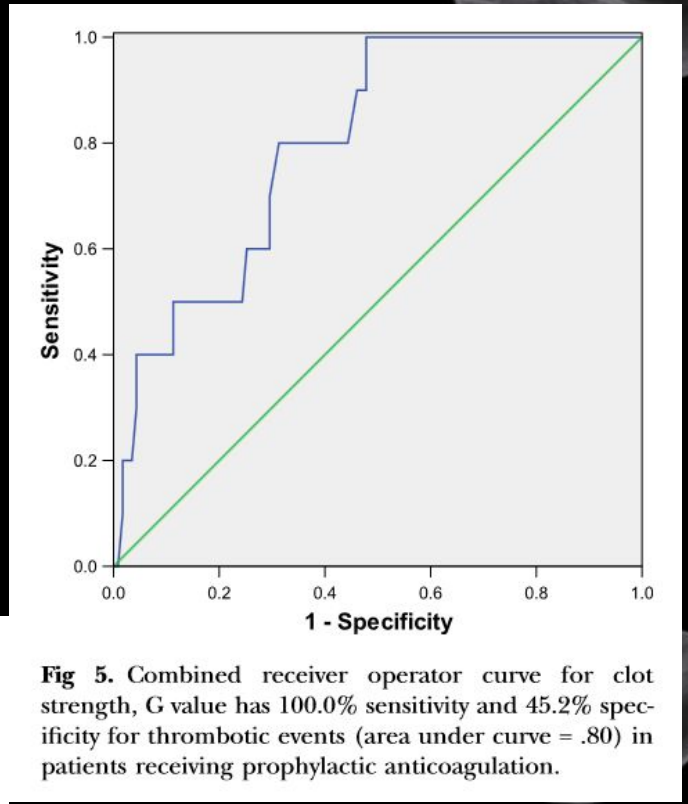


Fig 5. Combined receiver operator curve for clot strength, G value has 100.0% sensitivity and 45.2% specificity for thrombotic events (area under curve = .80) in patients receiving prophylactic anticoagulation.

Rapid thrombelastography (r-TEG) identifies hypercoagulability and predicts thromboembolic events in surgical patients

Surgery
Volume 146, Number 4

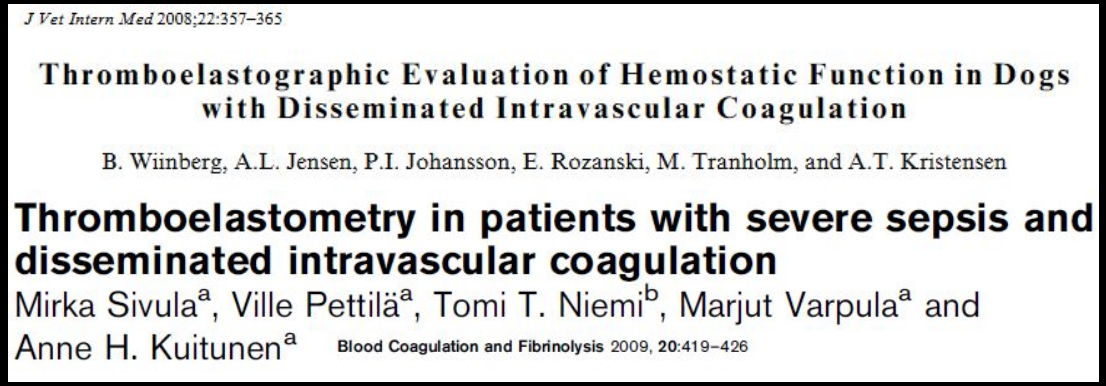
Jeffry L. Kashuk, MD,[a] Ernest E. Moore, MD,[a] Allison Sabel, MD, PhD, MPH,[c,d] Carlton Barnett, MD,[a] James Haenel, CRT,[a] Tuan Le, MD,[b] Michael Pezold, BA,[a] Jerry Lawrence, BA,[a] Walter L. Biffl, MD,[a] C. Clay Cothren, MD,[a] *and* Jeffrey L. Johnson, MD,[a] *Denver, CO*

TEG Interpretation

- LY30 correlates to clot breakdown
  - Depending on study, also correlates to d-dimers, FDPs
- ROTEM ML% (maximum lysis) in one study predicted post-traumatic hyperfibrinolysis better than plasma-based tests (FDPs, d-dimers)

TEG Interpretation

- Study of Dogs in DIC showed no correlation between LY30 and d-dimer concentrations
- Study of people in DIC showed prolonged lytic measurements despite higher d-dimers



J Vet Intern Med 2008;22:357–365

Thromboelastographic Evaluation of Hemostatic Function in Dogs with Disseminated Intravascular Coagulation

B. Wiinberg, A.L. Jensen, P.I. Johansson, E. Rozanski, M. Tranholm, and A.T. Kristensen

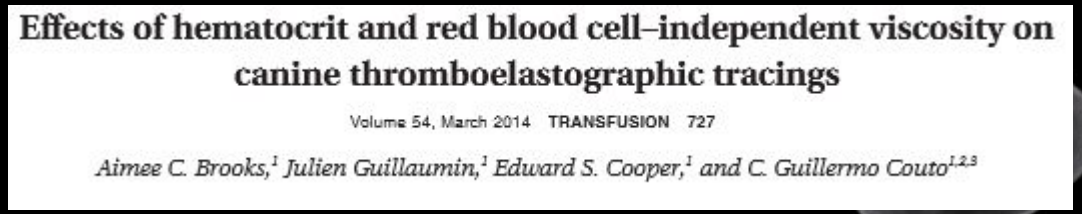
Thromboelastometry in patients with severe sepsis and disseminated intravascular coagulation

Mirka Sivula[a], Ville Pettilä[a], Tomi T. Niemi[b], Marjut Varpula[a] and Anne H. Kuitunen[a]

Blood Coagulation and Fibrinolysis 2009, **20**:419–426

Thromboelastography (TEG) Considerations

- Factor XIIa is not calcium dependant
  - Delay in running sample results in thrombin formation from factor XIIa
- HCT changes create artifactual changes in TEG tracings due to changes of viscosity
  - Decreased blood viscosity creates hypercoagulable TEG tracings



Effects of hematocrit and red blood cell–independent viscosity on canine thromboelastographic tracings

Volume 54, March 2014 TRANSFUSION 727

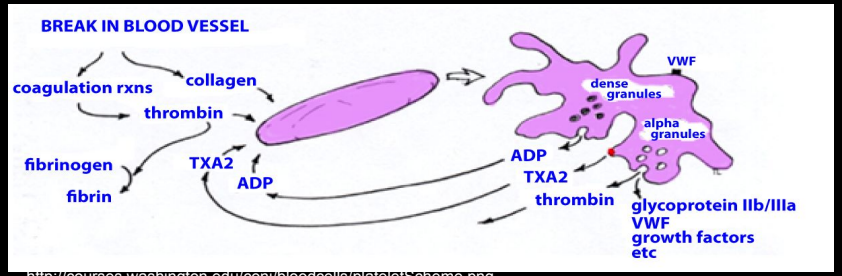
Aimee C. Brooks,[1] Julien Guillaumin,[1] Edward S. Cooper,[1] and C. Guillermo Couto[1,2,3]

TEG PlateletMapping

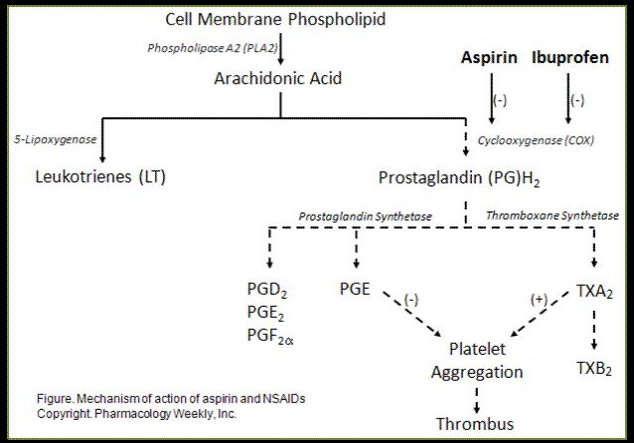
- Special use of TEG to determine the function on platelets in the presence of different activators

http://wolfspirit395.deviantart.com/art/blood-stained-map-164566046

Activation of Platelets

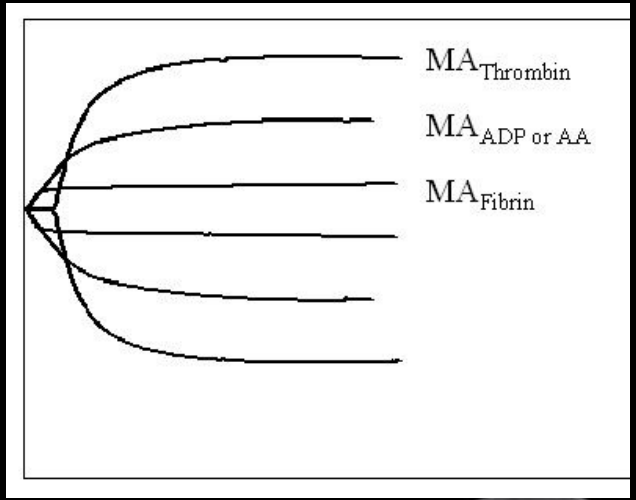


http://courses.washington.edu/conj/bloodcells/plateletScheme.png



TEG PlateletMapping

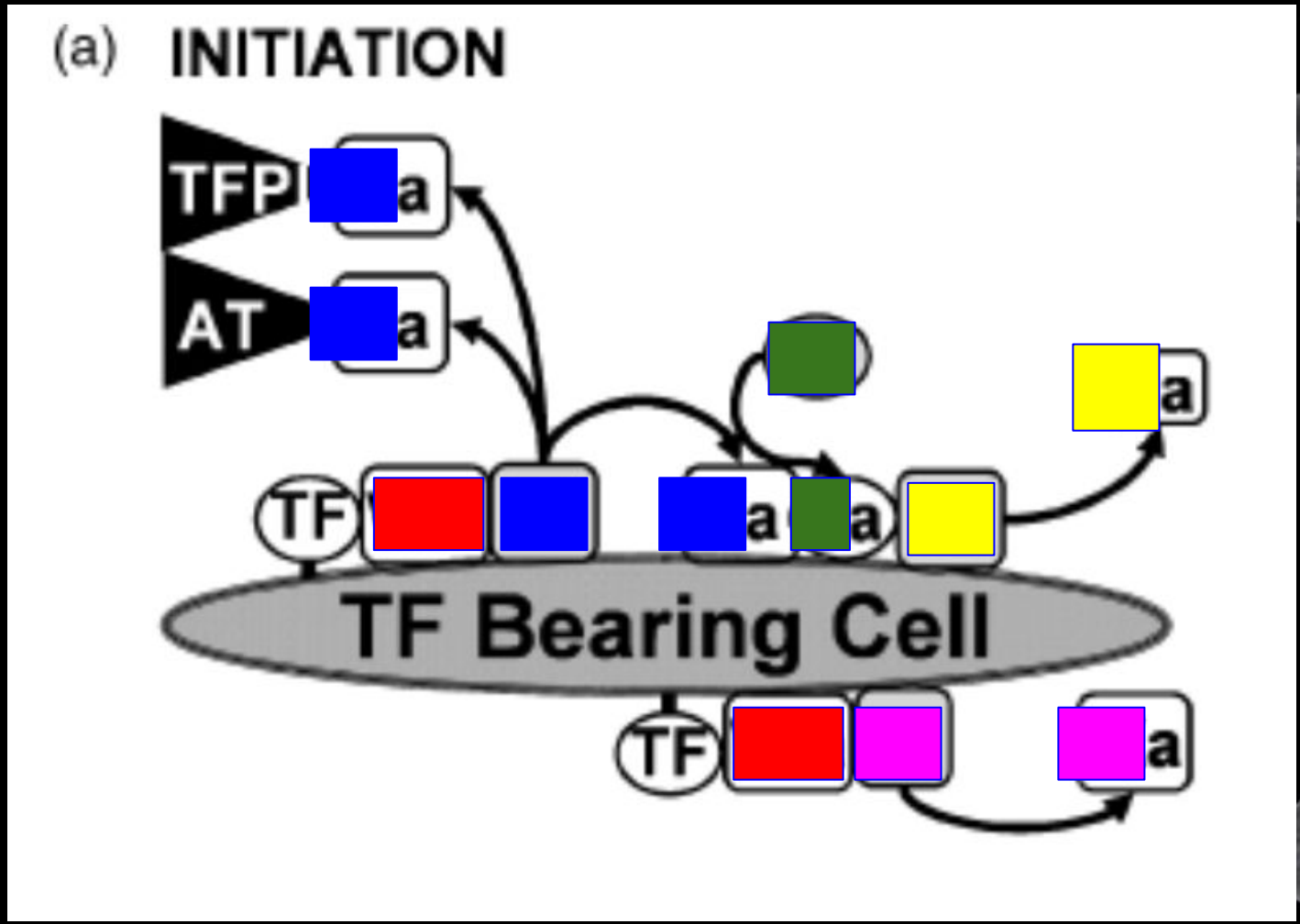
- Requires 4 cups
  - Cup with heparinized blood combined with XIIIa and reptilase (similar to thrombin) to form fibrin scaffold without thrombin
    - Measures clot formation from non-platelet activation dependent parts
  - Cup with ADP platelet activations and arachidonic acid activator
  - 4th cup with heparinase and kaolin activator
- Equations are used to determine the effect of each activator on MA

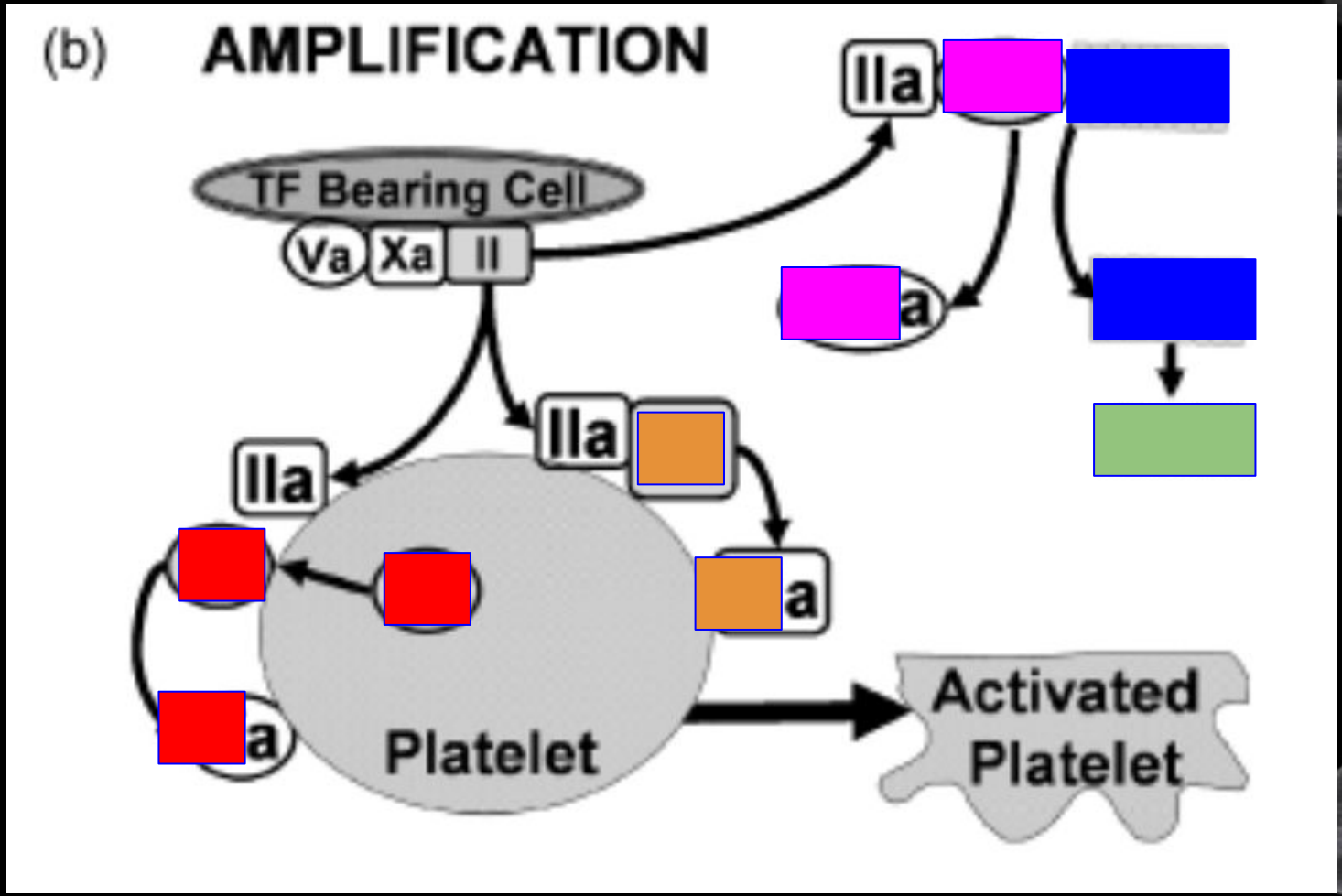


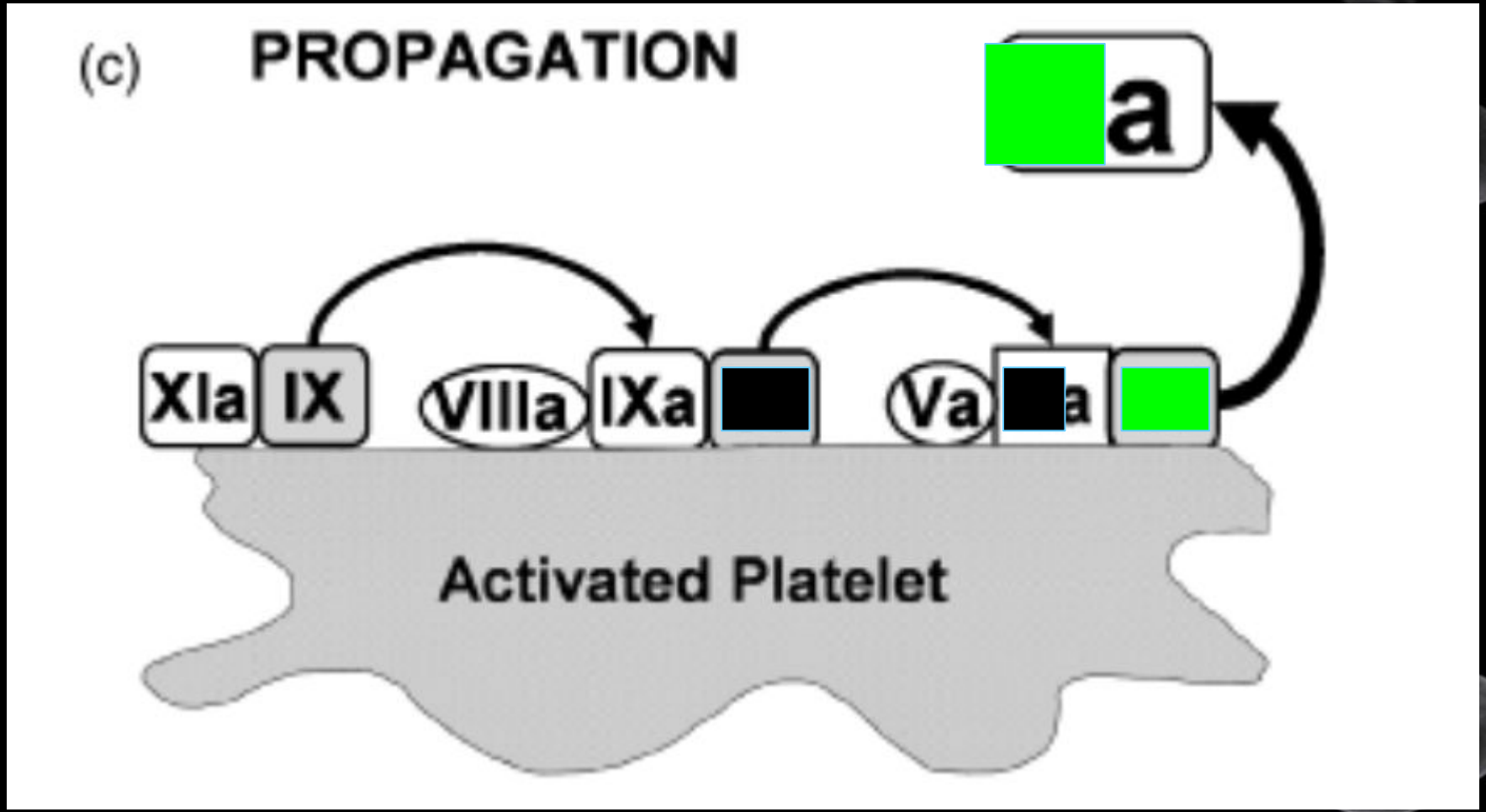
http://www.thrombosisjournal.com/content/figures/1477-9560-5-3-1-l.jpg

Conclusions

- Platelet testing - 20k/HPF is better #
  - EXTREMELY important part of coag picture
- PT/aPTT - not very sensitive tests for clinical bleeding
- D-Dimers much more specific for thrombosis than FDPs
- Fibrinogen - Correlates with lots but not super helpful
- TEG - Many factors interfere with results, but good test of overall hemostatic system


(a) INITIATION
TFP
a
AT
a
a
TF
a
a
TF Bearing Cell
TF
a


(b)
AMPLIFICATION
IIa
TF Bearing Cell
Va
Xa
II
a
IIa
IIa
a
a
Platelet
Activated
Platelet


(c)
PROPAGATION
a
XIa
IX
VIIIa
IXa
Va
Activated Platelet

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