Phenotypes of blood failure. One size fits all biology and resuscitation is the real blood failure.

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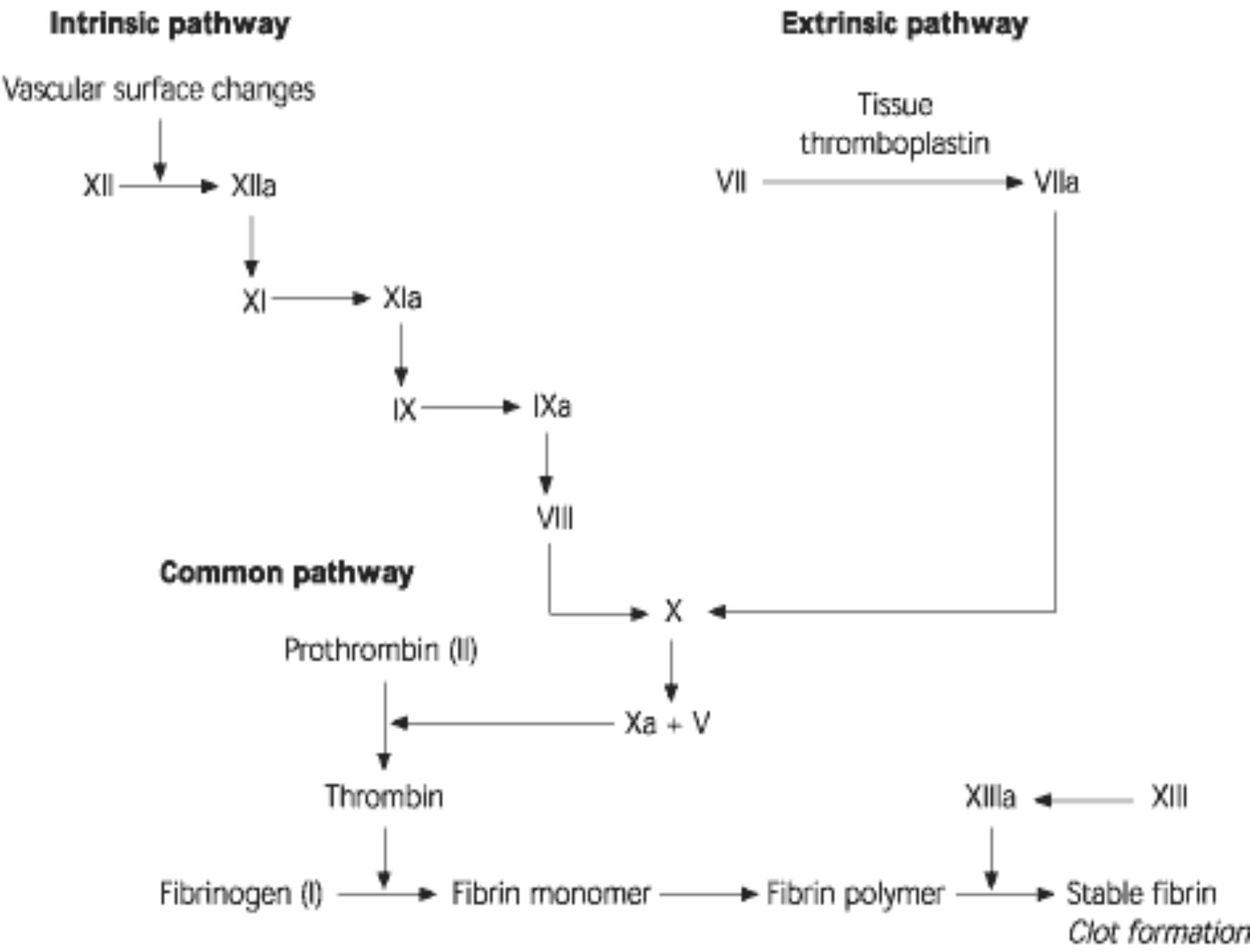
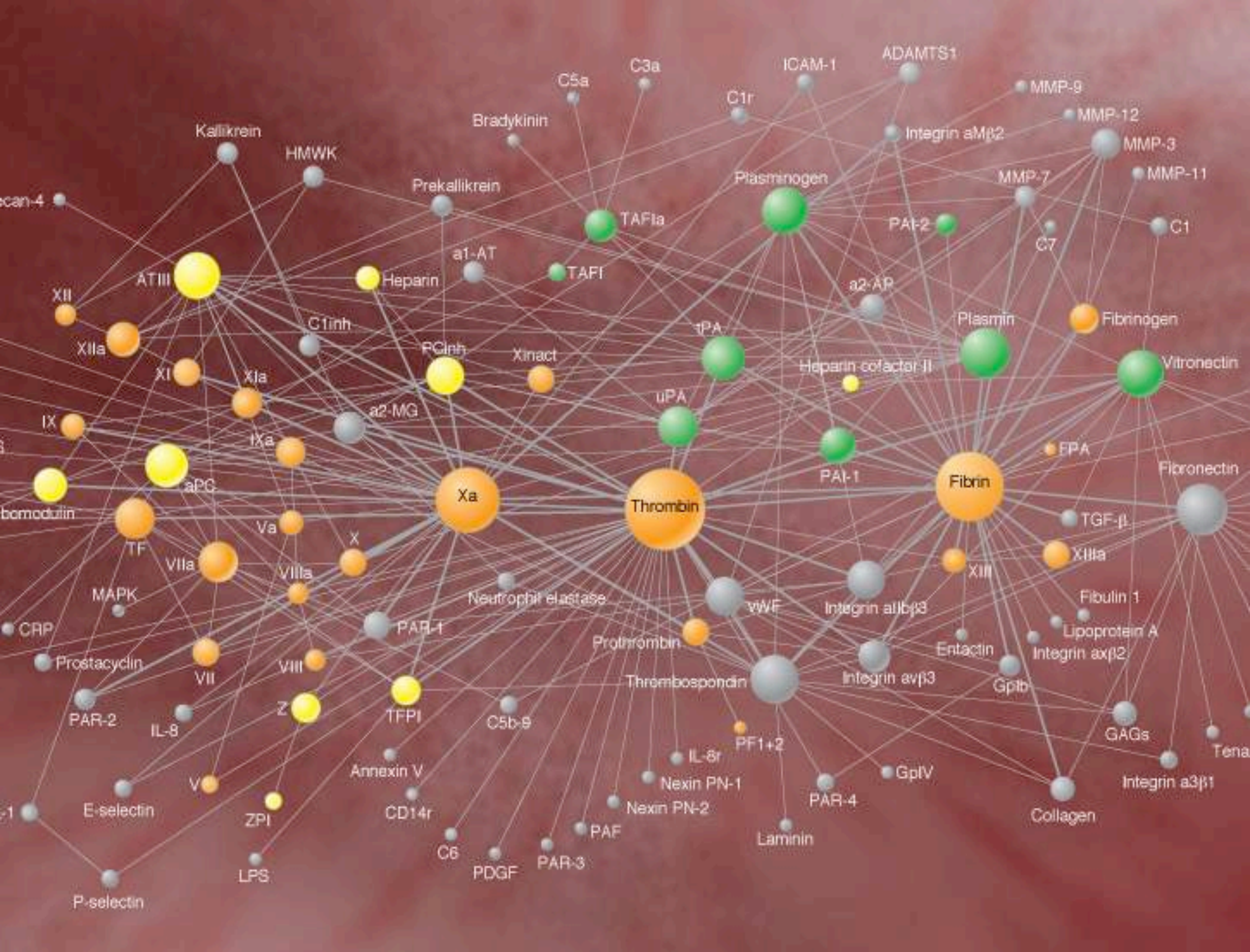
The Bruce Rockwell Distinguished Chair of Trauma Surgery
Denver Health Medical Center
Professor and Vice Chair
University of Colorado School of Medicine

What problem are we trying to solve when we resuscitate?

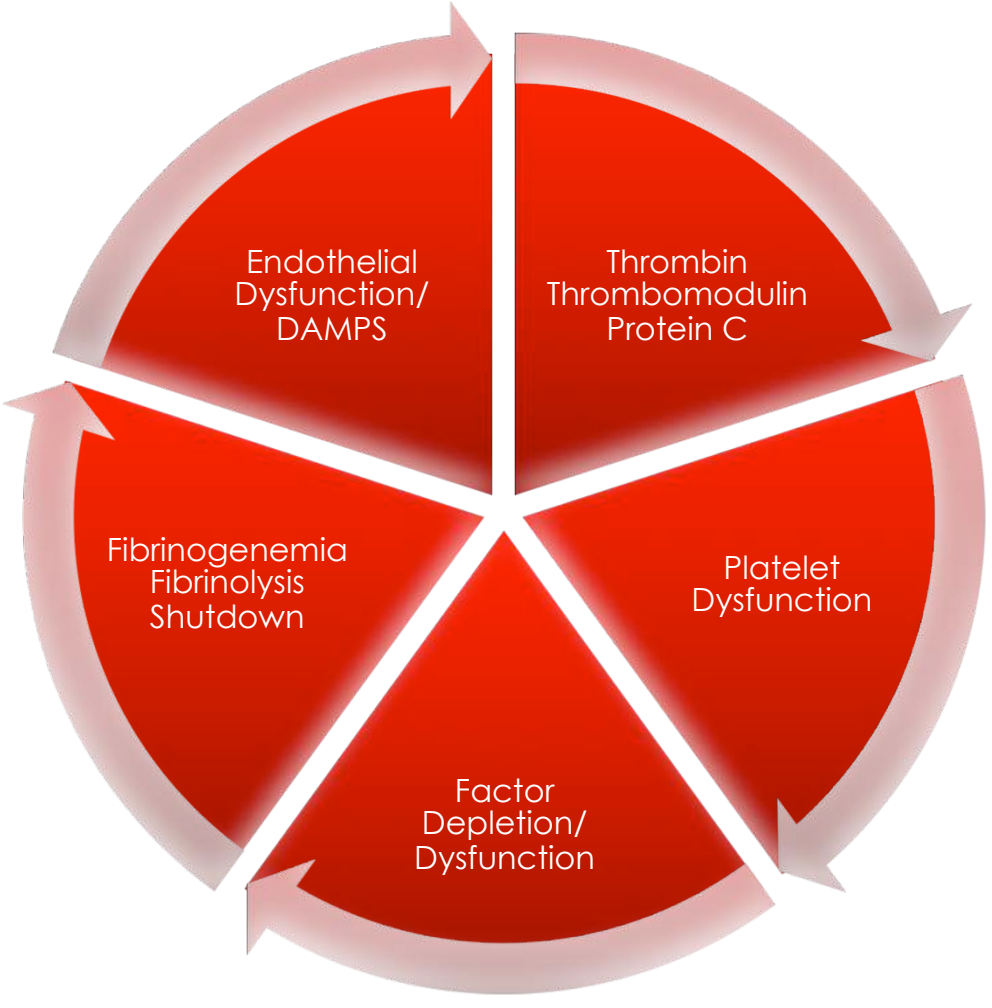
- Stop bleeding/progression?
- Treat coagulopathy?
- Prevent coagulopathy?
- Treat endotheliopathy?
- Prevent endotheliopathy?

- It is not the same in every patient and not the same minute to minute.


Intrinsic pathway
Extrinsic pathway
Vascular surface changes
Tissue thromboplastin
XII
XIIa
VII
VIIa
XI
XIa
IX
IXa
VIII
Common pathway
X
Prothrombin (II)
Xa + V
Thrombin
XIIIa
XIII
Fibrinogen (I)
Fibrin monomer
Fibrin polymer
Stable fibrin
Clot formation


ADAMTS1
ICAM-1
C3a
C5a
C1r
MMP-9
MMP-12
Bradykinin
Integrin aMβ2
MMP-3
Kallikrein
HMWK
MMP-11
Prekallikrein
Plasminogen
MMP-7
TAFIa
PAI-2
C1
C7
a1-AT
TAFI
ATIII
Heparin
a2-AP
XII
C1inh
Plasmin
Fibrinogen
tPA
XIIa
PCInh
Xinact
Heparin cofactor II
Vitronectin
XI
XIa
uPA
a2-MG
IX
IXa
EPA
Fibronectin
aPC
PAI-1
Fibrin
Xa
Thrombin
TGF-β
TF
Va
X
XIIIa
VIIa
VIIIa
XIII
MAPK
Neutrophil elastase
vWF
Integrin aIIbβ3
Fibulin 1
CRP
PAR-1
Lipoprotein A
Prothrombin
Entactin
Integrin axβ2
Prostacyclin
VII
VIII
Integrin avβ3
Thrombospondin
GpIb
PAR-2
IL-8
Z
TFPI
C5b-9
GAGs
PF1+2
IL-8r
Annexin V
GpIV
Integrin a3β1
V
Nexin PN-1
E-selectin
PAR-4
Nexin PN-2
CD14r
Collagen
ZPI
PAF
Laminin
C6
PDGF
PAR-3
LPS
P-selectin

Multiple overlapping phenotypes.



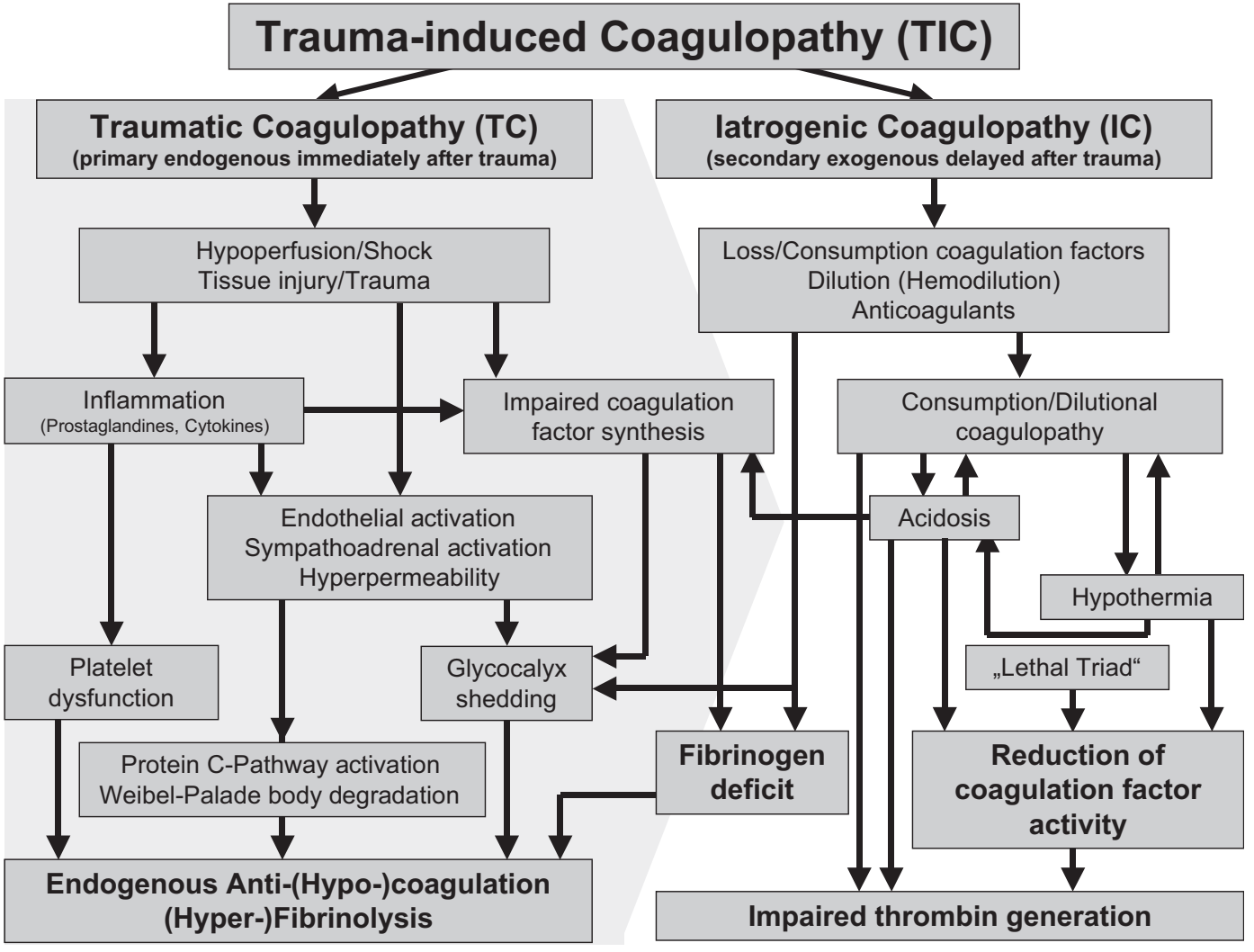
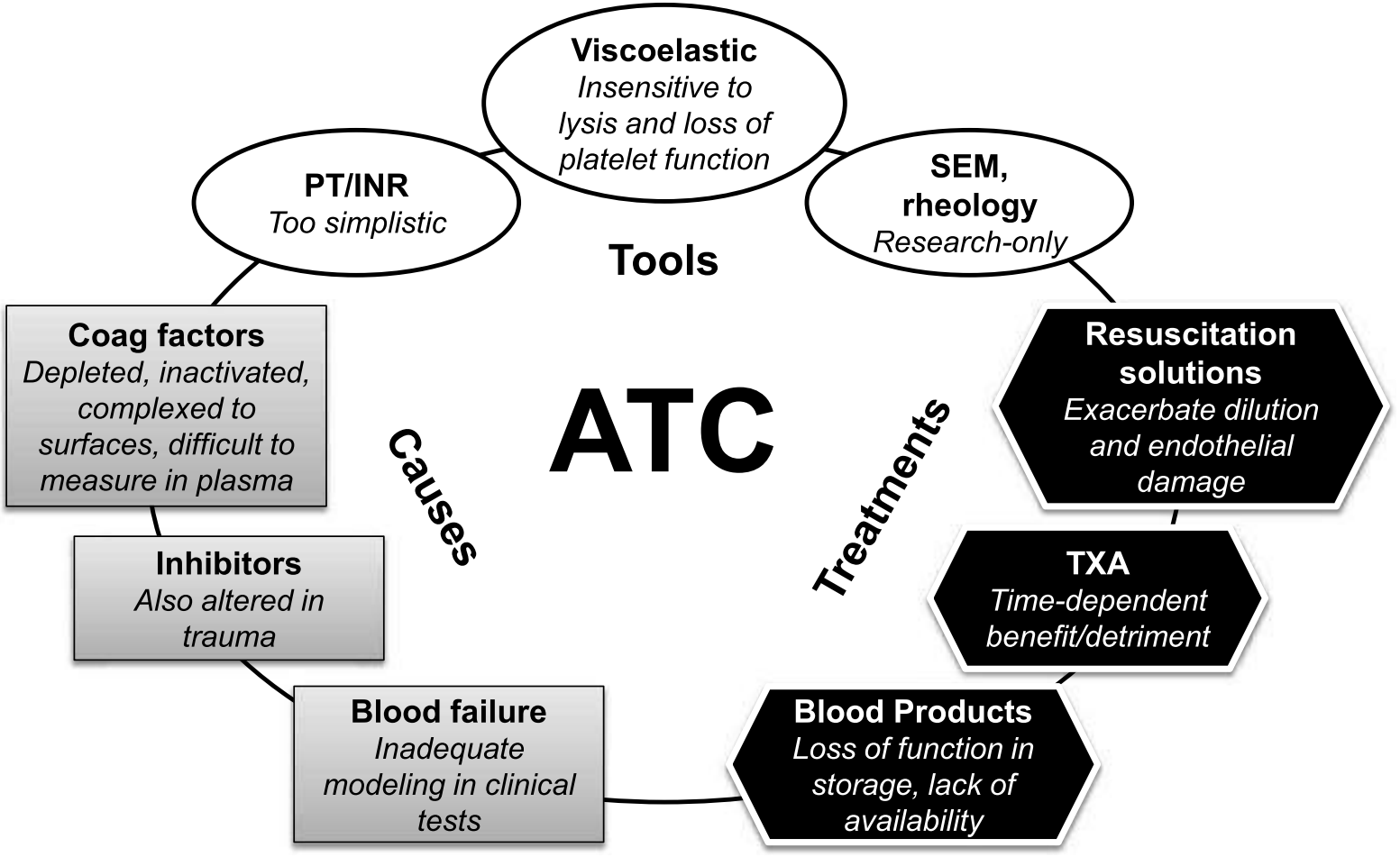
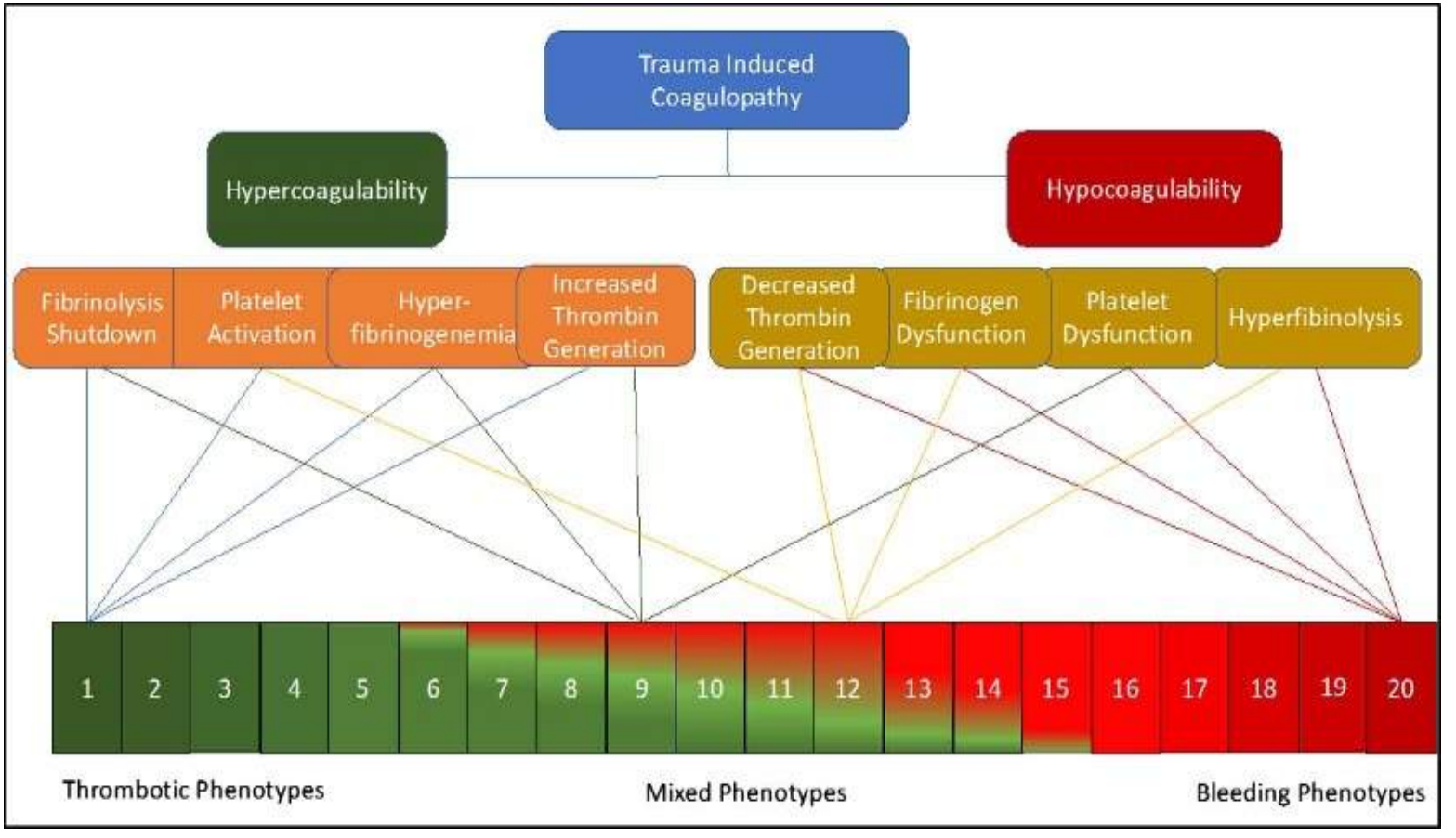


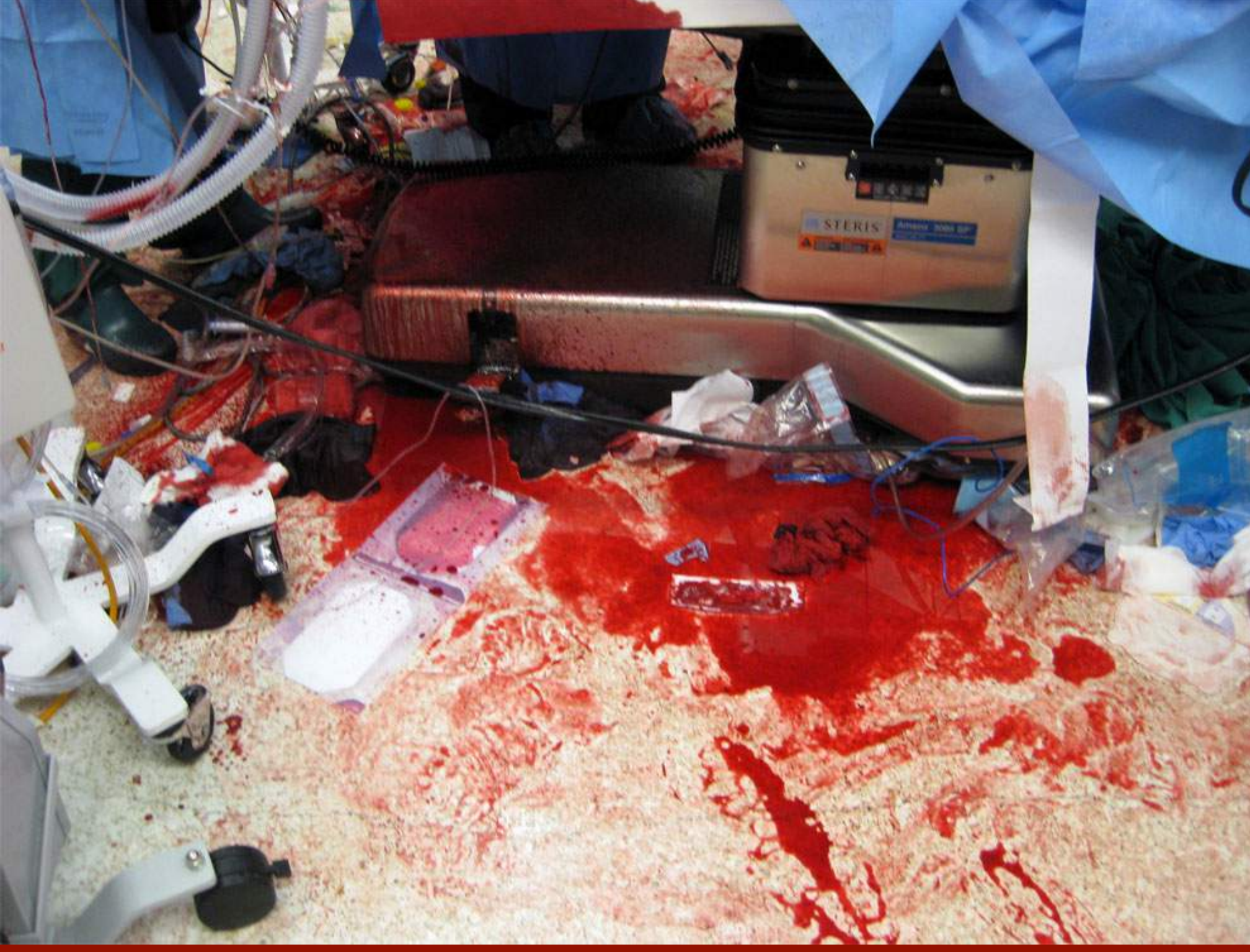
Fig. 1. Current concept and understanding of the mechanisms underlying TIC.

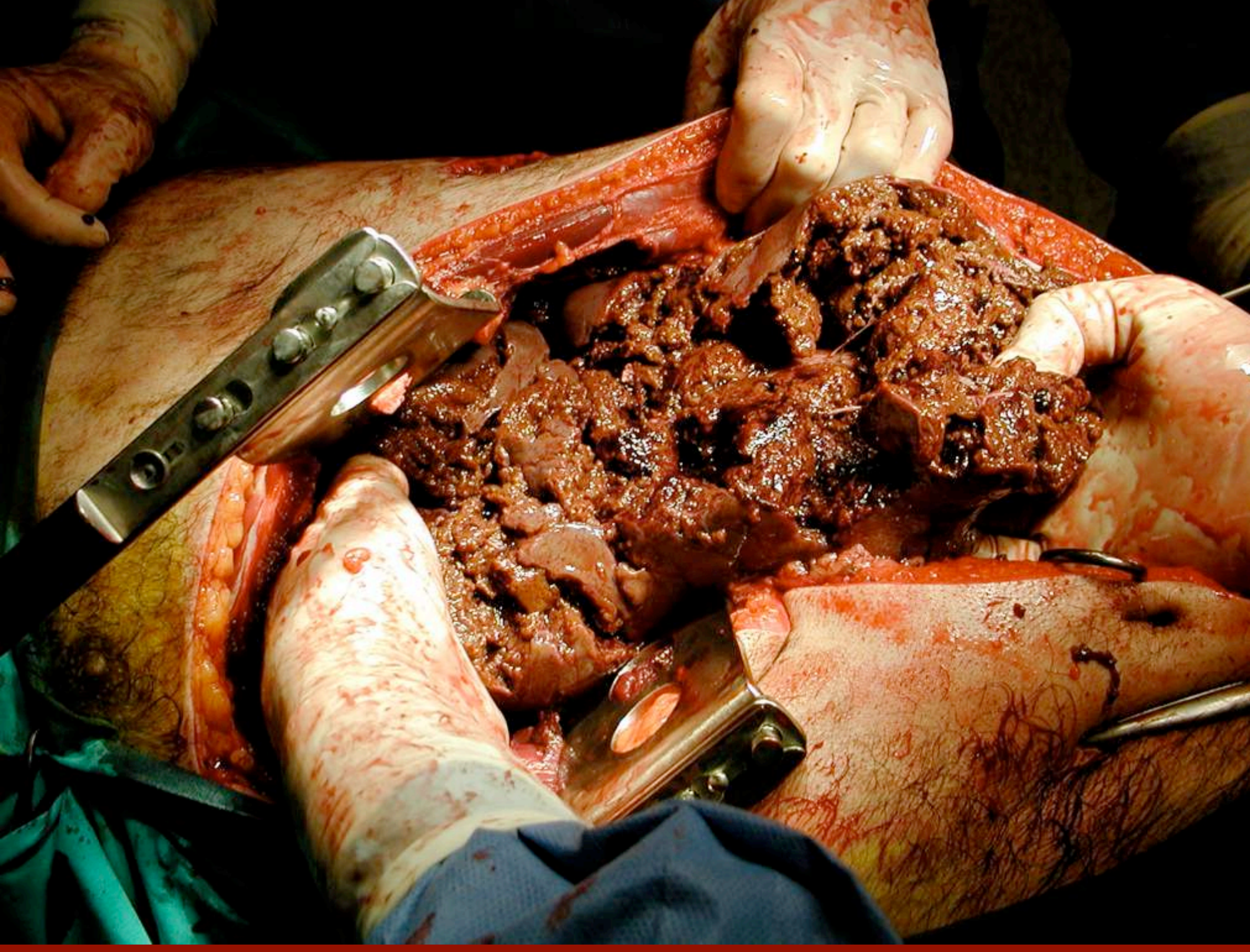

ATC
Tools
Viscoelastic
Insensitive to lysis and loss of platelet function
PT/INR
Too simplistic
SEM, rheology
Research-only
Causes
Coag factors
Depleted, inactivated, complexed to surfaces, difficult to measure in plasma
Inhibitors
Also altered in trauma
Blood failure
Inadequate modeling in clinical tests
Treatments
Resuscitation solutions
Exacerbate dilution and endothelial damage
TXA
Time-dependent benefit/detriment
Blood Products
Loss of function in storage, lack of availability

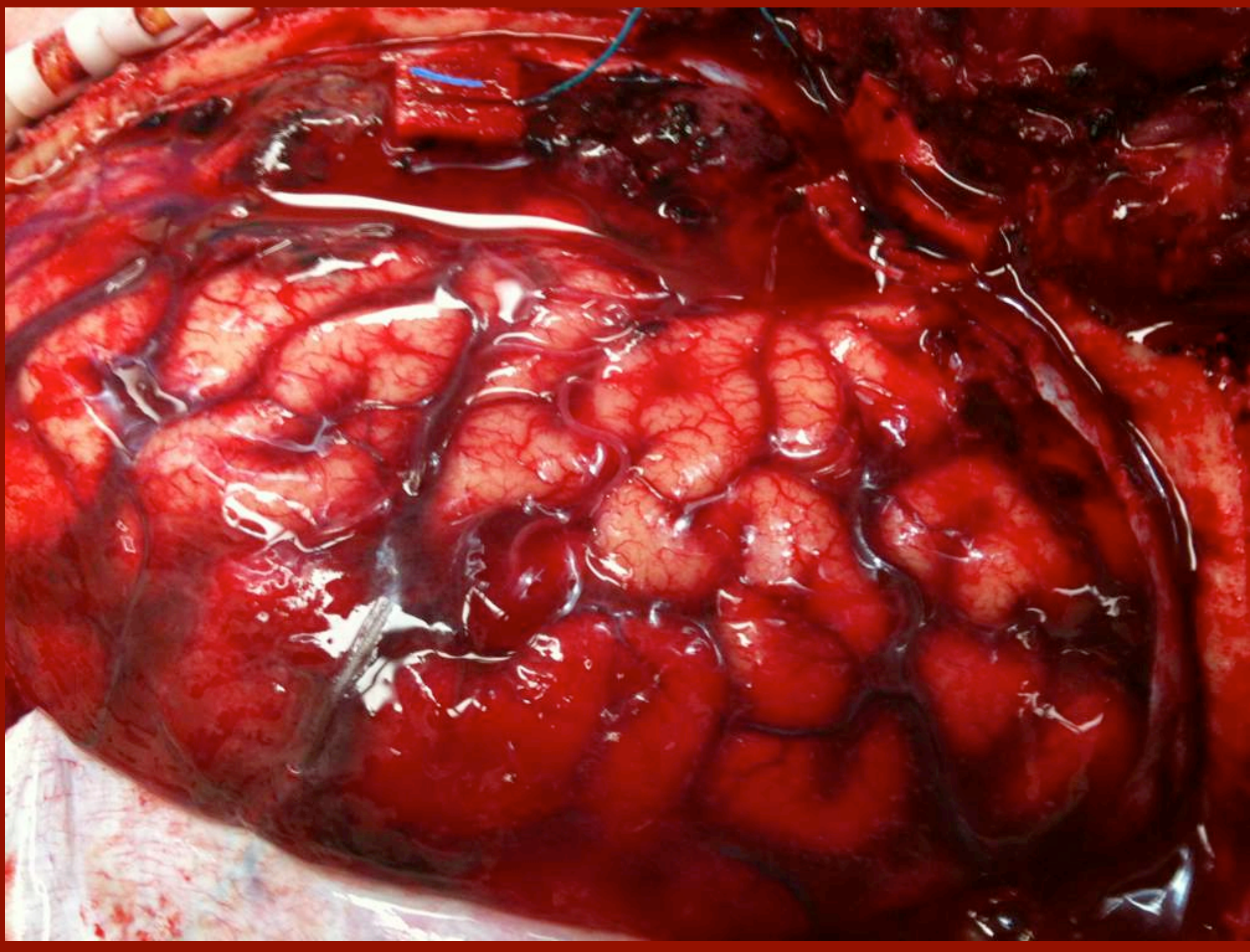

Trauma Induced Coagulopathy
Hypercoagulability
Hypocoagulability
Fibrinolysis Shutdown
Platelet Activation
Hyper-fibrinogenemia
Increased Thrombin Generation
Decreased Thrombin Generation
Fibrinogen Dysfunction
Platelet Dysfunction
Hyperfibinolysis
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Thrombotic Phenotypes
Mixed Phenotypes
Bleeding Phenotypes

Coagulopathy in the wild...


B
NO POSITIVE
O
NO POSITIVE


STERIS






LIVE
BREAKING NEWS
PLANE CRASHES AT SFO
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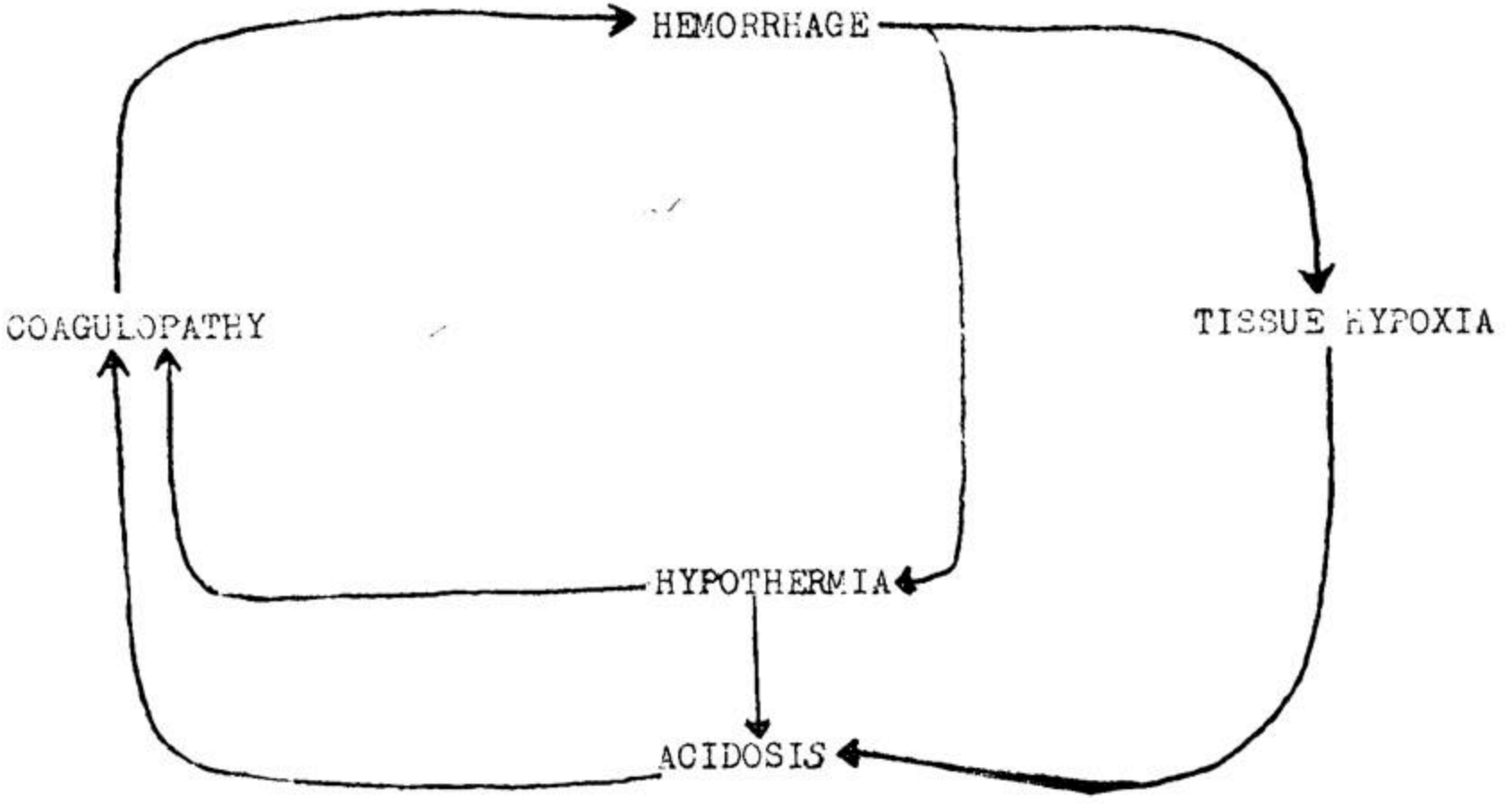
ON THE PHONE: TOM VACAR

Coagulopathy after trauma



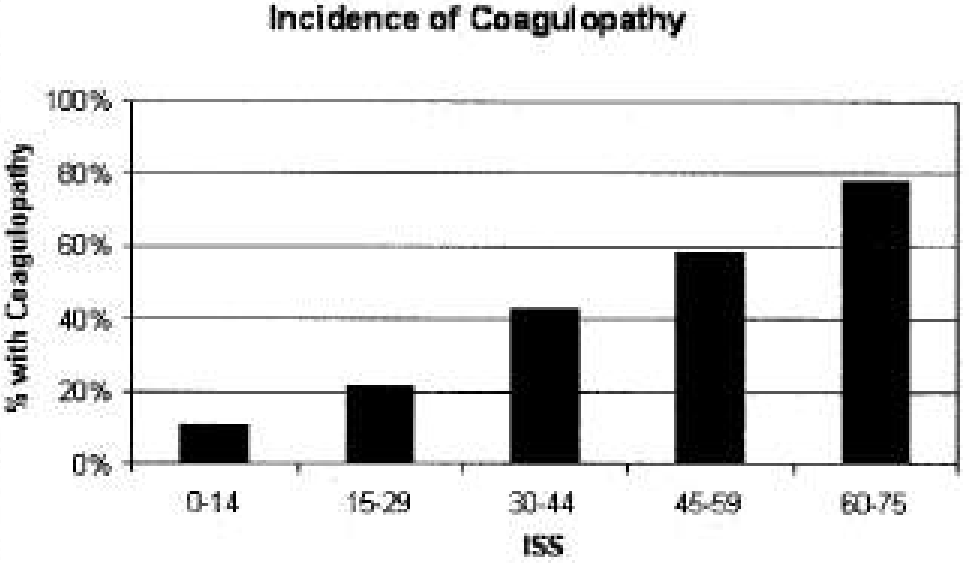
Kashuk *et al.* (1982). *J Trauma* 22(8):672.

The Journal of TRAUMA® Injury, Infection, and Critical Care

Acute Traumatic Coagulopathy

J Trauma, 2003.

Karim Brohi, BSc, FRCS, FRCA, Jasmin Singh, MB, BS, BSc, Mischa Heron, MRCP, FFAEM, and Timothy Coats, MD, FRCS, FFAEM

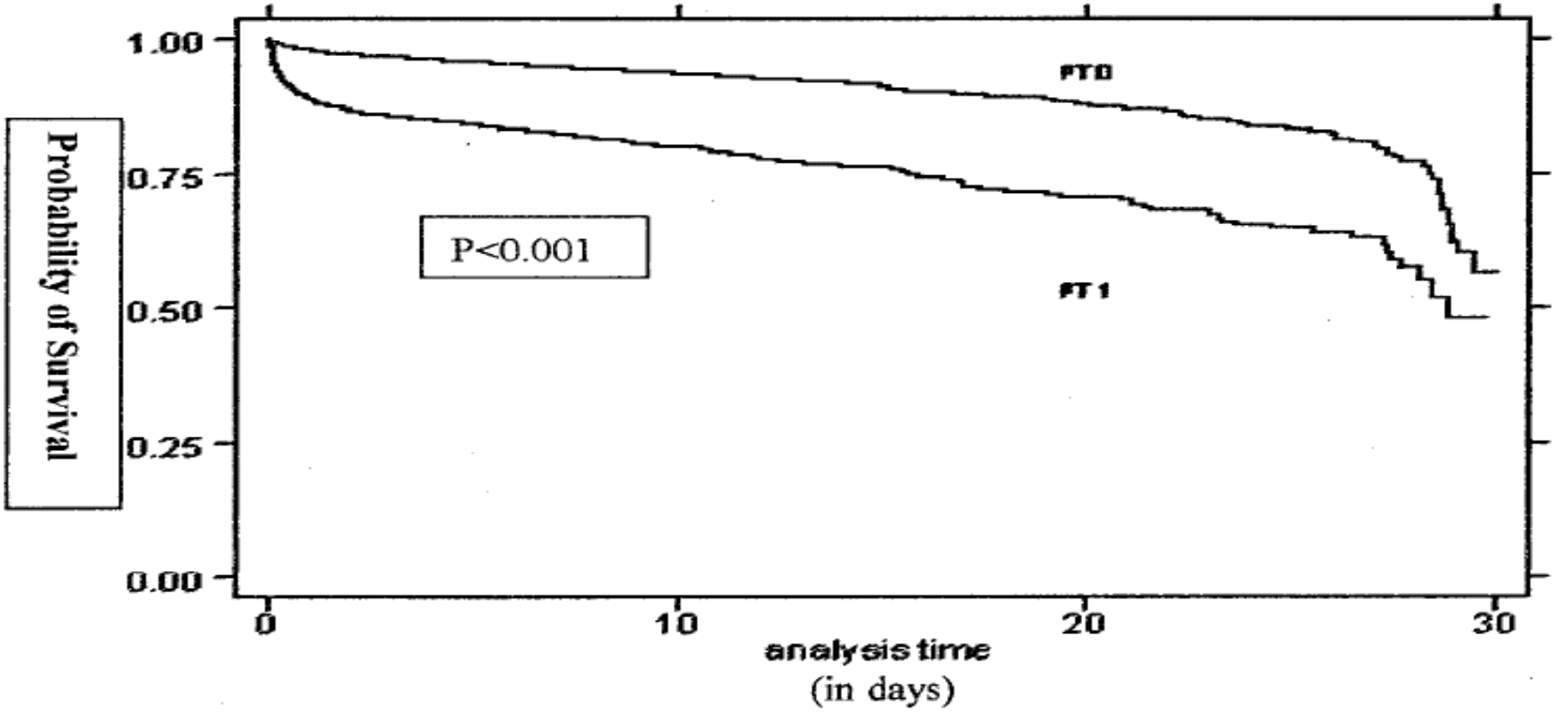


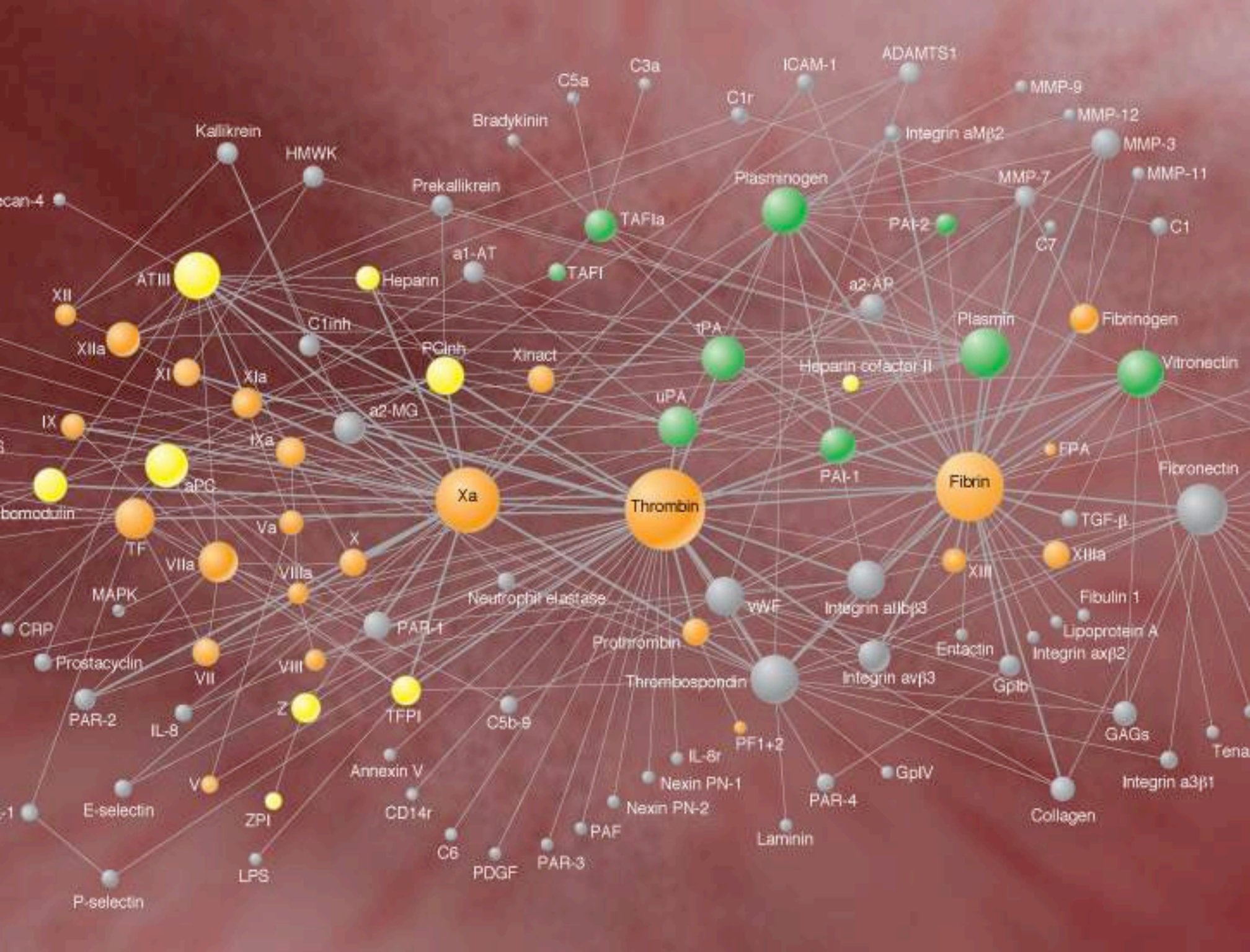
The Journal of TRAUMA® Injury, Infection, and Critical Care

J Trauma, 2003.

Early Coagulopathy Predicts Mortality in Trauma

Jana B. A. MacLeod, MD, MSc, Mauricio Lynn, MD, Mark G. McKenney, MD, Stephen M. Cohn, MD, and Mary Murtha, RN

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TAFIa
PAI-2
C1
C7
a1-AT
TAFI
ATIII
Heparin
a2-AP
XII
C1inh
Plasmin
Fibrinogen
tPA
XIIa
PCInh
Xinact
Heparin cofactor II
Vitronectin
XI
XIa
uPA
a2-MG
IX
IXa
EPA
Fibronectin
aPC
PAI-1
Fibrin
Xa
Thrombin
TGF-β
TF
Va
X
XIIIa
VIIa
VIIIa
XIII
MAPK
Neutrophil elastase
vWF
Integrin aIIbβ3
Fibulin 1
CRP
PAR-1
Lipoprotein A
Prothrombin
Entactin
Integrin axβ2
Prostacyclin
VII
VIII
Integrin avβ3
Thrombospondin
GpIb
PAR-2
IL-8
Z
TFPI
C5b-9
GAGs
PF1+2
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Annexin V
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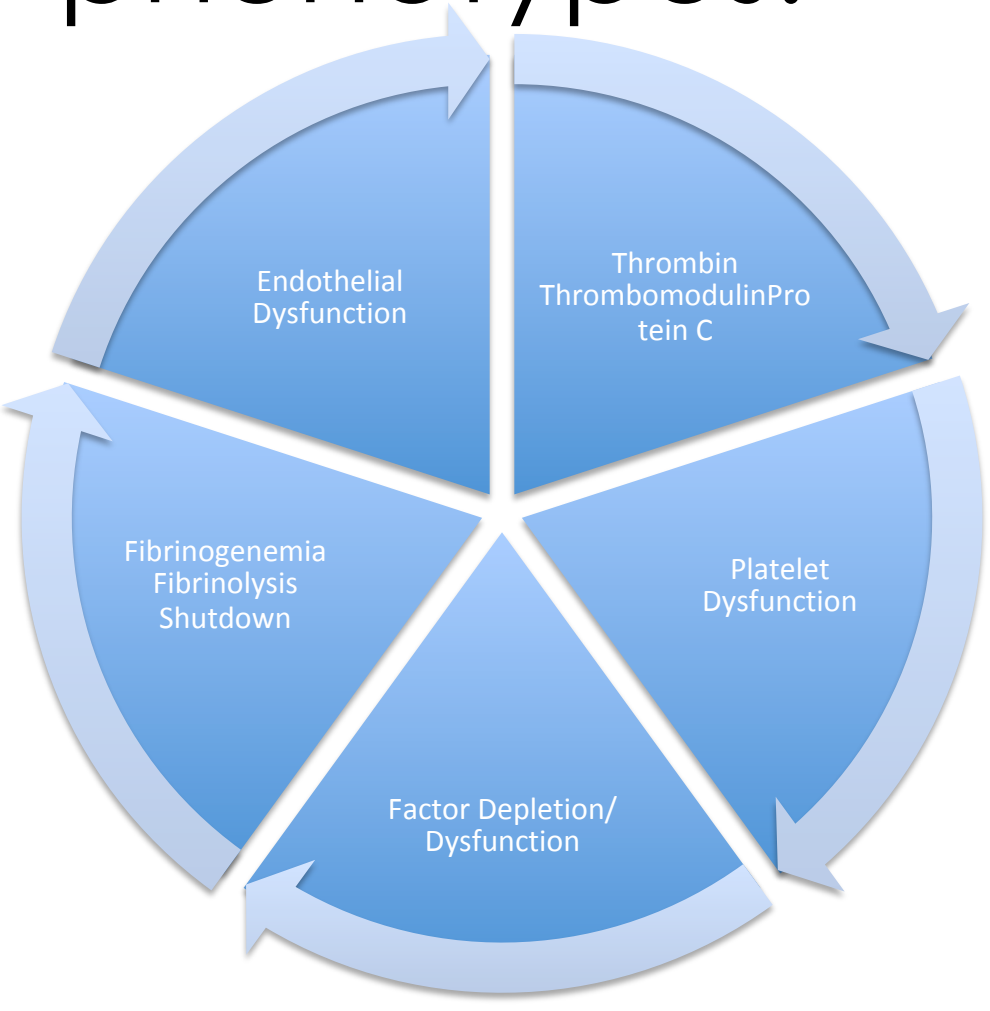
V
Nexin PN-1
E-selectin
PAR-4
Nexin PN-2
CD14r
Collagen
ZPI
PAF
Laminin
C6
PDGF
PAR-3
LPS
P-selectin

How to study a problem:
Clinical

Multiple overlapping phenotypes.



Acute Traumatic Coagulopathy: Initiated by Hypoperfusion

Modulated Through the Protein C Pathway?

Karim Brohi, FRCS, FRCA, Mitchell J. Cohen, MD,* Michael T. Ganter, MD,†*
Michael A. Matthay, MD,‡ Robert C. Mackersie, MD, and Jean-François Pittet, MD†‡*

- Study at San Francisco General Hospital
- Ann Surg 245:812-818,

- 209 severely traumatized patients admitted to SFGH

- Median time injury – hospital admission: 28 minutes

- If patients were severely injured (ISS>15) and hypoperfused (BD >6) they were coagulopathic.

PROTEIN C

-42 MWQLTSLLLFVATWGISGTPAPLDSVFSSSERAHQVLRIRKR -1

1 ANSFLEELRHSSLERECIEEICDFEEAKEIFQNVDDTLAFWSKHVDGDQC 50

51 LVLPLEHPCASLCCGHGTCIDGIGSFSCDCRSGWEGRFCQREVSFLNCSL 100

101 DNGGCTHYCLEEVGWRRCSCAPGYKLGDDLLQCHPAVKFPCGRPWKRMEK 150

151 KRSHLKRDTEDQEDQVDPRLIDGKMTRRGDSPWQVVLLDSKKKLACGAVL 200

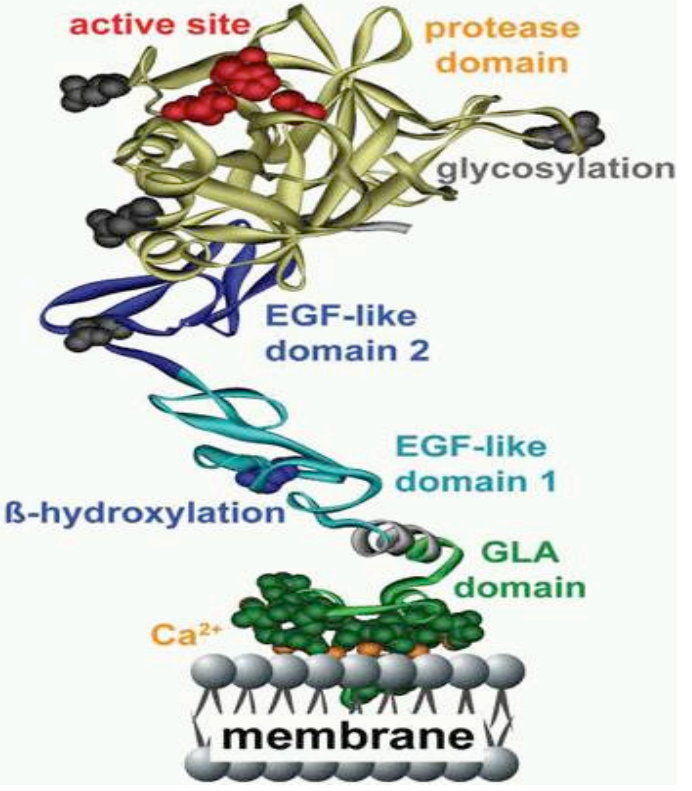
201 IHPSWVLTAAHCMDESKKLLVRLGEYDLRRWEKWELDLDIKEVFVHPNYS 250

251 KSTTDNDIALLHLAQPATLSQTIVPICLPDSGLAERELNQAGQETLVTGW 300

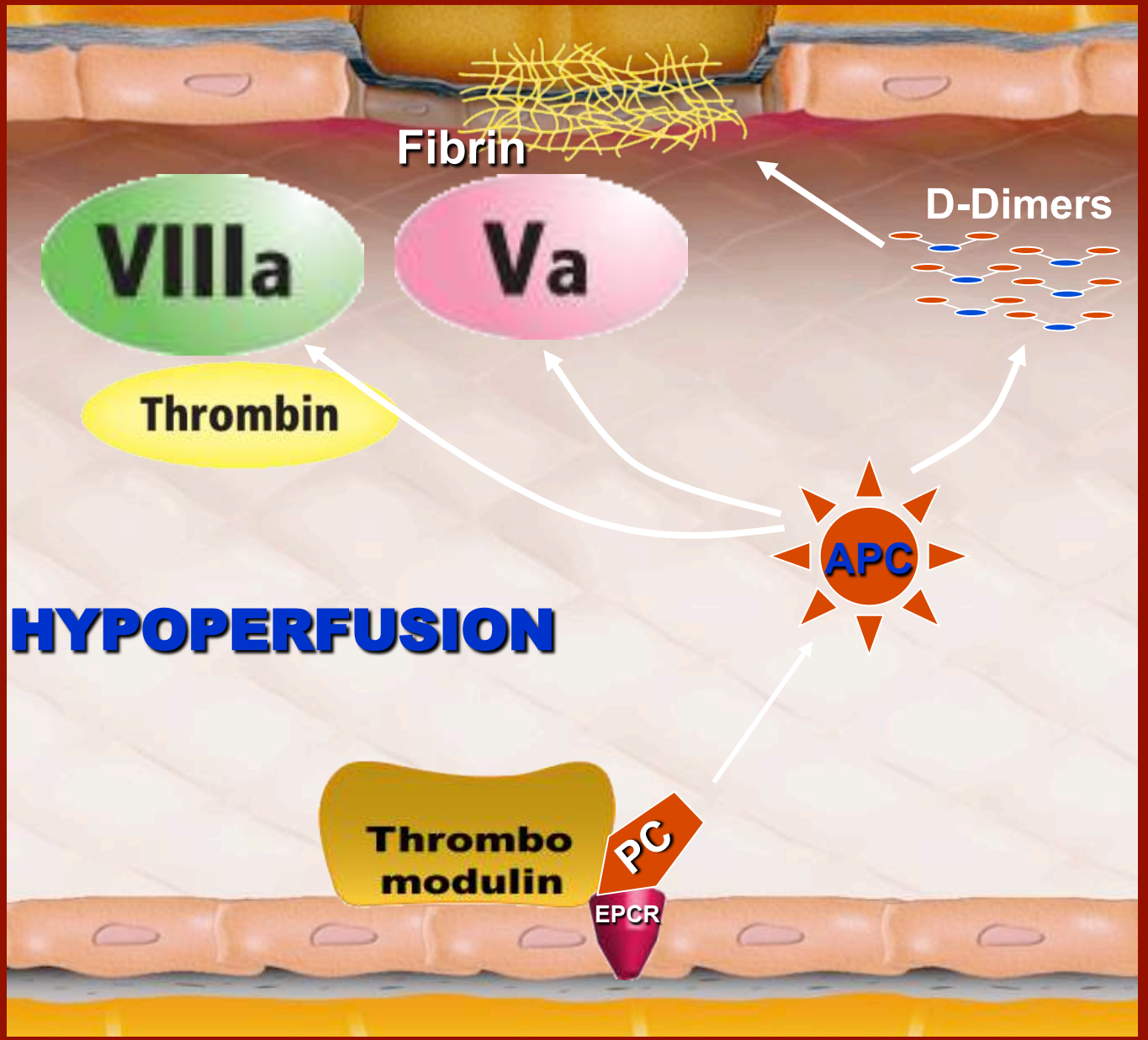
301 GYHSSREKEAKRNRTFVLNFIKIPVVPHNECSEVMSNMVSENMLCAGILG 350

351 DRQDACEGDSGGPMVASFHGTWFLVGLVSWGEGCGLLHNYGVYTKVSRYL 400

401 DWIHGHIRDKEAPQKSWAP 419



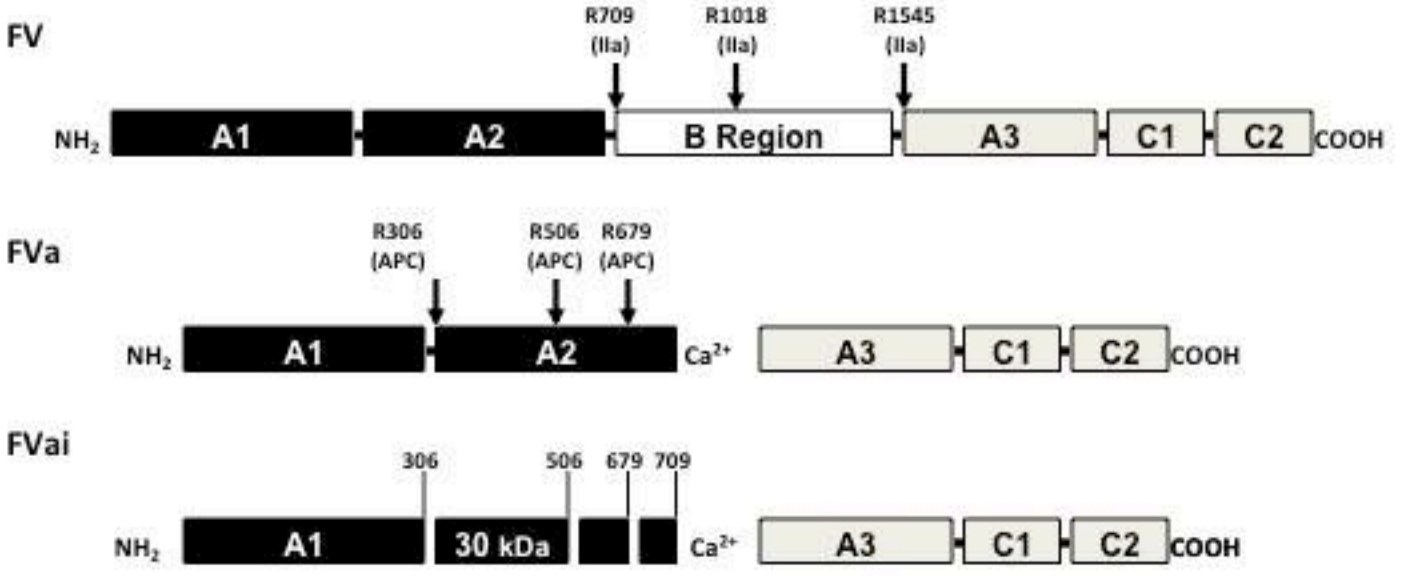
Activated protein C pathway

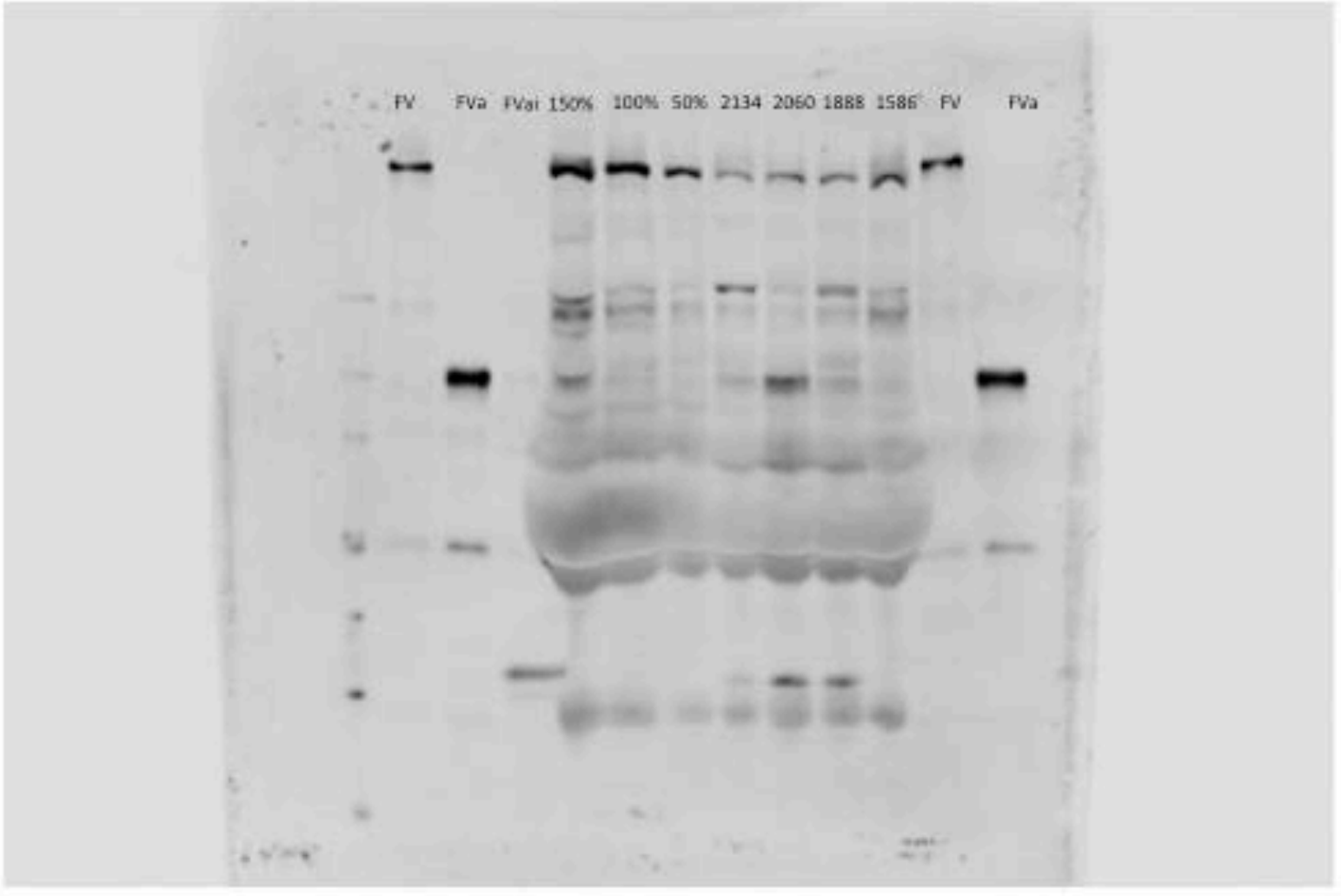


Thrombin binds Thrombomodulin

The complex Thrombin-Thrombomodulin activates Protein C

APC decreases FVIIIa and FVa and derepresses fibrinolysis


FV
R709
(IIa)
R1018
(IIa)
R1545
(IIa)
NH2
A1
A2
B Region
A3
C1
C2
COOH
FVa
R306
(APC)
R506
(APC)
R679
(APC)
NH2
A1
A2
Ca2+
A3
C1
C2
COOH
FVai
306
506
679
709
NH2
A1
30 kDa
Ca2+
A3
C1
C2
COOH


FV
FVa
FVai
150%
100%
50%
2134
2060
1888
1586
FV
FVa

Group 1: No Injury, No Shock

ID	Activity (%)*	Intact FV +, -, n.d.** (% of 10 donor)	Fragments +,- (identity)	αTAT, nM***	PAP, nM	TFPI, nM
134	104	+ (103)	+	0	2.6	1.54
148	48	+ (78)	-	0	9.2	1.15
173	78	+ (178)	-	0	7.5	1.70
1619	46	+ (106)	-	0	3.3	1.14
1693	n.a.	+ (123)	-	0	2.2	1.50
474	60	+ (88)	-	0	1.7	1.29
589	57	+ (149)	+ (HC)	0	5.6	0.88
1379	n.a.	+ (229)	-	1.3	5.3	1.53
1067	40	+ (105)	-	0	2.0	1.19
1890	15	+ (229)	-	0	2.9	2.06
1783	34	+ (113)	-	0	1.9	1.26
881	34	- (32)	+	9.4	2.7	1.48
879	91	+ (178)	-	0	2.0	1.68
1760	n.a.	- (57)	-	0	1.8	1.37
1338	98	- (44)	+	11.4	6.0	2.39
75	33	+ (60)	-	0	6.4	1.19
76	n.a.	- (56)	-	5.9	4.8	1.66
81	41	- (49)	+ (HC)	8.0	52.5	1.20
513	32	+ (76)	+ (HC)	8.4	40.9	2.37
865	102	+ (94)	+ (HC)	0	2.1	1.86

Group 2: No Injury, Shock

ID	Activity (%)*	Intact FV +, -, n.d.** (% of 10 donor)	Fragments +,- (identity)	αTAT, nM***	PAP, nM	TFPI, nM
899	n.a.	-, n.d	+	23.1	3.6	1.56
864	40	-, n.d	+	11.8	44.1	2.37
1729	n.a.	+ (80)	-	0	1.4	1.86
2013	116	+ (211)	+	0	2.9	1.72
2204	n.a.	+ (84)	-	0	2.9	1.50
2205	n.a.	+ (91)	-	0	9.6	0.99
2256	24	+ (108)	-	0	2.2	0.41
2157	87	+ (158)	-	0	2.8	1.56
2224	162	+ (262)	-	0	2.3	1.42
2117	32	+ (63)	-	0	3.2	0.41
2146	43	- (52)	+	0	31.6	1.04
1427	n.a.	- (53)	+ (HC)	1.3	35.8	1.70
2086	57	+ (73)	+	0	2.8	1.37
2050	94	- (47)	+	0	2.2	1.33
164	n.a.	- (50)	+	0	4.0	1.29
2175	64	+ (104)	+	0	2.6	1.34
219	73	+ (85)	+	0	3.8	1.35
1977	38	+ (69)	+ (HC)	0	6.8	0.96
2194	49	+ (140)	+	0	10.3	1.60
1964	45	+ (65)	-	0	1.7	1.32

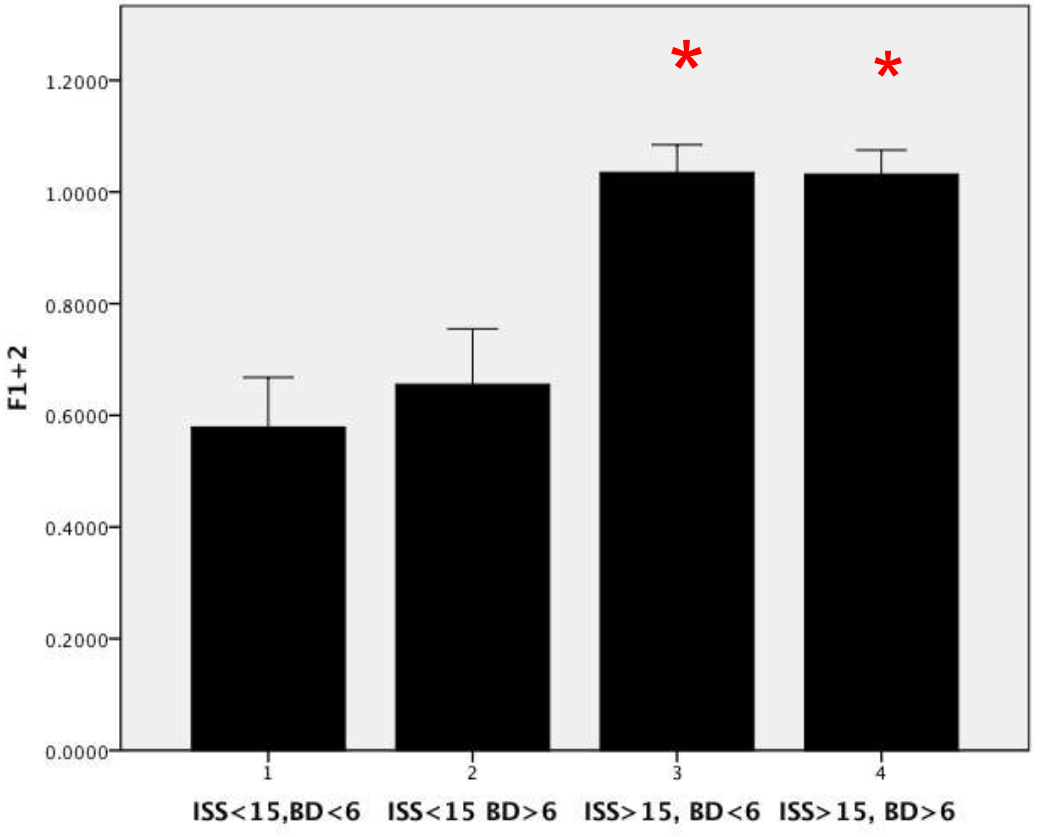
Group 3: Injury, No Shock

ID	Activity (%)*	Intact FV +, -, n.d.** (% of 10 donor)	Fragments +,- (identity)	αTAT, nM***	PAP, nM	TFPI, nM
252	n.a.	+ (153)	+ (HC)	5.3	31.7	2.83
1063	46	- (40)	-	4.8	25.0	1.20
920	58	- (49)	+	14.5	7.0	1.97
1046	30	+ (93)	+ (HC)	1.5	43.7	1.98
854	49	+ (96)	+ (HC)	9.7	44.9	1.94
1000	29	n.d.	+ (30 KD)	29.7	49.0	2.75
447	33	+ (78)	+ (30 KD)	2.3	5.6	1.55
204	87	+ (148)	+	4.3	11.9	1.49
361	68	+ (111)	+	4.7	13.7	1.21
955	68	n.d.	+	34.2	18.0	1.42
992	46	+ (79)	+ (HC)	5.4	28.9	2.38
676	62	+ (130)	+ (HC)	0	7.9	0.93
951	21	n.d.	+ (HC, 30KD)	27.3	44.9	3.10
685	116	+ (205)	-	1.0	6.3	1.76
163	59	+ (77)	-	0	15.4	1.20
761	101	+ (139)	+	2.7	4.3	2.34
1008	26	+ (126)	-	2.5	19.0	1.69
11	51	+ (68)	-	4.1	32.2	2.02
21	21	+ (83)	+ (HC)	0	19.7	0.82
3	83	+ (63)	+ (HC)	0	15.6	1.39

Group 4: Injury and Shock

ID	Activity (%)*	Intact FV +, -, n.d.** (% of 10 donor)	Fragments +,- (identity)	αTAT, nM***	PAP, nM	TFPI, nM
1891	15	- (25)	+ (30KD)	5.1	49.5	0.58
2134	n.a.	- (21)	+ (HC, 30KD)	0	40.4	0.82
2060	44	- (26)	+ (HC, 30KD)	11.7	49.1	0.95
1888	10	- (25)	+ (HC, 30KD)	10.5	59.5	1.48
1586	n.a.	- (45)	-	0	1.9	1.38
1747	17	+ (67)	+ (HC)	8.9	43.2	2.52
1827	7	- (13)	+ (30KD)	22.3	59.5	1.03
1991	46	- (59)	+ (HC)	4.9	14.4	1.25
2031	32	- (43)	-	0	11.3	0.77
1612	n.a.	- (51)	-	0	1.9	1.13
1637	35	- (28)	-	0	4.8	3.00
2226	21	- (38)	+ (HC)	6.5	44.9	3.15
2231	n.a.	+ (71)	-	0	21.5	0.90
1771	n.a.	+ (99)	+	0	19.1	1.02
2140	46	+ (139)	+ (HC)	14.4	41.0	2.27
1848	n.a.	- (49)	+ (HC, 30KD)	5.7	40.7	1.46
1839	n.a.	- (30)	+ (HC, 30KD)	15.4	44.7	1.94
1966	64	- (44)	+ (HC, 30KD)	1.7	21.2	1.39
1643	4	n.d.	+ (30KD)	49.0	44.9	2.06
1535	19	- (22)	+ (30KD)	5.4	46.5	0.79

This is (not?) thrombin dependent.



Clotting factor differences in coagulopathy

- Significant differences in serial clotting factor deficits associated with coagulopathy

	Unadjusted		Adjusted for injury	
	OR	P	OR	P
Prothrombin	0.928	<0.001	0.935	<0.001
Factor V	0.953	<0.001	0.957	<0.001
Factor VII	0.965	<0.001	0.965	<0.001
Factor VIII	0.997	0.002	0.996	0.002
Factor IX	0.977	<0.001	0.977	<0.001
Factor X	0.938	<0.001	0.948	<0.001
ATIII	0.962	<0.001	0.965	<0.001
aPC	1.053	<0.001	1.041	0.001
PC	0.972	<0.001	0.975	<0.001
PAI-1	0.993	0.324	0.982	0.123
D-Dimer	1.025	0.009	1.012	0.265
tPA	1.011	0.272	0.999	0.925

Clotting factor differences in coagulopathy

- Logistic regression model controlling for all measured factors simultaneously

	OR	P	95% CI
Prothrombin	0.946	0.261	(0.859 - 1.042)
Factor V	0.967	0.155	(0.924 - 1.013)
Factor VII	1.000	0.939	(0.974 - 1.025)
Factor VIII	1.003	0.337	(0.997 - 1.008)
Factor IX	0.988	0.343	(0.963 - 1.013)
Factor X	0.960	0.244	(0.897 - 1.028)
ATIII	1.018	0.425	(0.974 - 1.065)
aPC	1.080	0.005	(1.023 - 1.140)
PC	0.981	0.303	(0.945 - 1.018)
D-dimer	0.955	0.127	(0.901 - 1.013)

Clotting factor differences in coagulopathy

- Logistic regression model controlling for all measured factors simultaneously

	OR	P	95% CI
Factor V	**0.973**	**0.004**	**(0.956 - 0.991)**
aPC	1.080	0.005	(1.023 - 1.140)

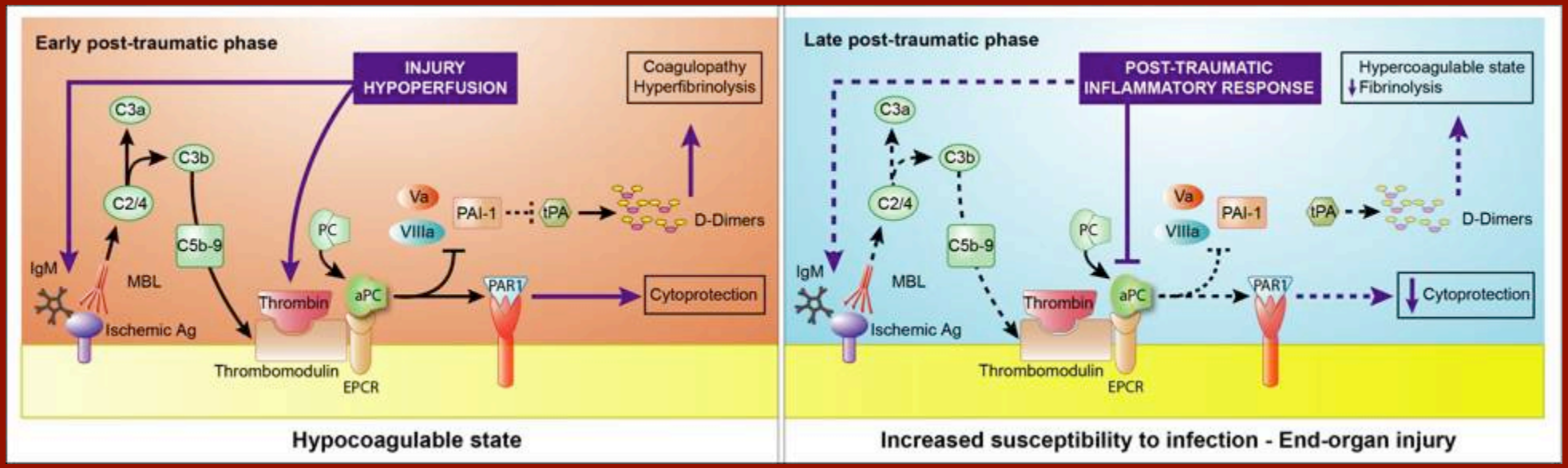
Clotting factor differences in early mortality

- Cox proportional hazards model controlling for all measured factors

	HR	P	95% CI
Factor V	**0.987**	**0.025**	**(0.976 – 0.998)**
Factor VIII	**0.998**	**0.019**	**(0.995 – 1.000)**
aPC	1.023	<0.001	(1.011 - 1.035)

Early Activation..
Later depletion?

Maladaptive response to trauma. Early coagulopathy, later hypercoagulable state and loss of cytoprotectivity.



Don’t forget platelets?

A Normal Platelet Count May Not Be Enough: The Impact of Admission Platelet Count on Mortality and Transfusion in Severely Injured Trauma Patients

Lisa M. Brown, MD, MAS, Mariah S. Call, BS, M. Margaret Knudson, MD, Mitchell J. Cohen, MD, and the Trauma Outcomes Group

Background: Platelets play a central role in hemostasis after trauma. However, the platelet count of most trauma patients does not fall below the normal range ($100–450 \times 10^9$/L), and as a result, admission platelet count has not been adequately investigated as a predictor of outcome. The purpose of this study was to examine the relationship between admission platelet count and outcomes after trauma.

Methods: A retrospective cohort study of 389 massively transfused trauma patients. Regression methods and the Kruskal-Wallis test were used to test the association between admission platelet count and 24-hour mortality and units of packed red blood cells (PRBCs) transfused.

Results: For every 50×10^9/L increase in admission platelet count, the odds of death decreased 17% at 6 hours ($p = 0.03$; 95% confidence interval [CI], 0.70–0.99) and 14% at 24 hours ($p = 0.02$; 95% CI, 0.75–0.98). The probability of death at 24 hours decreased with increasing platelet count. For every 50×10^9/L increase in platelet count, patients received 0.7 fewer units of blood within the first 6 hours ($p = 0.01$; 95% CI, −1.3 to −0.14) and one less unit of blood within the first 24 hours ($p = 0.002$; 95% CI, -1.6 to -0.36). The mean number of units of PRBCs transfused within the first 6 hours and 24 hours decreased with increasing platelet count.

Conclusions: Admission platelet count was inversely correlated with 24-hour mortality and transfusion of PRBCs. A normal platelet count may be insufficient after severe trauma, and as a result, these patients may benefit from a lower platelet transfusion threshold. Future studies of platelet number and function after injury are needed.

Key Words: Platelet count, Massive transfusion, Mortality.

(*J Trauma.* 2011;71: S337–S342)

Uncontrolled hemorrhage is a major cause of mortality in both civilian and military trauma patients.[1,2] Only 2% of severely injured trauma patients arrive to the hospital in hemorrhagic shock requiring a massive transfusion,[1] defined as transfusion of ≥10 units of packed red blood cells (PRBCs) over 24 hours. However, the mortality rate in this subset of trauma patients is ~40%, with half of these deaths occurring within the first 24 hours.[3] Several studies indicate that many of these traumatic deaths caused by hemorrhage are preventable,[2,4] and therefore a significant amount of research has been done to investigate resuscitation strategies and other therapeutic measures, which may lead to improved survival in these patients. Most of these studies have focused exclusively on determining the optimal ratio of fresh frozen plasma (FFP) to PRBCs needed to prevent and reverse the coagulopathy of trauma.[5–7] However, one landmark study examined platelet:PRBC ratio in addition to FFP:PRBC ratio and demonstrated that patients who received an FFP:PRBC ratio ≥1:2 in addition to a platelet:PRBC ratio ≥1:2 had the greatest overall survival, compared with patients who received lower ratios.[1]

Platelets serve two critical functions of the coagulation process. Platelet adhesion and aggregation at the site of endothelial injury forms a hemostatic plug, and platelets enhance activation of coagulation proteases leading to thrombus formation.[8,9] Despite these important roles, there are very few studies investigating the effects of platelet function in severely injured trauma patients[9,10] and even fewer studies investigating the effect of platelet count on trauma outcomes.[11] We investigated the effect of admission platelet count on mortality and the number of units of PRBCs transfused in a cohort of massively transfused civilian trauma patients. In addition, we examined whether platelet count is associated with injury severity and coagulopathy at admission.

METHODS

The cohort for this study included 389 massively transfused (≥10 units of PRBCs within the first 24 hours of admission) trauma patients. These patients are a subset of patients from an Institutional Review Board approved, retrospective, multicenter study that included adult trauma patients who arrived from the scene and received at least one unit of PRBCs in the emergency department (ED).[1] The multicenter trial included patients from 16 Level I trauma centers between July 2005 and June 2006.

The primary outcome of this study was mortality. We explored mortality at two time points, i.e., 6 hours and 24

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Presented at the American Association for the Surgery of Trauma meeting September 22–25, 2010, Boston, Massachusetts.
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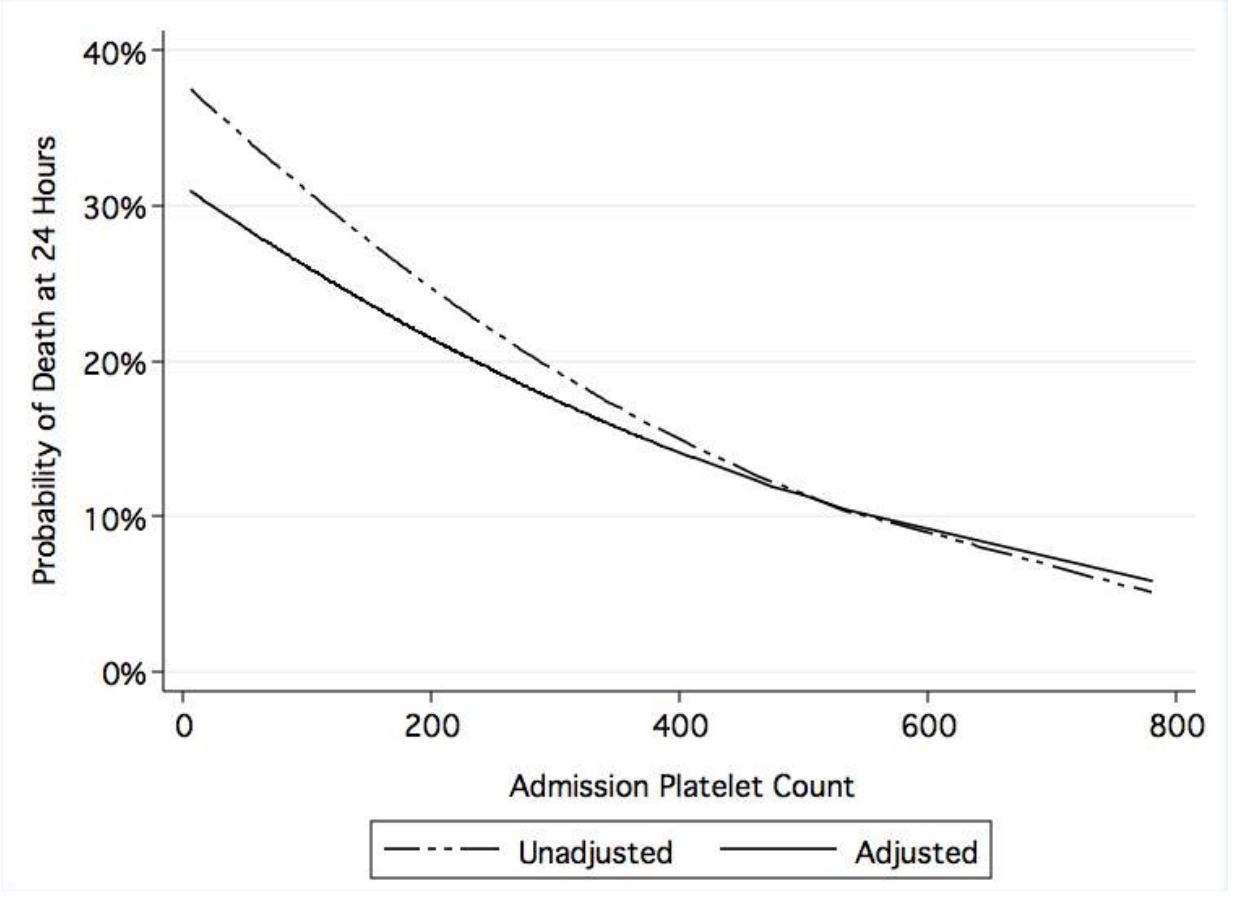
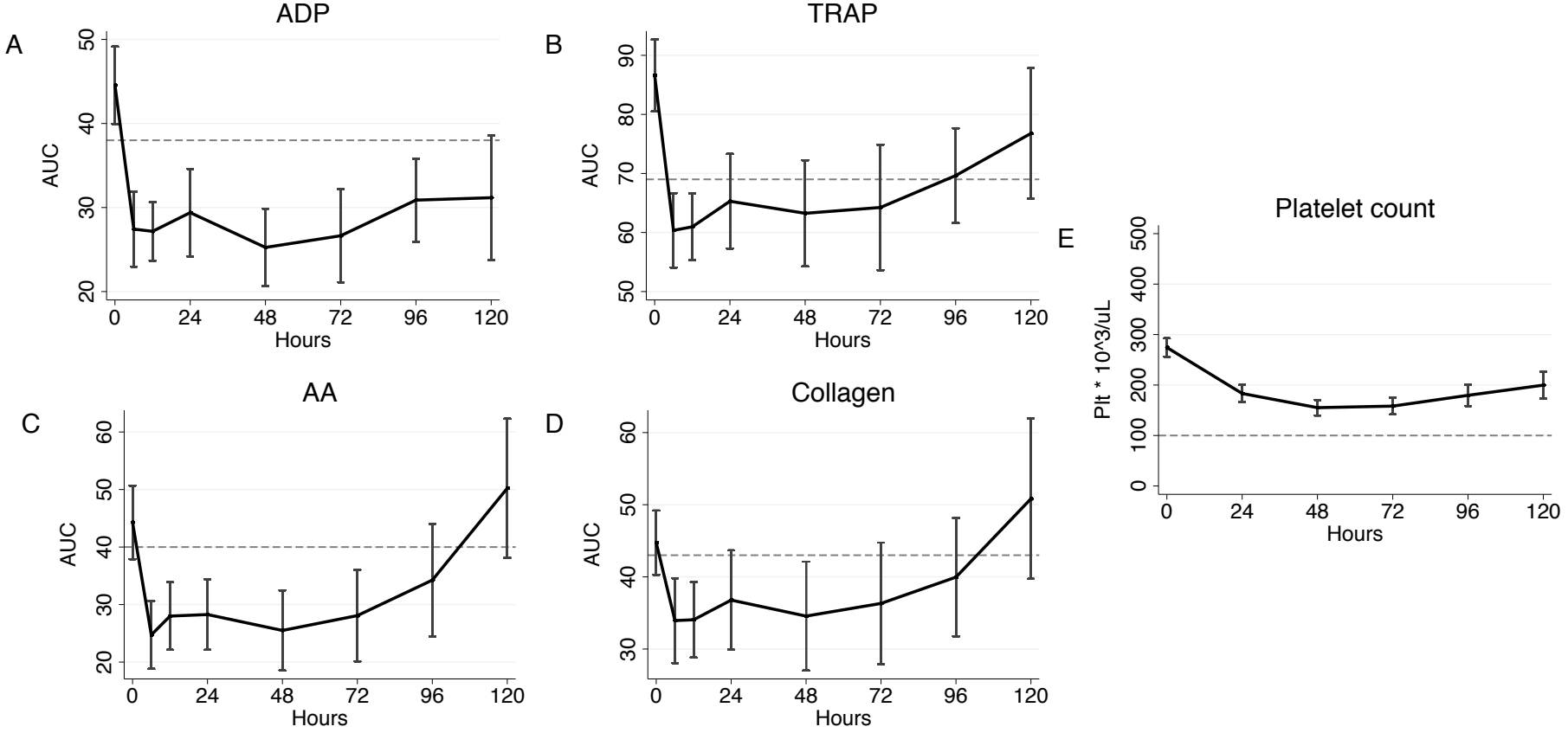
DOI: 10.1097/TA.0b013e318227f67c

Platelet Number and Mortality



Brown L, Cohen M
J Trauma 2011

Platelet function over time



Platelet hypofunction: Outcomes

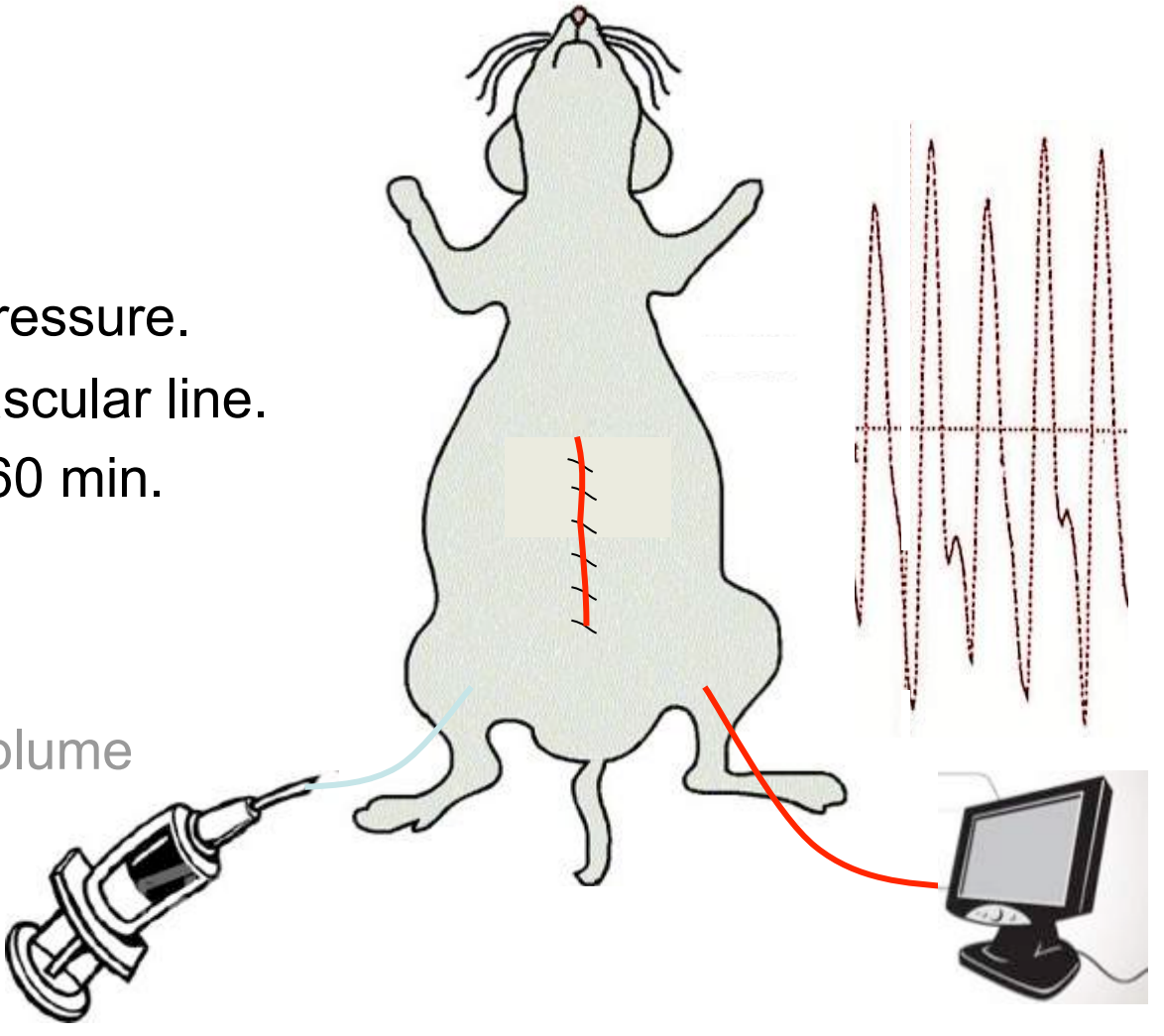
	Platelet hypofunction (N=39)	Normal function (N=52)	P-value
Hospital LOS	6 (2-27)	10 (6.5-20)	0.090
ICU LOS	3.5 (1-14)	3 (2-14)	0.436
Vent-free days	12 (0-26)	26 (7.5-27)	0.040
24h mortality	20.0%	2.1%	0.009

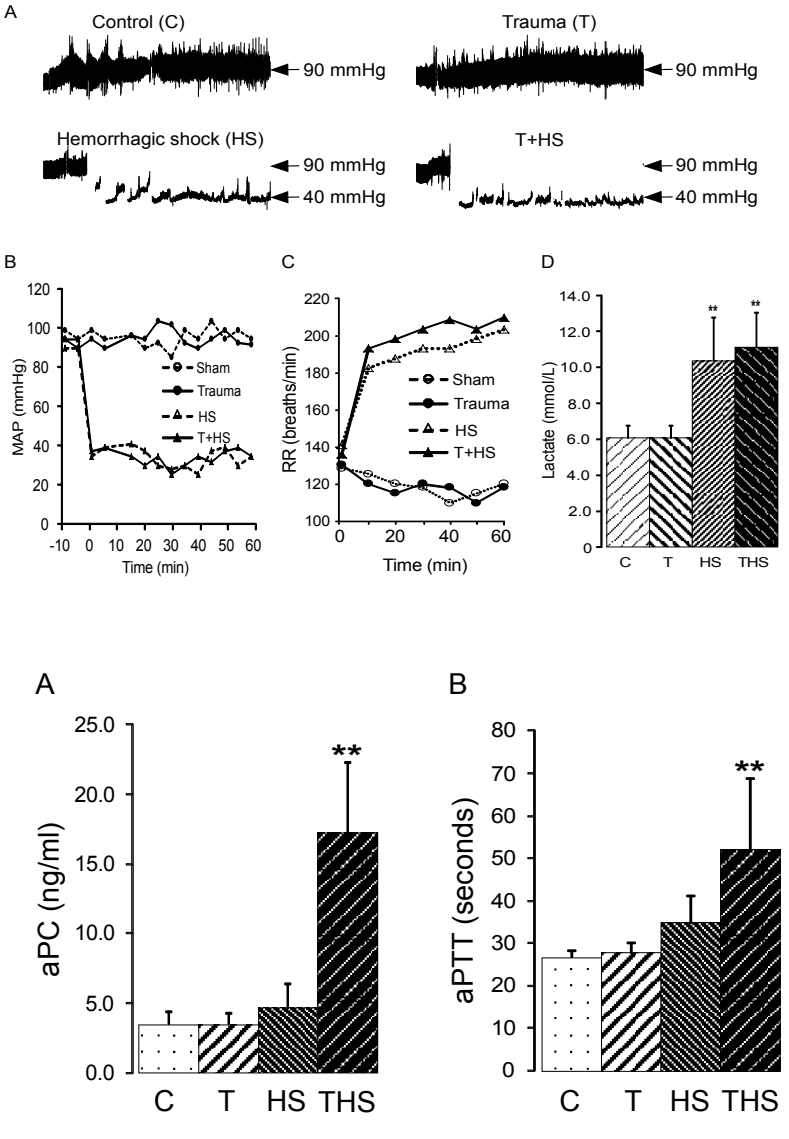
How to study a problem: Stepping toward mechanism

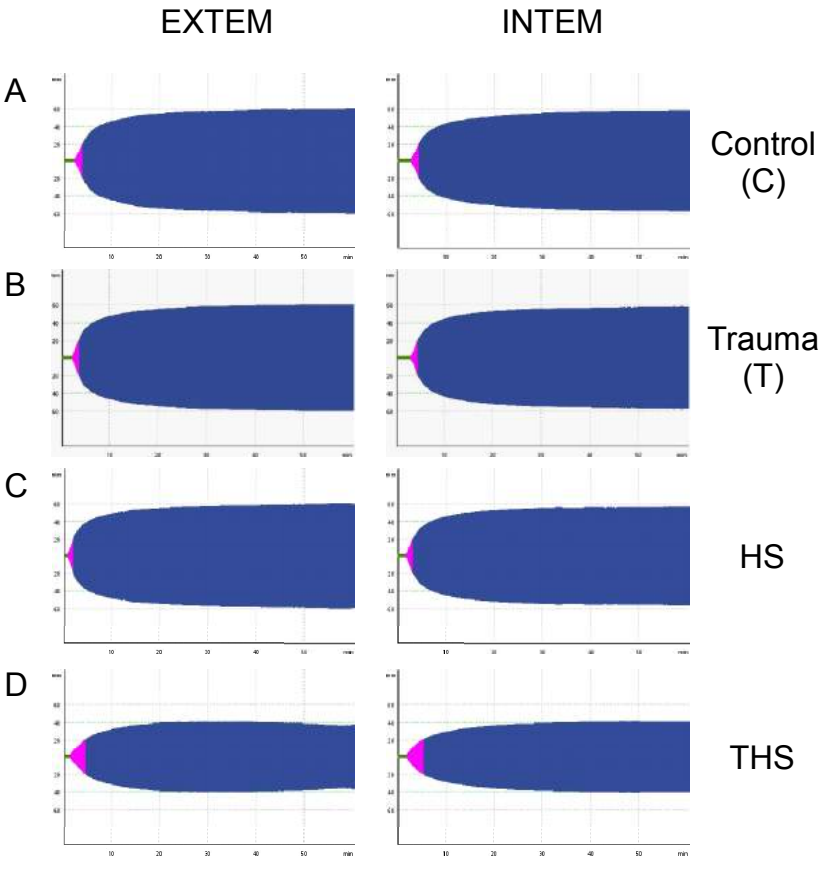
In vivo

Animal Model: Traumatic Coagulopathy

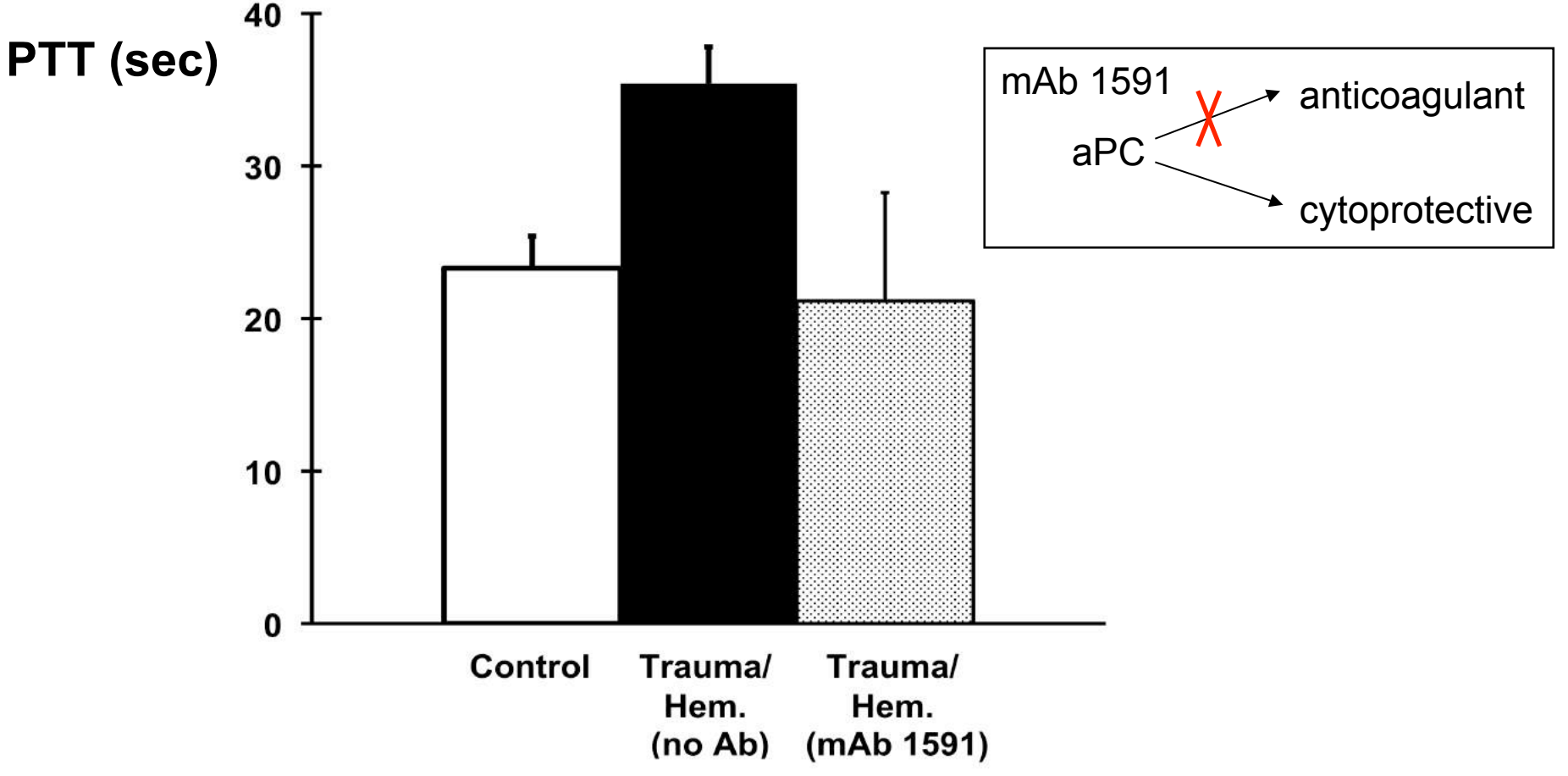
- Brain injury
- Hemorrhagic shock:
  - Non-ventilated, fixed-pressure.
  - Blood withdrawn via vascular line.
  - MAP 35 +/- 5mmHg x 60 min.
- Resuscitation:
  - LR @ 2x shed blood volume
    + shed blood



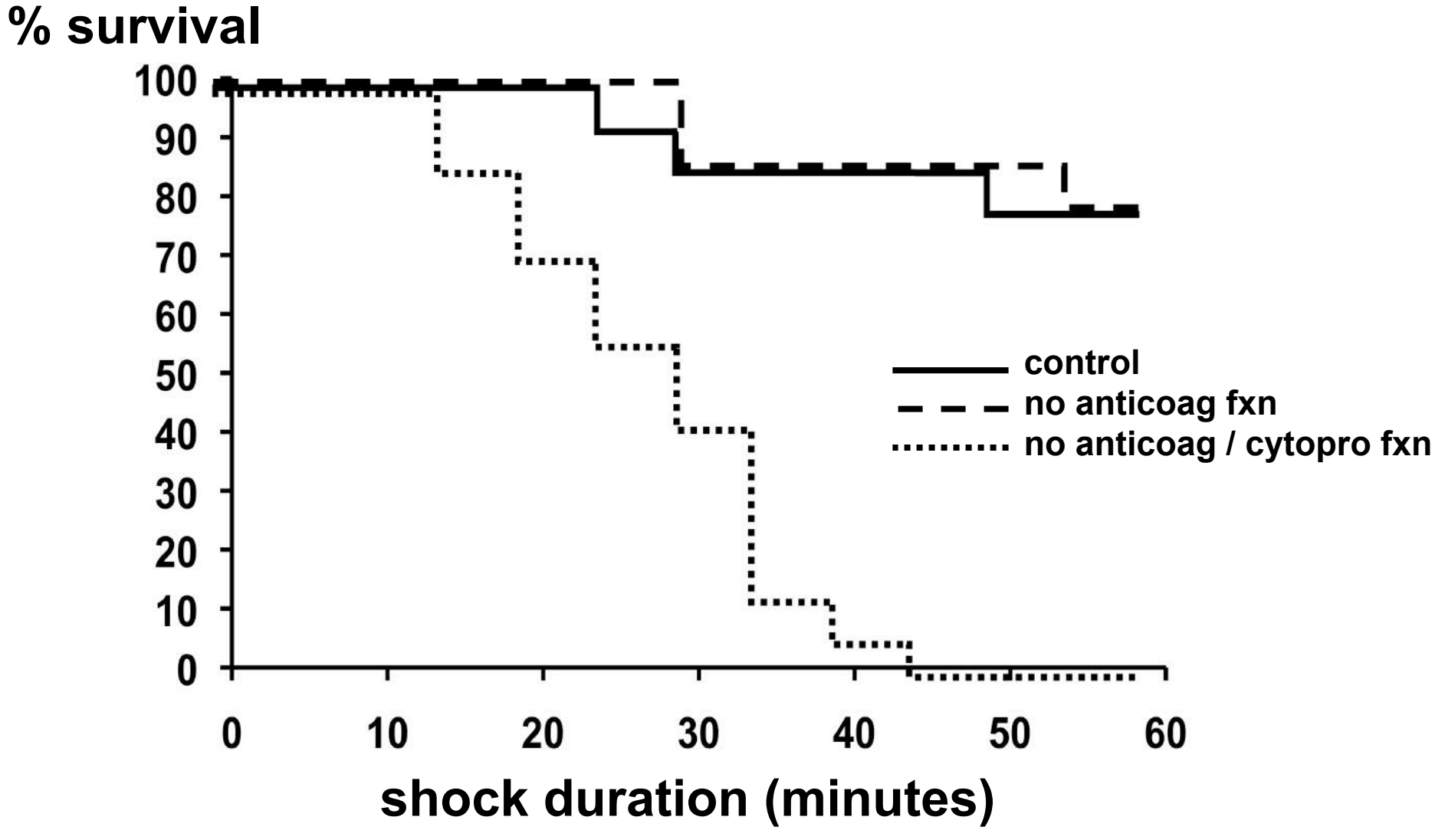

A
Control (C)
90 mmHg
Trauma (T)
90 mmHg
Hemorrhagic shock (HS)
90 mmHg
40 mmHg
T+HS
90 mmHg
40 mmHg
B
MAP (mmHg)
Sham
Trauma
HS
T+HS
Time (min)
C
RR (breaths/min)
Sham
Trauma
HS
T+HS
Time (min)
D
Lactate (mmol/L)
**
**
C
T
HS
THS
A
aPC (ng/ml)
**
C
T
HS
THS
B
aPTT (seconds)
**
C
T
HS
THS


EXTEM
INTEM
A
Control (C)
B
Trauma (T)
C
HS
D
THS

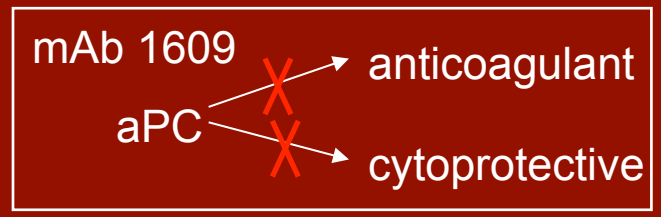
Acute Traumatic Coagulopathy: mediated by aPC *anticoagulant* function



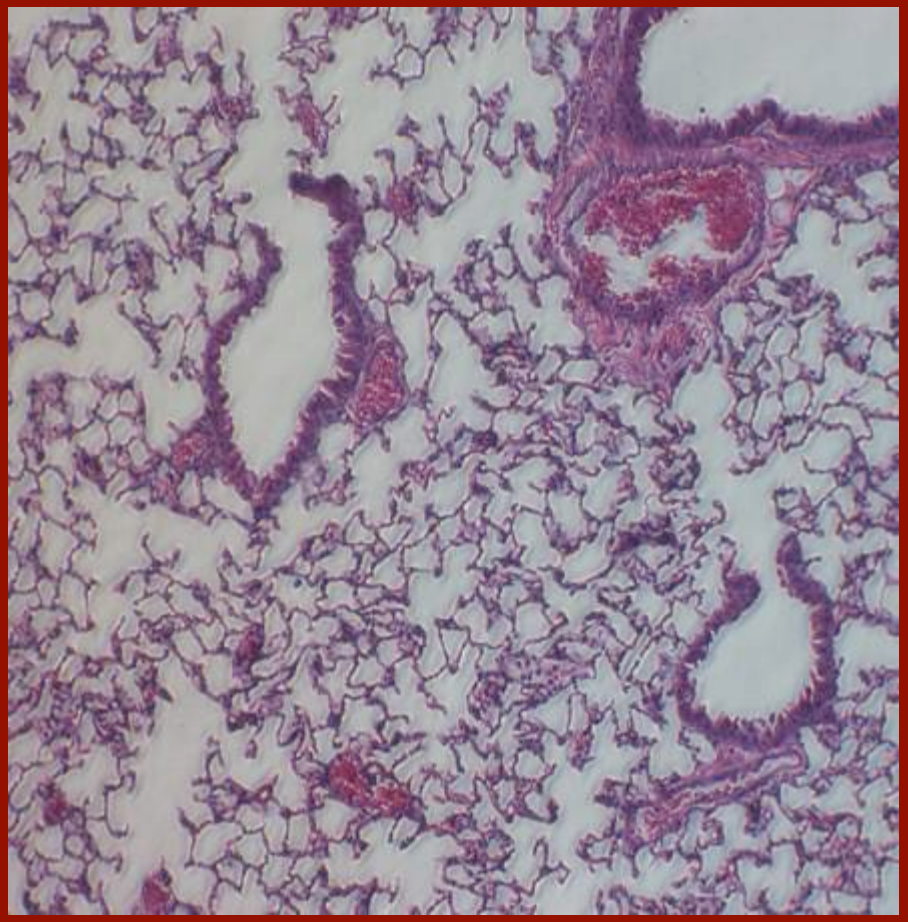
aPC is required for survival of Trauma/Hemorrhage



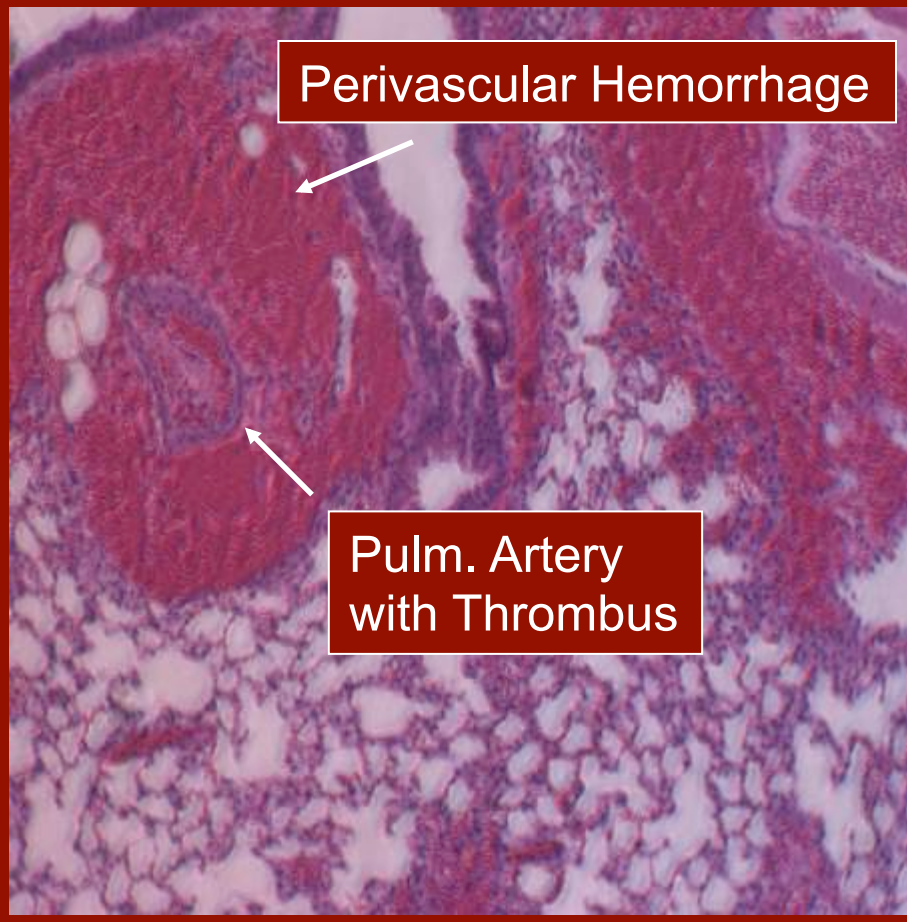
COMPLETE inhibition of Protein C causes diffuse intravascular coagulation & pulmonary injury.



A. Control mAb



B. mAb 1609



How to study a problem:
The next step towards mechanism
In vitro

PLOS | ONE

RESEARCH ARTICLE

Inducing Acute Traumatic Coagulopathy *In Vitro*: The Effects of Activated Protein C on Healthy Human Whole Blood

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Competing Interests: The authors have declared that no competing interests exist.

Abstract

Introduction

Acute traumatic coagulopathy has been associated with shock and tissue injury, and may be mediated via activation of the protein C pathway. Patients with acute traumatic coagulopathy have prolonged PT and PTT, and decreased activity of factors V and VIII; they are also hypocoagulable by thromboelastometry (ROTEM) and other viscoelastic assays. To test the etiology of this phenomenon, we hypothesized that such coagulopathy could be induced *in vitro* in healthy human blood with the addition of activated protein C (aPC).

Methods

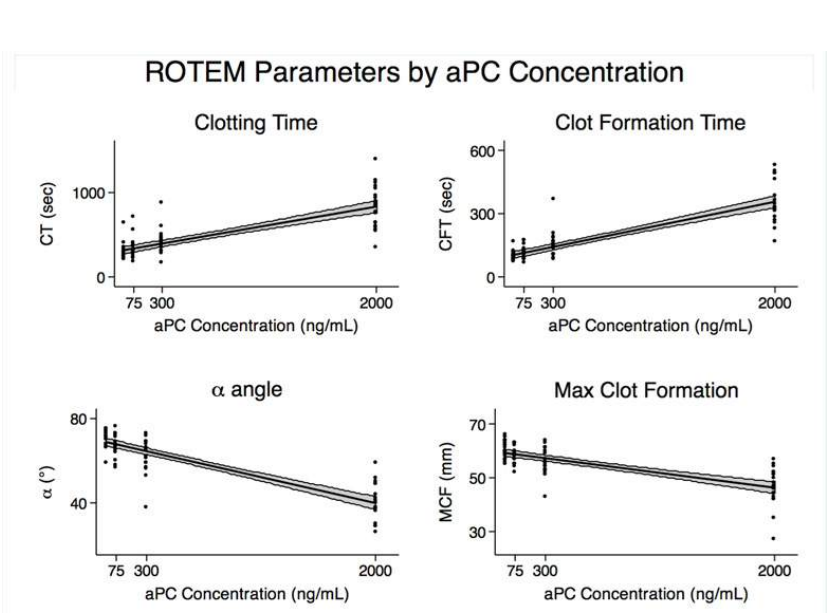
Whole blood was collected from 20 healthy human subjects, and was "spiked" with increasing concentrations of purified human aPC (control, 75, 300, 2000 ng/mL). PT/PTT, factor activity assays, and ROTEM were performed on each sample. Mixed effect regression modeling was performed to assess the association of aPC concentration with PT/PTT, factor activity, and ROTEM parameters.

Results

In all subjects, increasing concentrations of aPC produced ROTEM tracings consistent with traumatic coagulopathy. ROTEM EXTEM parameters differed significantly by aPC concentration, with stepwise prolongation of clotting time (CT) and clot formation time (CFT), decreased alpha angle (α), impaired early clot formation (a10 and a20), and reduced maximum clot firmness (MCF). PT and PTT were significantly prolonged at higher aPC concentrations, with corresponding significant decreases in factor V and VIII activity.

Conclusion

A phenotype of acute traumatic coagulopathy can be induced in healthy blood by the *in vitro* addition of aPC alone, as evidenced by viscoelastic measures and confirmed by



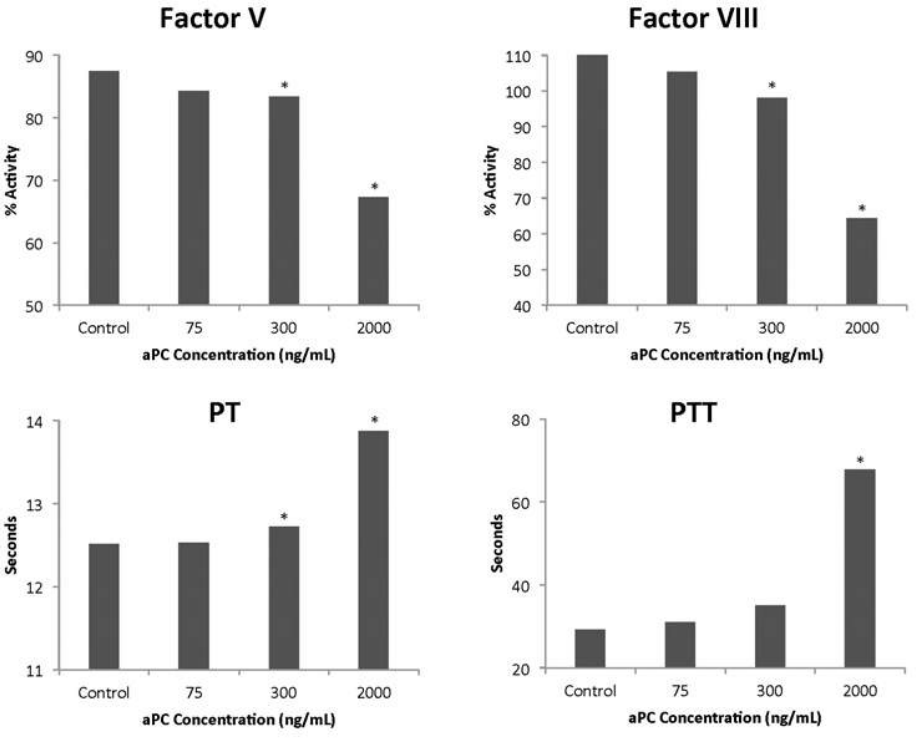


Fig 2. Linear regression analysis of ROTEM parameters. ROTEM EXTEM parameters changed significantly by aPC concentration, with strong linear correlation between aPC concentration and prolonged clotting time (CT) and clot formation time (CFT), decreased alpha angle (α), and reduced maximum clot firmness (MCF). The coefficients of these changes are delineated in Table 1.

doi:10.1371/journal.pone.0150930.g002

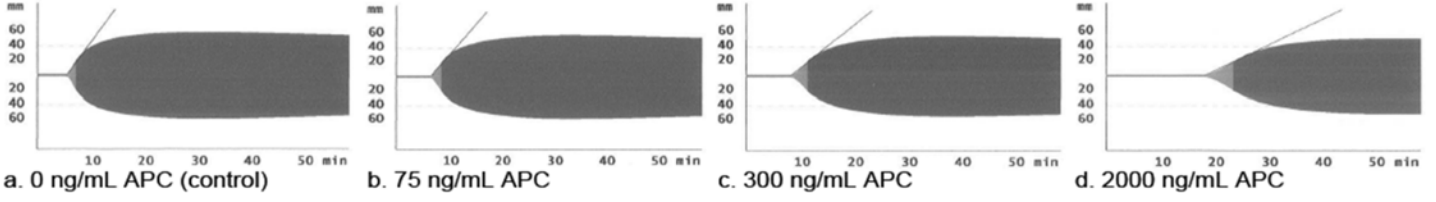


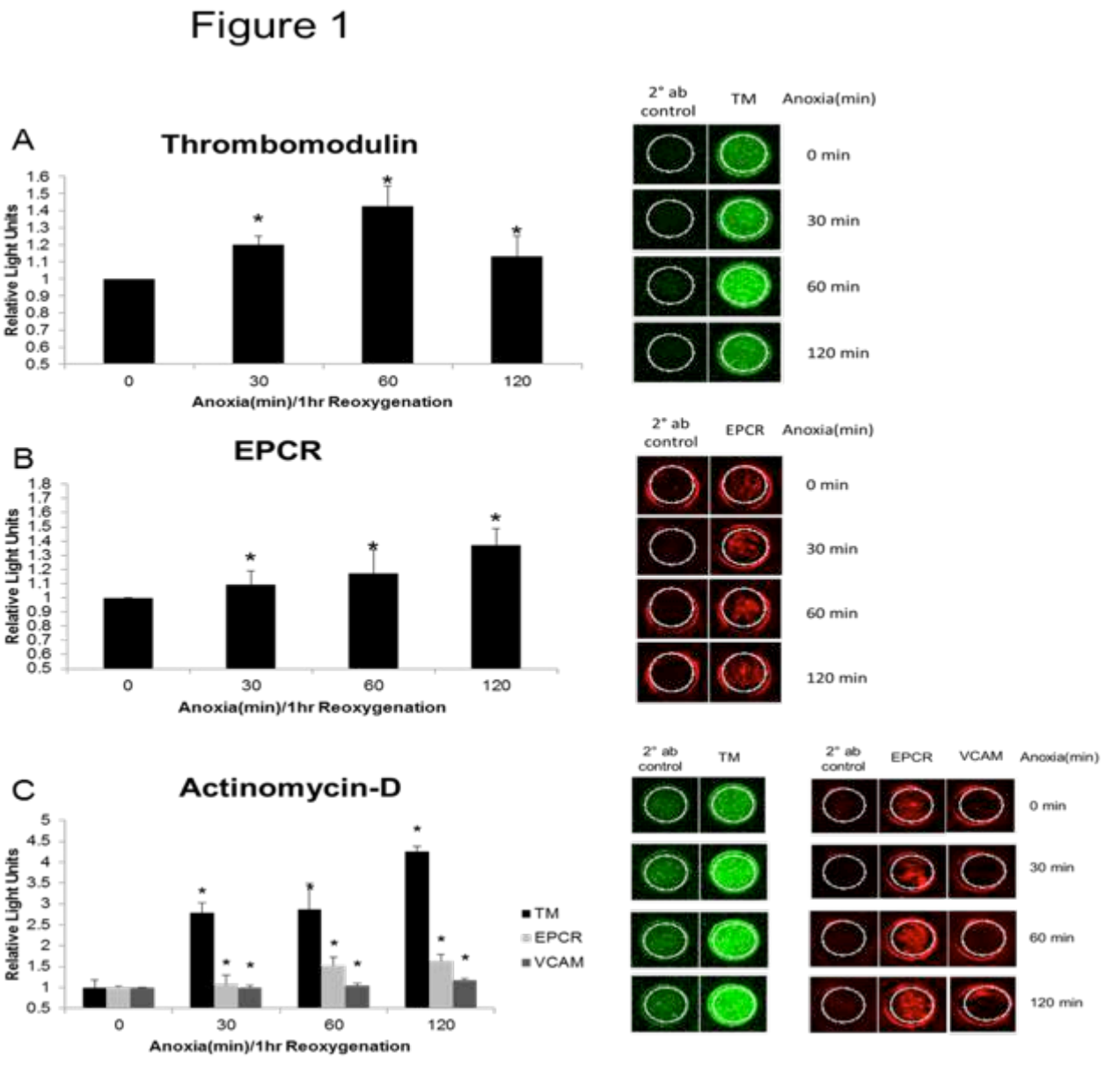
Fig 1. Characteristic ROTEM EXTEM tracings from a study subject. In every single one of the 20 subjects, as depicted here, increasing concentration of aPC produced ROTEM tracings consistent with worsening acute traumatic coagulopathy.

doi:10.1371/journal.pone.0150930.g001

Endothelial cell model

- HUVEC cells exposed to hypoxia for varying lengths.
- Complement activated with 30% human sera.
- Reoxygenated and cell surface thrombomodulin and EPCR measured by ‘on-cell western’
- Functional assay for activated protein C.

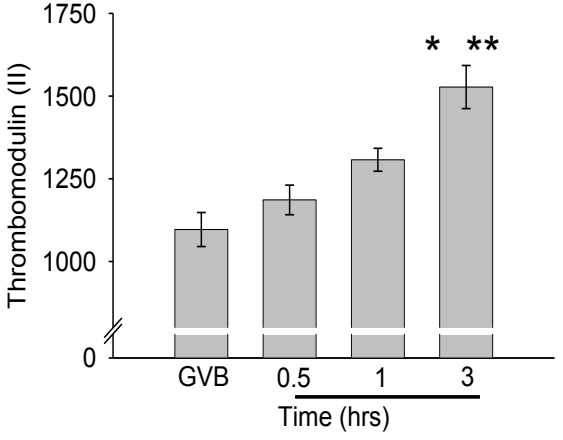
Hypoxia and reoxygenation results in increased TM and EPCR at the surface of HUVECs

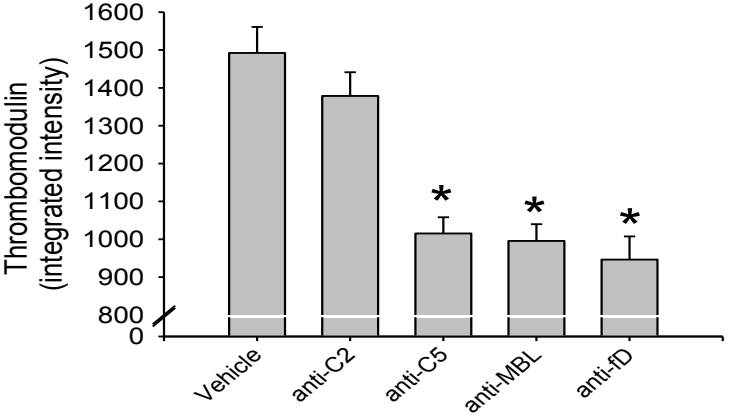


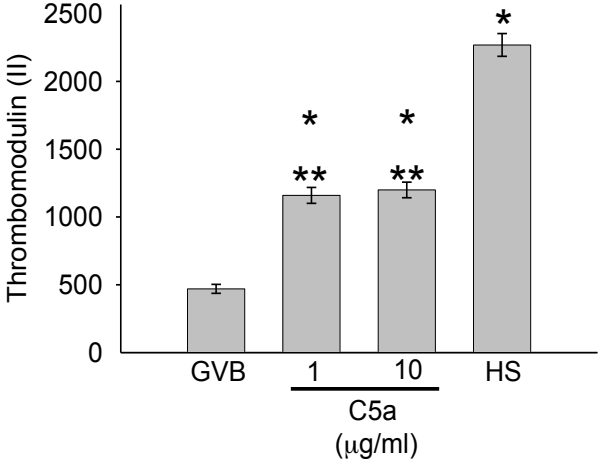
Unpublished

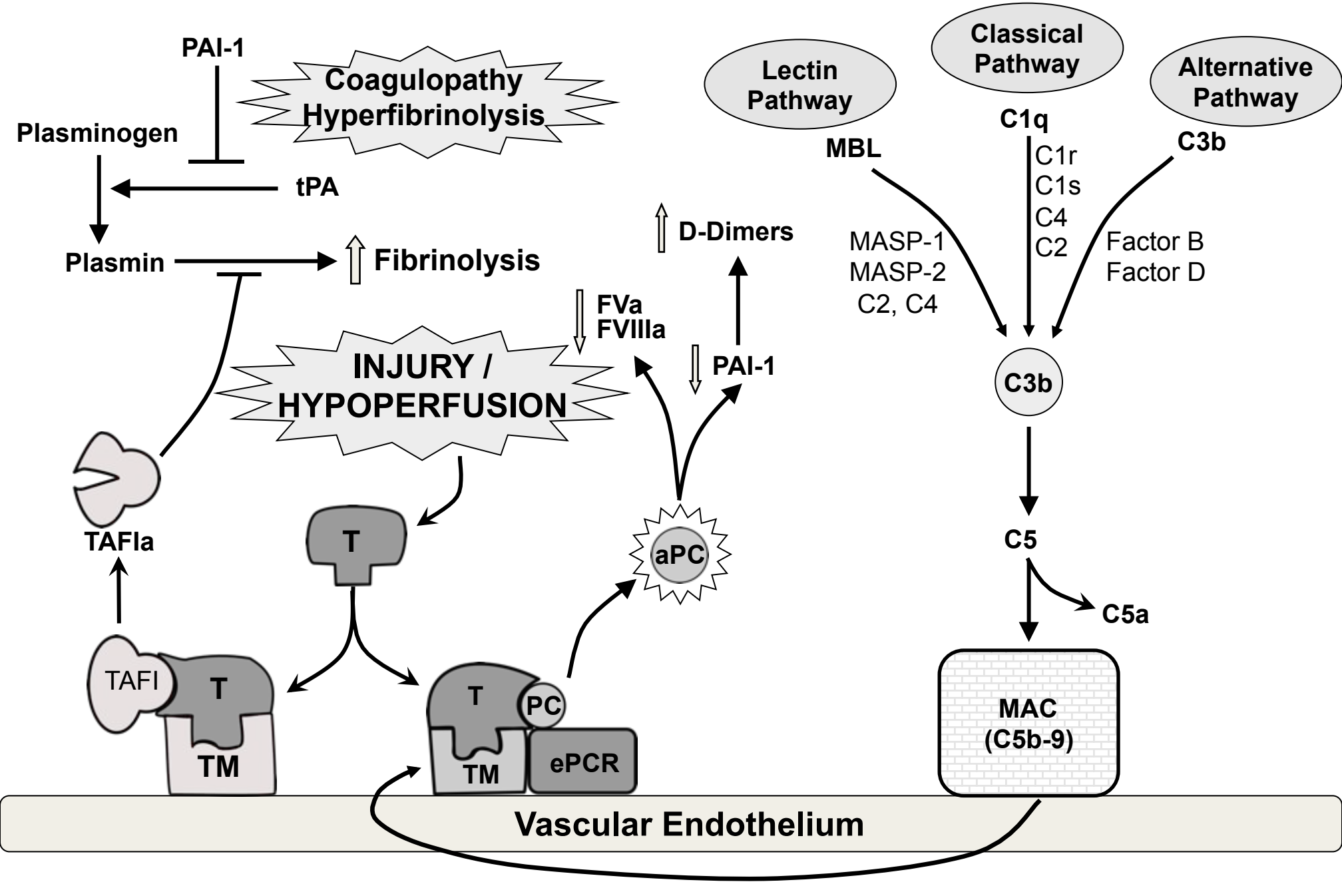
Complement and hypoxia induce TM expression and PC activation.

Complement inhibition at the level of factor D (fD), C5 or MBL, but not C2 attenuates complement induced expression of TM.



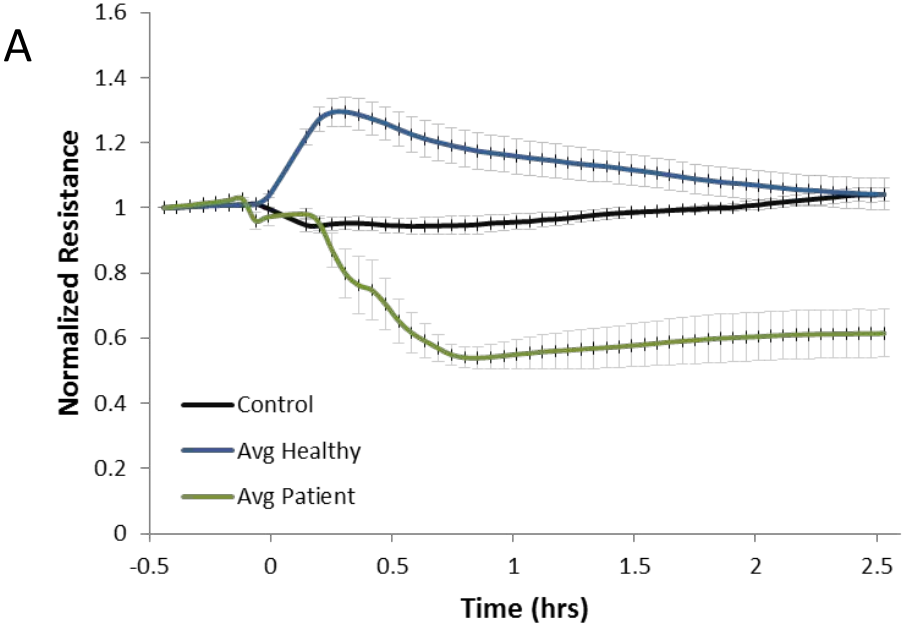


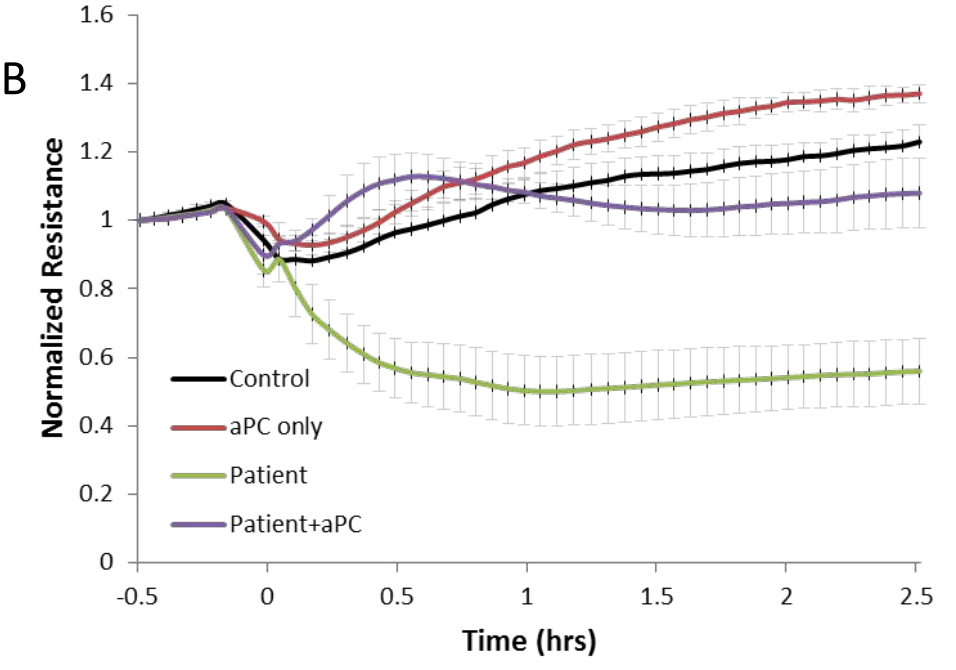


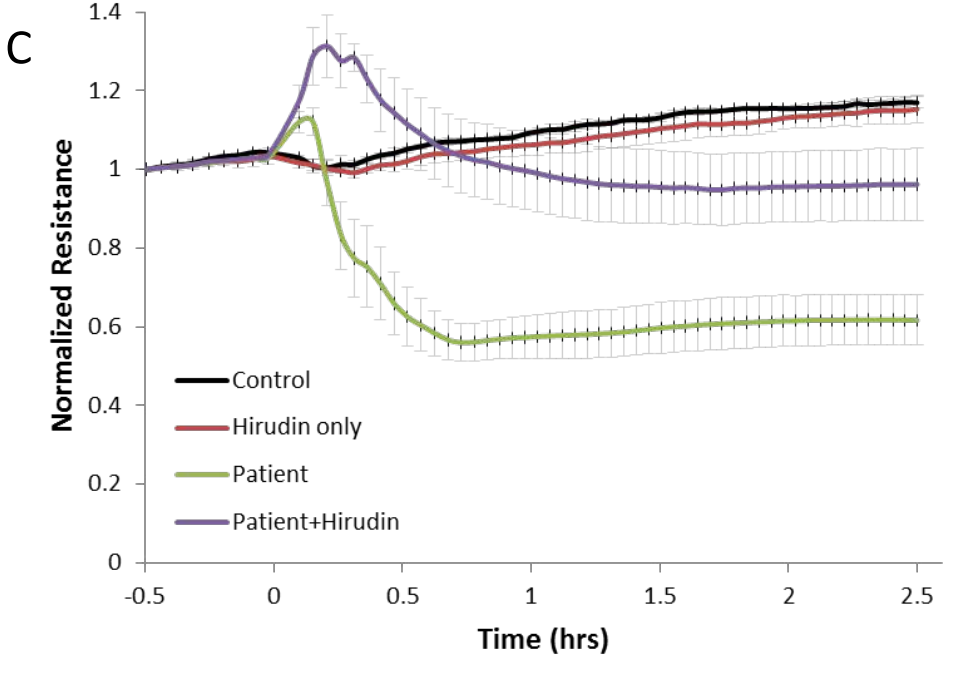

PAI-1
Coagulopathy
Hyperfibrinolysis
Plasminogen
tPA
Plasmin
Fibrinolysis
D-Dimers
FVa
FVIIIa
PAI-1
INJURY /
HYPOPERFUSION
TAFIa
T
aPC
TAFI
T
TM
T
PC
TM
ePCR
Lectin
Pathway
Classical
Pathway
Alternative
Pathway
MBL
C1q
C1r
C1s
C4
C2
C3b
MASP-1
MASP-2
C2, C4
Factor B
Factor D
C3b
C5
C5a
MAC
(C5b-9)
Vascular Endothelium

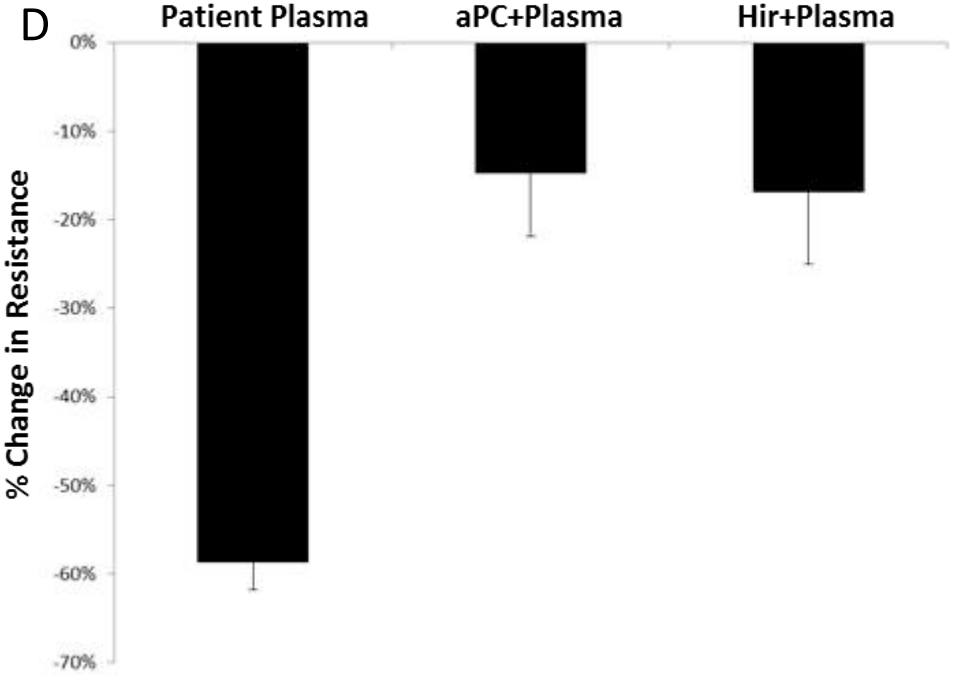
The endotheliopathy of trauma.

Fig. 1 Patient Plasma Induces Barrier Dysfunction.

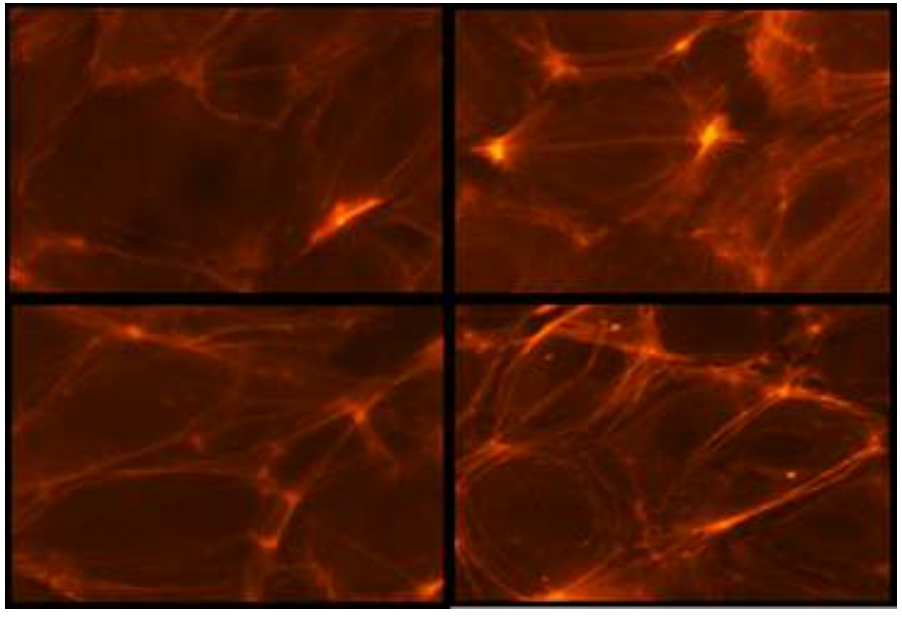




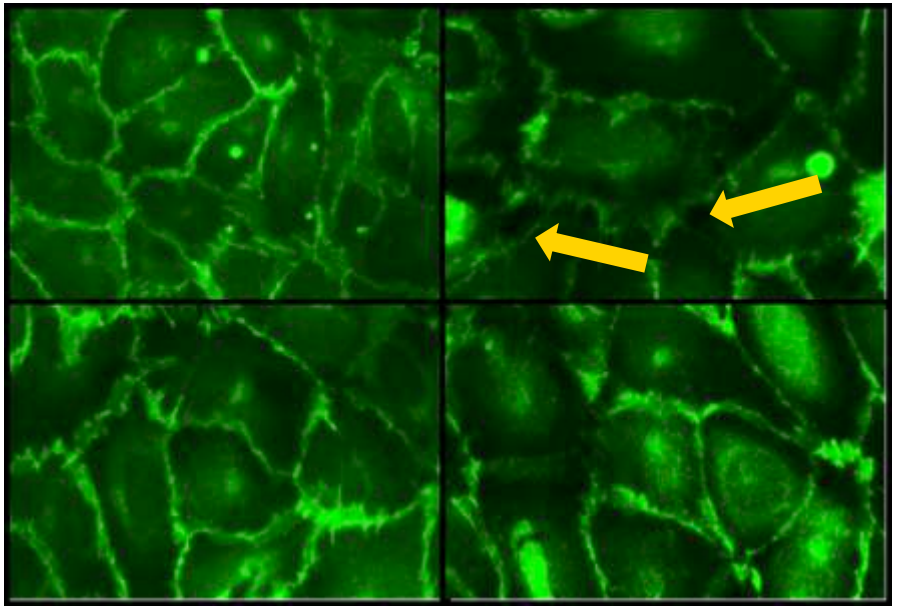




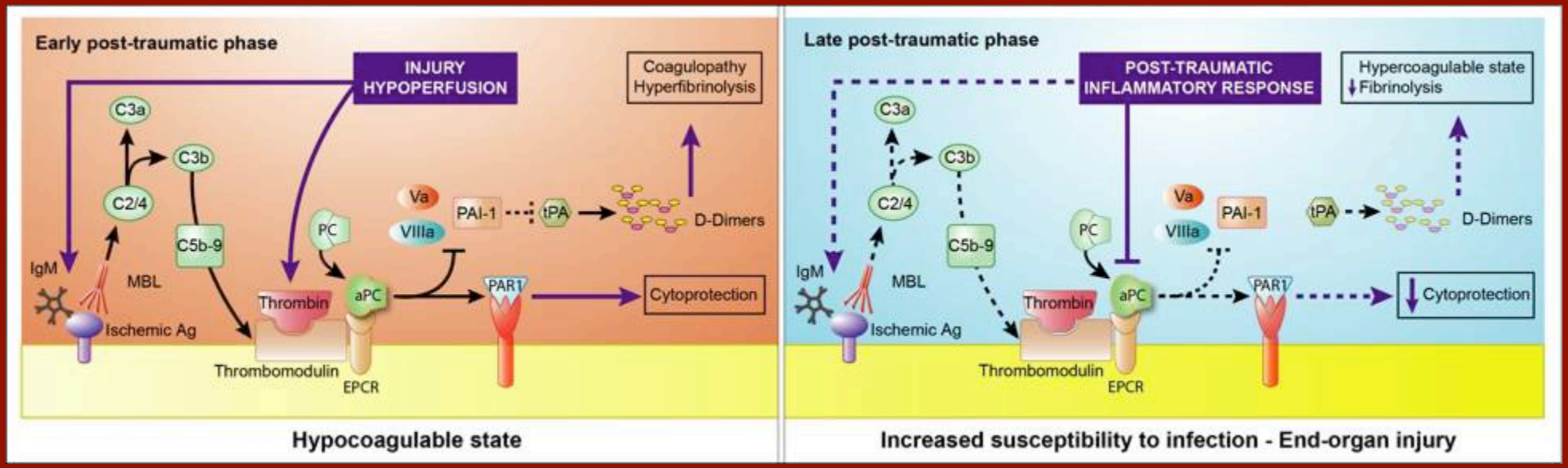
A


Untreated
Plasma
aPC Only
aPC+Plasma

B

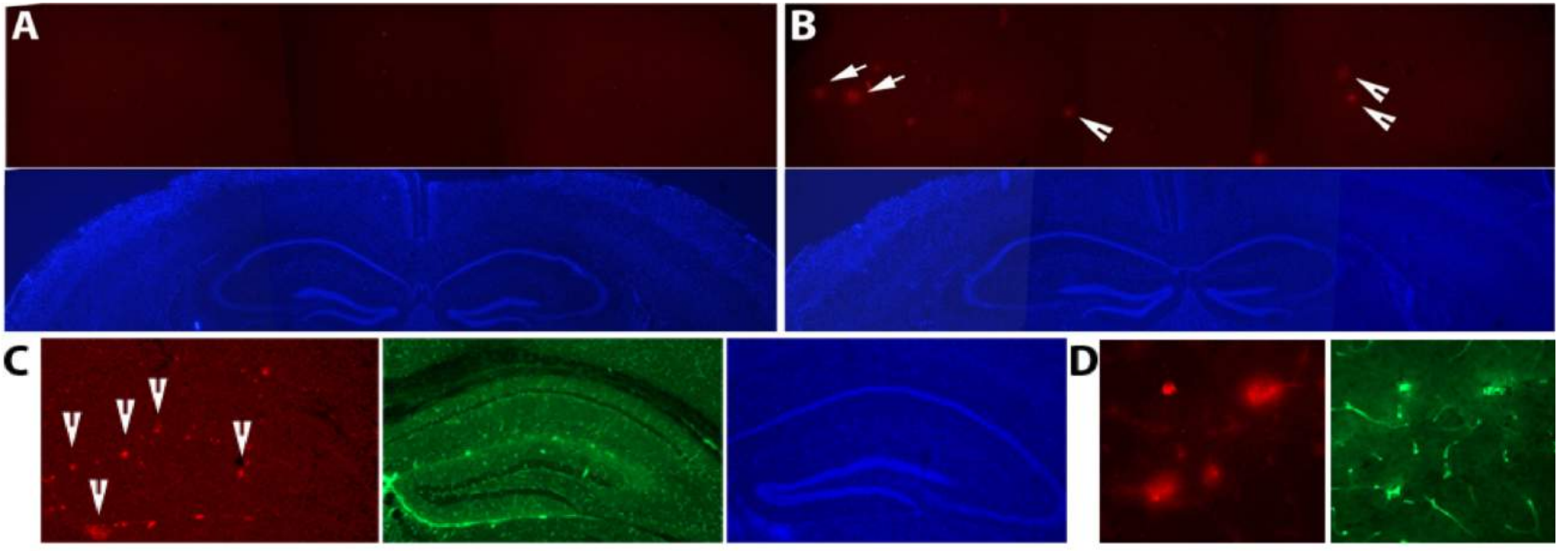

Untreated
Plasma
aPC Only
aPC+Plasma

Maladaptive response to trauma. Early coagulopathy, later hypercoagulable state and loss of cytoprotectivity.

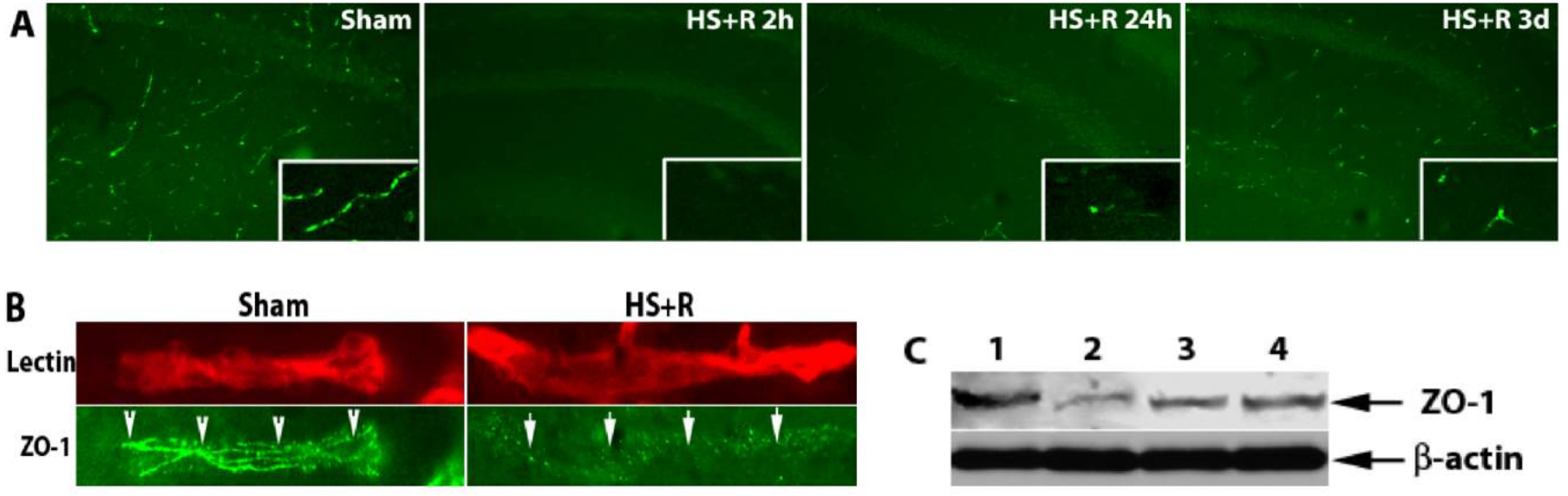


The link between brain injury and acute traumatic coagulopathy.

BBB permeability after non-TBI polytrauma



Adherens junction protein downregulation after non-TBI brain injury



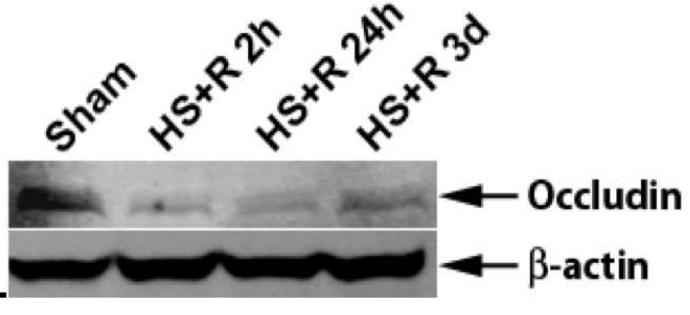
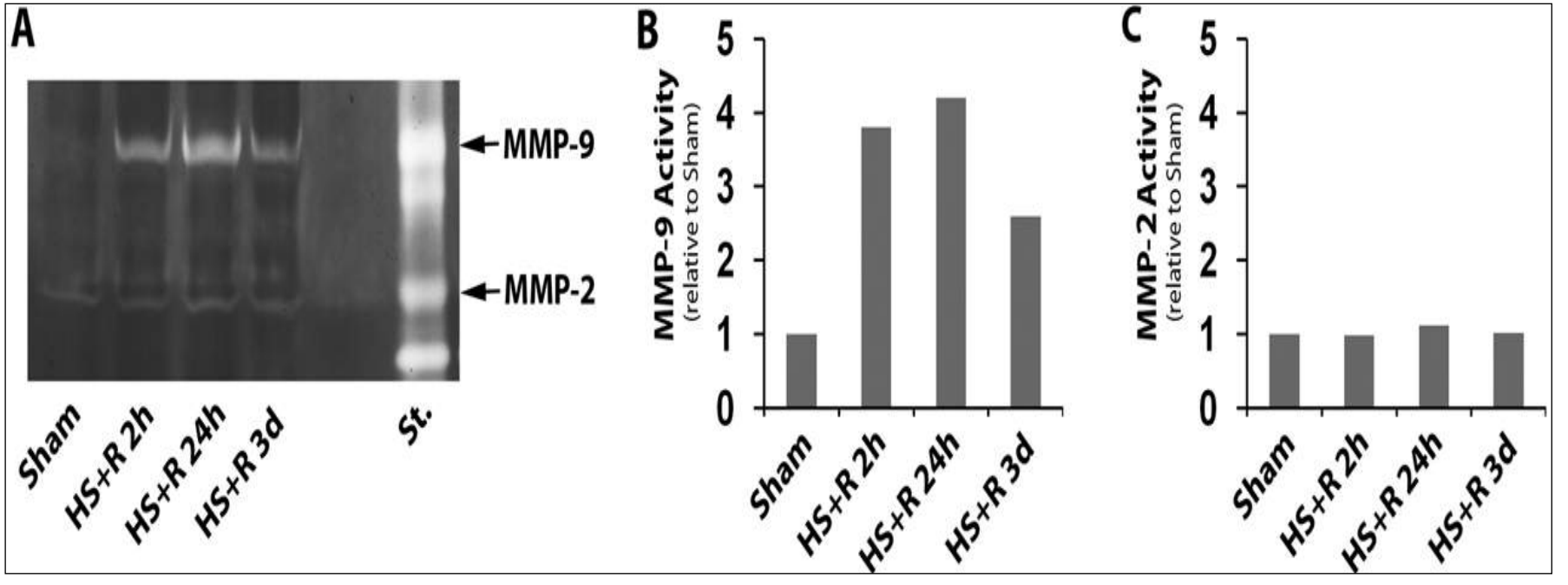


Figure3. Decreased Occludin expression in the mouse brain following HS and resuscitation. **A.** Western blot analysis showed decreased Occludin expression in the HS+R groups. **B.** Occludin staining in the mouse brain.

Junctional protein regulation via MMP-9



What don't we have time to discuss?

- Fibrinolysis/Fibrinolysis shutdown?
- Other thrombin phenotypes?
- Other inhibitors/anti coagulant pathways?
- Inflammatory phenotypes?
- Tissue specific coagulation?

- It is not the same in every patient and not the same minute to minute.

PRECISION MEDICINE:
Combining mechanism, prediction and targeted care.
In silico coagulation modeling.

Trauma scoring systems…

Trauma scoring systems…

- Many from rules of thumb to prediction of massive transfusion, need for LSI, development of MOF/ARDS and mortality.
- Most are sparsely used due to being non dynamic, too complicated or overfit/misspecified abstractions.

Early Predictors of Massive Transfusion in Combat Casualties

Martin A Schreiber, MD, FACS, Jeremy Perkins, MD, Laszlo Kiraly, MD, Samantha Underwood, MS, Charles Wade, PhD, John B Holcomb, MD, FACS

BACKGROUND: An early predictive model for massive transfusion (MT) is critical for management of combat casualties because of limited blood product availability, component preparation, and the time necessary to mobilize fresh whole blood donors. The purpose of this study was to determine which variables, available early after injury, are associated with MT. We hypothesized that

Table 2. Results of Stepwise Logistic Regression Analysis Revealing Variables That Are Independently Predictive of the Need for Massive Transfusion

	Value	Odds ratio	95% CI
HGB (g/dL)	≤11	7.7	5.0–11.9
INR	>1.5	5.9	3.5–10.2
Penetrating mechanism	Yes	2.6	1.4–4.8

HGB, hemoglobin; INR, International Normalized Ratio.

blood in the non-MT group ($p < 0.001$). Mortality was 39% in the MT group and 1% in the non-MT group ($p < 0.001$). Variables that independently predicted the need for MT were: hemoglobin ≤ 11 g/dL, International Normalized Ratio > 1.5, and a penetrating mechanism. The area under the receiver operator characteristic curve was 0.804 and Hosmer-Lemeshow goodness-of-fit test was 0.98.

CONCLUSION: MT after combat injury is associated with high mortality. Simple variables available early after admission allow accurate prediction of MT. (J Am Coll Surg 2007;205:541–545. © 2007 by the American College of Surgeons)

Association of Shock, Coagulopathy, and Initial Vital Signs With Massive Transfusion in Combat Casualties

Claire R. Larson, MD, Christopher E. White, MD, MSc, FACS, Philip C. Spinella, MD, John A. Jones, BS, John B. Holcomb, MD, FACS, Lorne H. Blackbourne, MD, FACS, and Charles E. Wade, PhD

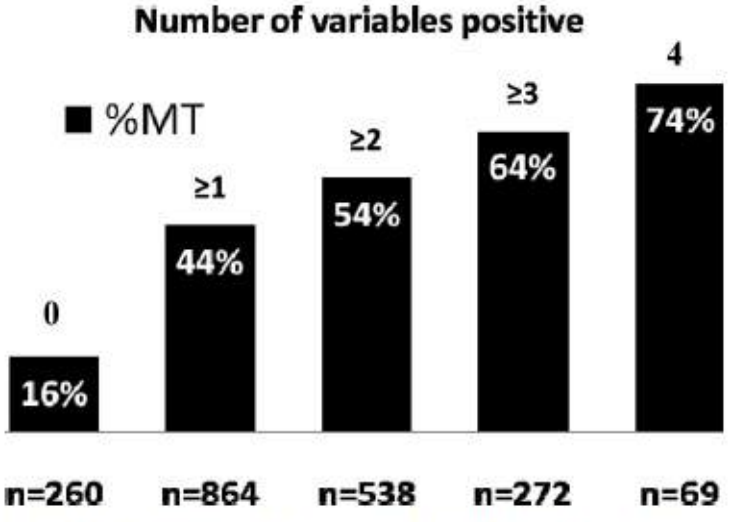


Figure 1. Mortality rates associated with multiple variables present in our clinical model.

- BD ≥ 6
- HR > 110
- SBP < 110 mm Hg
- Hgb < 11

(*J Trauma.* 2010;69: S26–S32)

A Predictive Model for Massive Transfusion in Combat Casualty Patients

Daniel F. McLaughlin, MD, Sarah E. Niles, MD, MPH, Jose Salinas, PhD, Jeremy G. Perkins, MD, E. Darrin Cox, MD, Charles E. Wade, PhD, and COL John B. Holcomb, MC

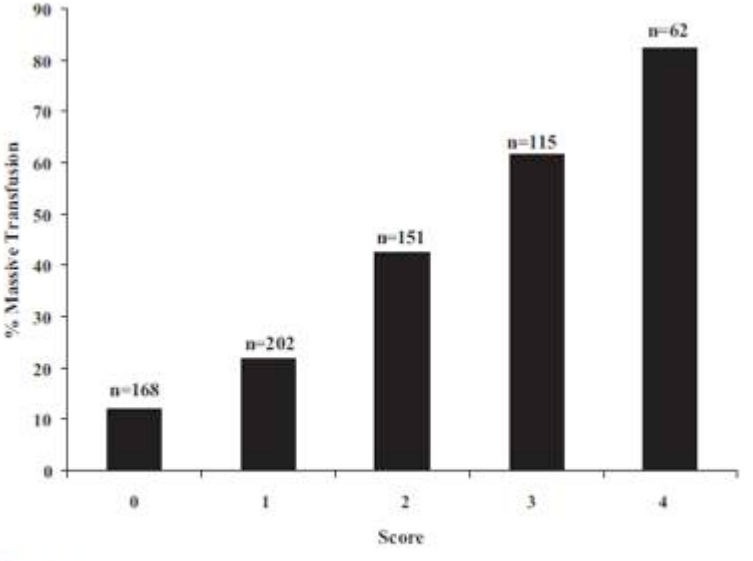


Fig. 4. *Observed percentage of massive transfusion for each number of variables with values associated with massive transfusion.*

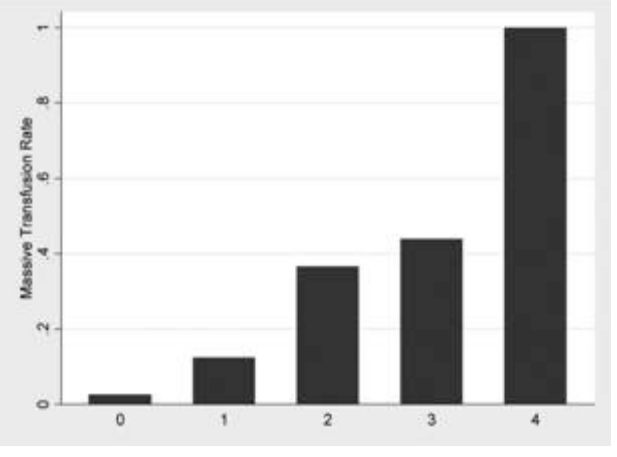
- BD ≥ 6
- HR > 105
- Acidosis (ph<7.25)
- Hgb < 11

J Trauma. 2008;64:S57–S63.

Multiple Scoring Systems

ABC Score

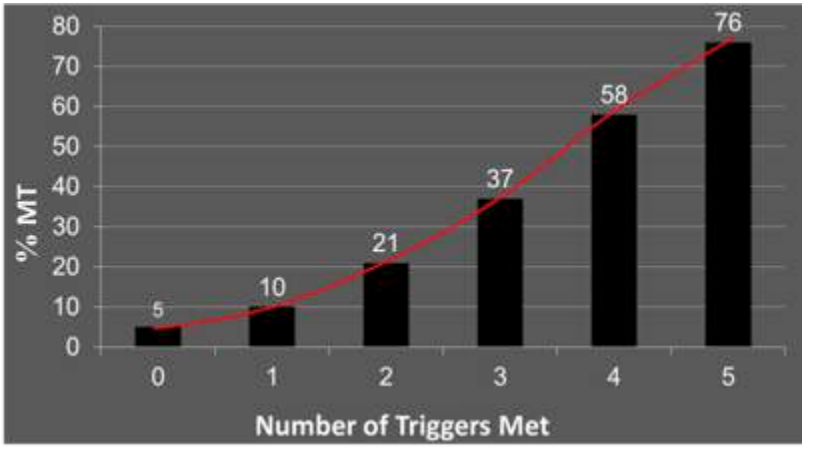
- Penetrating mechanism
- ED SBP of 90 mm Hg or less
- ED HR of 120 bpm or greater
- Positive FAST



Cotton et al, J Trauma 2009

Massive Transfusion Score

- SBP<90mmHg
- BD>=-6
- Temp<35.5 C
- INR>1.5
- Hgb <11g/dL



Callcut et al, J Trauma 2011

Emergency Department Crystalloid Resuscitation of 1.5 L or More is Associated With Increased Mortality in Elderly and Nonelderly Trauma Patients

Eric J. Ley, MD, Morgan A. Clond, PhD, Marissa K. Srour, BS, Moshe Barnajian, MD, James Mirocha, MS, Dan R. Margulies, MD, and Ali Salim, MD

- 3137 patients
- Prospectively recorded IVF volumes
- Compared elderly (>=70) vs. non-elderly
- Multivariate analysis

TABLE 3. Estimated Odds Ratios for Various Fluid Resuscitation Volumes in the Nonelderly

Volume (L)	Odds Ratio (95% Wald CI)	*p*
IVF ≥1	1.69 (1.00–2.87)	0.051
IVF ≥1.5	2.09 (1.31–3.33)	0.002
IVF ≥2	2.27 (1.41–3.65)	0.0007
IVF ≥3	2.69 (1.53–4.73)	0.0006

IVF, intravenous fluid (L).

TABLE 5. Odds Ratio for Mortality With Crystalloid Resuscitation in the Elderly

Volume (L)	Odds Ratio (95% Wald CI)	*p*
IVF ≥1	1.10 (0.48–2.49)	0.82
IVF ≥1.5	2.89 (1.13–7.41)	0.027
IVF ≥2	4.57 (1.55–13.53)	0.006
IVF ≥3	8.61 (1.55–47.75)	0.014

IVF, intravenous fluid (L).

(*J Trauma*. 2011;70: 398–400)

We can do better than overfit models.

1. Data Driven Prediction

Precision Medicine. Prediction Without Overfitting

Methods allow for complete agnosticism with regards to candidate variables for predicting outcomes of interest (thus, can use them all).

Dynamic (time-adaptive) prognosis scoring

Dynamic variable importance – the independent predictive value of different variables and how this changes over time.

Optimal Treatment regimes

Planned sub-group analysis

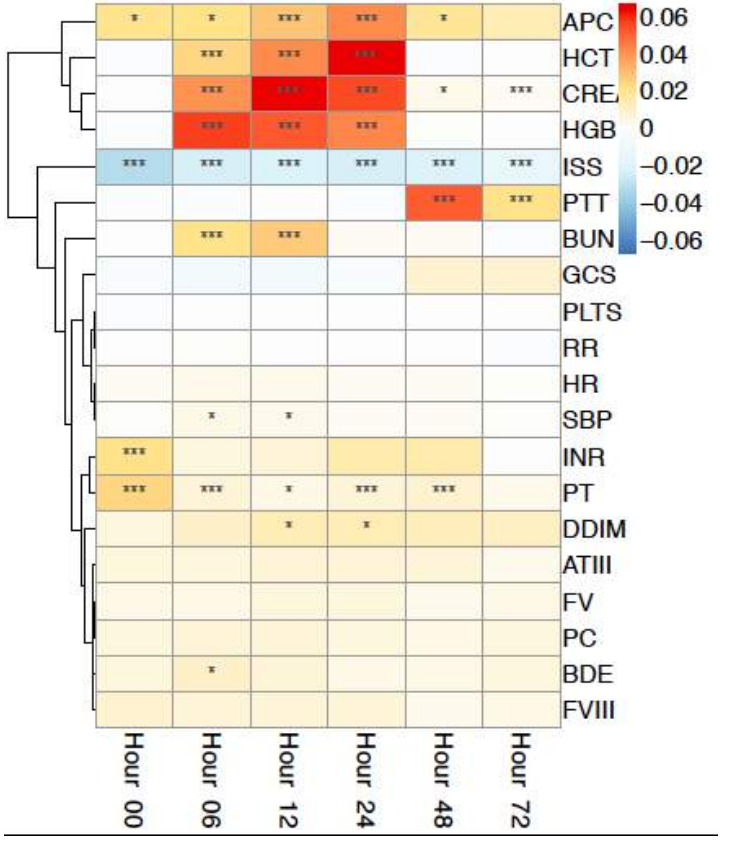
Unplanned sub-group analysis (data adaptive target parameters).

We can determine, in the context of many competitors, which variables contribute most to diagnosis of outcome and how these change over time.

TABLE 2. Variable Importance Analysis

		30–90 Min			90–180 Min		
Variable	Delta/binary	Double Robust	Stepwise	Unadjusted	Double Robust	Stepwise	Unadjusted
bdresd	0.1	−3.5E−3 (0.16)	−2.2E−4 (0.01)	−2.3E−4 (<0.01)	7.9E−4 (0.73)	−1.6E−4 (0.14)	−2.6E−4 (<0.01)
ctdhed	Binary	5.4E−3 (0.59)	2.0E−2 (0.7)	2.6E−2 (0.02)	1.3E−2 (0.18)	3.9E−2 (0.46)	5.1E−2 (<0.01)
fistresd*	Binary*	−1.2E−2 (0.32)	−1.3E−4 (0.99)	2.5E−3 (0.79)	−1.6E−2 (0.19)	1.0E−2 (0.45)	1.4E−2 (0.33)
fibresd	1	1.4E−2 (0.02)	−1.2E−4 (0.43)	−2.2E−4 (0.1)	1.4E−2 (0.04)	−4.4E−4 (0.03)	−4.8E−4 (0.02)
gcsd	1	−4.3E−4 (0.92)	−1.7E−3 (0.59)	−2.5E−3 (0.07)	−2.1E−4 (0.96)	−2.7E−3 (0.06)	−2.9E−3 (<0.01)
glucd	3.4	1.1E−3 (0.28)	4.9E−4 (0.22)	5.5E−4 (<0.01)	−2.4E−4 (0.77)	3.6E−4 (0.03)	4.4E−4 (0.01)
hctresd*	1*	−3.5E−3 (<0.01)*	−2.2E−3 (0.01)*	−2.4E−3 (<0.01)*	6.9E−4 (0.88)*	−6.2E−4 (0.68)*	−1.1E−3 (0.12)*
hgbresd	0.1	−1.1E−3 (0.2)	−7.3E−4 (0.2)	−7.5E−4 (<0.01)	−3.7E−4 (0.21)	−4.6E−4 (0.72)	−5.2E−4 (0.01)
hrsd1	1	3.0E−4 (0.82)	−1.8E−5 (0.84)	−4.9E−5 (0.8)	1.2E−3 (0.17)	2.0E−4 (0.47)	1.2E−4 (0.63)
inresd	0.1	−2.3E−3 (0.57)	2.7E−4 (1)	3.5E−4 (0.06)	1.4E−2 (0.17)	4.1E−4 (1)	4.6E−4 (0.1)
intubed	Binary	−1.3E−2 (0.21)	4.5E−3 (0.64)	8.5E−3 (0.43)	−1.8E−3 (0.87)	2.5E−2 (0.09)	3.4E−2 (0.03)
ins	1	3.3E−4 (0.76)	7.1E−4 (0.04)	7.3E−4 (0.04)	2.0E−3 (0.22)	1.2E−3 (<0.01)	1.2E−3 (<0.01)
ndeconsd	Binary	9.1E−2 (0.25)	1.1E−1 (0.3)	2.1E−1 (0.15)	−4.8E−2 (<0.01)	−2.6E−2 (0.05)	−2.5E−2 (<0.01)
plasmaumn	1	1.1E−2 (0.11)	2.1E−3 (0.09)	3.0E−3 (0.01)	7.8E−3 (0.11)	4.2E−3 (<0.01)	4.7E−3 (<0.01)
pltresd*	4*	−6.3E−4 (<0.01)*	−5.7E−4 (0.25)*	−6.9E−4 (0.02)*	−1.0E−3 (0.05)*	−1.1E−3 (0.15)*	−9.9E−4 (<0.01)*
plteum	1	−7.8E−3 (0.32)	−1.3E−3 (0.75)	4.6E−4 (0.93)	−7.9E−3 (0.5)	1.7E−3 (0.37)	4.1E−3 (0.04)
RBCsurv*	1*	3.8E−3 (0.09)	1.7E−3 (0.06)	2.4E−3 (<0.01)	7.7E−3 (<0.01)*	3.3E−3 (<0.01)*	3.9E−3 (<0.01)*
rfvisiad*	Binary*	−4.1E−2 (<0.01)*	0.0E+0 (1)*	−1.9E−2 (<0.01)*	−4.2E−2 (<0.01)*	−2.5E−2 (0.03)*	−2.5E−2 (<0.01)*
shpod1	1	−1.6E−3 (0.18)	−2.0E−4 (0.21)	−2.3E−4 (0.17)	−2.0E−4 (0.58)	8.9E−5 (0.6)	1.4E−4 (0.49)
sked	1	3.8E−3 (0.71)	4.7E−3 (0.49)	7.9E−3 (0.31)	2.5E−2 (0.16)	1.9E−2 (0.05)	2.5E−2 (0.03)
snand	1	−5.1E−3 (<0.01)	−2.7E−4 (0.63)	−1.8E−4 (0.8)	6.3E−3 (0.52)	−8.2E−5 (0.9)	−1.0E−4 (0.89)
tcsurd*	Binary*	−1.8E−3 (0.94)	1.1E−2 (0.77)	8.2E−3 (0.77)	−4.5E−2 (<0.01)*	−2.6E−2 (<0.01)*	−2.6E−2 (<0.01)*
traxrd*	Binary*	1.5E−4 (0.99)	2.4E−2 (0.68)	2.4E−2 (0.49)	−2.9E−2 (0.02)*	−2.5E−3 (0.99)*	−3.5E−3 (0.88)*

Variable importance analysis (Ω_{VIM} for binary, Ω_β for continuous), for death (with p values), where delta (δ_{VIM}) is the chosen potential change in the corresponding variable of interest for estimates of Ω_β, and binary indicates that the variable is binary, and thus, the Ω_{VIM} estimate is reported.
*Discussed in the text.



Dynamic prediction modeling and variable importance.

PLOS | ONE

RESEARCH ARTICLE

Variable Importance and Prediction Methods for Longitudinal Problems with Missing Variables

Iván Díaz[1]*, Alan Hubbard[2], Anna Decker[2], Mitchell Cohen[3]

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* idiaz@jhu.edu

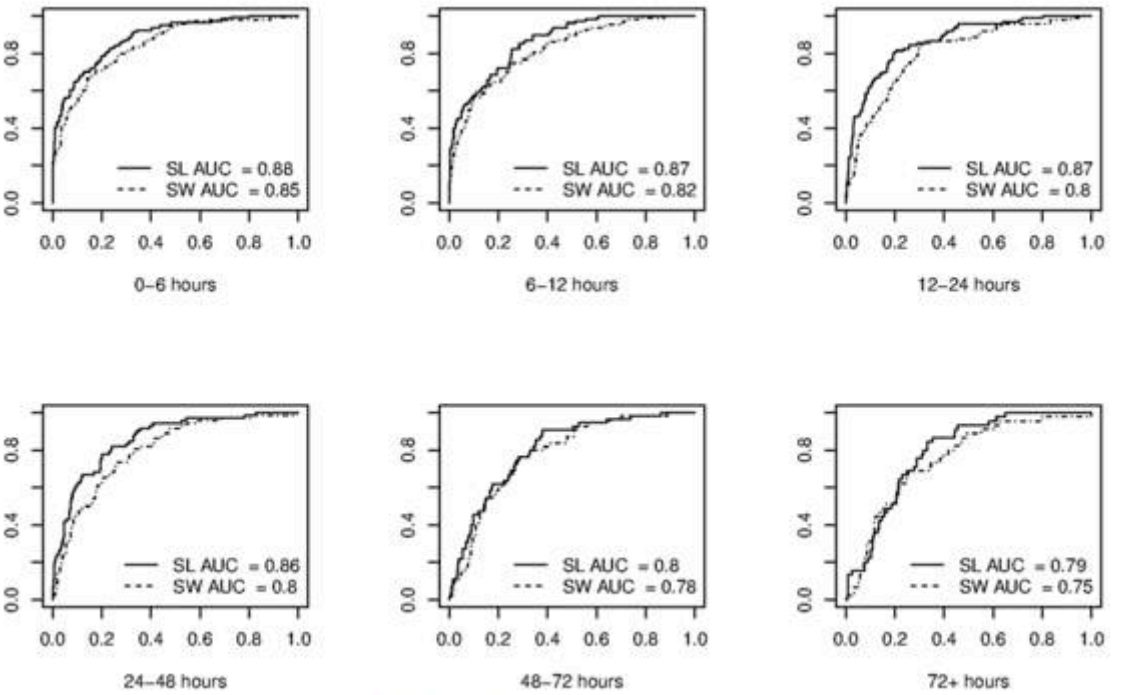
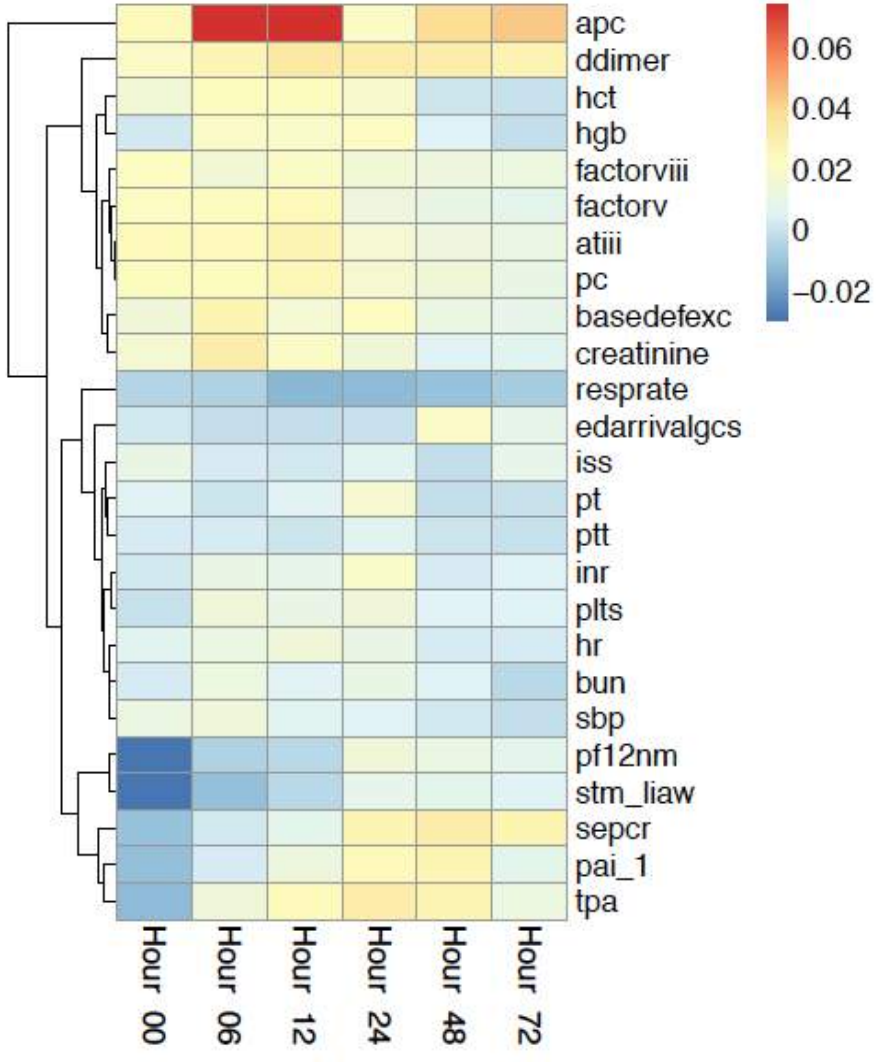
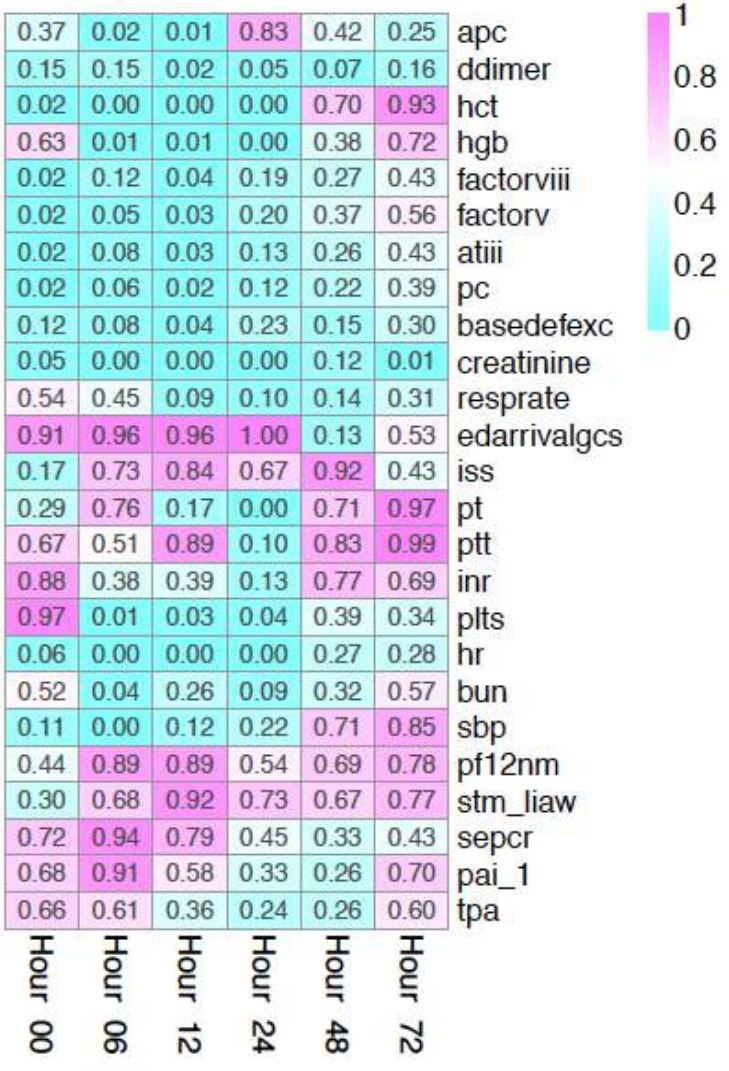


Fig 2. ROC curves of cross-validated prediction for the super learner (SL) and the logistic step-wise regression (SW), for different time intervals.

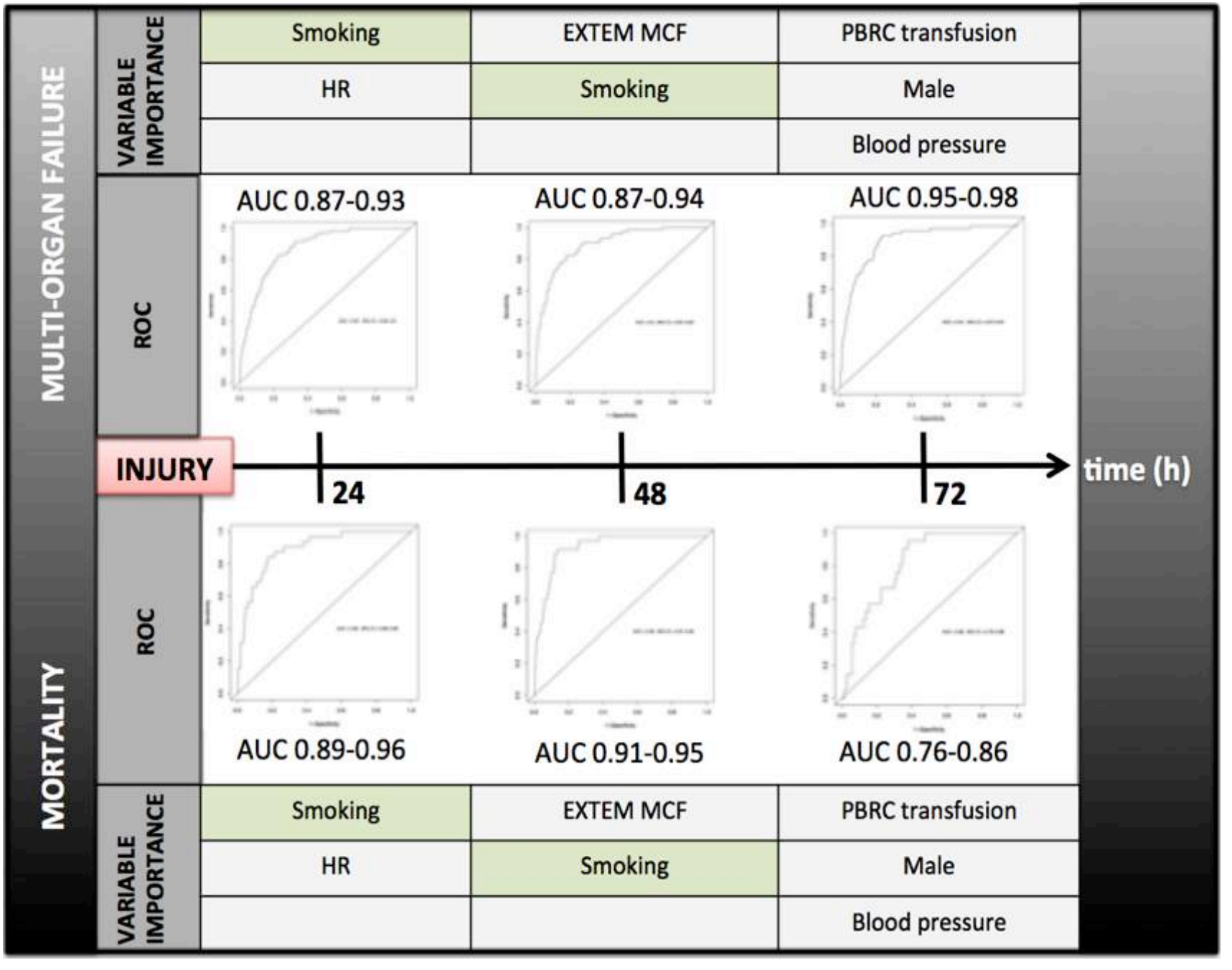
Variable Importance: What drives outcome at each time iteration.



(a) Effect size



(b) P-values


MULTI-ORGAN FAILURE
MORTALITY
VARIABLE IMPORTANCE
Smoking
EXTEM MCF
PBRC transfusion
HR
Smoking
Male
Blood pressure
ROC
AUC 0.87-0.93
AUC 0.87-0.94
AUC 0.95-0.98
INJURY
24
48
72
time (h)
ROC
AUC 0.89-0.96
AUC 0.91-0.95
AUC 0.76-0.86
VARIABLE IMPORTANCE
Smoking
EXTEM MCF
PBRC transfusion
HR
Smoking
Male
Blood pressure

A principal component analysis of coagulation after trauma

Matthew E. Kutcher, MD, Adam R. Ferguson, PhD, *and* **Mitchell J. Cohen, MD,** *San Francisco, California*

BACKGROUND: Clotting factor abnormalities underlying acute traumatic coagulopathy are poorly understood, with application of traditional regression techniques confounded by colinearity. We hypothesized that principal components analysis (PCA), a pattern-finding and data reduction technique, would identify clinically predictive patterns in the complex clotting factor milieu after trauma.

METHODS: Plasma was prospectively collected from 163 critically injured trauma patients. Prothrombin; factors V, VII, VIII, IX, X; D-dimer; activated and native protein C; and antithrombin III levels were assayed and subjected to nonlinear PCA to identify principal components (PCs).

RESULTS: Of 163 patients, 19.0% were coagulopathic on admission. PCA identified 3 significant PCs, accounting for 67.5% of overall variance. PC1 identified global clotting factor depletion; PC2 the activation of protein C and fibrinolysis; and PC3 factor VII elevation and VIII depletion. PC1 score correlated with penetrating injury and injury severity, predicting coagulopathy (odds ratio [OR], 4.67; $p < 0.001$) and mortality (OR, 1.47; $p = 0.032$). PC2 score correlated with injury severity, acidosis, and shock, and significantly predicted ventilator-associated pneumonia (OR, 1.59; $p = 0.008$), acute lung injury (OR, 2.24; $p < 0.001$), multiorgan failure (OR, 1.83; $p = 0.002$), and mortality (OR, 1.62; $p = 0.006$) but was not associated with international normalized ratio (INR)–based or partial thromboplastin time (PTT)–based coagulopathy ($p > 0.200$). PC3 did not significantly predict outcomes.

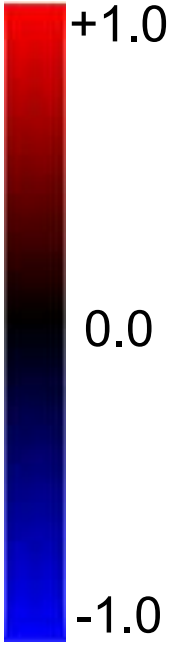
CONCLUSION: PCA identifies distinct patterns of coagulopathy: depletion coagulopathy predicts mortality and INR/PTT elevation, while fibrinolytic coagulopathy predicts infection, end-organ failure, and mortality, without detectable differences in INR or PTT. While depletion coagulopathy is intuitive, fibrinolytic coagulopathy may be a distinct but often overlapping entity with differential effects on outcomes. (*J Trauma Acute Care Surg*. 2013;74: 1223–1230. Copyright © 2013 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Prognostic study, level III.

KEY WORDS: Coagulopathy; principal components analysis; fibrinolysis.

PCA model construction

	PC1	PC2	PC3
Percent variance	43.91	13.45	10.12
Prothrombin	**-0.86**	-0.04	0.11
Factor V	**-0.78**	0.01	-0.11
Factor VII	**-0.62**	0.01	**0.47**
Factor VIII	**-0.35**	**0.34**	**-0.73**
Factor IX	**-0.69**	0.07	0.03
Factor X	**-0.88**	-0.01	0.20
D-dimer	0.25	**0.80**	0.00
aPC	0.20	**0.74**	**0.39**
Protein C	**-0.80**	0.11	-0.05
AT III	**-0.74**	0.16	-0.17



- Identify factor patterns

PCA model: PC1

- 43.91% variance
- Negative correlation:
  - All numbered factors
  - Anticoagulants PC & AT3
- **Depletion coagulopathy**

	PC1
Variance	43.91%
Prothrombin	**-0.86**
Factor V	**-0.78**
Factor VII	**-0.62**
Factor VIII	**-0.35**
Factor IX	**-0.69**
Factor X	**-0.88**
D-dimer	0.25
aPC	0.20
Protein C	**-0.80**
AT III	**-0.74**

PCA model: PC2

- 13.45% variance
- Positive correlation:
  - D-dimer & aPC
  - Factor VIII
- **Fibrinolytic coagulopathy**

	PC2
Variance	13.45%
Prothrombin	-0.04
Factor V	0.01
Factor VII	0.01
Factor VIII	**0.34**
Factor IX	0.07
Factor X	-0.01
D-dimer	**0.80**
aPC	**0.74**
Protein C	0.11
AT III	0.16

PCA model: outcomes

		PC1	PC2	PC3
Odds ratio	Mortality	**1.48**	**1.62**	-
	Multiorgan failure	-	**1.83**	-
	Acute lung injury	-	**2.24**	-
	VAP	-	**1.59**	-
	INR ≥1.3	**4.68**	-	-
	PTT ≥30	**3.10**	-	**1.44**

A principal component analysis of postinjury viscoelastic assays: Clotting factor depletion versus fibrinolysis

Theresa L. Chin, MD,[a] Ernest E. Moore, MD,[a,b] Hunter B. Moore, MD,[a] Eduardo Gonzalez, MD,[a] Michael P. Chapman, MD,[a] John R. Stringham, MD,[a] Christopher R. Ramos, MD,[a] Anirban Banerjee, PhD,[a] *and* **Angela Sauaia, MD, PhD,[a]** *Denver, CO*

Introduction. *The mechanisms driving trauma-induced coagulopathy (TIC) remain to be defined, and its therapy demands an orchestrated replacement of specific blood products. Thrombelastography (TEG) is a tool to guide the TIC multicomponent therapy. Principal component analysis (PCA) is a statistical approach that identifies variable clusters; thus, we hypothesize that PCA can identify specific combinations of TEG-generated values that reflect TIC mechanisms.*

Methods. *Adult trauma patients admitted from September 2010 to October 2013 for whom a massive transfusion protocol was activated were included. Rapid TEG values obtained within the first 6 hours after injury were included in the PCA. PCA components with an eigenvalue >1 were retained, and, within components, variable loadings (equivalent to correlation coefficients) $>|60|$ were considered significant. Component scorings for each patient were calculated and clinical characteristics of patients with high and low scores were compared.*

Results. *Of 98 enrolled patients, 67% were male and 70% suffered blunt trauma. Median age was 41 years (interquartile range 28–55) and median Injury Severity Score was 31.5 (interquartile range 24–43). PCA identified three principal components (PCs) that together explained 93% of the overall variance. PC1 reflected global coagulopathy with depletion of platelets and fibrinogen whereas PC3 indicated hyperfibrinolysis. PC2 may represent endogenous anticoagulants such as the activation of protein C.*

Conclusion. *PCA suggests depletion coagulopathy is independent from fibrinolytic coagulopathy. Furthermore, the distribution of mortality suggests that low levels of fibrinolysis may be beneficial in a select group of injured patients. These data underscore the potential of risk for concurrent presumptive treatment for preserved depletion coagulopathy and possible fibrinolysis. (Surgery 2014;156:570-7.)*

From the University of Colorado Denver[a] and Denver Health Medical Center,[b] Denver, CO

Individual clotting factor contributions to mortality following trauma

Ryan C. Kunitake, Benjamin M. Howard, MD, MPH, Lucy Z. Kornblith, MD, Sabrinah A. Christie, MD, Amanda S. Conroy, Mitchell J. Cohen, MD, *and* **Rachael A. Callcut, MD, MSPH**, *San Francisco, California*

BACKGROUND: Acute traumatic coagulopathy affects 20% to 30% of trauma patients, but the extensive collinearity of the coagulation cascade complicates attempts to clarify global clotting factor dysfunction. This study aimed to characterize phenotypes of clotting factor dysfunction and their contributions to mortality after major trauma.

METHODS: This prospective cohort study examines all adult trauma patients of the highest activation level presenting to San Francisco General Hospital between February 2005 and February 2015. Factors II, V, VII, VIII, IX, and X and protein C activity on admission and mortality status at 28 days were assessed. Predictors of 28-day mortality in univariate analysis were included in multiple logistic regression controlling for traumatic brain injury (TBI), acidosis, age, and mechanism of injury. Principal component analysis was utilized to identify phenotypic coagulation.

RESULTS: Complete coagulation factor data were available for 876 (61%) of 1,429 patients. In multiple logistic regression, factors V (odds ratio [OR], 0.86; 95% confidence interval [CI], 0.76–0.97), VIII (OR, 0.97; 95% CI, 0.95–0.99), and X (OR, 0.79; 95% CI, 0.68–0.92) and protein C (OR, 1.17; 95% CI, 1.05–1.30) significantly predicted 28-day mortality after controlling for age, base deficit, mechanism of injury, and TBI. Principal component analysis identified two significant principal components (Phenotypes 1 and 2) that accounted for 66.3% of the total variance. Phenotype 1 (factors II, VII, IX, and X and protein C abnormalities) explained 49.3% and was associated with increased injury, coagulopathy, TBI, and mortality. Phenotype 2 (factors V and VIII abnormalities) explained 17.0% and was associated with increased coagulopathy, blunt injury, and mortality. Only Phenotype 2 remained significantly associated with 28-day mortality in multiple logistic regression.

CONCLUSIONS: Principal component analysis identified two distinct phenotypes within the entirety of global clotting factor abnormalities, and these findings substantiate the crucial association of factors V and VIII on mortality following trauma. This may be the first step toward identifying unique phenotypes after injury and personalizing hemostatic resuscitation. (*J Trauma Acute Care Surg.* 2017;82: 302–308.

LEVEL OF EVIDENCE: Prognostic study, level III.

KEY WORDS: Clotting factors; hemorrhage; trauma-related mortality.

TABLE 3. Principal Component Analysis

	Phenotype 1	Phenotype 2	Total
Eigenvalue	3.45	1.19	
Percent variance	49.3%	17.0%	66.3%
Factors			
II (% activity)	0.47	−0.06	
V (% activity)	0.22	0.47	
VII (% activity)	0.44	−0.21	
VIII (% activity)	−0.10	0.85	
IX (% activity)	0.41	0.01	
X (% activity)	0.49	−0.03	
Protein C (% activity)	0.36	0.11	

Eigenvalues greater than 1 were considered significant. Loading values greater than |0.30| were considered significant.

Surgery 163 (2018) 827–831

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Trauma/Critical Care
Presented at the Academic Surgical Congress 2017

Principal component analysis of coagulation assays in severely injured children

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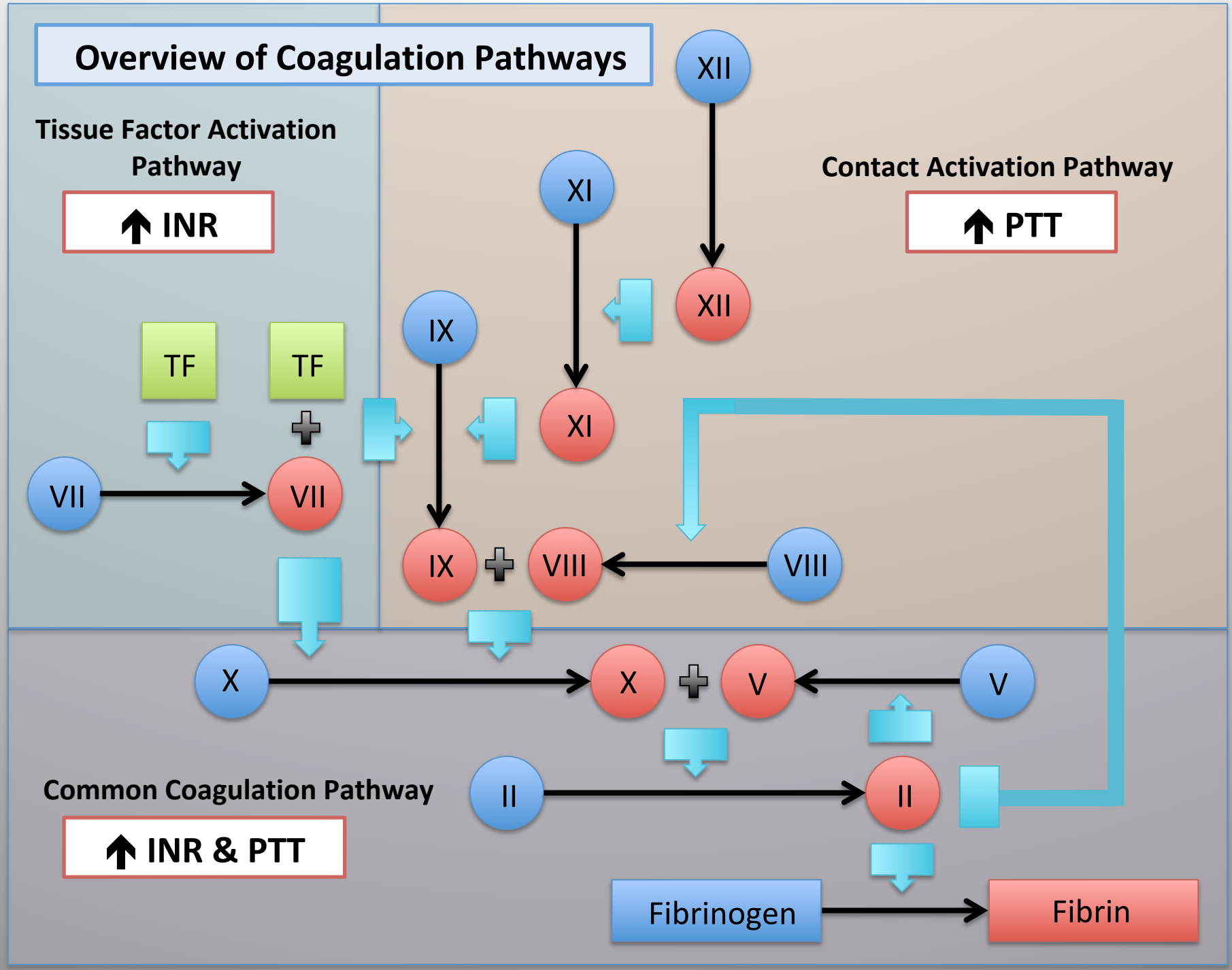
[a] Division of General Surgery and Trauma, Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA
[b] Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA

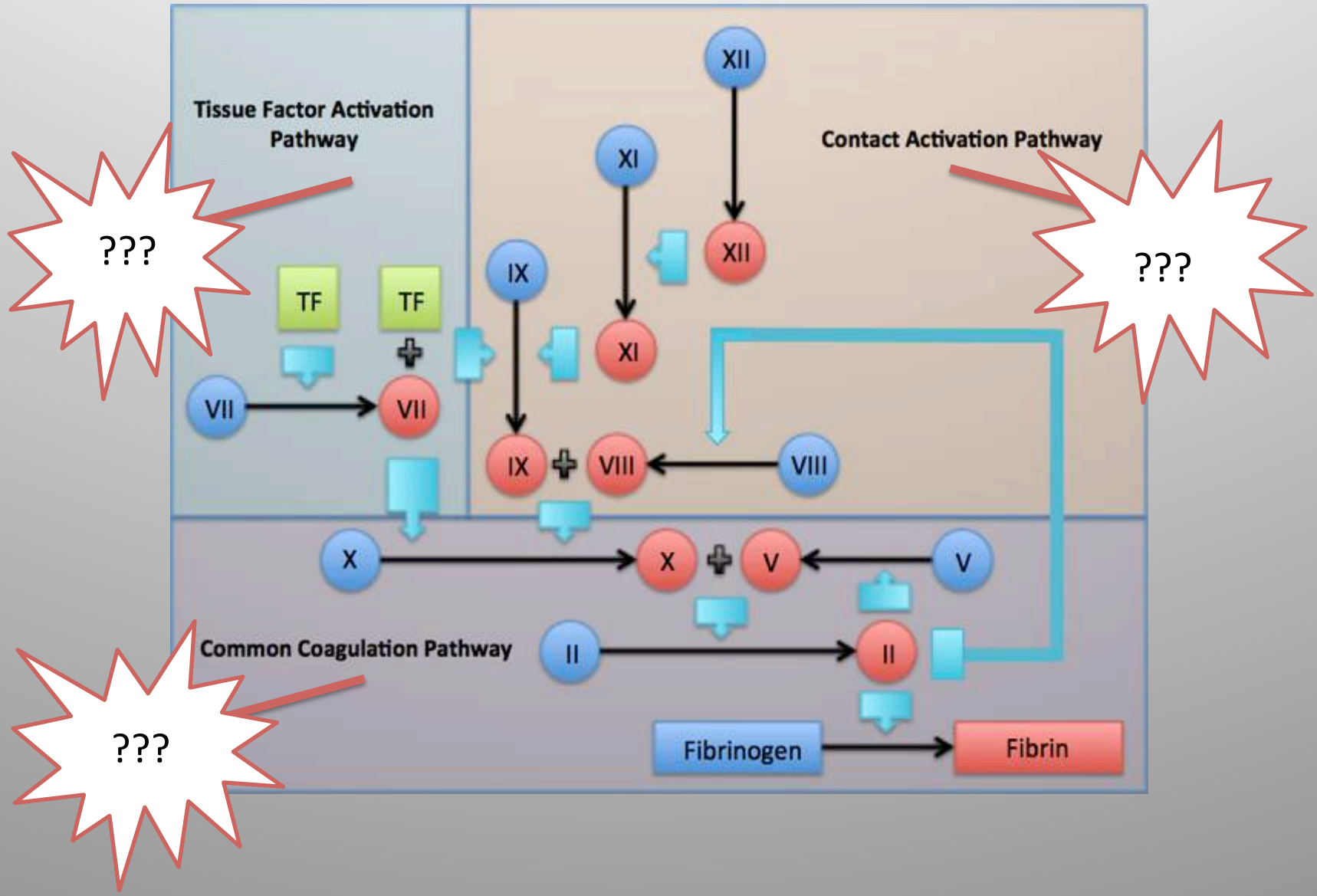
Table 4
Review of mechanisms and principal components in studies of critically injured patients.

Study	Cohort	Inclusion criteria	n	Mechanism			
				Fibrinolysis	Clot strength/ kinetics	Global factor depletion	Endothelial contribution
Leeper et al 2017[26]	Pediatric	Highest-level trauma activation	133	LY30, INR	Platelets, MA, K	ACT, K	
Chin et al 2014[22]	Adult	Massive transfusion	98	LY30	K, angle, MA, MRTG, TTG	ACT, TMRTG	
Kutcher et al 2013[23]	Adult	Highest-level trauma activation	163	Factor VIII(+), d-dimer, Protein C		Factors V, VII, VIII, IX, X, Protein C, antithrombin III	Factor VIII(−), Factor VII, Protein C
Kunitake et al 2017[24]	Adult	Highest-level trauma activation	876			Factors II, VII, IX, and X, Protein C	Factors V and VIII

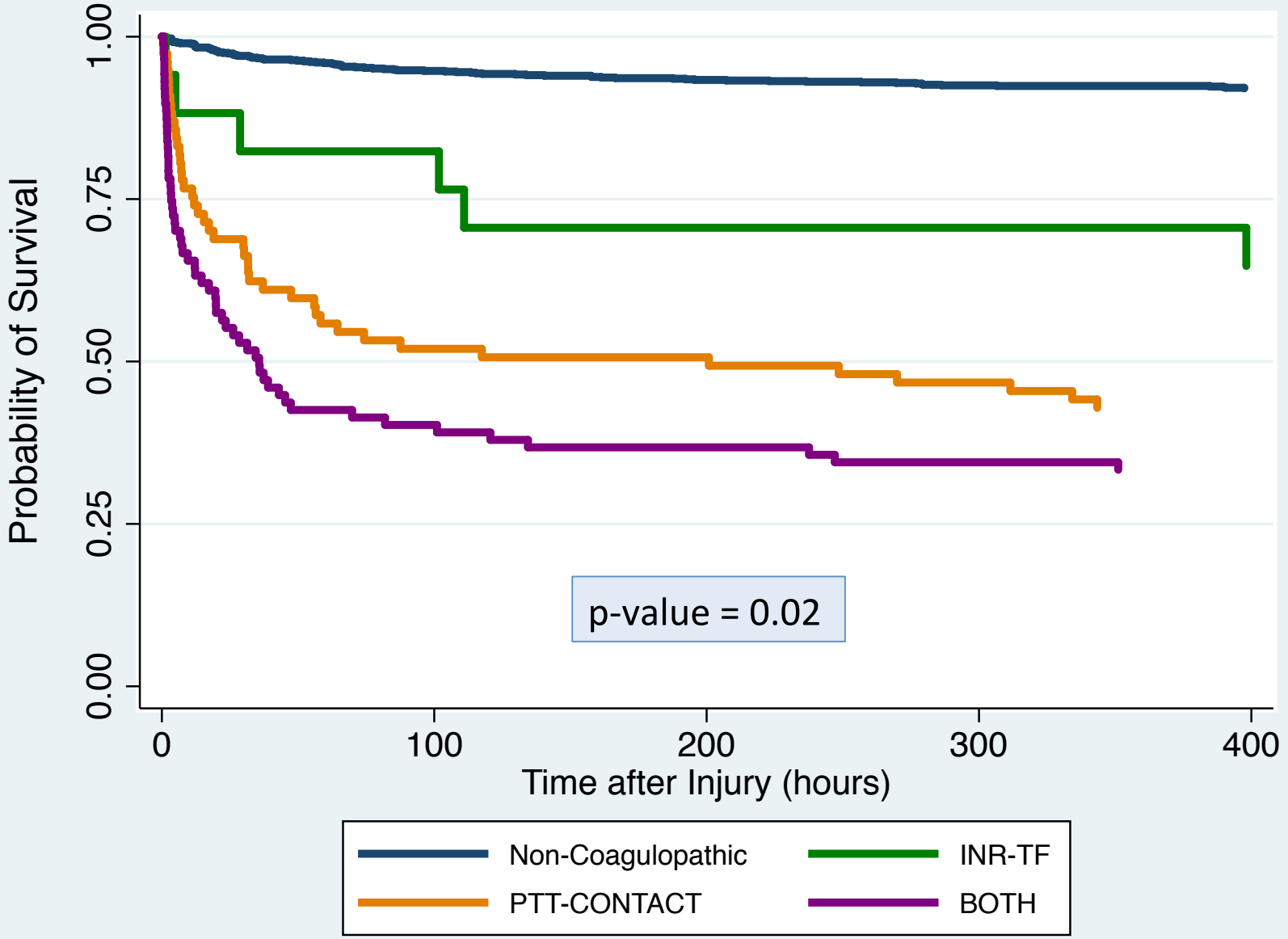
More Phenotypes:
Conventional Coagulation Tests


Overview of Coagulation Pathways
Tissue Factor Activation Pathway
INR
Contact Activation Pathway
PTT
XII
XI
XII
IX
TF
TF
XI
VII
VII
IX
VIII
VIII
X
X
V
V
Common Coagulation Pathway
INR & PTT
II
II
Fibrinogen
Fibrin

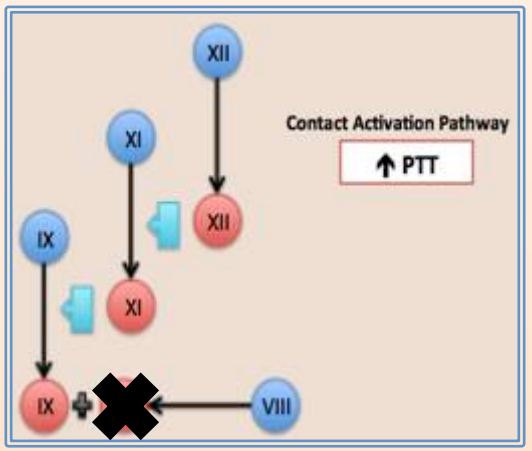
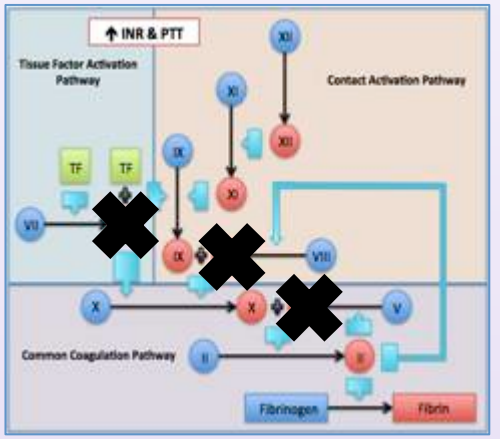
ATC- MULTIPLE PHENOTYPES REQUIRING PRECISION MEDCINE?



SURVIVAL AFTER INJURY BY COAGULOPATHIC GROUP



SUMMARY OF COAGULOPATHIC PHENOTYPES

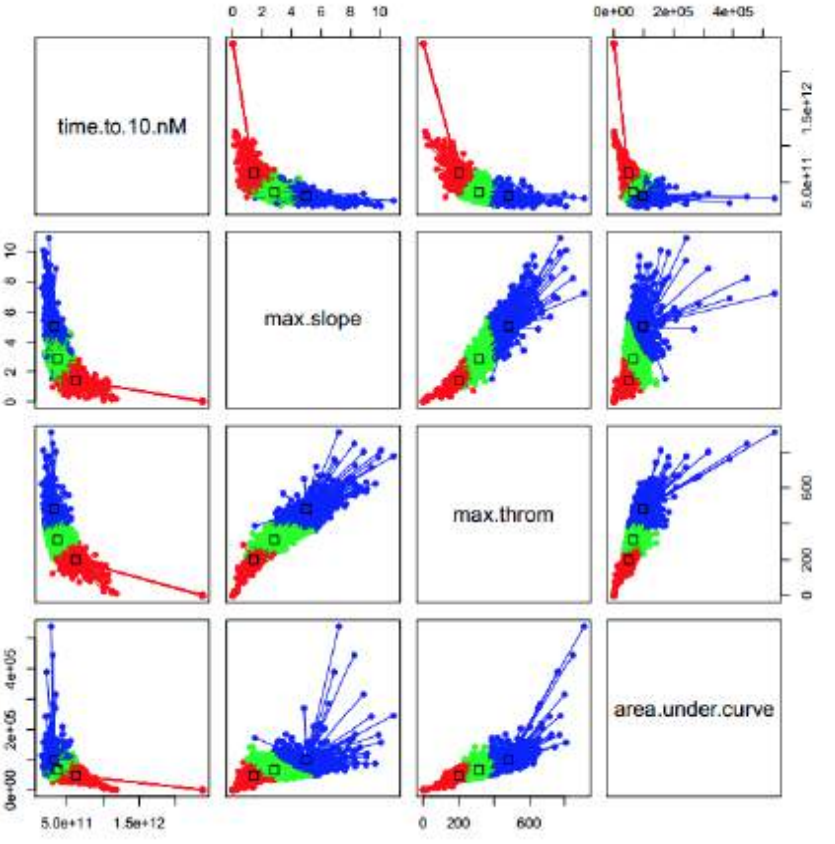
TARGET:			

		INR-TF	PTT-CONTACT	BOTH
Demographics			↓ GCS	↓ GCS
Coagulation Profile	↓	Factor VII Protein C	Factor VIII	Factors V, VII, VIII Protein C, Fibrinogen, Anti-thrombin III
	↑		D-dimer	D-dimer
Outcomes		↑ PRBC, FFP	↓ PRBC, FFP	↑ PRBC, FFP
		↑ Mortality	↑↑ Mortality	↑↑↑ Mortality
POTENTIAL THERAPY:		FFP rfVII APC Inhibitors	Cryoprecipitate rfVIII PCC	Multimodal: FFP, Cryoprecipitate, PCC, APC Inhibitors DVT ppx/surveillance

More Phenotypes:
More Complex Variables.

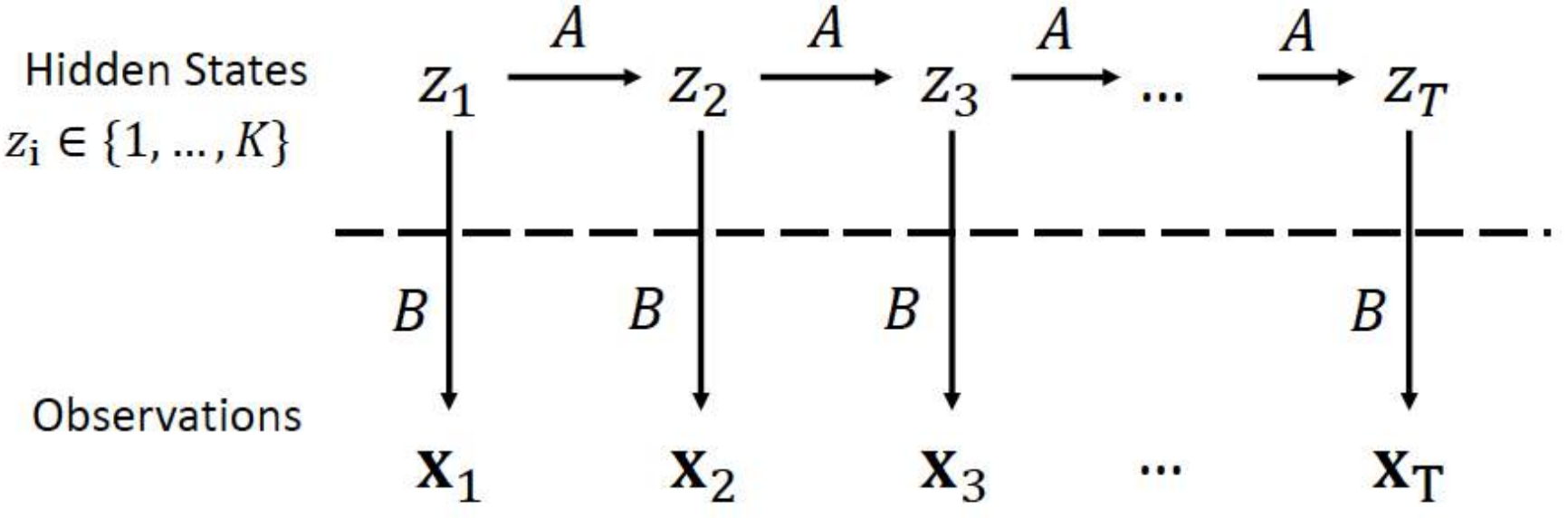
Phenotype Clustering

- Cluster 1: Factors depletion. High PTT, INR. Coagulopathic.
- Cluster 2: Medium PTT, PT. Factors in the middle. High head injury score.
- Cluster 3: High factors. Low PTT, INR. Relative healthy patients.



	Time to 10 nM	Max Slope	Max Throm	AUC (Throm)
C1	626.32	1.453e-09	2.0041e-07	4.8205e-05
C2	367.14	2.8317e-09	3.1334e-07	6.5896e-05
C3	316.07	5.0057e-09	4.842e-07	9.8347e-05

Hidden Markov Model

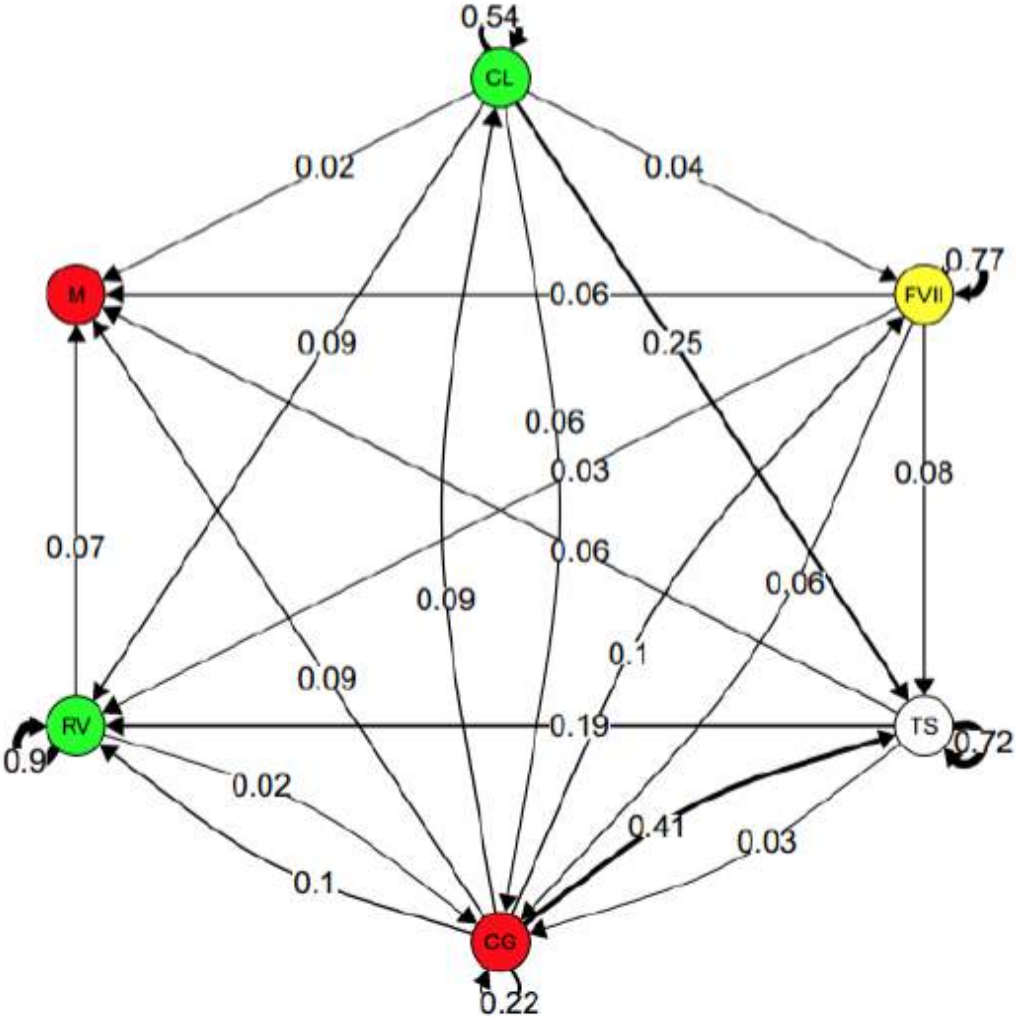


$$\theta \begin{cases} A & \text{Transition probability} & a_{ij} = P(z_{t+1} = i | z_t = j) \\ B & \text{Emission probability} & b_k = P(\mathbf{x}_t | z_t = k) \\ \pi & \text{Initial state distribution} & \pi_i = P(z_1 = i) \end{cases}$$

$$p(\mathbf{z}_{1:T}, \mathbf{x}_{1:T}) = p(\mathbf{z}_{1:T}) p(\mathbf{x}_{1:T} | \mathbf{z}_{1:T}) = \left[p(z_1) \prod_{t=2}^{T} p(z_t | z_{t-1}) \right] \left[\prod_{t=1}^{T} p(\mathbf{x}_t | z_t) \right]$$

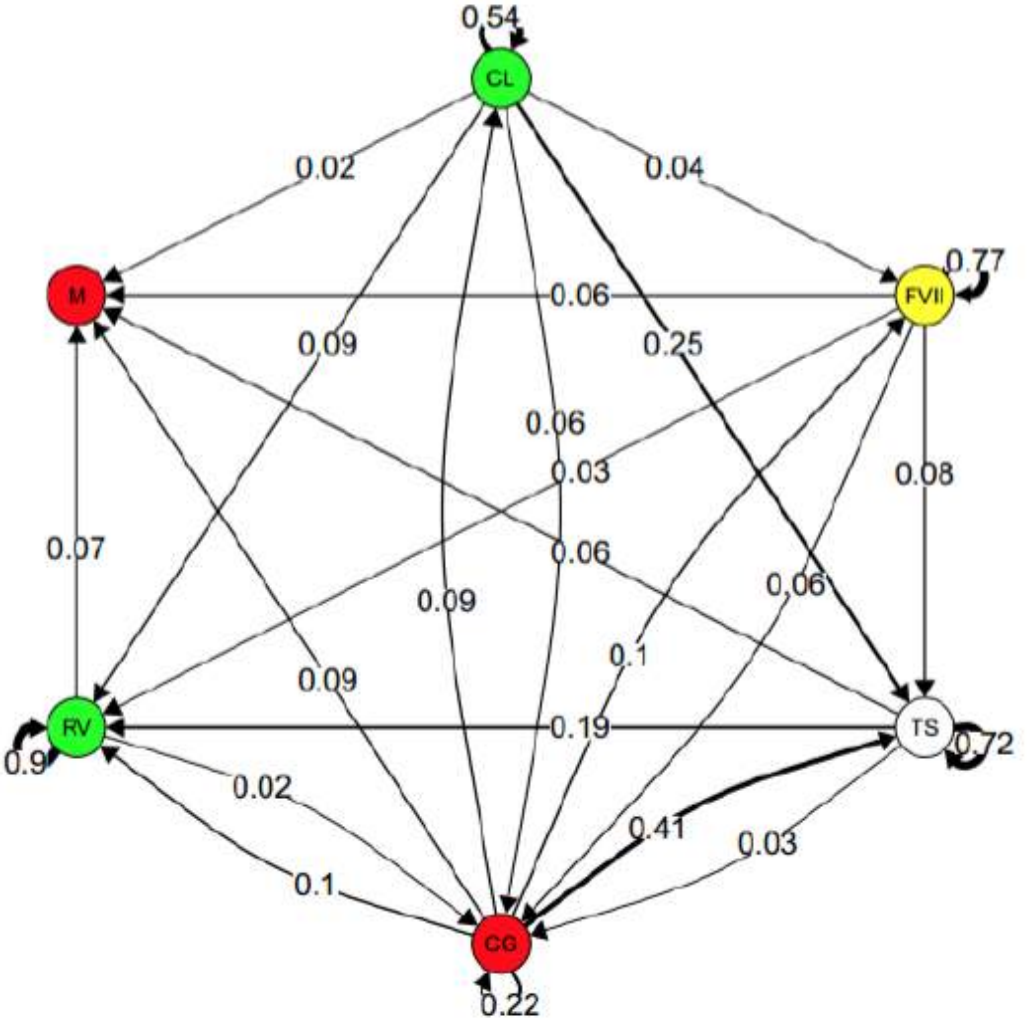
Hidden States Transitions

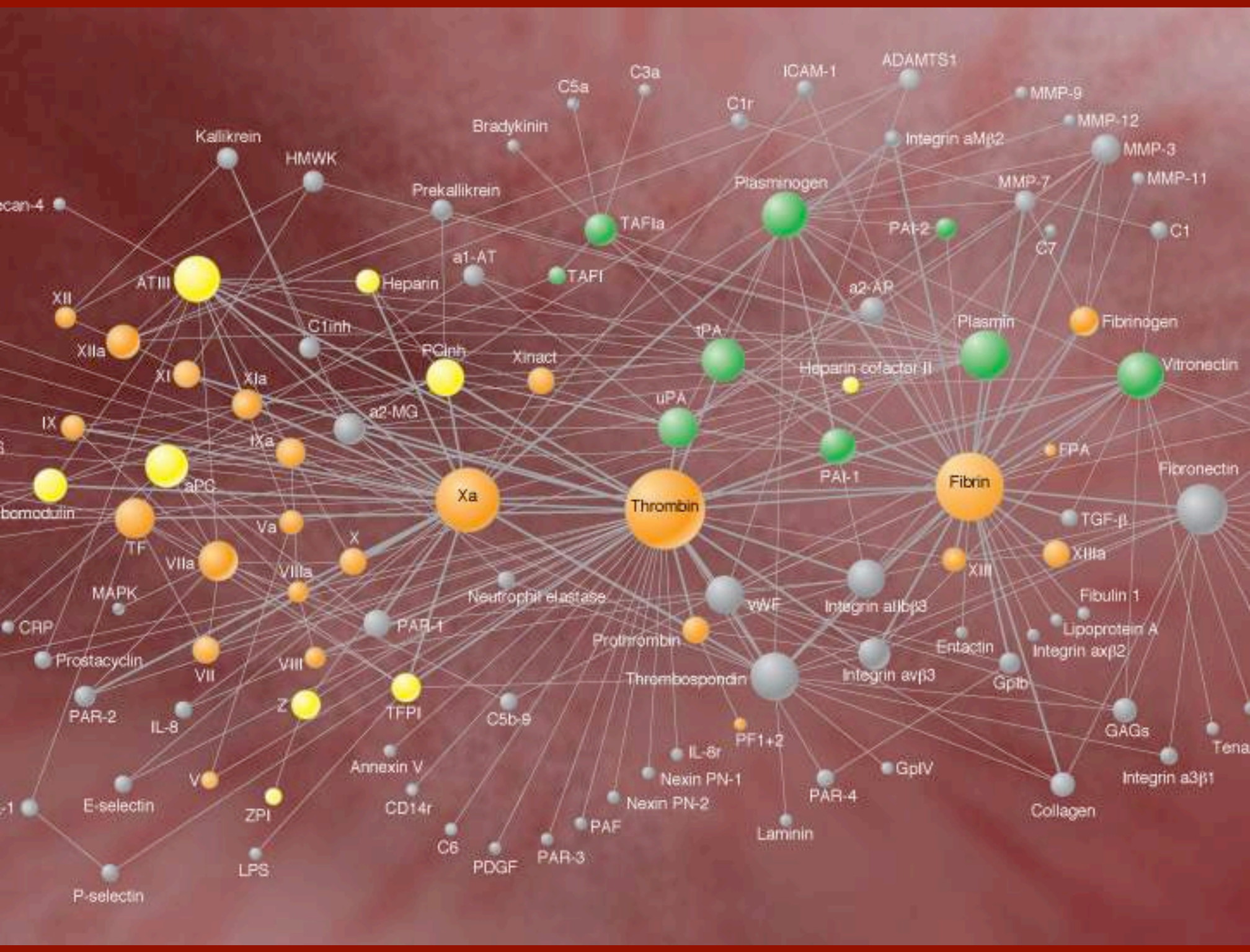
- State 1: Clotting State (CL)
- State 2: Factor VII State (FVII)
- State 3: Transition State (TS)
- State 4: Coagulopathic State (CG)
- State 5: Recovery State (RV)
- Mortality



Other Findings

- Main trajectories
  - Clotting state → Transition state → Recovery state
  - Coagulopathy state → Transition state → Mortality
- Critical states
  - Coagulopathy state
  - Transition state

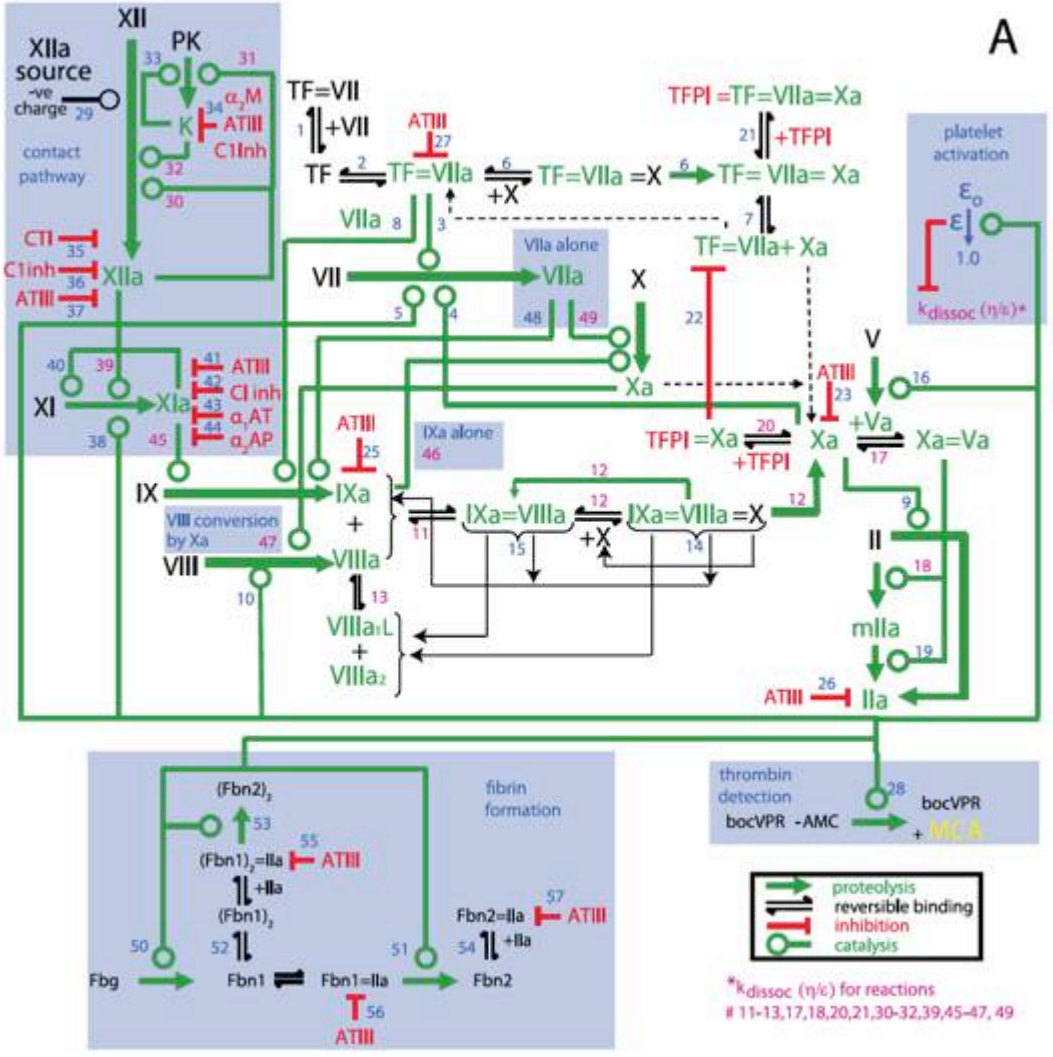



ADAMTS1
ICAM-1
C3a
C5a
C1r
MMP-9
MMP-12
Integrin aMβ2
MMP-3
MMP-11
Kallikrein
HMWK
Bradykinin
Prekallikrein
Plasminogen
MMP-7
TAFIa
PAI-2
C1
C7
a1-AT
TAFI
ATIII
Heparin
a2-AP
XII
C1inh
tPA
Plasmin
Fibrinogen
XIIa
PCInh
Xinact
Heparin cofactor II
Vitronectin
XI
XIa
uPA
a2-MG
IX
IXa
aPC
PAI-1
FPA
Fibronectin
Xa
Thrombin
Fibrin
TF
Va
X
TGF-β
XIIIa
VIIa
VIIIa
XIII
MAPK
Neutrophil elastase
vWF
Integrin αIIbβ3
Fibulin 1
CRP
PAR-1
Protrombin
Entactin
Lipoprotein A
Integrin axβ2
Prostacyclin
VII
VIII
Integrin avβ3
Gpib
PAR-2
IL-8
Z
TFPI
C5b-9
Thrombospondin
GAGs
PF1+2
IL-8r
Annexin V
GpIV
V
Nexin PN-1
Integrin a3β1
E-selectin
CD14r
Nexin PN-2
PAR-4
ZPI
PAF
Collagen
C6
Laminin
PDGF
PAR-3
LPS
P-selectin

Combining mechanism, prediction and targeted care.

2. Model Driven Dynamics

Building an autonomous controller: Coagulation control systems.


A
XII
XIIa source
-ve charge
contact pathway
PK
α2M
ATIII
C1inh
CTI
C1inh
ATIII
XIIa
XI
XIa
ATIII
CI inh
α1AT
α2AP
TF=VII
+VII
TF
TF=VIIa
+X
TF=VIIa =X
TF= VIIa= Xa
TFPI =TF=VIIa=Xa
+TFPI
platelet activation
ε0
ε
1.0
kdissoc (η/ε)*
VIIa
VII
VIIa alone
VIIa
X
Xa
TF=VIIa+ Xa
TFPI =Xa
+TFPI
Xa
V
+Va
Xa=Va
IX
IXa
IXa alone
VIII conversion by Xa
VIII
VIIIa
IXa=VIIIa
IXa=VIIIa =X
+X
VIIIa1L
+
VIIIa2
II
mIIa
IIa
fibrin formation
(Fbn2)2
(Fbn1)2=IIa
+IIa
(Fbn1)2
Fbn2=IIa
Fbg
Fbn1
Fbn1=IIa
Fbn2
thrombin detection
bocVPR -AMC
bocVPR
+ MCA
proteolysis
reversible binding
inhibition
catalysis
*kdissoc (η/c) for reactions
11-13,17,18,20,21,30-32,39,45-47, 49

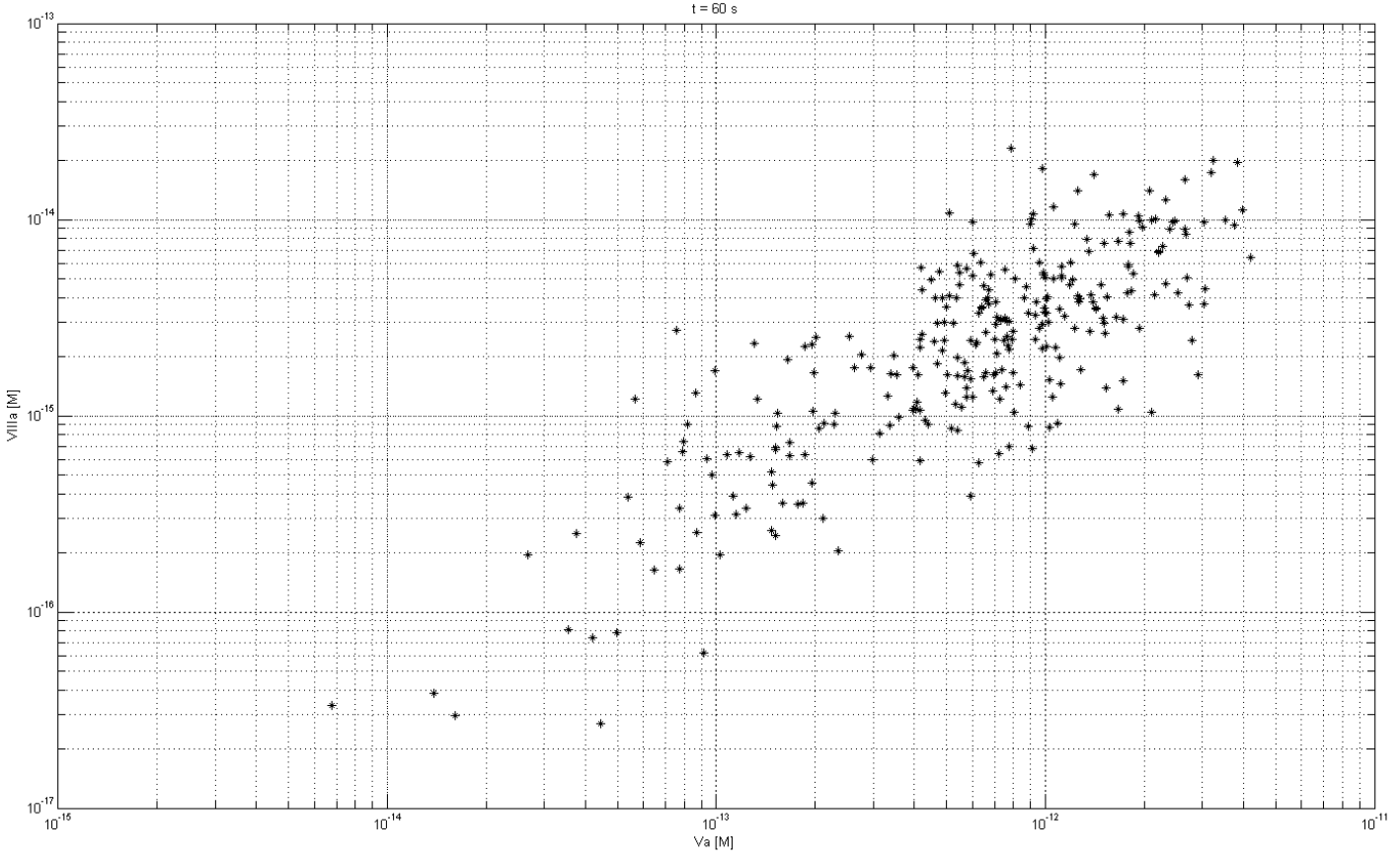
Hockin-Mann Chemical Kinetic Equations

1 TF + VII <1–2> TF═VII
2 TF + VIIa <3–4> TF═VIIa
3 TF═VIIa + VII-5 > TF═VIIa + VIIa
4 Xa + VII-6 > Xa + VIIa
5 IIa + VII-7 > IIa + VIIa
6 TF═VIIa + X <8–9> TF═VIIa═X-10 > TF═VIIa═Xa
7 TF═VIIa + Xa <11–12> TF═VIIa═Xa
8 TF═VIIa + IX<13–14>TF═VIIa═IX-15 > TF═VIIa + IXa
9 Xa + II-16 > Xa + IIa
10 IIa + VIII-17 > IIa + VIIIa
11 VIIIa + IXa <18–19> IXa═VIIIa
12 IXa═VIIIa + X <20–21> IXa═VIIIa═X-22 >
IXa═VIIIa + Xa
13 VIIIa <23–24> $VIIIa_1 \cdot L + VIIIa_2$
14 IXa═VIIIa═X-25 > $VIIIa_1 \cdot L + VIIIa_2$ + X + IXa
15 IXa═VIIIa-25 > $VIIIa_1 \cdot L + VIIIa_2$ + IXa
16 IIa + V-26 > IIa + Va
17 Xa + Va <27–28> Xa═Va
18 Xa═Va + II <29–30> Xa═Va═II-31 > Xa═Va + mIIa
19 mIIa + Xa═Va-32 > IIa + Xa═Va
20 Xa + TFPI <33–34> Xa═TFPI
21 TF═VIIa═Xa + TFPI <35–36> TF═VIIa═Xa═TFPI
22 TF═VIIa + Xa═TFPI-37 > TF═VIIa═Xa═TFPI
23 Xa + ATIII-38 > Xa═ATIII
24 mIIa + ATIII-39 > mIIa═ATIII
25 IXa + ATIII-40 > IXa═ATIII
26 IIa + ATIII-41 > IIa═ATIII
27 TF═VIIa + ATIII-42 > TF═VIIa═ATIII

- 34 states, 43 chemical kinetic equations. No Protein C or Activated Protein C effects.
- Rate constants aggregated from 2002 literature.
- Initial conditions specify mean plasma concentrations for proteins, with tissue factor (TF) variable.

Using the H-M Model

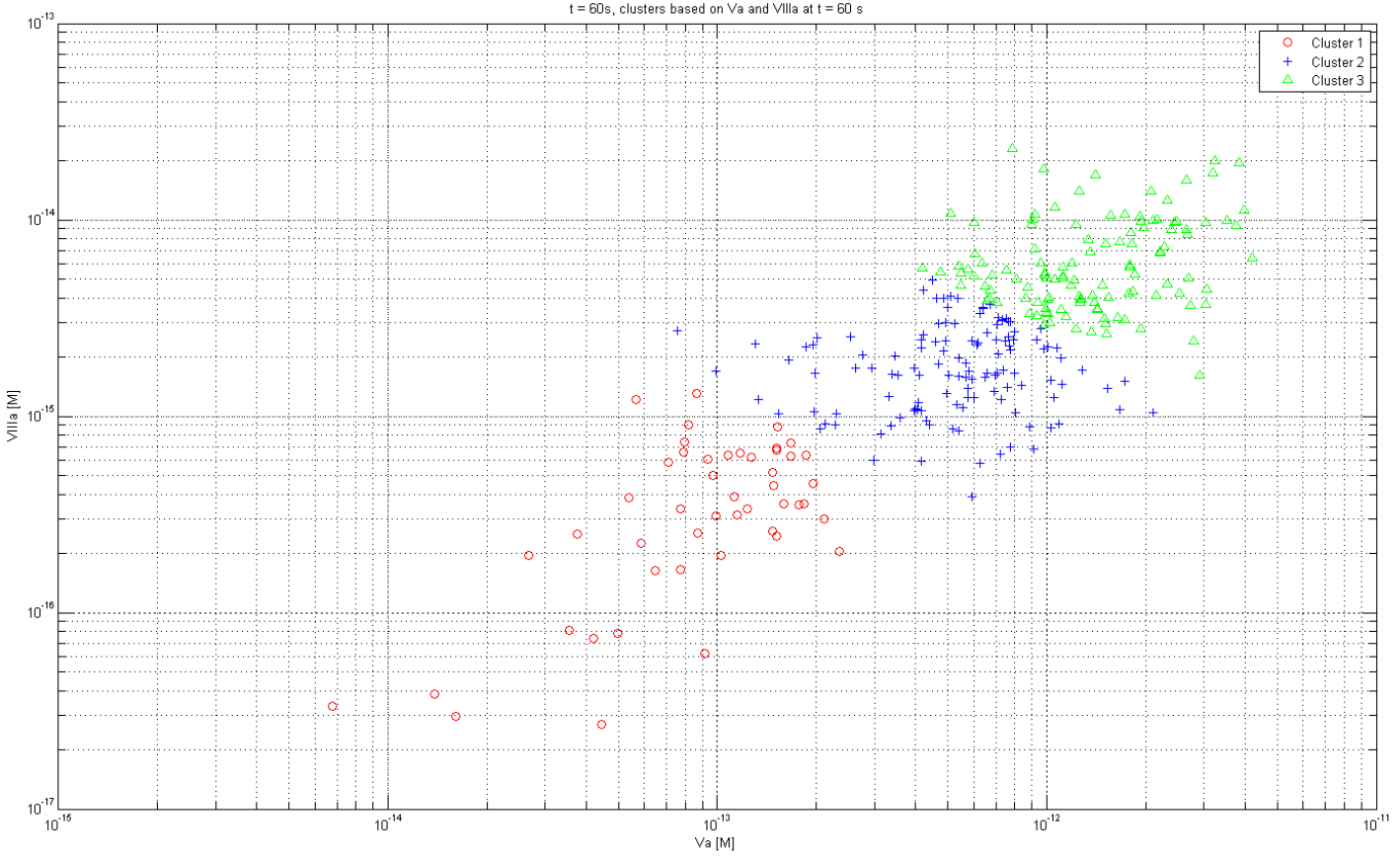
- Deploy the model to determine species concentrations 60s after measurements.



VIIIa [M] vs. Va [M] on a log-log scale, to check aPC effects.

Using the H-M Model

- Can cluster the output.



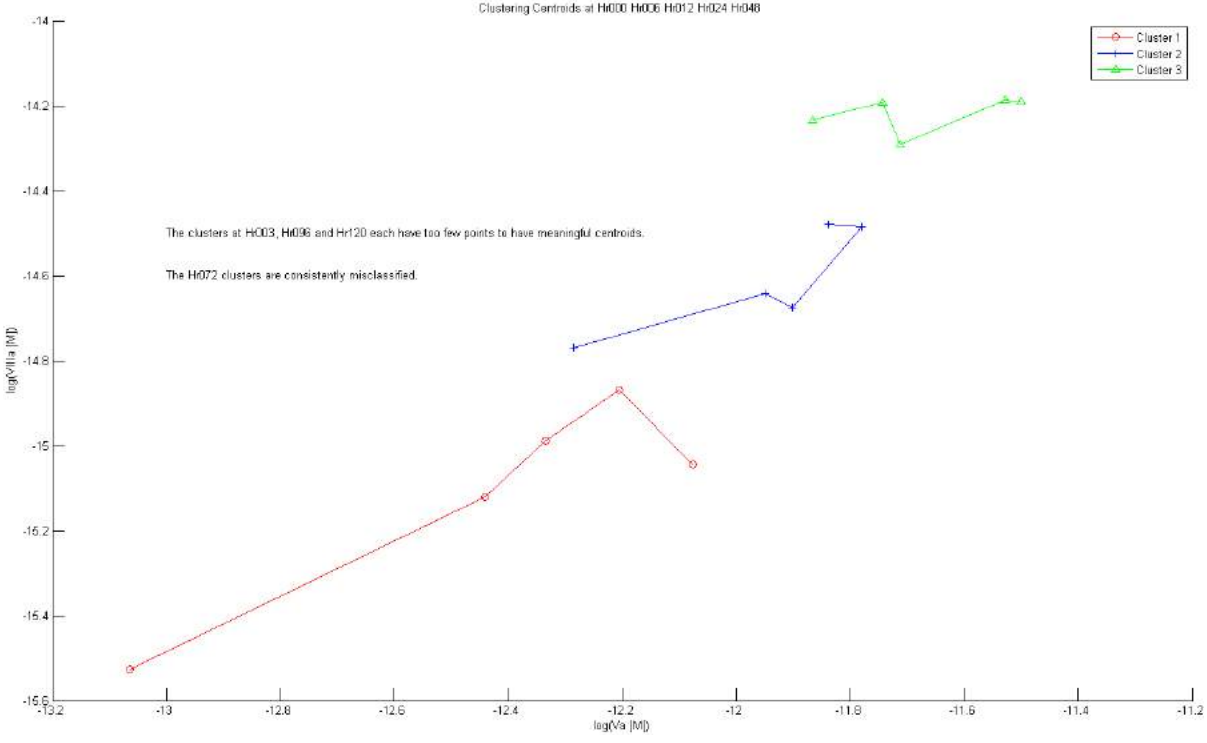
VIIIa [M] vs. Va [M] on a log-log scale with *k-Means* clusters.

Clustering Results

	Cluster 1 (Low 8/5) (n=48)	Cluster 2 (Medium 8/5) (n=125)	Cluster 3 (High 8/5) (n=118)	P-value
Age	46.7±24.2	45.3±19.0	38.2±18.0	0.006
BMI	26.4±4.5	28.0±6.2	26.8±4.9	0.138
%penetrating	29.2%	30.0%	42.7%	0.084
ISS	35.8±18.9	25.6±13.7	26.6±15.1	<0.001
BD	-8.9±6.7	-6.4±5.5	-6.4±5.9	0.038
GCS	5 (3-10)	8 (3-14)	9 (4-14)	0.051
Arrival temp	35.2±1.1	35.5±0.9	35.7±0.8	0.026
Prehosp. IVF	25 (0-200)	100 (0-300)	175 (34-500)	0.303
pH	7.23±0.17	7.28±0.14	7.27±0.15	0.134
INR	1.25 (1.1-1.6)	1.1 (1.0-1.2)	1.1 (1.1-1.2)	0.004
PT	16 (14.4-20.2)	14.5 (13.6-15.8)	14.4 (13.5-15.4)	<0.001
PTT	32.5 (28.6-49.8)	28.4 (26.1-33.1)	26.9 (25.0-30.0)	<0.001
aPC	13.0 (3.6-20.2)	2.6 (1.0-11.2)	3.1 (1.5-12.3)	0.010
24h RBC	4 (0-14)	1 (0-5)	2 (0-5)	0.014
24h FFP	3 (0-11)	0 (0-2)	0 (0-4)	0.013
24h plt	0 (0-2)	0 (0-0)	0 (0-0)	0.043
Hospital LOS	8 (2-25)	8 (2-24)	8 (3-24)	0.780
ICU LOS	4 (2-13.5)	4 (2-12)	4 (2-11)	0.946
Vent-free days	0 (0-10)	14 (0-26)	19 (0-26)	0.001
Mortality	58.3.%	30.9%	27.1%	0.001

Clustering Results

- Can cluster the 60s-after-measurement output for measurements at other times: 3h, 6h, 12h, 24h, 48h, 72h, 96h, 120h.



k-Means cluster centroids move up and to the right, in the direction of aPC improvement.

COAGULATION

Targeted clinical control of trauma patient coagulation through a thrombin dynamics model

Amor A. Menezes,[1,2] Ryan F. Vilardi,[3] Adam P. Arkin,[1,2,4]* Mitchell J. Cohen[5,6]*

We present a methodology for personalizing the clinical treatment of severely injured patients with acute traumatic coagulopathy (ATC), an endogenous biological response of impaired coagulation that occurs early after trauma and shock and that is associated with increased bleeding, morbidity, and mortality. Despite biological characterization of ATC, it is not easily or rapidly diagnosed, not always captured by slow laboratory testing, and not accurately represented by coagulation models. This lack of knowledge, combined with the inherent time pressures of trauma treatment, forces surgeons to treat ATC patients according to empirical resuscitation protocols. These entail transfusing large volumes of poorly characterized, nontargeted blood products that are not tailored to an individual, the injury, or coagulation dynamics. Massive transfusion mortality remains at 40 to 70% in the best of trauma centers. As an alternative to blunt treatments, time-consuming tests, and mechanistic models, we used dynamical systems theory to create a simple, biologically meaningful, and highly accurate model that (i) quickly forecasts a driver of downstream coagulation, thrombin concentration after tissue factor stimulation, using rapidly measurable concentrations of blood protein factors and (ii) determines the amounts of additional coagulation factors needed to rectify the predicted thrombin dynamics and potentially remedy ATC. We successfully demonstrate in vitro thrombin control consistent with the model. Compared to another model, we decreased the mean errors in two key trauma patient parameters: peak thrombin concentration after tissue factor stimulation and the time until this peak occurs. Our methodology helps to advance individualized resuscitation of trauma-induced coagulation deficits.

INTRODUCTION

Trauma is the leading cause of death and disability between the ages of 1 and 44 (*1*), with bleeding contributing to the vast majority of these deaths (*2*). Such hemorrhage is a clinical problem that is complicated by an endogenous biological response called acute traumatic coagulopathy (ATC) (*3*). ATC results in impaired coagulation, increased bleeding, greater transfusion needs, and a fourfold increase in mortality (*3*). After the initial phase of hypocoagulobility, ATC patients often dynamically transition to a hypercoagulable thrombotic state manifested by excessive clotting (*3*). The resulting deep vein thrombosis, myocardial infarction, stroke, and organ failure (*4*) all contribute to an extremely poor outcome in patients who survive their initial injuries.

Despite considerable research (*4*) on the molecular mechanisms of ATC, there remains a mechanistic and predictive knowledge gap that stems from an inadequate understanding of coagulation mechanisms after an injury and a lack of adequate prediction and real-time decision support for clinicians who care for the severely injured. These failings impede improvements to urgent resuscitation. Thus, there is a need to characterize coagulation mechanisms in trauma patients and to use this characterization to improve the precision of individual treatments.

In the absence of dynamic diagnostics and decision support, current trauma resuscitation practices (*4*) center on the nontargeted repair of the coagulation cascade (*5*) (Fig. 1A) and the production of its principal protein thrombin through the transfusion of large volumes of poorly characterized fresh-frozen plasma containing multiple clotting proteins and inhibitors in concentrations that vary from unit to unit. These urgent-care therapies indiscriminately actuate many interacting elements of the coagulation process, resulting in variable untargeted treatment for every patient and with every administration, which is further exacerbated by a lack of clarity about treatment effects on the patient's physiological and biological trajectories resulting from the missing diagnostics and decision support. Such blunt treatment is often either not enough (ATC and bleeding continue) or too much (thrombosis occurs). Both of these extremes contribute to dysregulated inflammation and poor outcomes (*4*). The mortality from massive transfusion remains at 40 to 70% in the best of trauma centers (*6*). Retrospective (*7*) and prospective (*8*) studies connect the blunt addition of fresh-frozen plasma to poor outcomes, even when the plasma is augmented with empiric ratios of platelets and red blood cells. Transfusion of fresh-frozen plasma is independently associated with a higher risk of multiple organ failure and poor outcomes in patients with hemorrhagic shock (*9*). Meanwhile, individual interventions consisting of personalized blood protein factor concentrations that are tailored to specific clotting perturbations have been shown to be beneficial (*4*), although no consensus yet exists on the amount and type of coagulation factors to administer. There is, however, a clinical desire for specific blood products to treat trauma coagulopathy (*10*). In sum, in an era of increasing personalized medicine, there is an urgent need for targeted, patient-specific trauma coagulation therapies.

Current diagnostics and decision support suffer from a dearth of patient-specific coagulation measurements. Although clinical practice uses several global markers [international normalized ratio (INR), partial thromboplastin time (PTT), prothrombin time (PT), platelet count, fibrinogen concentration, etc.] to diagnose the presence of ATC, these conventional coagulation tests are not enough to tailor a specific intervention and support only the decision to administer plasma or not. Cell-based viscoelastic tests are insufficiently predictive, and their use in resuscitation algorithms also results in nontargeted treatment. Moreover,

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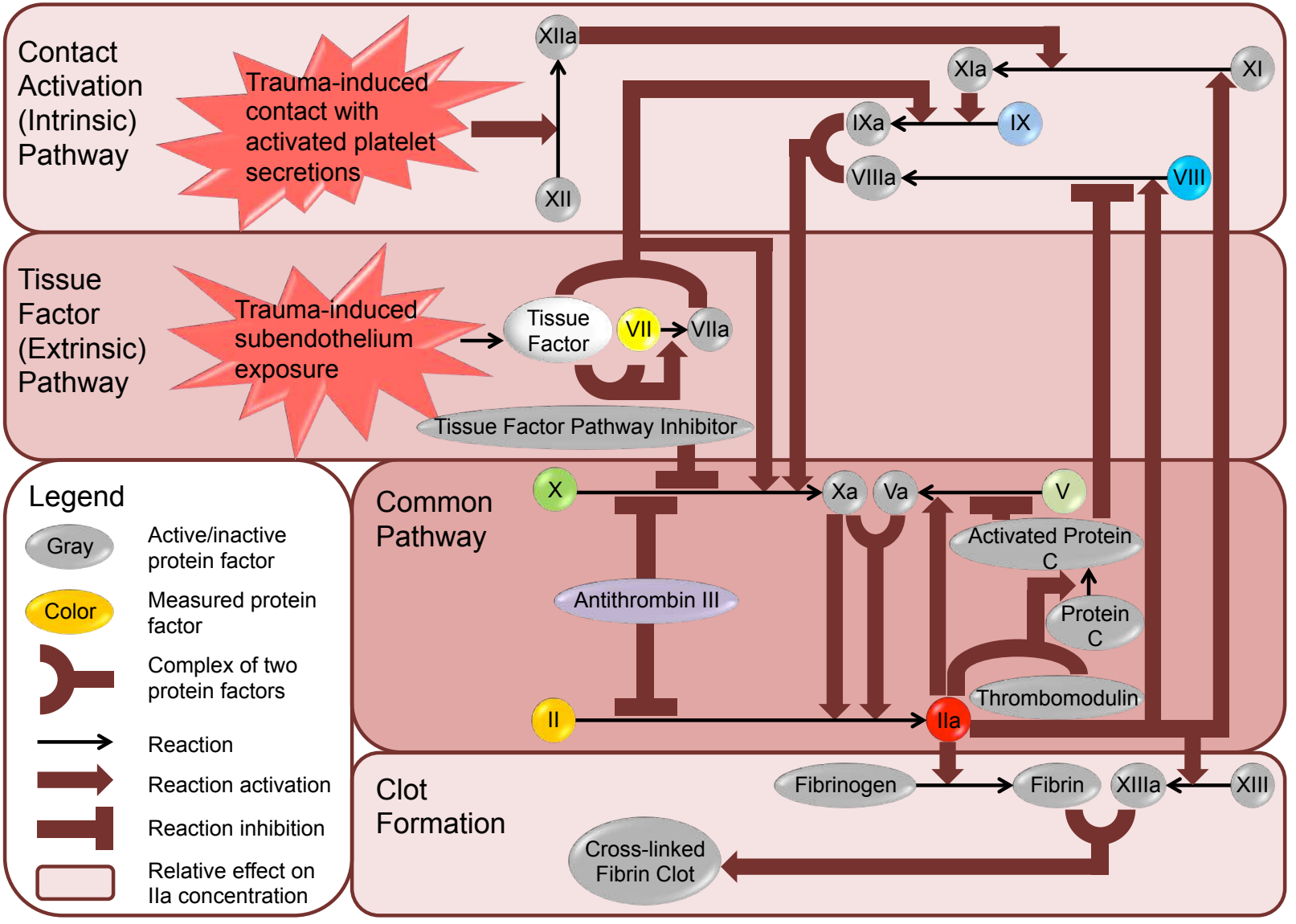
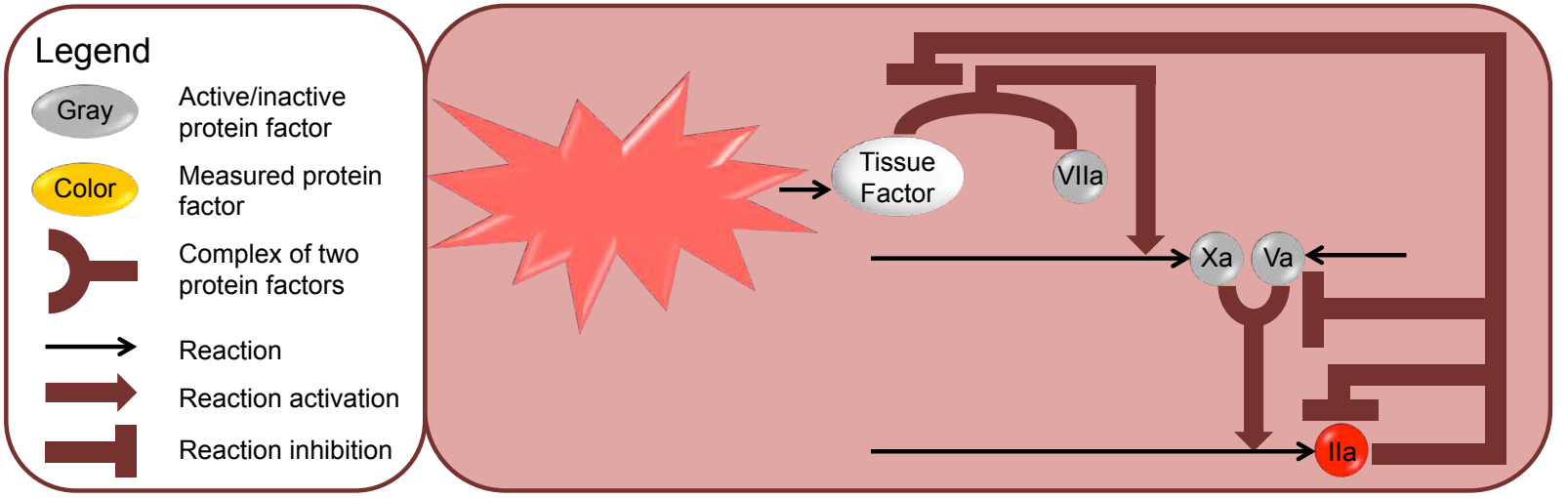
Current Understanding: Coagulation Cascade



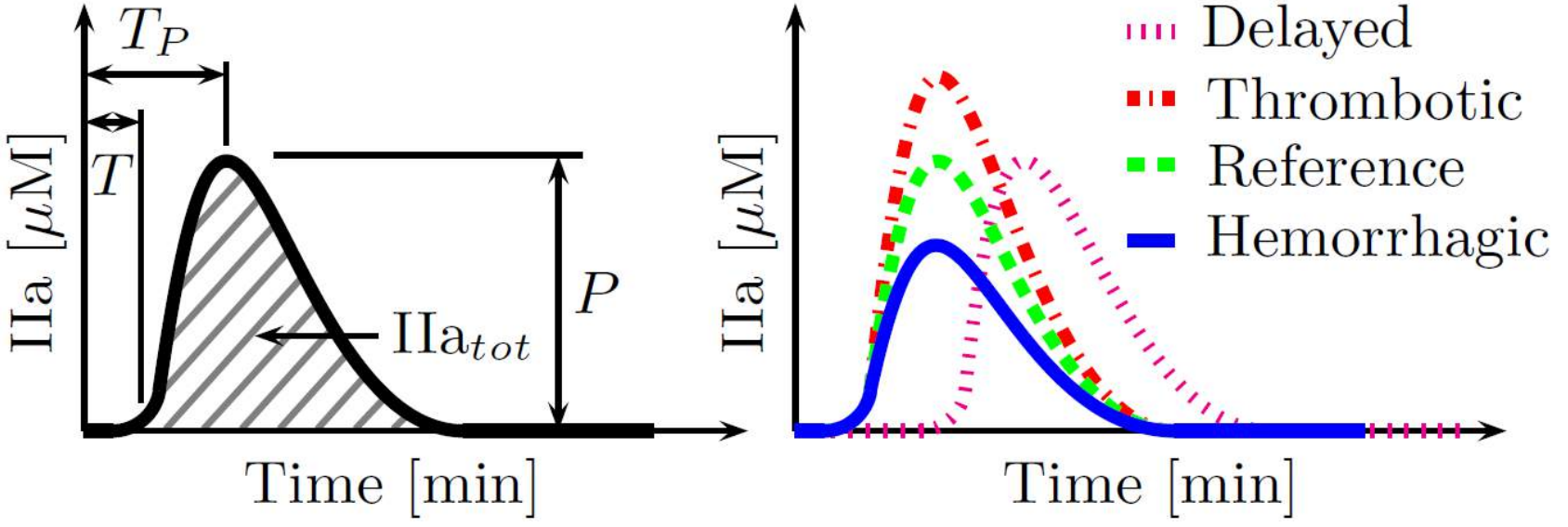
Claim: Possible to Simplify



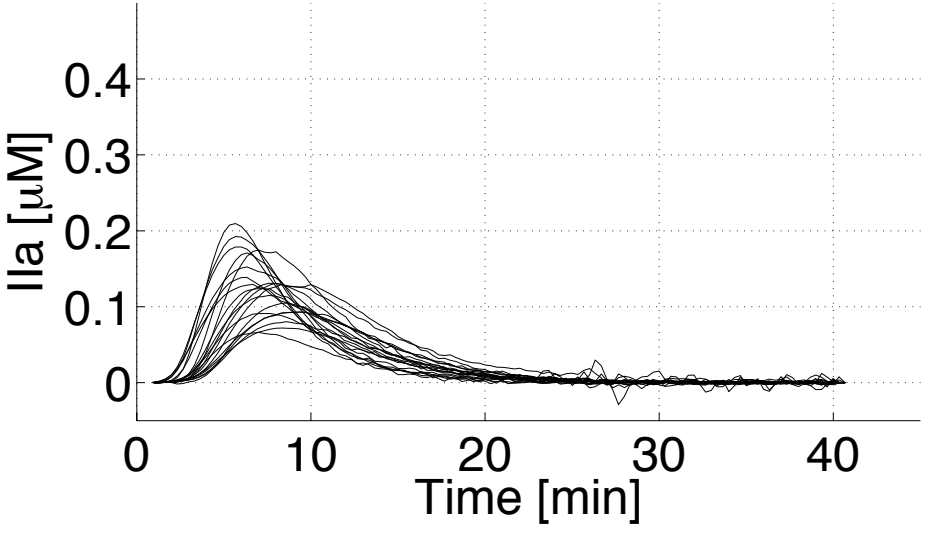
- Dynamical System Input: Tissue Factor
- Dynamical System Output: Thrombin
- Need an input-to-output measurement.

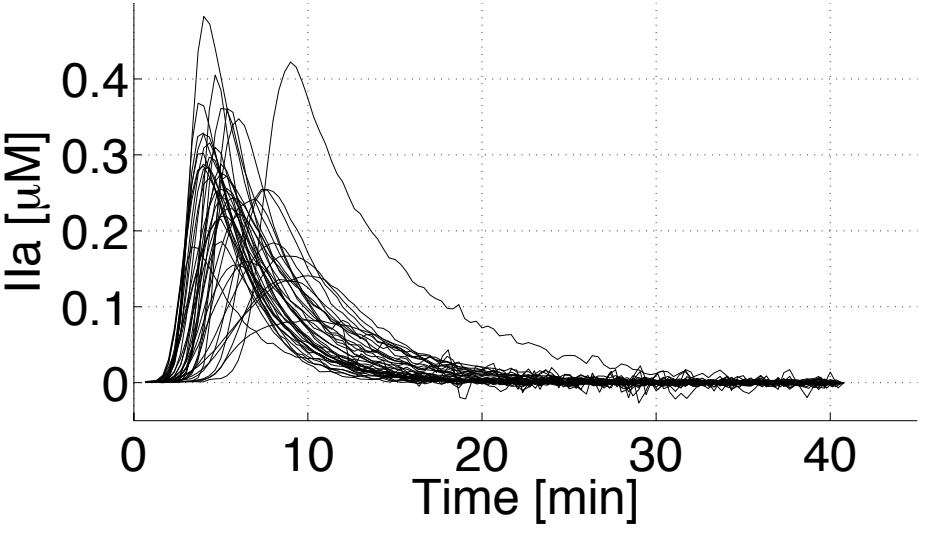
Thrombin Measurement

- The Calibrated Automated Thrombogram (CAT) is a fluorogenic assay that measures the time-history of thrombin generation in a blood sample upon the addition of (typically 5pM of) tissue factor.



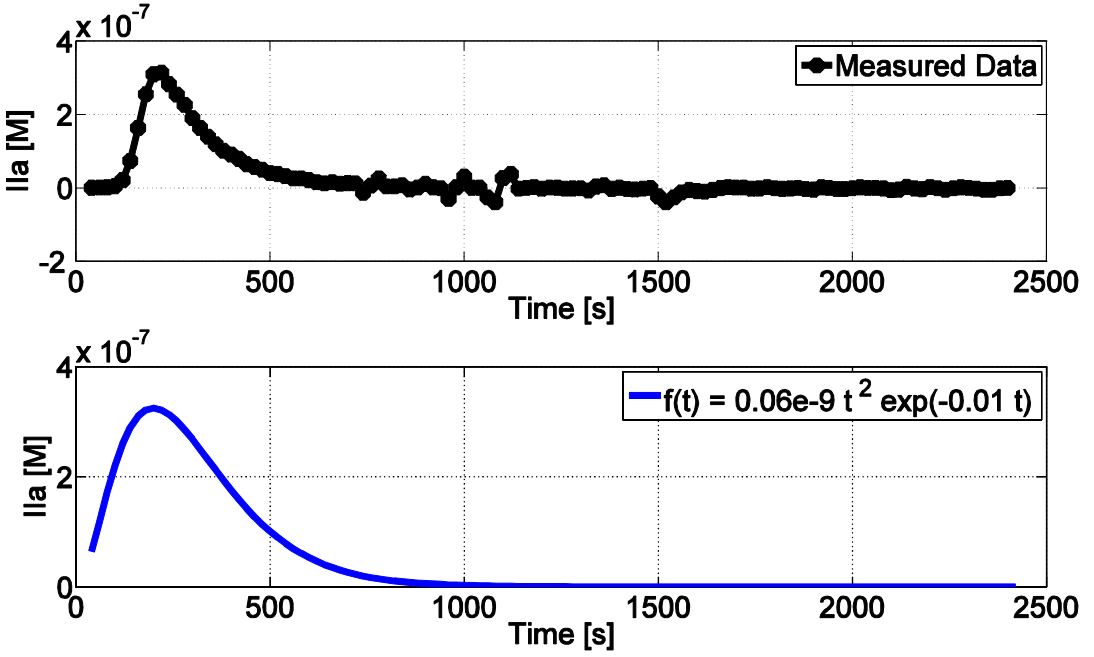
Normal vs. Trauma CATs





- Can we emulate trajectories with a single-input single-output thrombin dynamical system model with a separable delay for treatment guidance? What kind of model?

Building a Black-Box Model



- Can approximate a CAT peak.
- Suppose we choose the following non-delayed function as first approximation:

$$y(t) = \beta\, t^2\, e^{-\alpha t}$$

- t^2 → three states.

- Look at output in frequency domain as the result of some dynamical system:

$$Y(s) = \frac{2\beta}{(s+\alpha)^3} = \frac{2\beta}{s^3 + 3\alpha s^2 + 3\alpha^2 s + \alpha^3}$$

Building a Black-Box Model: 3 states, 5 pars.

- Suppose input is a (unit) impulse, *U(s)* = 1:

$$\frac{Y(s)}{U(s)} = \frac{2\beta}{(s+\alpha)^3} = \frac{2\beta}{s^3 + 3\alpha s^2 + 3\alpha^2 s + \alpha^3}$$

- System transfer function, including delay:

$$\frac{Y(s)}{U(s)} = \frac{b}{s^3 + a_2 s^2 + a_1 s + a_0} e^{-sT}$$

Building a Black-Box Model: Traditional Form

$$\frac{Y(s)}{U(s)} = \left(\frac{Kp}{s+p}\right)\left(\frac{\omega_n^2}{s^2 + 2\zeta\omega_n s + \omega_n^2}\right)e^{-sT}$$

- Define

$\sigma = \zeta\omega_n$ and $\omega_d = \omega_n\sqrt{1-\zeta^2}$ (i.e., $\omega_n^2 = \sigma^2 + \omega_d^2$), and let

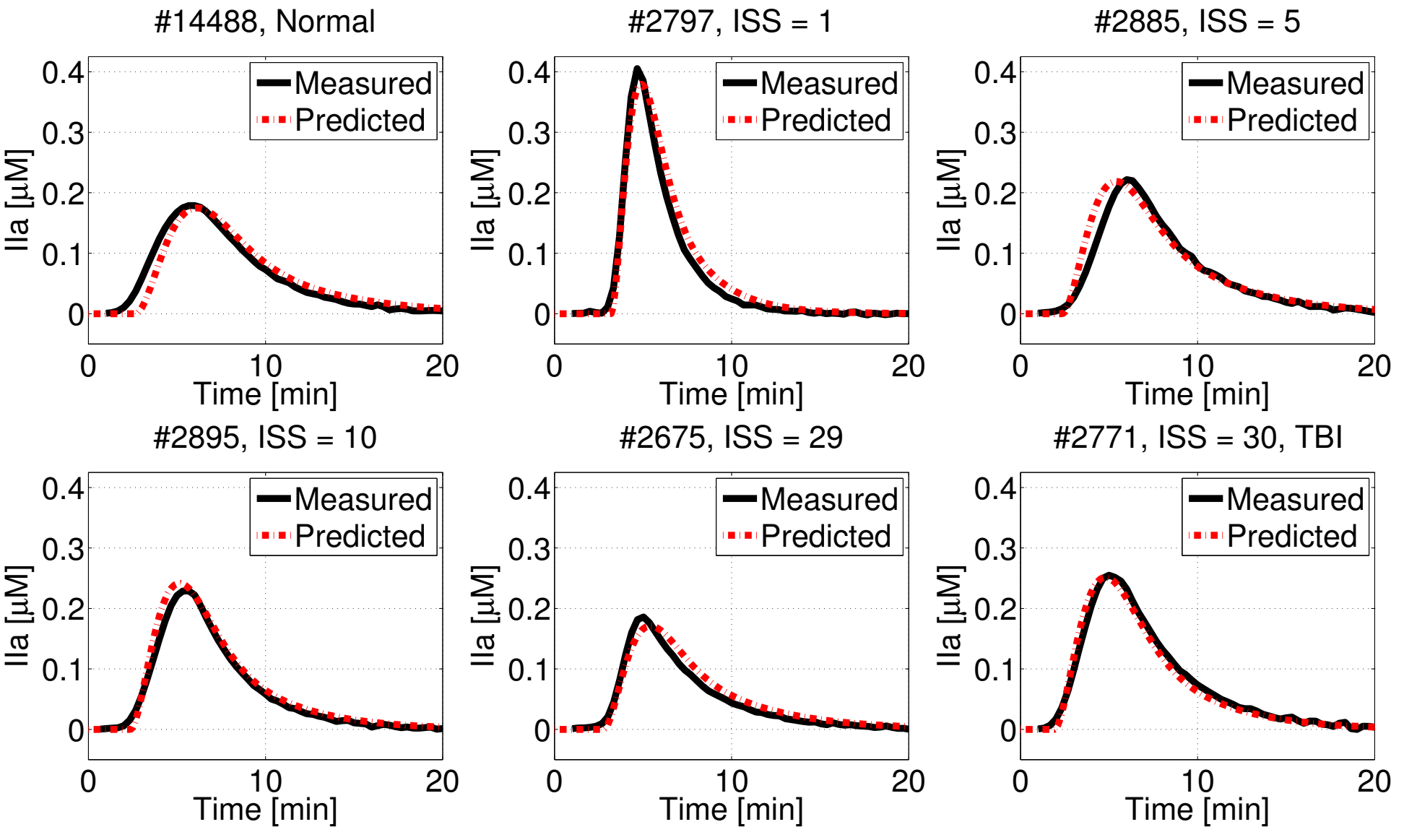
$A = \frac{Kp\omega_n^2}{p^2 - 2\zeta\omega_n p + \omega_n^2}$; $B = \frac{-Kp\omega_n^2}{p^2 - 2\zeta\omega_n p + \omega_n^2}$; $C = \frac{Kp\omega_n^2(p - 2\zeta\omega_n)}{p^2 - 2\zeta\omega_n p + \omega_n^2}$;

$D = \left(B\cos\left(\omega_d\left(t-T\right)\right) + \frac{C-\sigma B}{\omega_d}\sin\left(\omega_d\left(t-T\right)\right)\right)$. Then each fitted time-delayed CAT unit impulse response is given by

$$y(t) = \begin{cases} 0 & \text{if } t < T; \\ \left(Ae^{-p(t-T)} + De^{-\sigma(t-T)}\right)1(t-T) & \text{if } t \geq T, \end{cases}$$

for some p, ζ, ω_n and T, computed from a_2, a_1, a_0 and T.

Performance

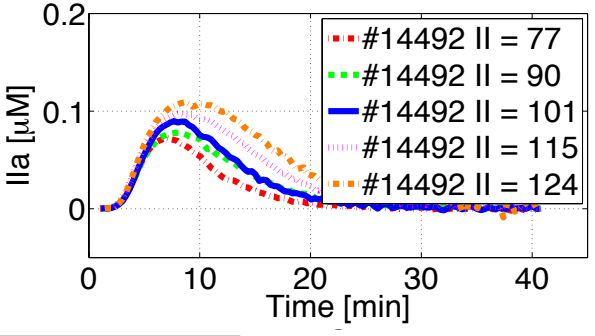


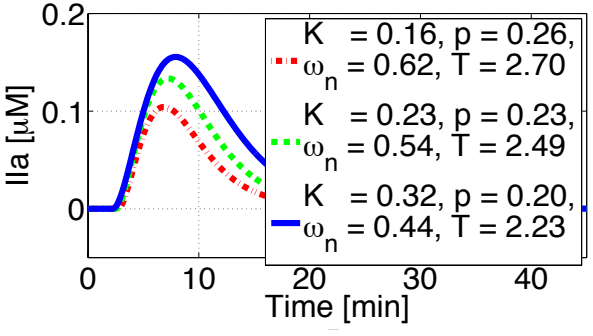
Targeted Clinical Control of Trauma Patient Coagulation Through a Thrombin Dynamics Model

Amor Menezes, Ryan Vilardi, Adam Arkin and Mitchell Cohen (UCB/LBNL, UCSF/SFGH)

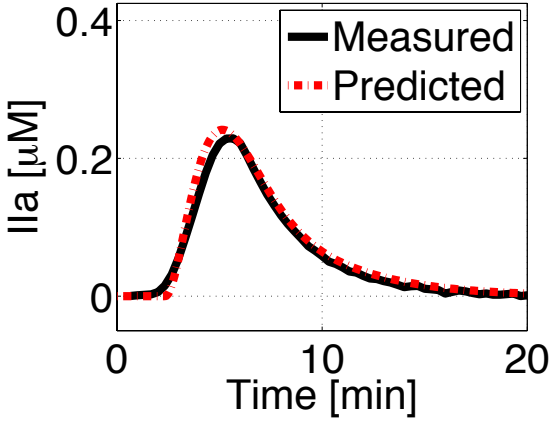
Benefit/Results

Parameters exactly capture behavior caused by protein factor addition (e.g., factor II to normal plasma)

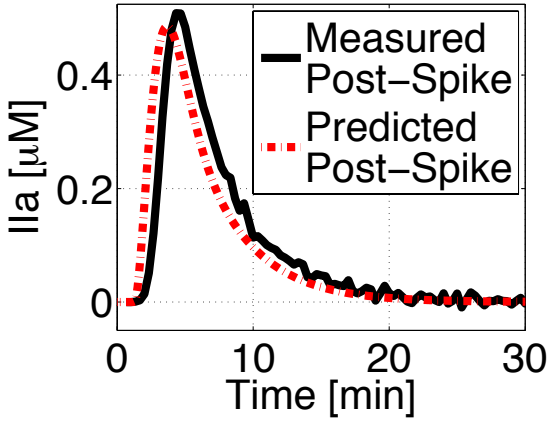




Initial protein factor concentrations can exactly predict a trauma patient CAT (e.g., for a moderate Injury Severity Score)



For this patient's plasma, after adding concentrations of factors II, VIII, X, we can still correctly predict the moved CAT



Have proved the likelihood of authority (at least *in vitro*) to achieve a standard desirable CAT trajectory.

Challenge/Computing Needs

1. Larger study to improve parametric inference and better validate predictions
   i. More data
   ii. Data-model reconciliation
2. Computer/model-aided investigation of controllability, control authority
3. Extensions of model's applicable range

Precision Medicine

British Journal of Hospital Medicine

November 2014

'Big data' approaches to trauma outcome prediction and autonomous resuscitation

Massive clinical digital data routinely collected by high throughput biomedical devices provide opportunities and challenges for optimal use. This article discusses how such data are used in learning prediction models at level 1 trauma centres to support decision making in trauma patients.

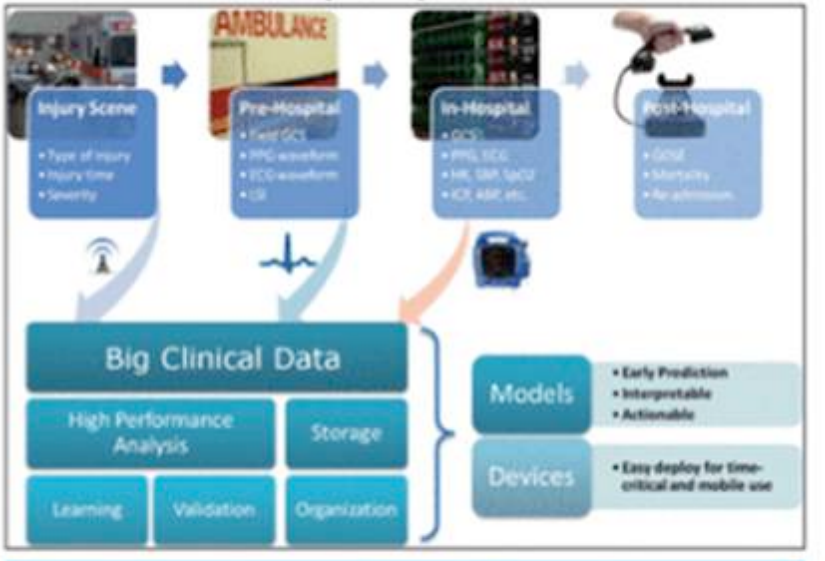
In 2011, the IBM Watson supercomputer beat two human contestants in the television game show *Jeopardy!*, empowered by 2880 processo 2013). After its impressive perfor IBM's Watson has made conque objective, and generated new idea be harnessed with supercomputin health. The big data analysis ph volumes of data analysed at high v sources (Laney, 2001). The goal efforts applied to health care is health information and recognize comes to develop actionable ther

In the clinical realm, the volu logical patient data has proliferat computer hardware and medical fidelity data are streamed into ph care planning, clinical decision su ment and remote patient moni extracting useful and actionable patient data also requires conside used to store, manage and anal Those techniques are far beyon tional database and spreadsheet-b common medical knowledge and of physiological signals and othe medicine considers these techniq develop combat casualty aut (Palmer, 2010; DuBose et al, 2 time field decision-making (Prov

For the purposes of demonstra eficial application, this article de 2 years, we may achieve the unre

and waveforms), radiological images, text (medical records, clinical notes), and other important data (e.g.

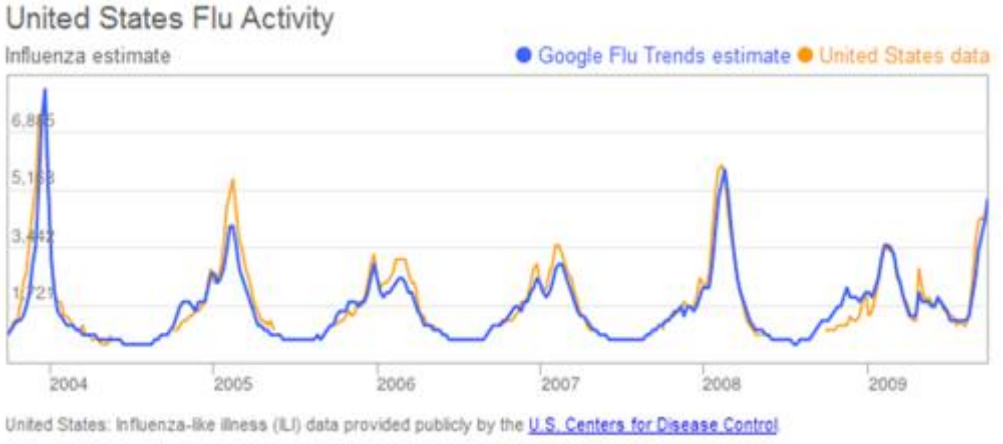
Figure 1. Data streams collected while a patient is transported, treated and discharged from a trauma centre. Critical components of the big data approach in handling those massive data are shown and the expected outputs.



Dr Shiming Yang *is Data Analyst,* **Dr Mary Njoku** *is Associate Professor of Anesthesiology and* **Dr Colin F Mackenzie** *is Professor of Anesthesiology in the Shock Trauma Anesthesiology Research Center and Department of Anesthesiology, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA*

Correspondence to: Dr CF Mackenzie (cmack003@umaryland.edu)

Google



Nature 2009

Detecting influenza epidemics using search engine query data

Jeremy Ginsberg[1], Matthew H. Mohebbi[1], Rajan S. Patel[1], Lynnette Brammer[2], Mark S. Smolinski[1] & Larry Brilliant[1]

[1]Google Inc. [2]Centers for Disease Control and Prevention

Epidemics of seasonal influenza are a major public health concern, causing tens of millions of respiratory illnesses and 250,000 to 500,000 deaths worldwide each year[1]. In addition to seasonal influenza, a new strain of influenza virus against which no prior immunity exists and that demonstrates human-to-human transmission could result in a pandemic with millions of fatalities[2]. Early detection of disease activity, when followed by a rapid response, can reduce the impact of both seasonal and pandemic influenza[3,4]. One way to improve early detection is to monitor health-seeking behavior in the form of online web search queries, which are submitted by millions of users around the world each day. Here we present a method of analyzing large numbers of Google search queries to track influenza-like illness in a population. Because the relative frequency of certain queries is highly correlated with the percentage of physician visits in which a patient presents with influenza-like symptoms, we can accurately estimate the current level of weekly influenza activity in each region of the United States, with a reporting lag of about one day. This approach may make it possible to utilize search queries to detect influenza epidemics in areas with a large population of web search users.

This paper was originally published in Nature Vol 457, 19 February 2009, doi:10.1038/nature07634

http://dx.doi.org/10.1038/nature07634

JAMA
Nov 15

Twitter Streams Fuel Big Data Approaches to Health Forecasting

Bridget M. Kuehn, MSJ

Within moments of the explosions at the finish line of the 2013 Boston marathon, Twitter messages began appearing describing the incident and casualties—some preceded the alerts from Massachusetts public health and emergency agencies sent to emergency departments (EDs) in the area (Cassa CA et al. *PLoS Curr*. Published online July 2, 2013).

The prospect of using such real-time data to provide early public health warnings—possibly within minutes—and timely alerts to hospitals about oncoming surges or emerging public health concerns has led to a new wave of studies probing ways to use Twitter in medicine and public health.

Infectious disease specialists and public health agencies were the first to mine social media data streams for early signs of cholera and influenza outbreaks (Chunara R, Andrews JR, Brownstein JS. *Am J Trop Med Hyg*. 2012;86[1]:39-45 and Shaman J et al. *Nat Commun*. 2013;4:10). At least 2 cities are already using social media data to monitor foodborne illness (Kuehn BM. *JAMA*. 2014; 312[2]:117-118).

Now, scientists are finding that Twitter data—especially when combined with other real-time data streams like environmental sensors or data from fitness apps—also have the potential to provide early warnings about chronic disease, emergencies, adverse drug reactions, or even safety problems like prescription drug misuse.

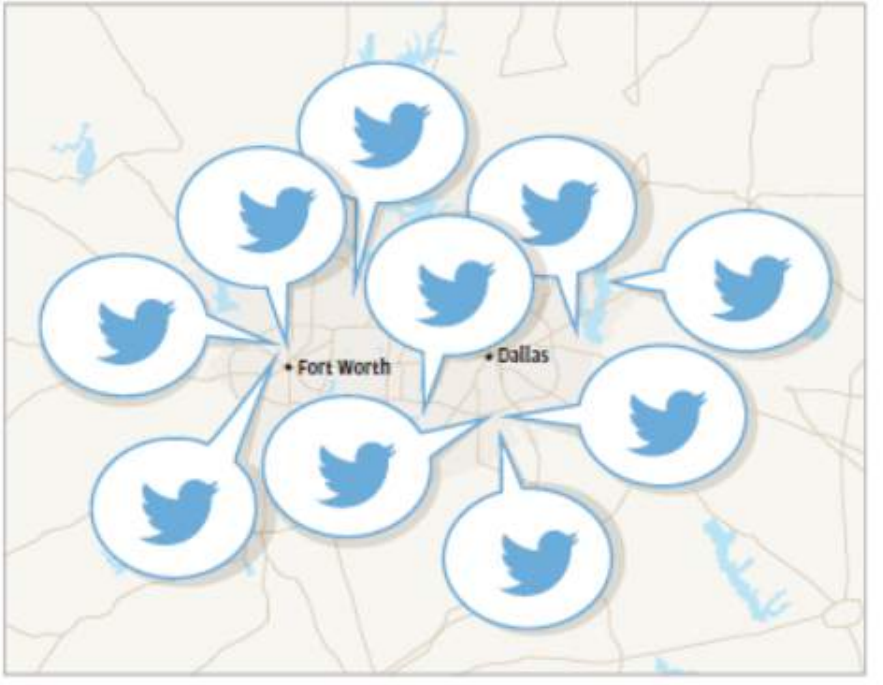
Finding the Signal

Enormous amounts of real-time data are generated each day as people use mobile devices and apps like Twitter. In fact, the average US resident now spends about 3 hours each day using a mobile device, according to analysts at Yahoo's Flurry Insights (http://bit.ly/1NzuROH).

"We live in the era of big data," said Sudha Ram, PhD, professor of management information systems and computer science at the University of Arizona, Tucson, whose research focuses on predicting asthma surges. "We have tons of data pouring out from everywhere. Why not look at [asthma surges] in a very different way and bring other data to bear?"

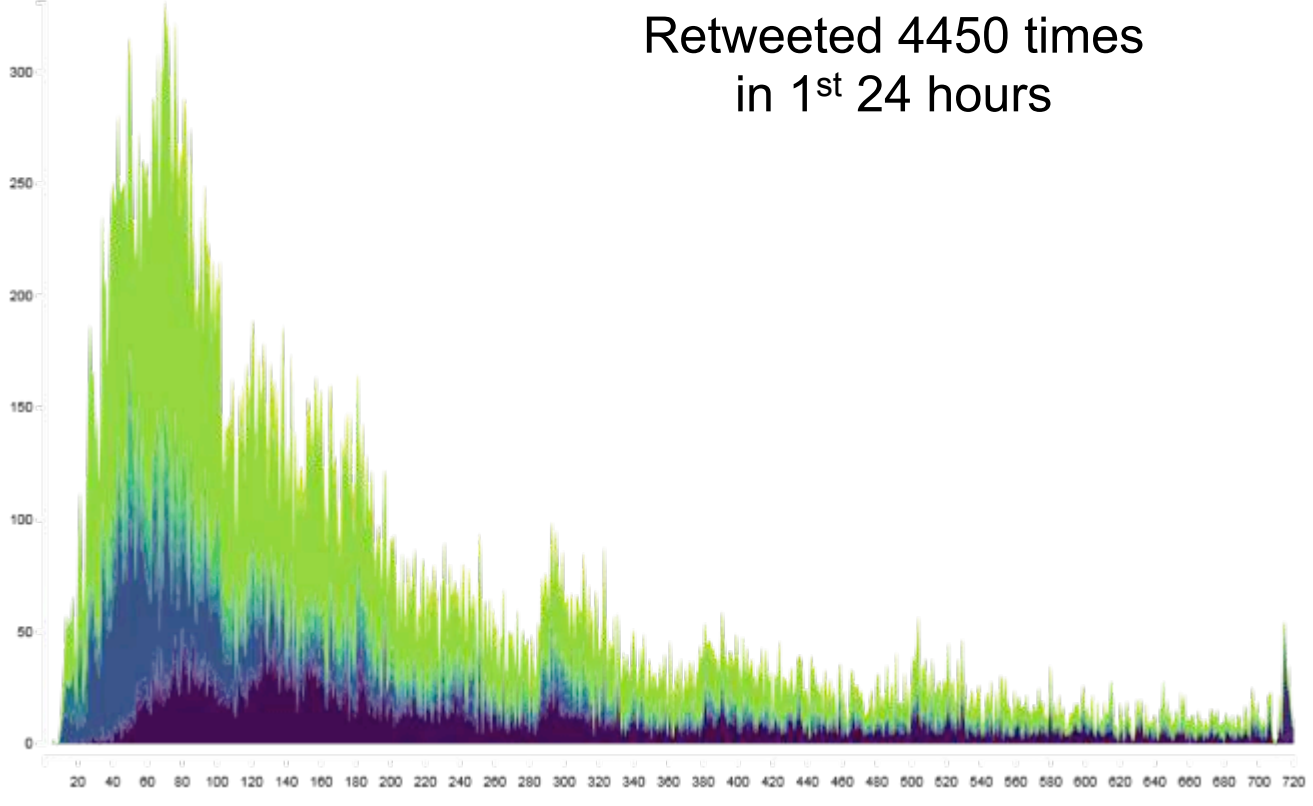
Ram's research focuses on extracting health signals from this fire hose of data using data mining techniques. In Twitter, Ram has found a particularly rich vein of information.

"A lot of people dismiss Twitter as frivolous, but my work has shown there



Instantaneous News

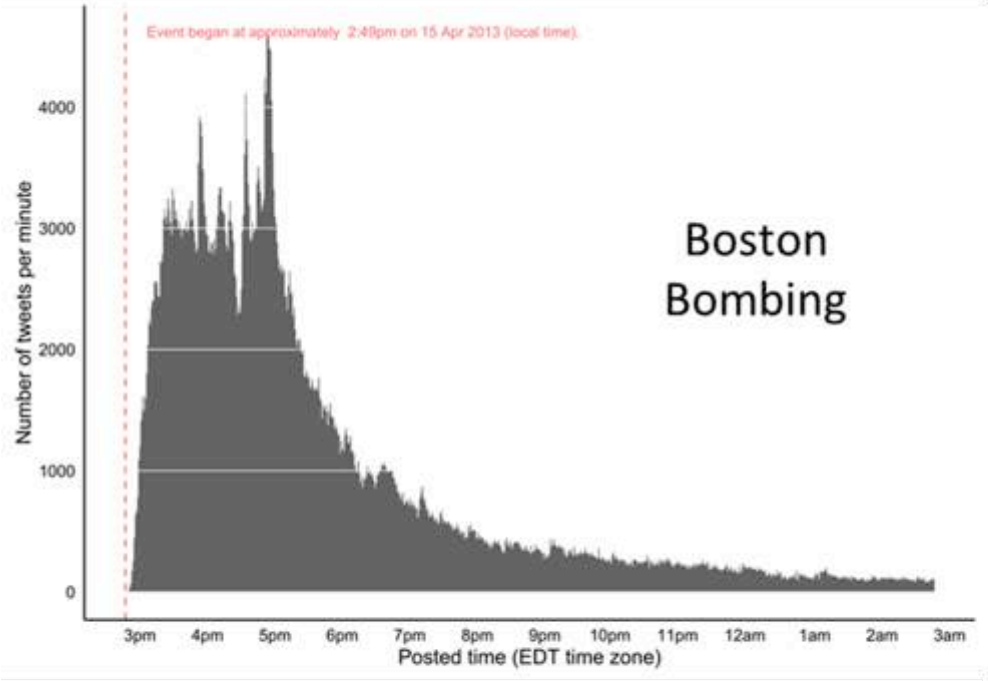
1st Twitter message/ photo 30 seconds after impact

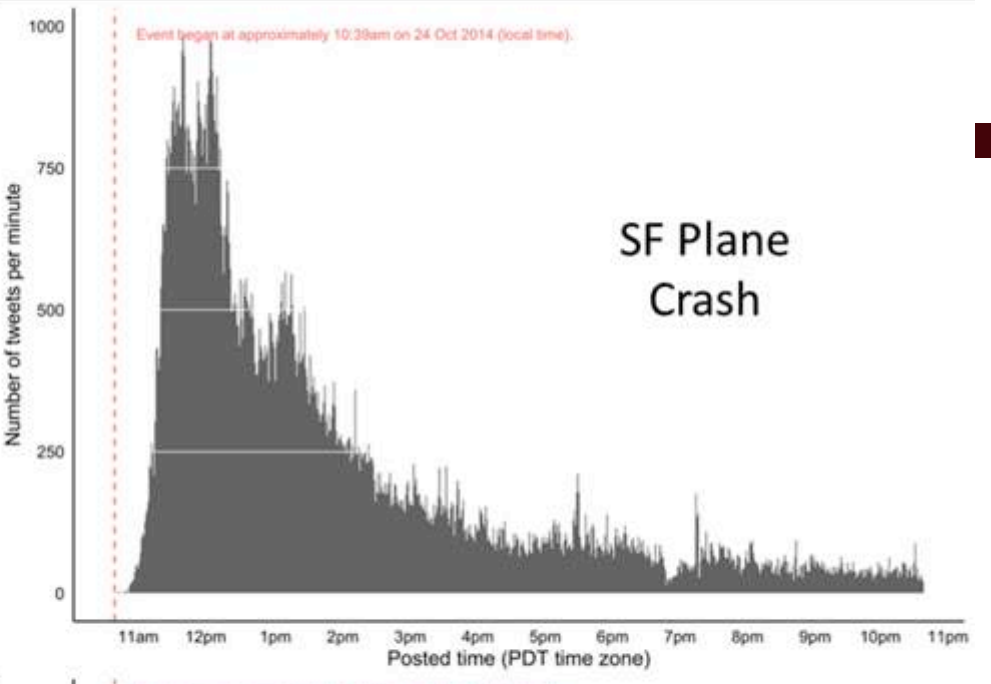


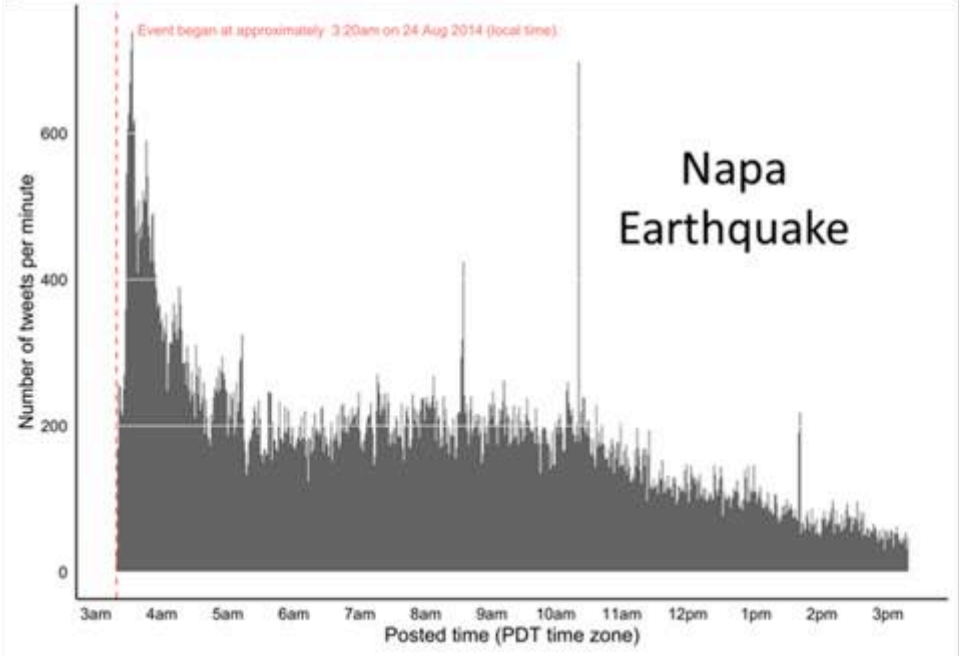
Retweeted 4450 times in 1st 24 hours

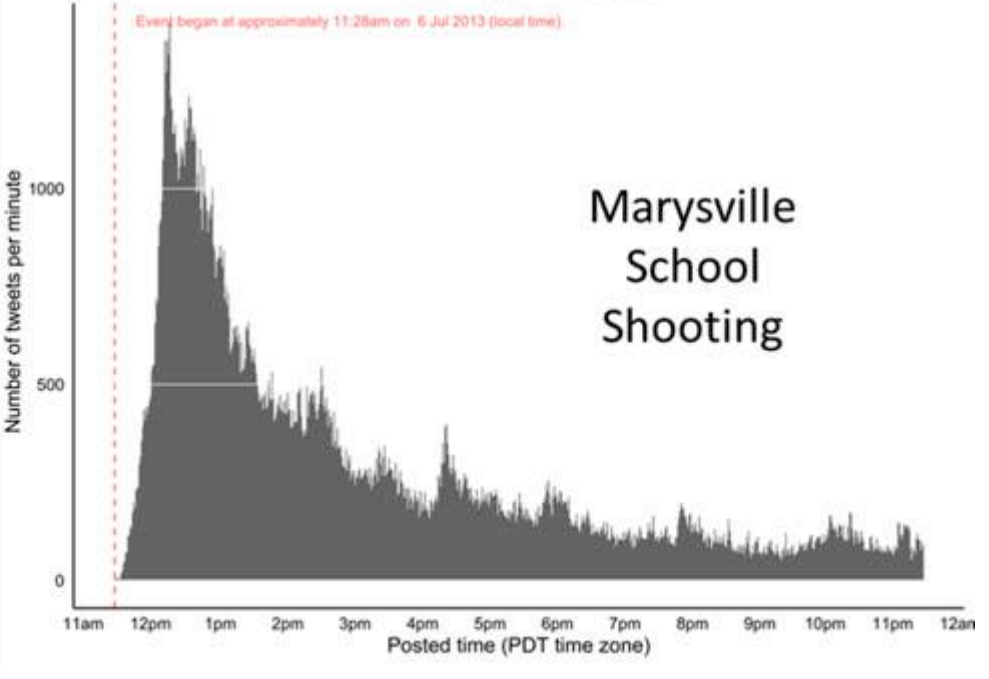
Impact of Social Media

Tweets Per Minute in 1st 12 Hrs Post-Event

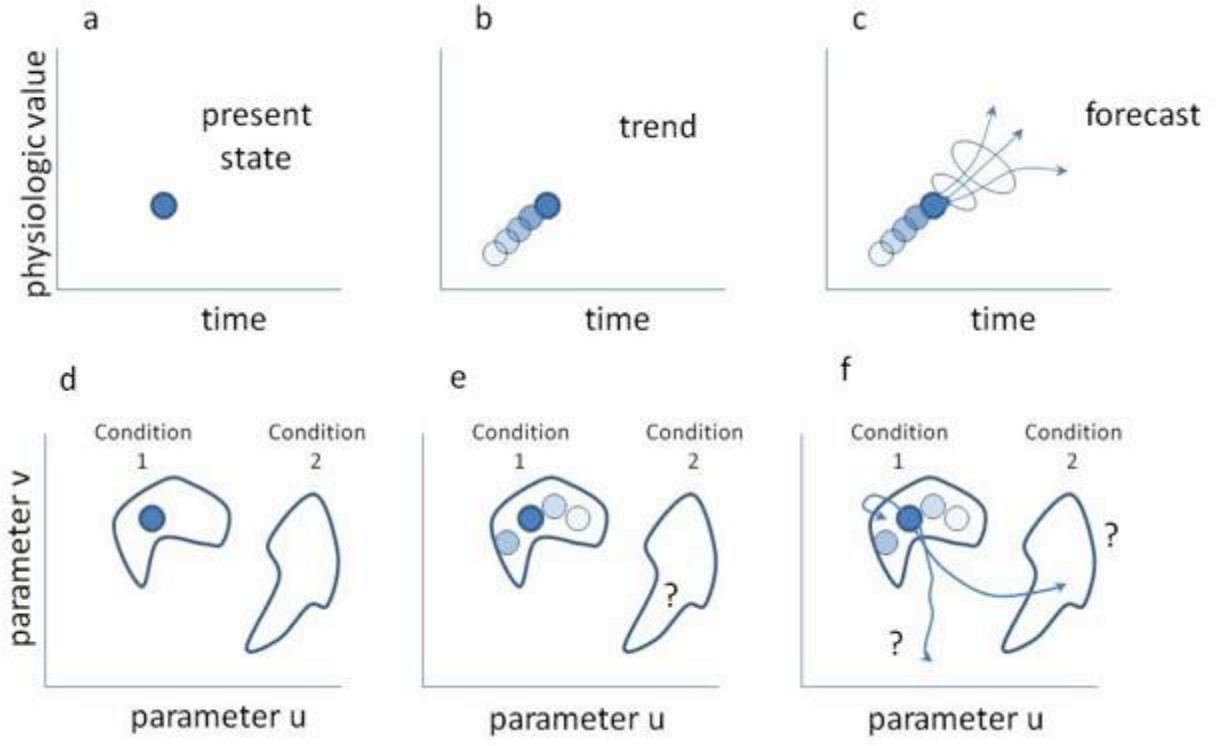






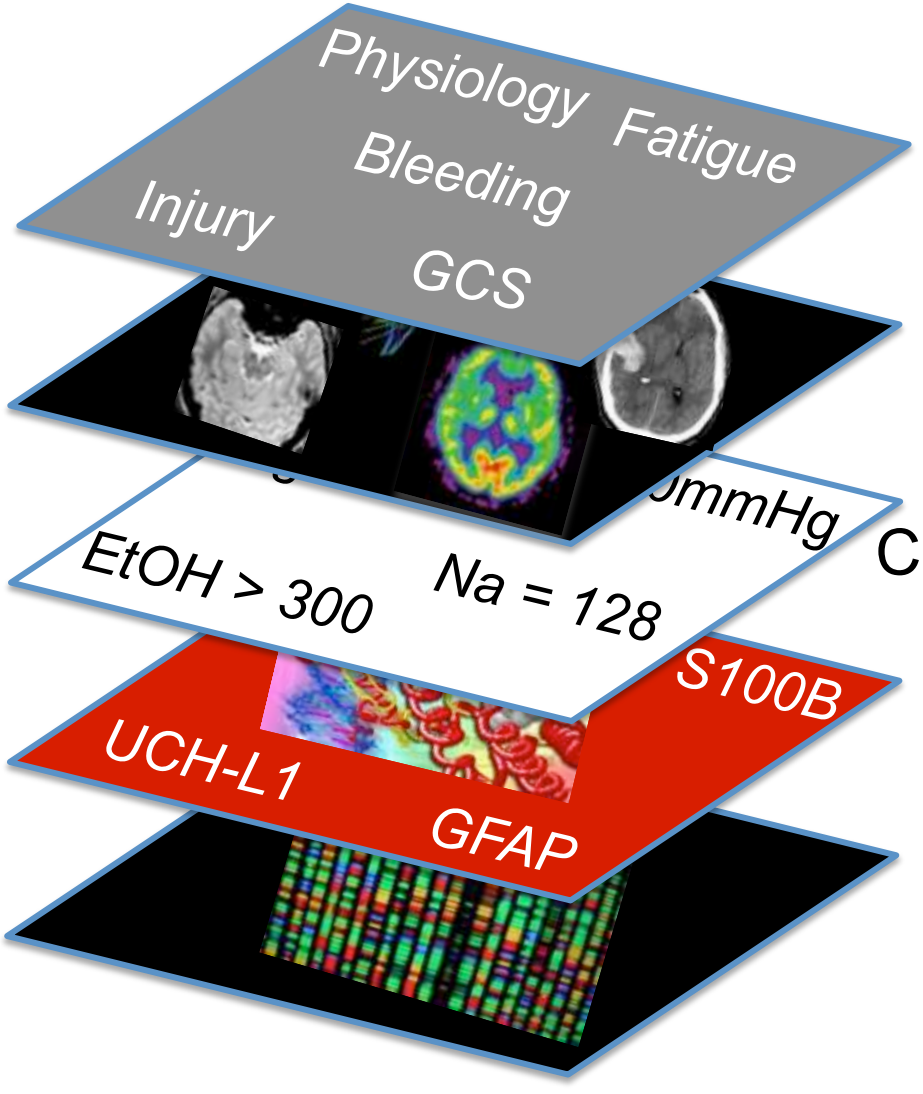


Dynamic physiologic states exist in a physiologic state space



Our patients move through these states optimally guided towards health

Trauma: a Precision Medicine Approach



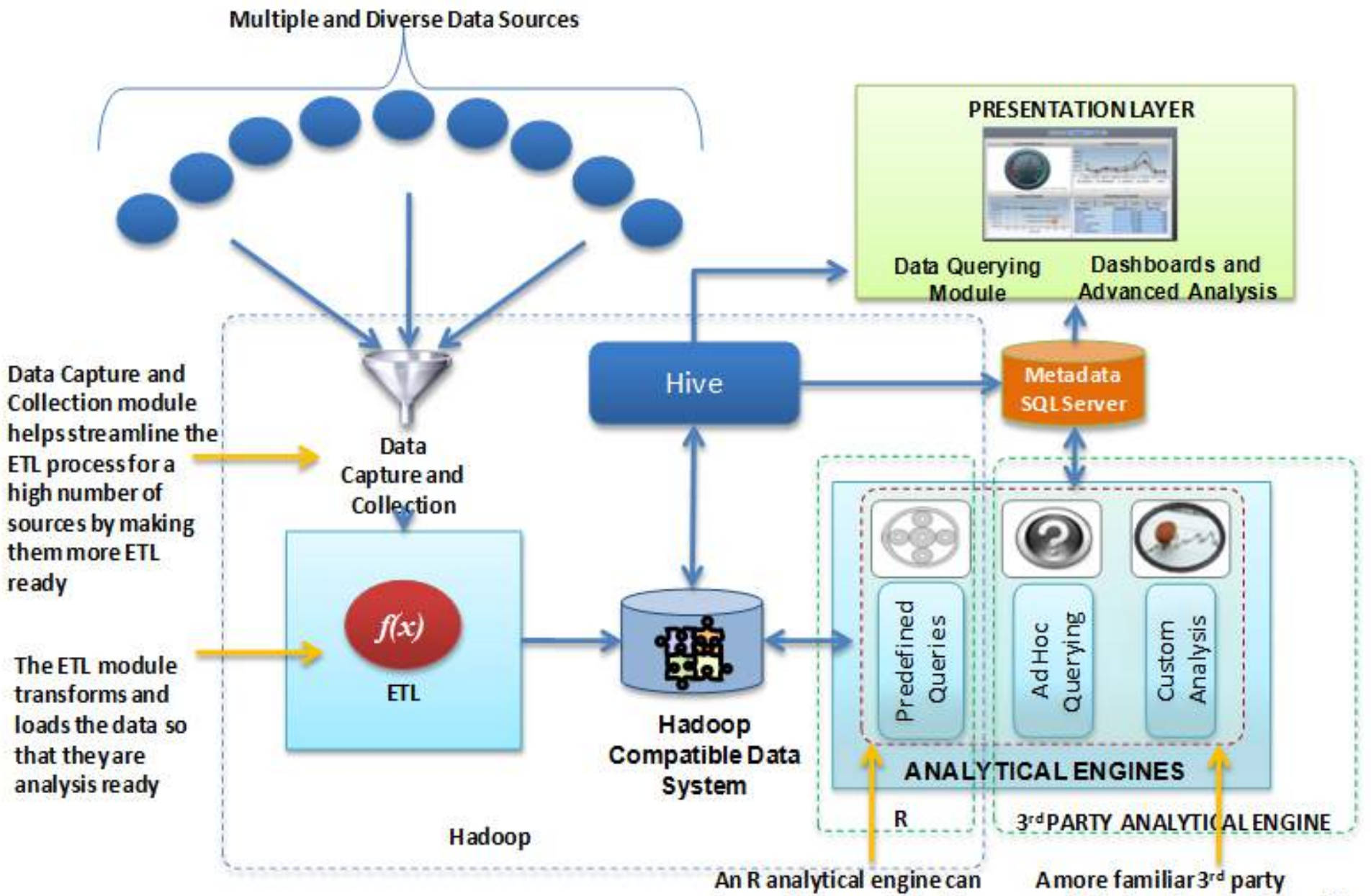
Demographic/Injury

Imaging

Clinical Data/Physiology

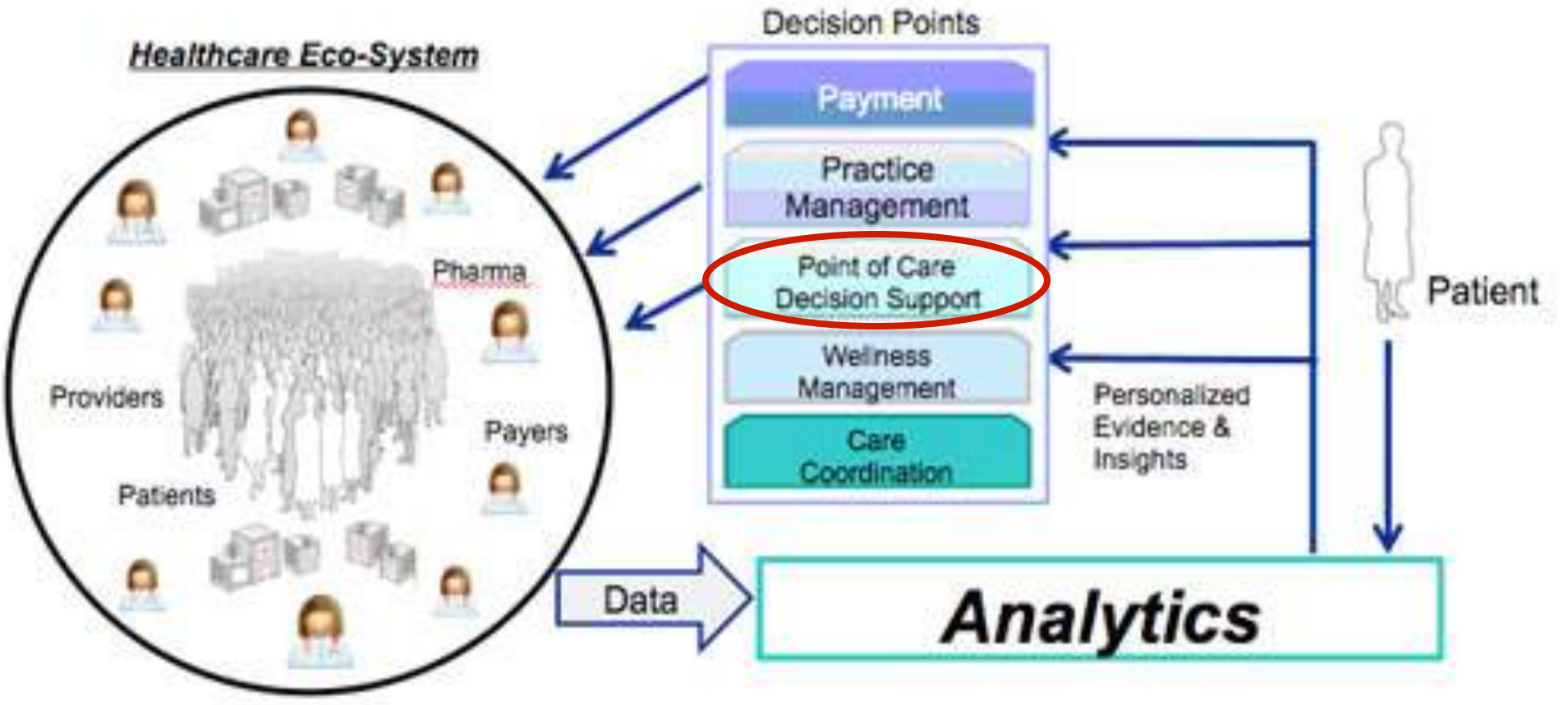
Proteome

Genome



What we want to do…

Simplified Version



Manipulate Care to Mitigate Risk


Da Hui

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