

The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

Hemostasis in the Operating Room [Also the Emergency Department] Viscoelastometry

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The Fritsma Factor, Your interactive Hemostasis Resource
www.fritsmafactor.com


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Bottom Line at the Start [BLAST]

- Perform and interpret the activated clotting time test.
- Describe and interpret viscoelastometry reports.
- Relate viscoelastometry [VET] reports to blood component management.




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Lab Responsibility; Do You...

- Know what coag tests your ER docs anesthetists/anesthesiologists perform?
- Know what tests are used for various procedures?
- Offer support to your ORs and ERs?
- Manage OR and ER quality assurance?
- Offer in-lab intraoperative platelet mapping — Aspirin or clopidogrel resistance



Thanks to Dr. **Oksana Volod**, LA Cedars-Sinai for her discussion of lab-OR collaboration.

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Preoperative Testing Only When Hx/Px Provide Indications

Test	Indication	Comments
HGB/HCT/MCV/RBC	Anemia, blood loss	Iron, erythropoietin
WBC count, diff	Fever, infection, hematologic disorder	
PLT count, function	Liver disorder, systemic bleeding	PLTs, TPA, factors
Pregnancy test	Women of child-bearing age	
Urinalysis, creatinine	Renal or gyny disorder, meds that damage kidneys	
Liver enzymes	Liver disorder, meds that damage liver	
Electrolytes	Systemic or metabolic disorder	IV Rx
Glucose, HGB A1C	Diabetes, metabolic syndrome	IV Rx
Coagulation studies	Hemorrhage	Factor replacement
Thrombosis studies	VTE—DVT and PE	Anticoagulation

Welch JM, Zhuang T, Shapiro LM, et al. Is low-value testing before low-risk hand surgery associated with increased downstream healthcare use and reimbursements? A national claims database analysis. Clin Orthop Relat Res. 2022. doi: 10.1097/CORR.0000000000002255.

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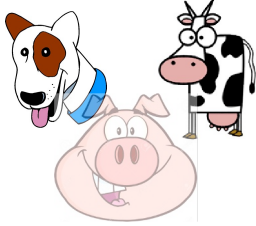

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Activated Clotting Time

"Heparin sodium"

Unfractionated heparin [UFH]

"Standard heparin"

Jay MacLean, med student at William Howell's Johns Hopkins lab in 1916 isolated a substance from dog liver and described its anticoagulant property. Howell named it heparin. 1935, prepared by Karolinska Institut, Stockholm, US-FDA-cleared in 1936 [first ever]

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UFH Rx \leq 5 days Venous Thromboembolic Disease [VTE]

- Prevent 2^o thrombosis in VTE
- Bolus: 5000–10,000 units or 80 IU/kg
- Maintenance: 1600 U/hour or 18 IU/kg/h, \geq 30,000/24 h
- Rx PTT target: ~85–120s
- Chromogenic anti-Xa Rx target: 0.3–0.7 IU/mL

Rasoli S, Zeinah M, Athanasiou T, Kourliouros A. Optimal intraoperative anticoagulation strategy in patients undergoing off-pump coronary artery bypass. Interact Cardiovasc Thorac Surg. 2012;14: 629–33

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Intraoperative UFH ≤ 5 days

- Applications
 - Cardiopulmonary bypass, [CPB]—coronary artery bypass graft [CABG]
 - Percutaneous intervention [PCI, cardiac catheterization]
 - Extracorporeal mechanical oxygenation [ECMO]
 - Hemodialysis, major orthopedic surgery, delivery and post-partum
- Supertherapeutic UFH dose 70–500 IU/kg, median 150 IU/kg
- $\gg 1.0$ IU/mL exceeds PTT and chromogenic anti-Xa linearity, use ACT or VET
- Postsurgical protamine sulfate reversal dose, half UFH dose
- UFH and protamine response measured by ACT

Burt C, Arrowsmith J, McKie MA, et al. Optimal protamine dosing after cardiopulmonary bypass: The PRODOSE adaptive randomised controlled trial. *PLoS Med.* 2021;18:e1003658. doi: 10.1371/journal.pmed.1003658.

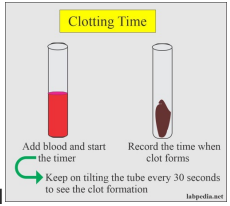
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Activated Coagulation Time [ACT]

- Improved Lee-White WB clotting time
- Activators
 - Kaolin in hydroxyethyl piperazine ethane sulfonic acid buffer, calcium, and sodium azide
 - Celite535®: SiO₂, diatomaceous earth
- Fresh WB + activator—record clot interval
 - Representative reference mean of reference interval [MRI]: 100 s
 - Therapeutic UFH Rx target range: 150–190s
 - Supertherapeutic UFH target: 400s
- Near-patient, broad linearity, CV 5–15 s
 - Hattersley P. Activated coagulation time of whole blood. *JAMA* 1966;136:436–40.



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Waived POC ACT Instruments

Per Dr. Oksana, Use ACT during CBP and in recovery up to 8 hours, as residual UFH is released from tissue, requiring additional protamine sulfate.

Ojito JW, Hannan RL, Burgos MM, et al. Comparison of point-of-care activated clotting time systems utilized in a single pediatric institution. *JECOT.* 2012;44:15–20

- Hemochron® Signature Elite WB Microcoagulation System
 - Werfen IL (previously International Technidyne), Bedford, MA
- Medtronic HMS+® Hemostasis Management System
- Medtronic ACT+® Automated Coagulation Timer System
 - Medtronic, Minneapolis, MN
- i-STAT® Handheld Test Cartridge Blood Analysis System
 - Abbott Point of Care Inc., Princeton, NJ


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Hemochron Signature Elite

Handheld device. Using test-specific cuvettes, system computes PT, PTT, or ACT. Select desired test cuvette, add a drop of WB. A measured volume is dispensed to a channel where it is mixed in a cuvette that contains kaolin or Celite. The sample oscillates. LED sensor detects reduced flow and records the endpoint when movement slows to a predetermined limit.



ACT MRI: 221.1 s SD: 14.8 s

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Medtronic HMS

System transfers fresh or citrated WB from syringe to each of six cartridges containing varied concentrations of heparin and kaolin.

Each cartridge contains a plunger that oscillates vertically until an optical sensor detects viscosity by detecting the rate of fall.

The system measures ACT and extrapolates heparin concentration, recommends heparin and protamine dose per body mass.



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Medtronic ACT +

Operator fills each of two kaolin cartridges, then places cartridges in warmed receptacle.

Each cartridge contains a plunger that oscillates vertically until an optical sensor detects viscosity by detecting the rate of fall.

ACTs from the cartridges are averaged and reported.



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Abbott i-STAT ACT

Hand-held analyzer that measures WB gases, chems, lytes, heme parameters, cardiac markers, PT and ACT.

Operator collects fresh WB to the ACT cartridge and places into a warmed well where the sample mixes with kaolin or Celite. Thrombin cleaves a reagent substrate. Circuitry detects the electrochemical product.

ACT MRI: 153.3 s | SD: 7.9 s

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Fibrinogen Deficiency

- Congenital hypo- and afibrinogenemia
- Dysfibrinogenemia in liver disease
- Hemodilution, blood loss, consumption
 - Trauma, massive hemorrhage, massive transfusion protocol, obstetrics, cardiac surgery, orthopedics, DIC, sepsis, hepatitis
- Rx: CRYO or lyophilized IV FBG concentrate RIASTAP® [CSL Behring, 2009] or Fibryga® [Octapharma, 2017]
- If FBG level is unknown, use 70 mg per kg IV
 - If patient's FBG level is known use FBG assay and compute:

Target FBG [mg/dL] – FBG level [mg/dL]
1.8 mg/dL Fibryga per kg body weight

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Clot-based Fibrinogen Assays

Fibrin Polymerization and Crosslinking

- TT-derived von Clauss FBG
- PT-derived FBG
- VET functional FBG

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Clauss Fibrinogen Assay

- Thrombin time modification
- Dilute plasma to minimize effect of inhibitors such as FDPs
- Pipette 50–100 units/mL thrombin
- Measure time to clot formation, compare to calibration curve
- Inverse relationship, CVs: 15–30%
- Interference: FDPs, heparin, lipemia and icterus if using optical measurement

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Clauss versus PT-derived Fg

PT-derived Fg estimate, interprets the opacity of PT reaction mixture. The line of best fit compares derived PT to the reference Clauss assay. Concordance is lost at the low and high ends.

Mackie J, et al. Thromb Haemost 2002; 87:997–1005

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Viscoelastometry [VET]

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Figure 1: The operating principle of the Sonoclot analyzer (Sienco Inc, Arvada, Colorado).

Sienco Sonoclot

Hett DA, Walker D, Pilkington SN, Smith DC.
Sonoclot analysis. Br J Anaesth. 1995; 75: 771-6.

Thanks to Jon Henderson, Sienco President

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Thromboelastograph [TEG 5000]

30 minutes

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TEG 5000 Parameters

Parameter	Symbol	Definition	RI
Clot rate	R	Period from 0-2 mm amplitude	4-8 m
Clot kinetics	K	Period from 2-22 mm amplitude	0-4 m
Clot strengthening angle	α	slope of tangent at 2-22 mm amplitude	47-74°
Maximum clot strength	MA	Maximum amplitude	54-72 mm
Clot lysis	LY30	MA at 30 minutes	0-8%

The TEG® hemostasis system continuously measures all phases of hemostasis as a net product of whole blood components.

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TEG 5000

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TEG 5000 Results For Oenophiles

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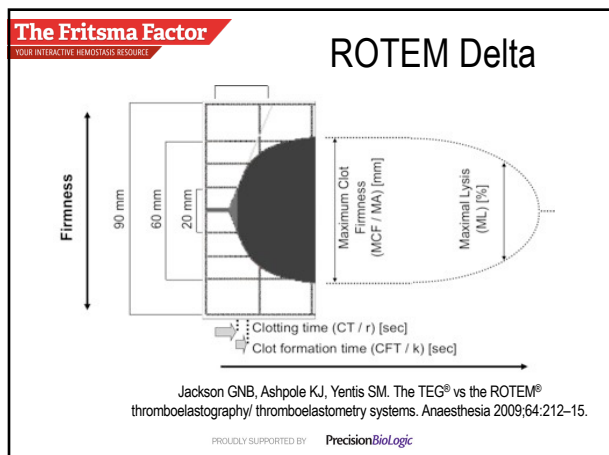
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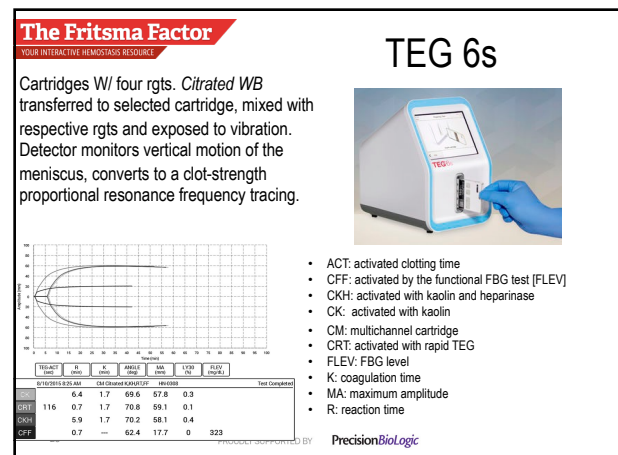
ROTEM Delta

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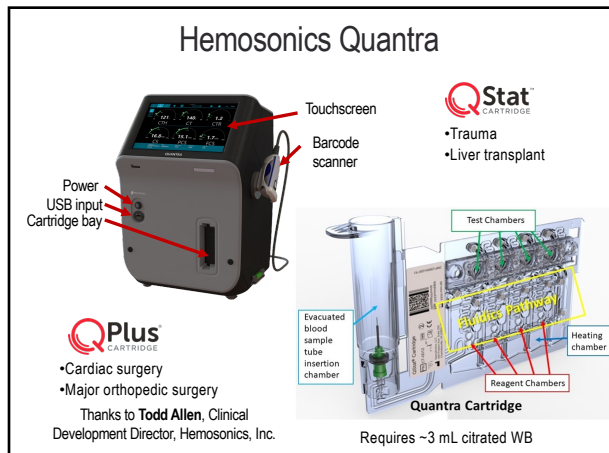
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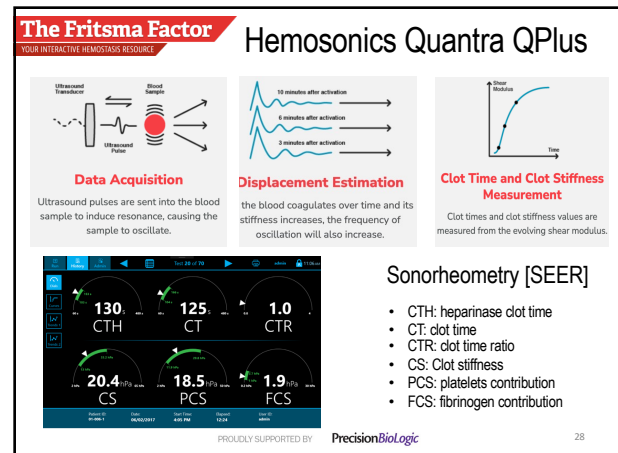
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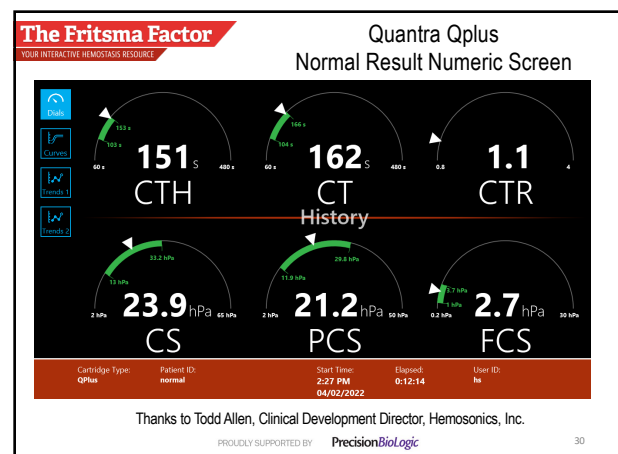
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Hemosonics Quantra Qplus Cartridge

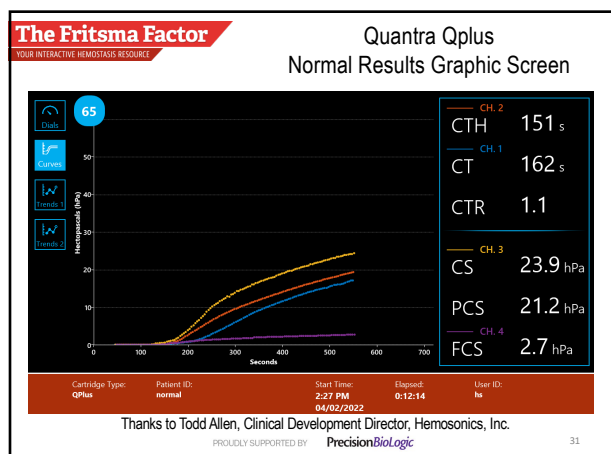
Parameter [Units]	Measurement
CT [s]	Intrinsic system clot time
CTH [s]	Intrinsic system clot time with heparinase neutralizer
CS [hPa]	Clot stiffness of WB, extrinsic activation [maximum amplitude]
FCS [hPa]	FBG contribution to clot stiffness
PCS [hPa, calculated]	PLT contribution to clot stiffness
CTR [ratio, calculated]	Clotting time ratio [CT/CTH]: Indicates intrinsic pathway function or UFH influence

Citrated WB; CTH, CS, FCS, and PCS are measureable while on bypass

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VET Assay Crosswalk

Quanta QPlus System	Units	Activates	ROTEM delta	TEG 6S
Clot time [CT]	sec		INTEM CT [sec]	Kaolin R [min]
CT with heparinase [CTH]	sec	Intrinsic pathway	HEPTEM CT [sec]	Heparinase Kaolin R [min]
Clot time ratio [CTR]	N/A		Not available	Not available
Clot stiffness [CS]	hPa		EXTEM MCF	Rapid TEG MA
FBG contribution [FCS]	hPa	Extrinsic pathway	FIBTEM MCF	Functional FBG MA
PLT contribution [PCS]	hPa		PLT mapping	Not available

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VET Applications

- ACT—all VETs: manage UFH and protamine sulfate
 - Dialysis, CABG, CPB, PCI, ECMO, VAD major orthopedic surgery
- FBG—All VETs
- Platelet function—Qplus, PLT mapping
- Fibrinolysis: TEG 5000 and ROTEM
- Platelet mapping: TEG 5000 and 6S
 - Moderate complexity—requires laboratory scientist
 - Detect and monitor anti-PLT Rx, PLT dysfunction prior to surgery

Liver transplant, trauma, obstetrics

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VET Applications
Cardiopulmonary Bypass Surgery

- Extracorporeal membrane oxygenation [ECMO]: passing blood through foreign surfaces
 - PLTs adhere, become activated or dysfunctional
 - EC disruption exposes TF, causing Fg & VWF activation & depletion
 - Surgery induces inflammation, activating platelets and procoagulants
- UFH hypertherapeutic up to 4 IU/mL plasma level during CPB, CABG, ECMO, VAD, dialysis, major orthopedic surgery
 - Exceeds PTT linearity
 - Anesthetists, anesthesiologists monitor UFH with ACT
- VET assesses coagulation in the presence of UFH and when it is neutralized by protamine sulfate
 - Directs concentrate selection, reduces the amount of blood transfused

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VET Applications
Non-surgical Cardiology

- Patient function monitoring when on antiplatelet therapy, such as GP IIb/IIIa antagonists [clopidogrel] or aspirin.
- VET is used in patients who appear to be "ASA resistant" as it permits *ex vivo* optimization of treatment
 - Raise ASA dosage, switch to clopidogrel, ticagrelor
- Platelet mapping predicts blood loss in CPB patients. This helps clinicians avoid or activate massive transfusion protocols.

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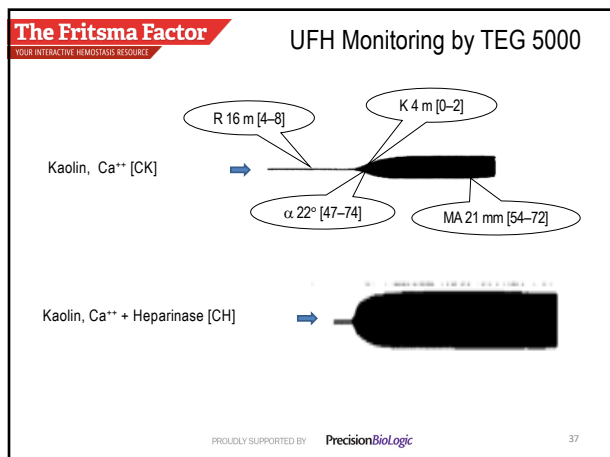
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ER VET Applications
Trauma-induced Coagulopathy & Traumatic Brain Injury

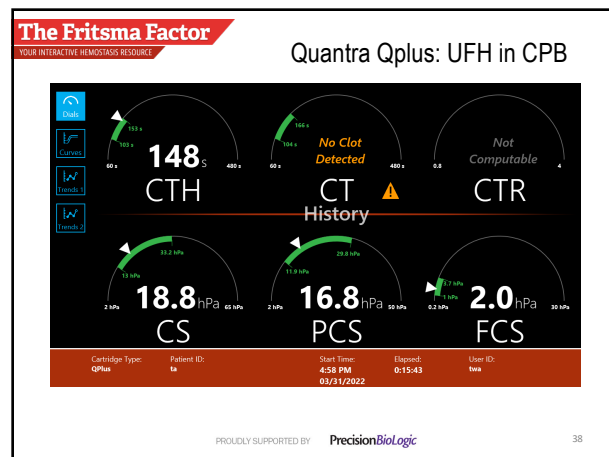
- Trauma-induced coagulopathy [TIC] is a consequence of tissue damage and systemic hypoperfusion [shock].
- Early, aggressive resuscitation with blood products is paramount to survival
 - Tranexamic acid, factor concentrates, ADAMTS13 concentrate, activated prothrombin complex concentrate [Kcentra], PLTs, plasma, massive transfusion protocol
- VET rapidly identifies TIC and traumatic brain injury [TBI] and platelet dysfunction and subsequently triggers massive transfusion protocols

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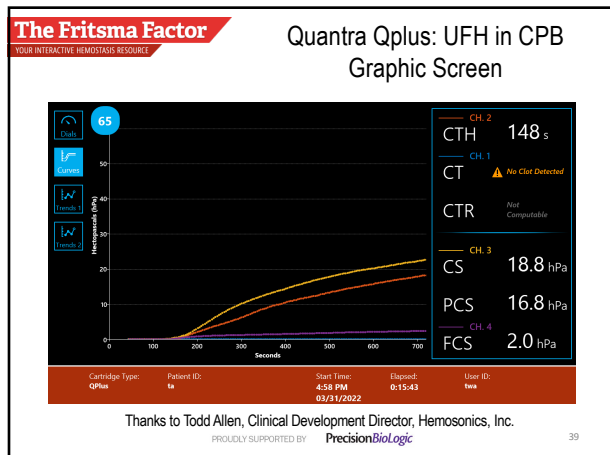
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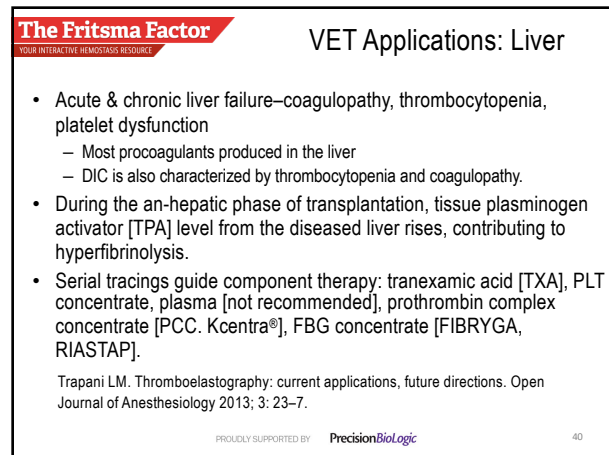
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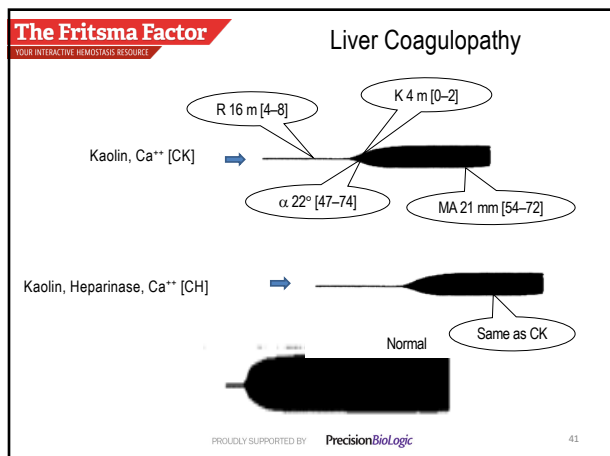
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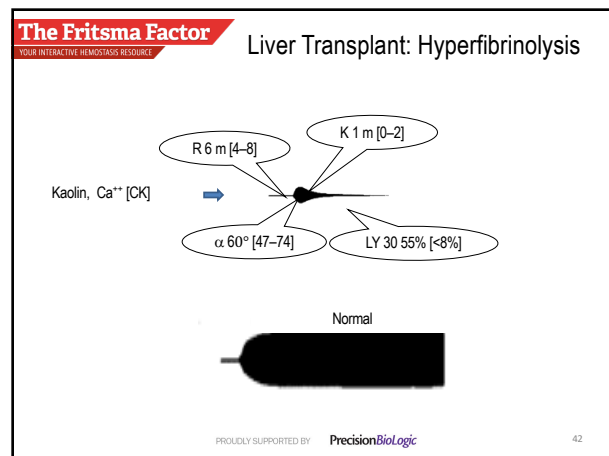
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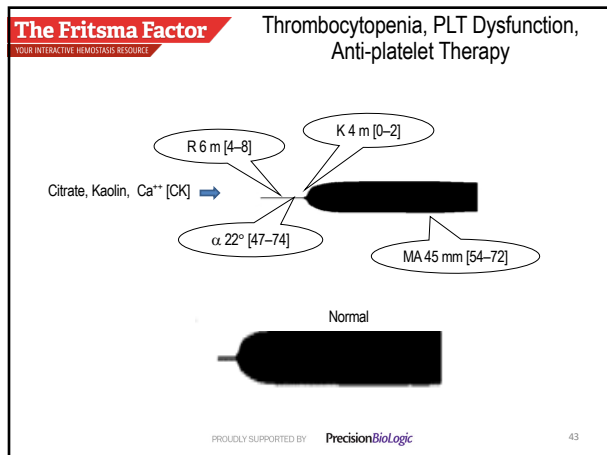
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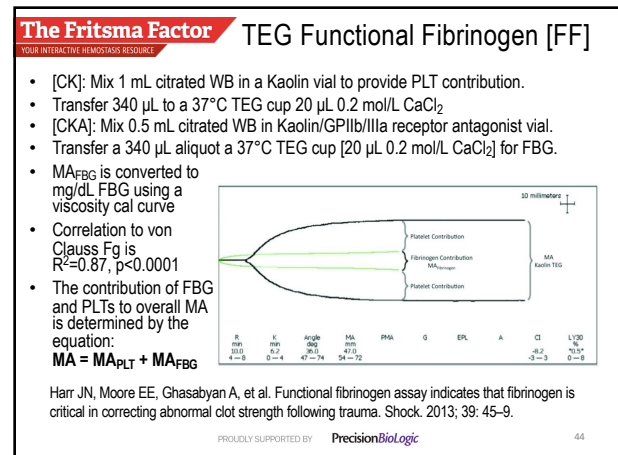
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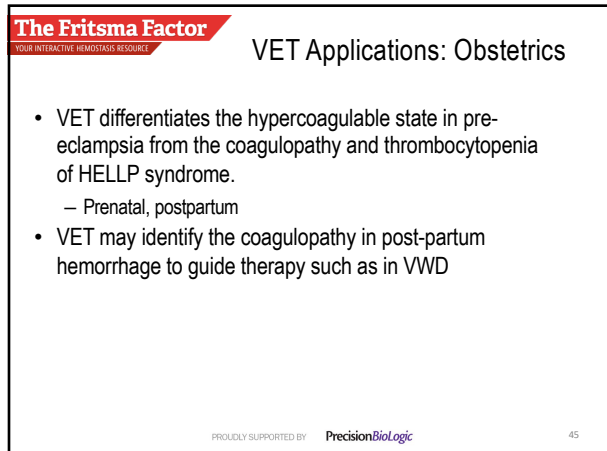
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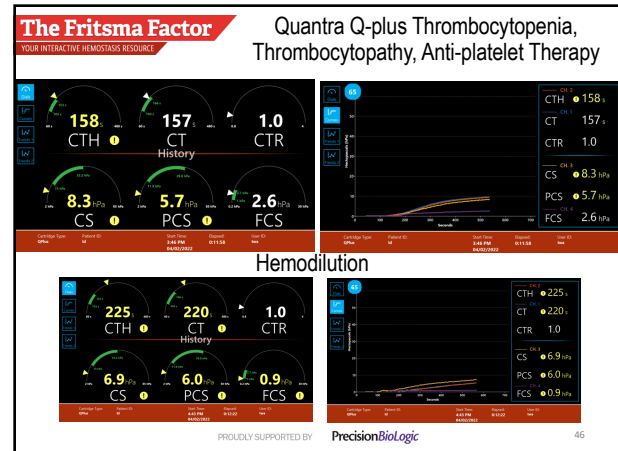
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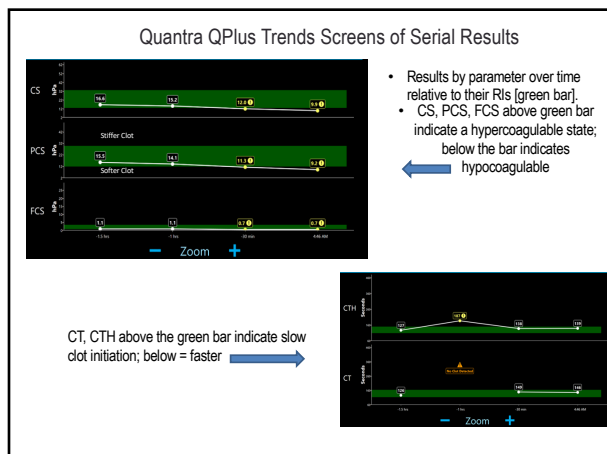
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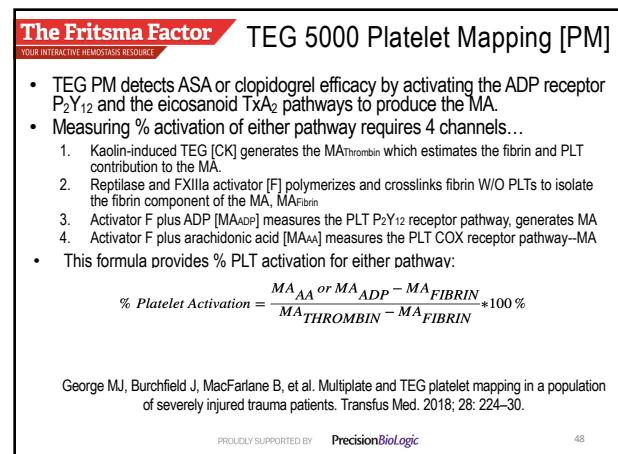
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TEG 5000 Platelet Map MRIs

Parameter	MRI All	MRI Female	MRI Male
MA _{Thrombin}	61 mm	63 mm	58 mm
MA _{Fibrin}	7.5 mm	8.1 mm	6.6 mm
MA _{ADP}	41 mm	53 mm	49 mm
MA _{AA}	65 mm	66 mm	63 mm
% ADP	18.6%	18.2%	19.4%
% TxA ₂	1.2%	1.3%	1.1%

Bochsen L, Winberg B, Kjølgaard-Hansen M, et al. Evaluation of the TEG® platelet mapping™ assay in blood donors Thrombos J 2007; 5, <https://doi.org/10.1186/1477-9560-5-3>

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Questions?

Biz Fisher, Rutgers DCLS Candidate, checked her ORs at Good Sam in Vincennes, Indiana and found their TEG 5000 patterns were uncontrolled and uninterpretable.



Am I supporting my ORs and the ER?

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Bottom Line at the End [BLEAT]

- Perform and interpret the activated clotting time test.
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- Relate viscoelastometry reports to blood component management.

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