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

George A Fritsma MS, MLS
The Fritsma Factor, Your interactive Hemostasis Resource
www.fritsmafactor.com

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.

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.

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

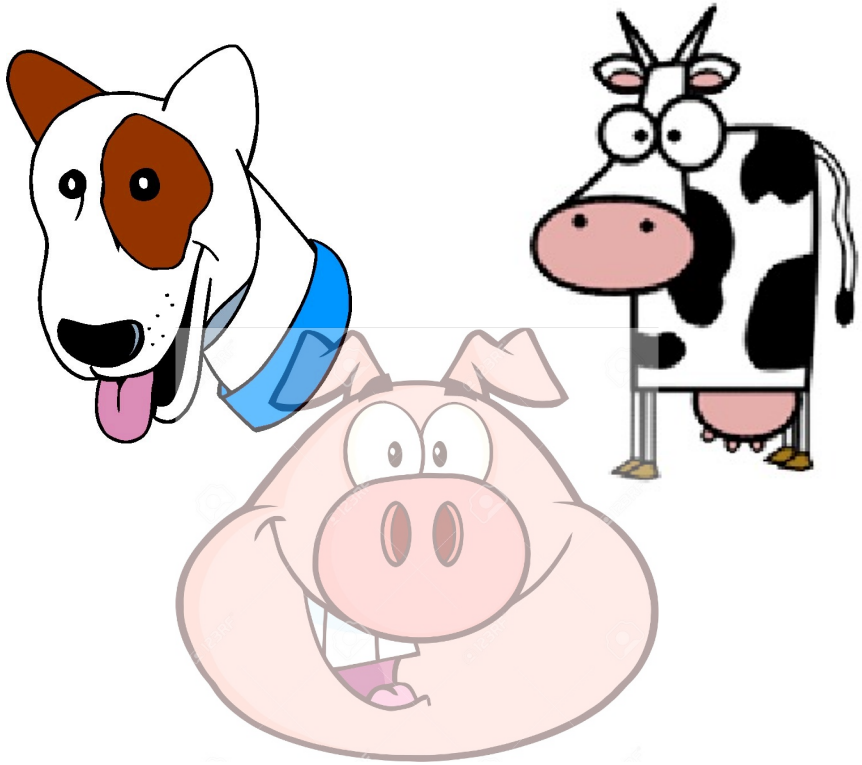
Welch JM, Zhuang T, Shapiro LM, et al. Is low-value testing before low-risk hand surgery associated with increased downstream healthcare use and reimbursements? A national claims database analysis. Clin Orthop Relat Res. 2022. doi: 10.1097/CORR.0000000000002255.

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]

UFH Rx ≤ 5 days
Venous Thromboembolic Disease [VTE]

- Prevent 2º thrombosis in VTE
- Bolus: 5000–10,000 units or 80 IU/kg
- Maintenance: 1600 U/hour or 18 IU/kg/h, ≥ 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

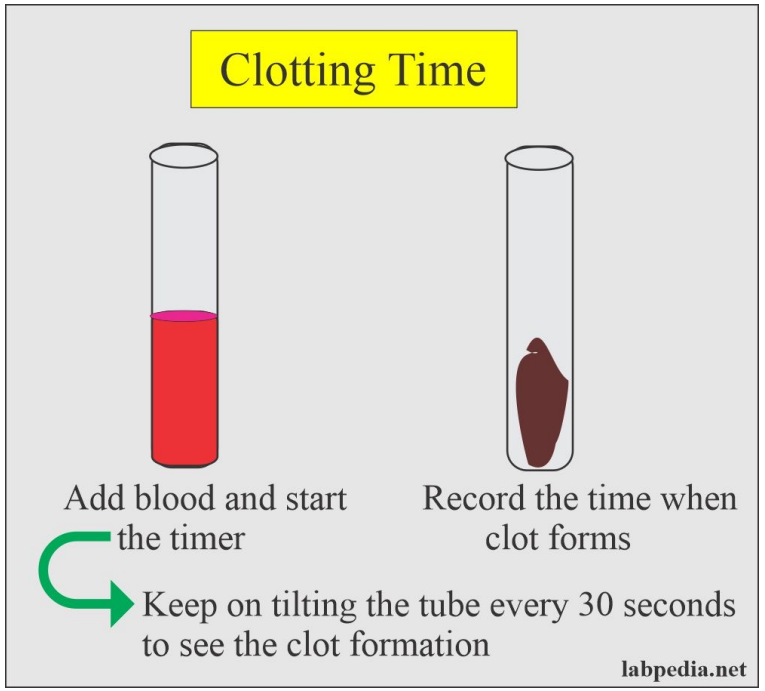
Intraoperative UFH ≤ 5 days

- 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
- >> 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.

Activated Coagulation Time [ACT]

- Improved Lee-White WB clotting time
- Activators
  - Kaolin in hydroxyethyl piperazine ethane sulfonic acid buffer, calcium, and sodium azide
  - Celite535®: SiO_2, 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.

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. JECT. 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

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

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.

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.

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

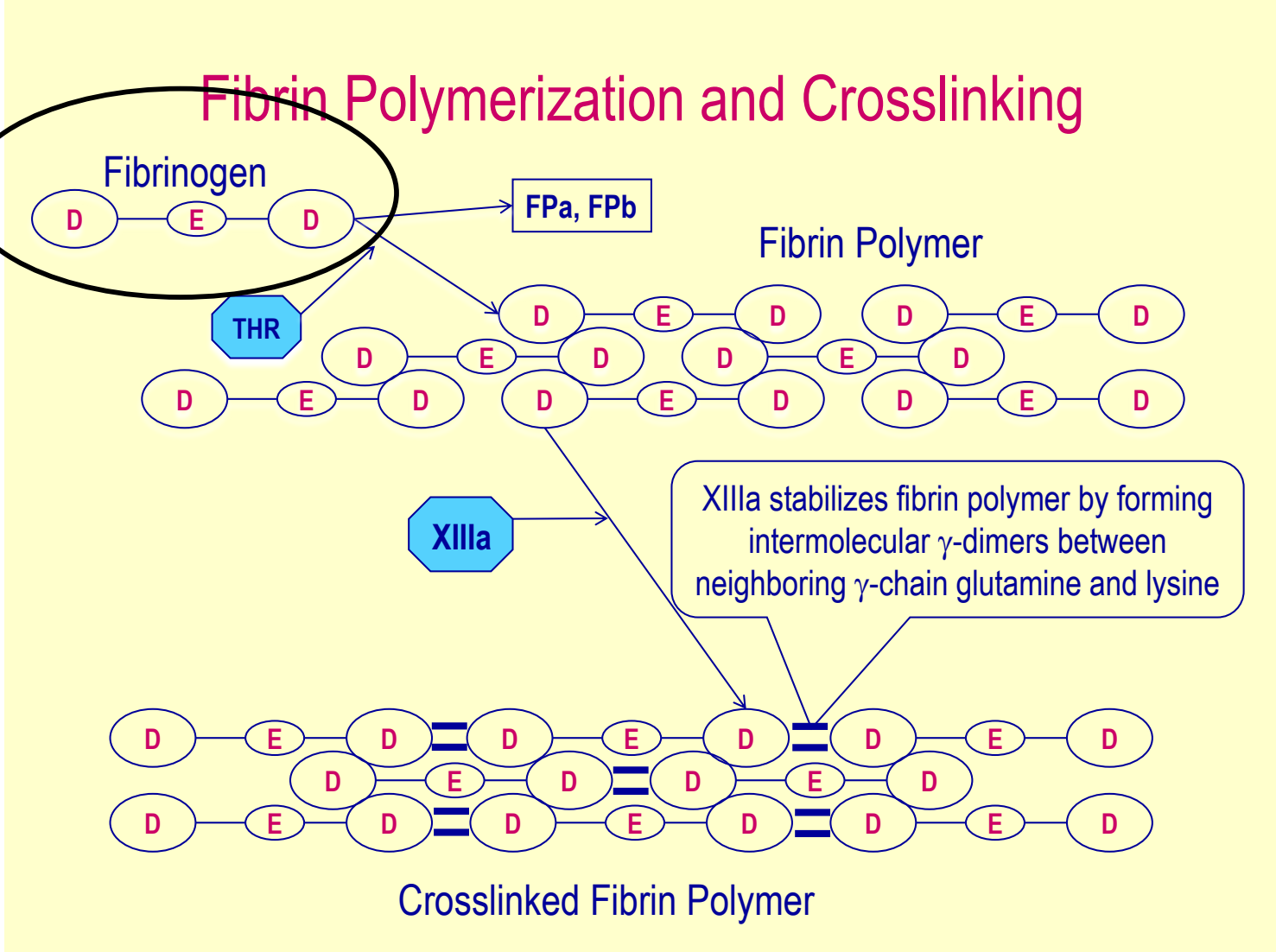
Fibrinogen Deficiency

- 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

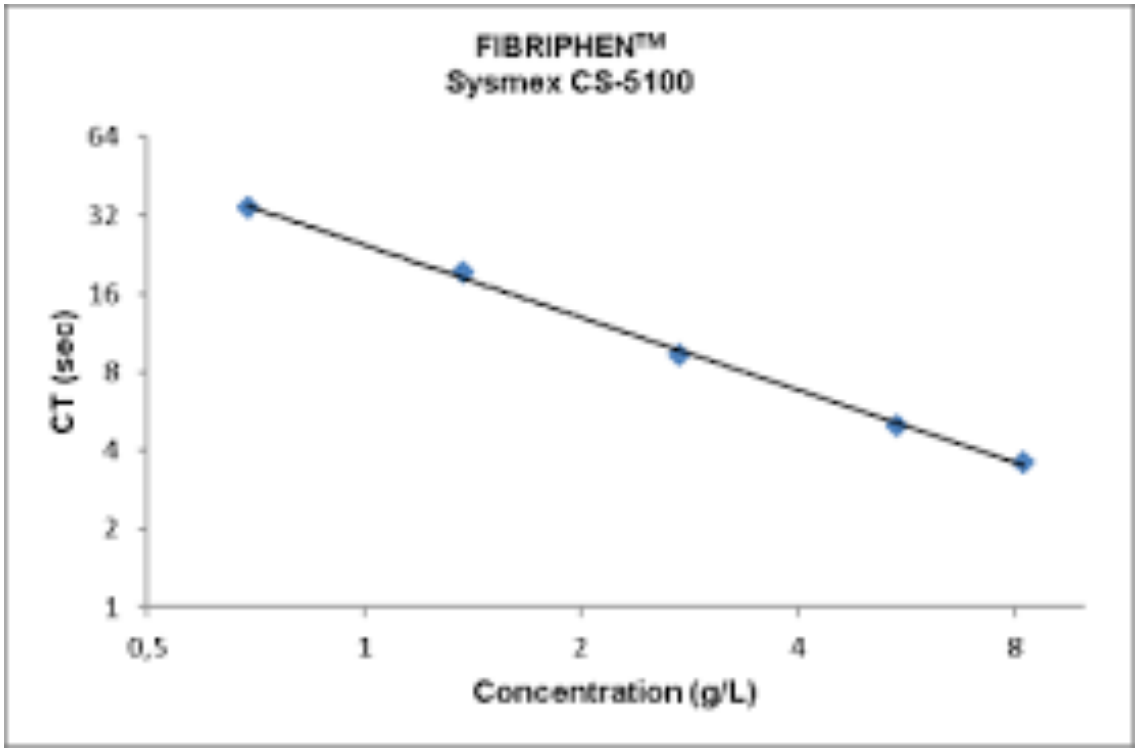
Clot-based Fibrinogen Assays

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



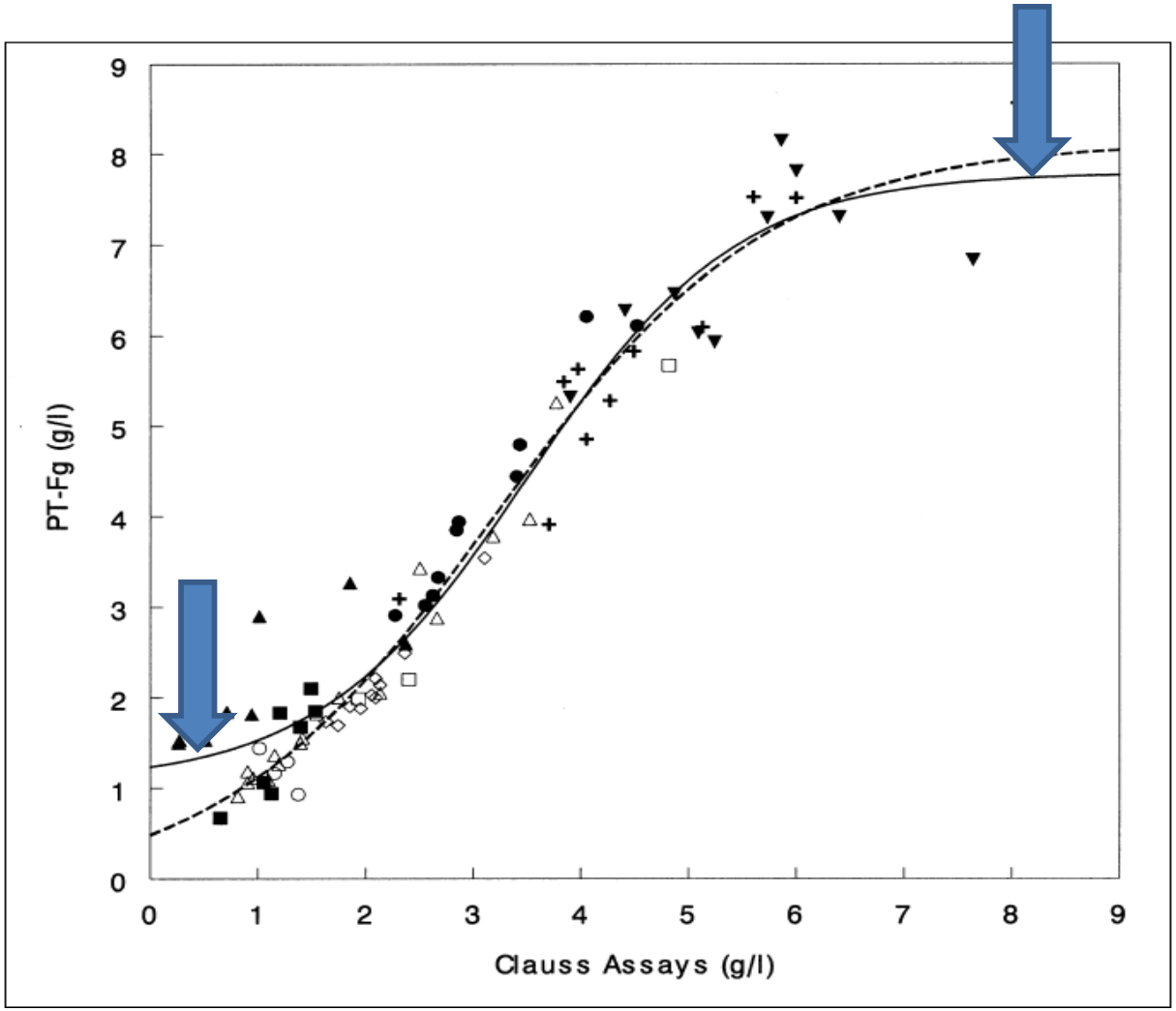
Clauss Fibrinogen Assay

- 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



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

Viscoelastometry [VET]

FDA 2021

Hemosonics
Quantra Qplus, Qstat

1946

FDA 2019

Hemonetics
Thromboelastograph—TEG 5000, TEG 6S

FDA 2010

Werfen IL
Rotational thromboelastometry—ROTEM Delta

FDA 1995, but available since 1979

Sienco
Sonoclot

Sienco Sonoclot

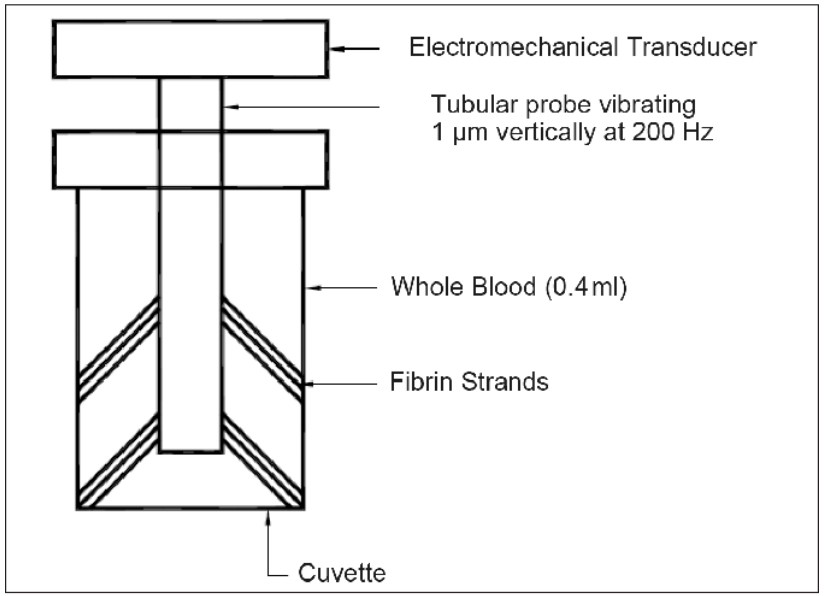
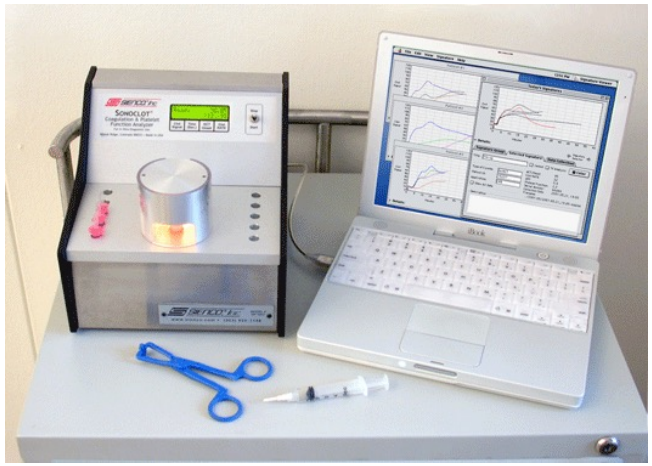
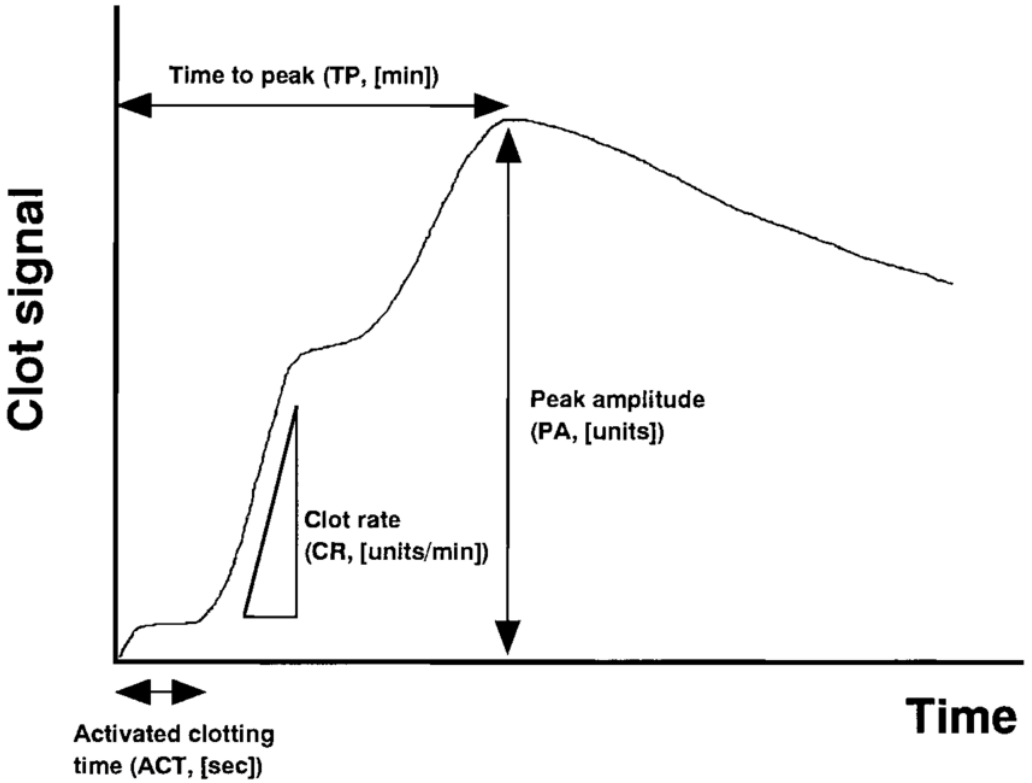


Figure 1: The operating principle of the Sonoclot analyser (Sienco Inc, Arvada,



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

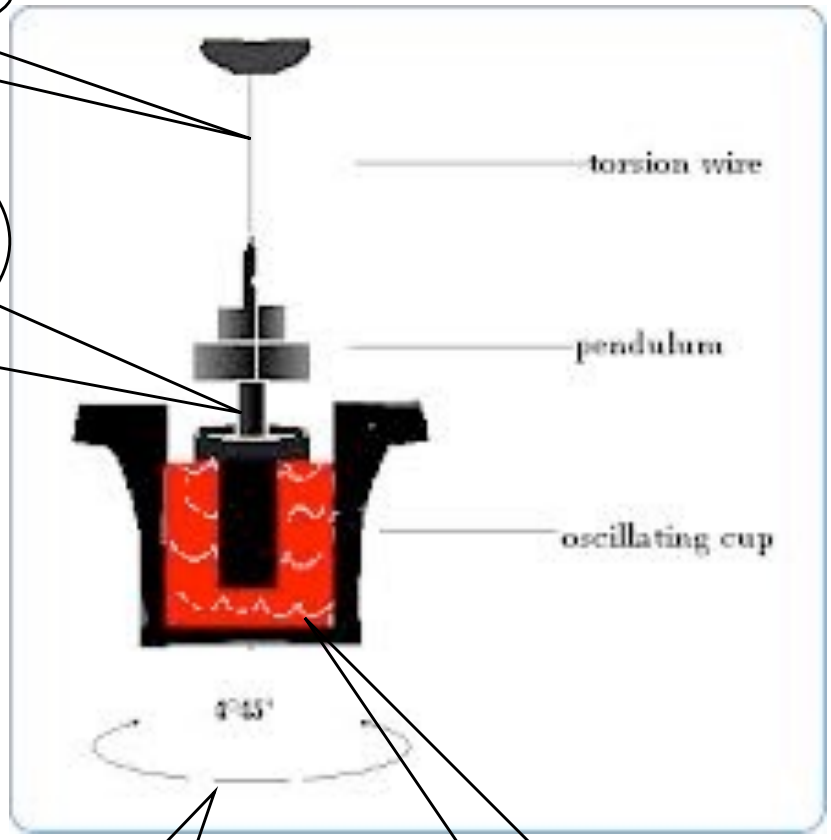


Thanks to **Jon Henderson**, Sienco President

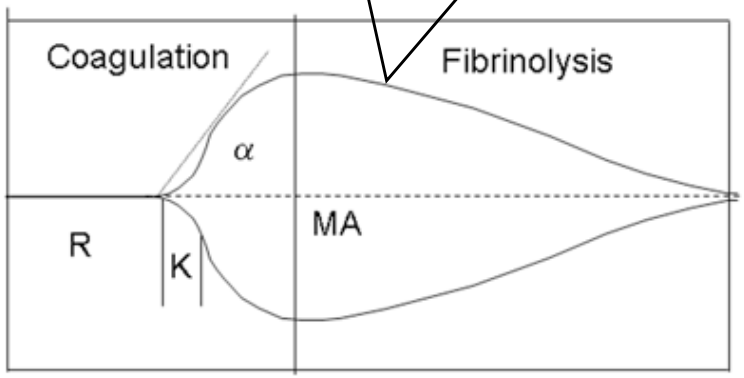
Thromboelastograph [TEG 5000]

Torsion recorded

Pendulum displaced by viscoelastic increases



Tracing reflects pendulum oscillation



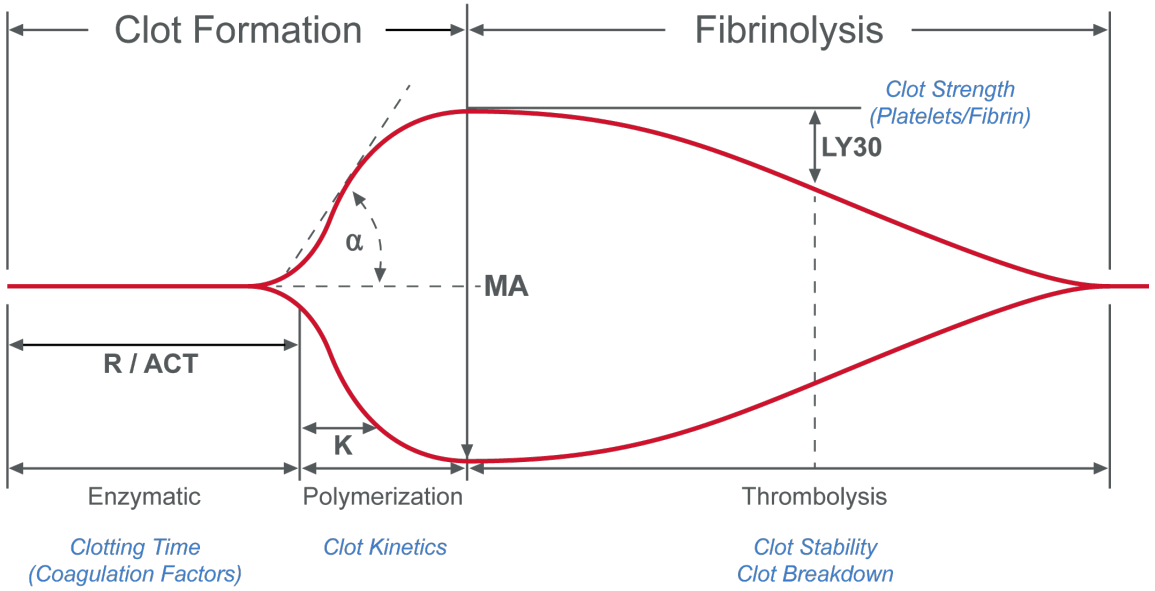
30 minutes

Cup oscillates

360 uL whole blood

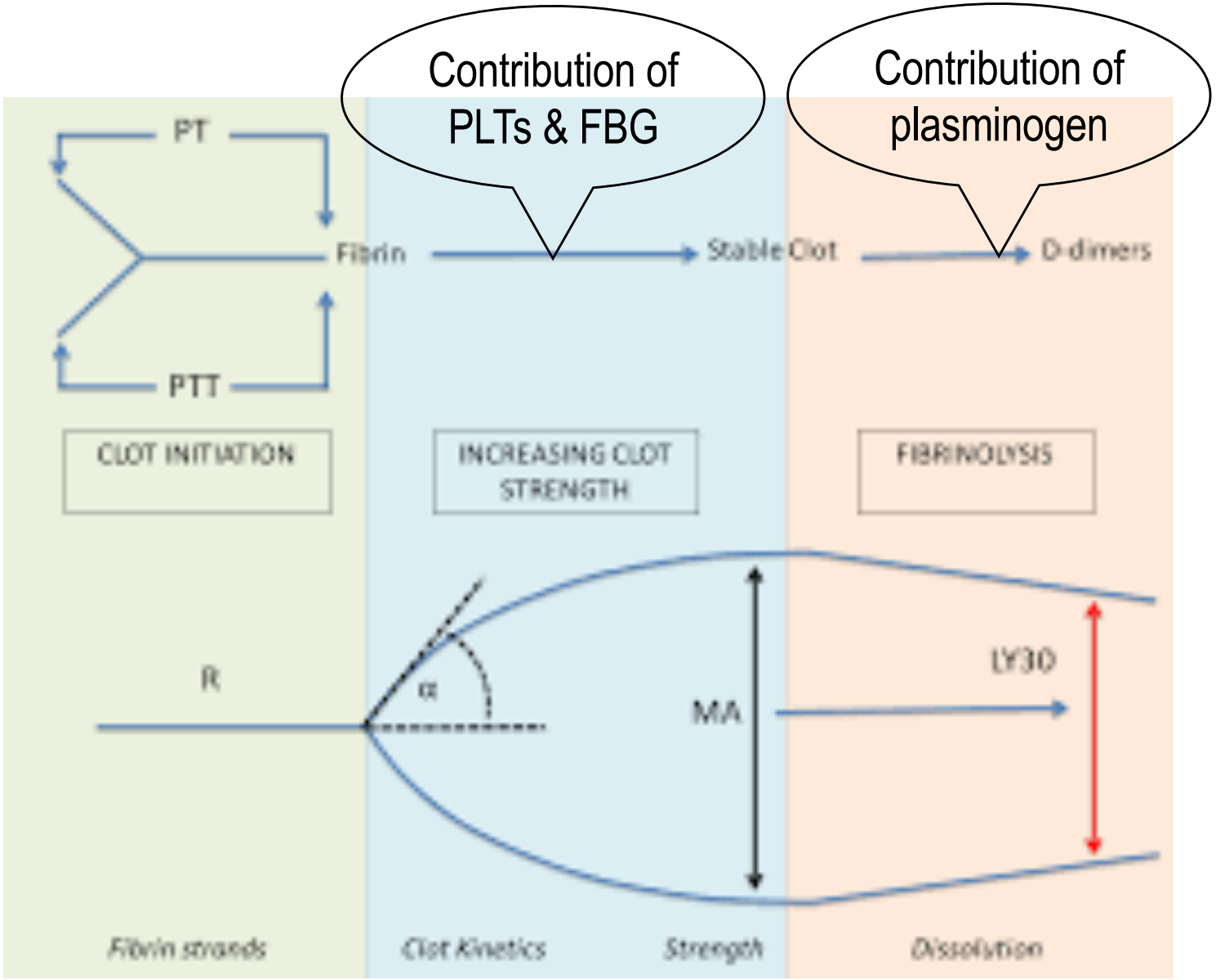
TEG 5000 Parameters

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%



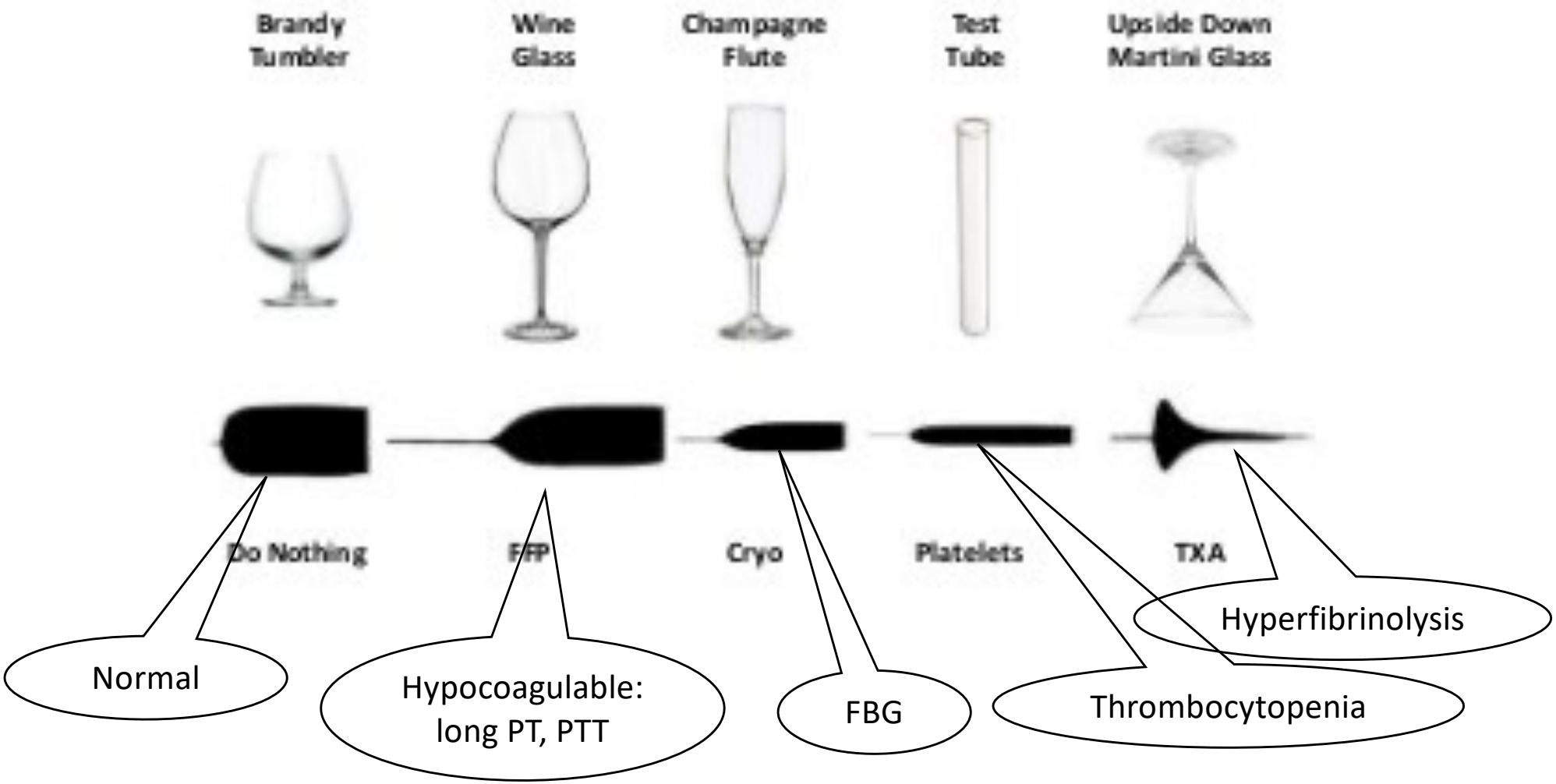
The TEG® hemostasis system continuously measures all phases of hemostasis as a net product of whole blood components.

TEG 5000


Contribution of PLTs & FBG
Contribution of plasminogen
PT
PTT
Fibrin
Stable Clot
D-dimers
CLOT INITIATION
INCREASING CLOT STRENGTH
FIBRINOLYSIS
R
α
MA
LY30
Fibrin strands
Clot Kinetics
Strength
Dissolution

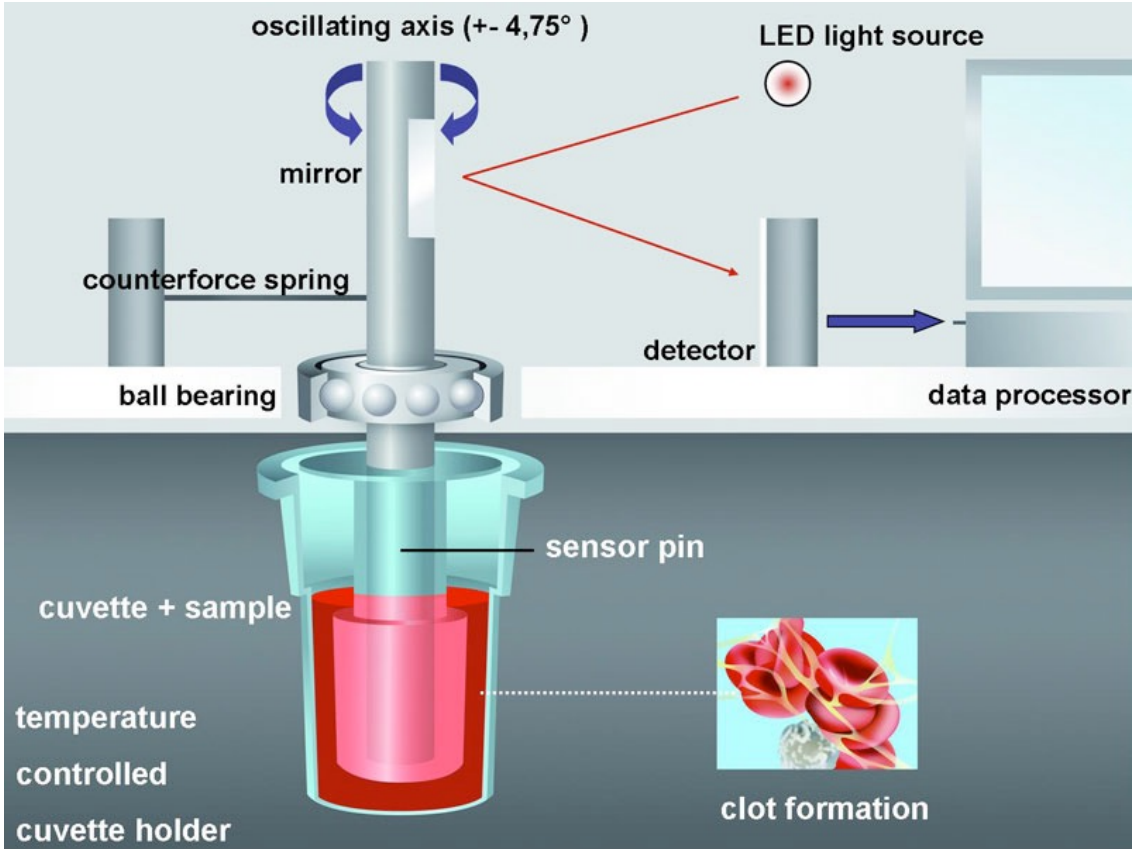
The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

TEG 5000 Results For Oenophiles



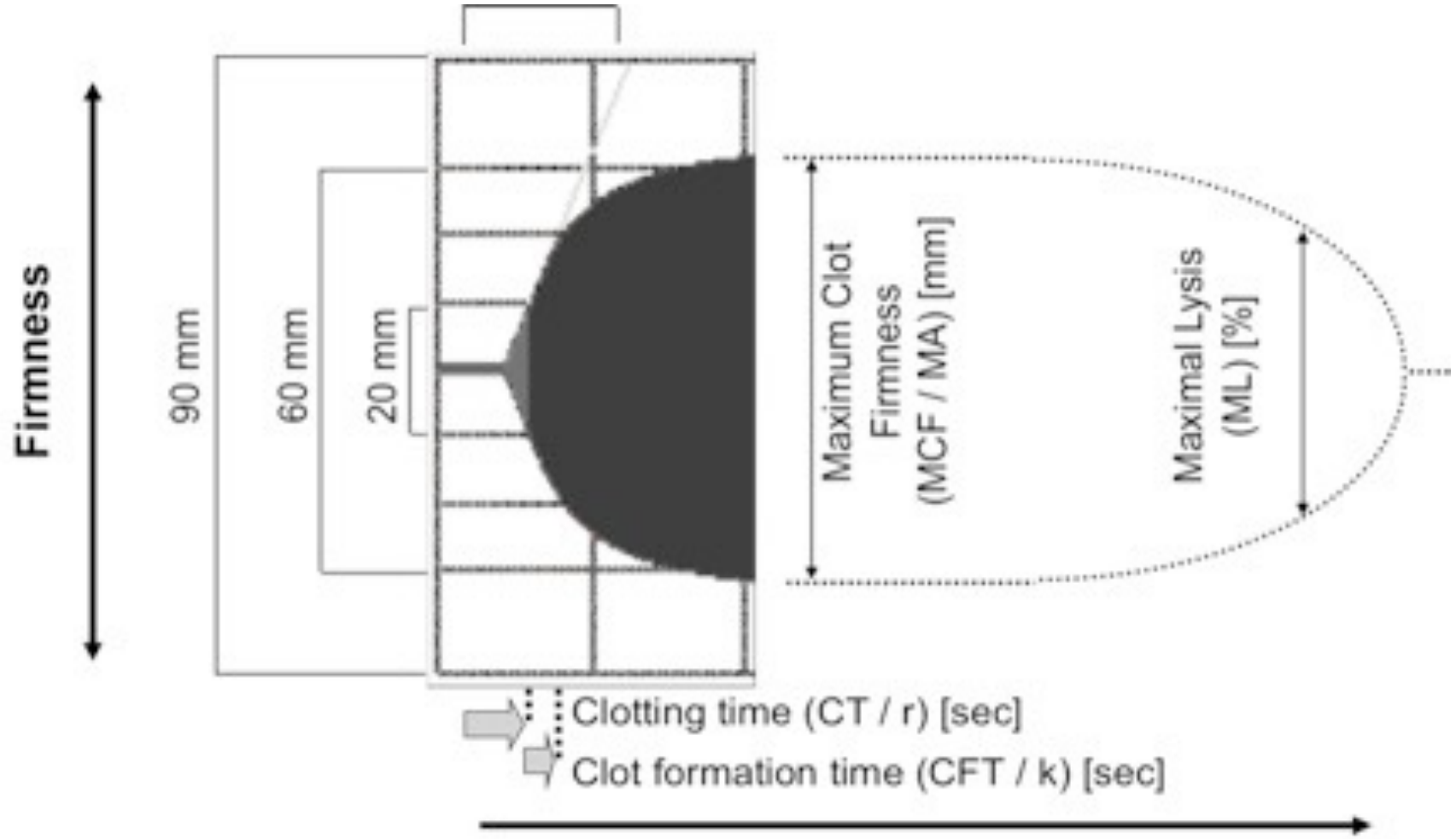
The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

ROTEM Delta



The Fritsma Factor
YOUR INTERACTIVE HEMOSTASIS RESOURCE

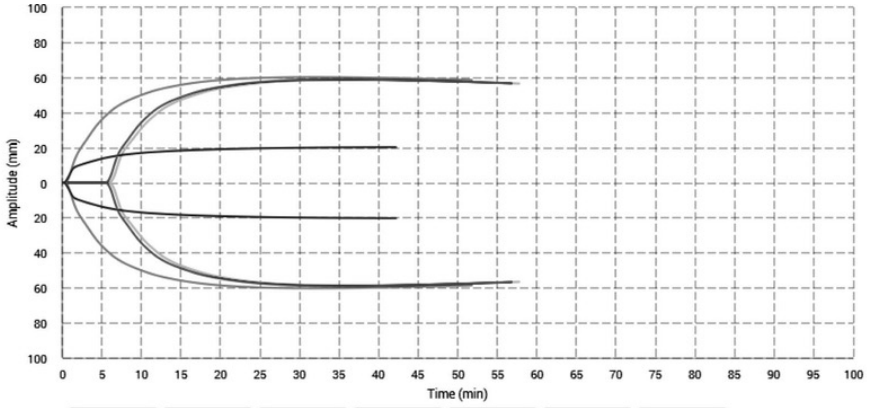
ROTEM Delta



Jackson GNB, Ashpole KJ, Yentis SM. The TEG® vs the ROTEM® thromboelastography/ thromboelastometry systems. Anaesthesia 2009;64:212–15.

TEG 6s

Cartridges W/ four rgts. *Citrated WB* transferred to selected cartridge, mixed with respective rgts and exposed to vibration. Detector monitors vertical motion of the meniscus, converts to a clot-strength proportional resonance frequency tracing.



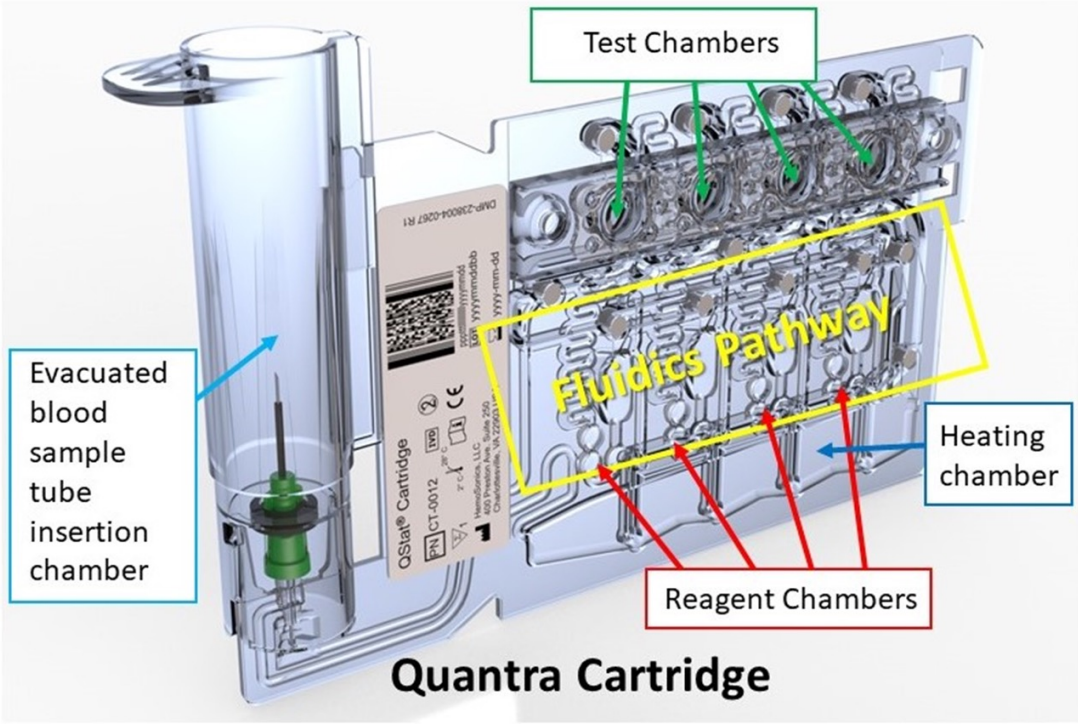
	TEG-ACT (sec)	R (min)	K (min)	ANGLE (deg)	MA (mm)	LY30 (%)	FLEV (mg/dL)
8/10/2015 8:25 AM	CM Citrated K,KH,RT,FF	HN-0308	Test Completed				
CK		6.4	1.7	69.6	57.8	0.3	
CRT	116	0.7	1.7	70.8	59.1	0.1	
CKH		5.9	1.7	70.2	58.1	0.4	
CFF		0.7	---	62.4	17.7	0	323

- ACT: activated clotting time
- CFF: activated by the functional FBG test [FLEV]
- CKH: activated with kaolin and heparinase
- CK: activated with kaolin
- CM: multichannel cartridge
- CRT: activated with rapid TEG
- FLEV: FBG level
- K: coagulation time
- MA: maximum amplitude
- R: reaction time

Hemosonics Quantra

QStat™ CARTRIDGE

- Trauma
- Liver transplant



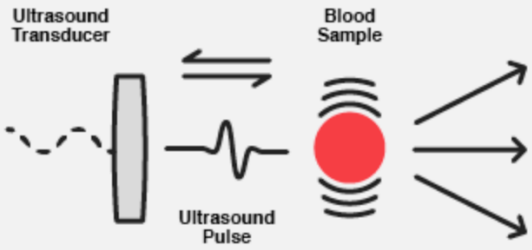
QPlus® CARTRIDGE

- Cardiac surgery
- Major orthopedic surgery

Thanks to **Todd Allen**, Clinical Development Director, Hemosonics, Inc.

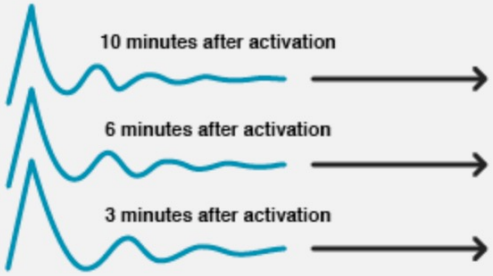
Requires ~3 mL citrated WB

Hemosonics Quantra QPlus



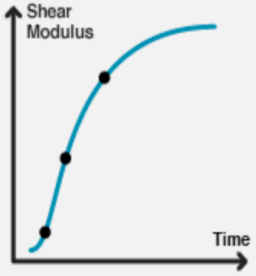
Data Acquisition

Ultrasound pulses are sent into the blood sample to induce resonance, causing the sample to oscillate.



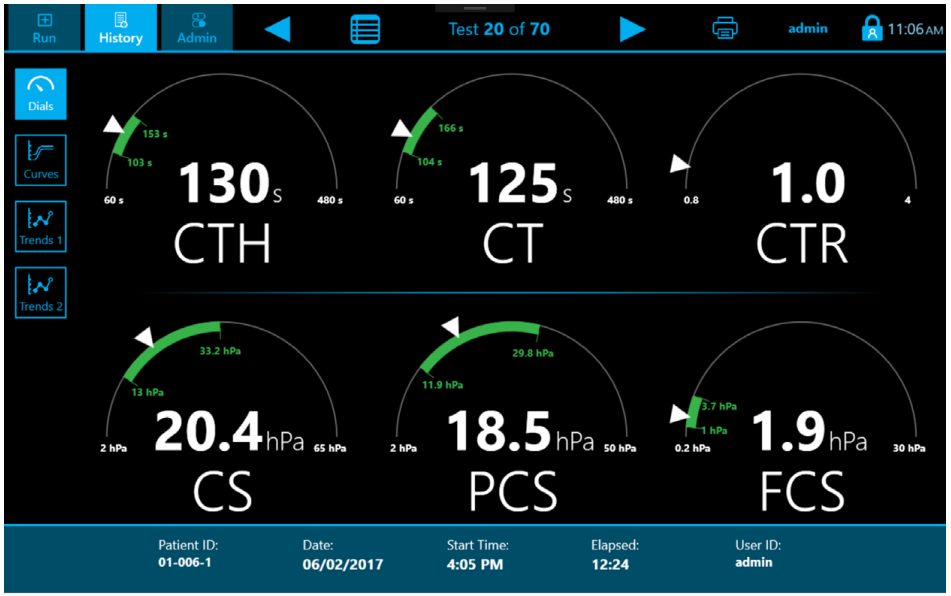
Displacement Estimation

the blood coagulates over time and its stiffness increases, the frequency of oscillation will also increase.



Clot Time and Clot Stiffness Measurement

Clot times and clot stiffness values are measured from the evolving shear modulus.



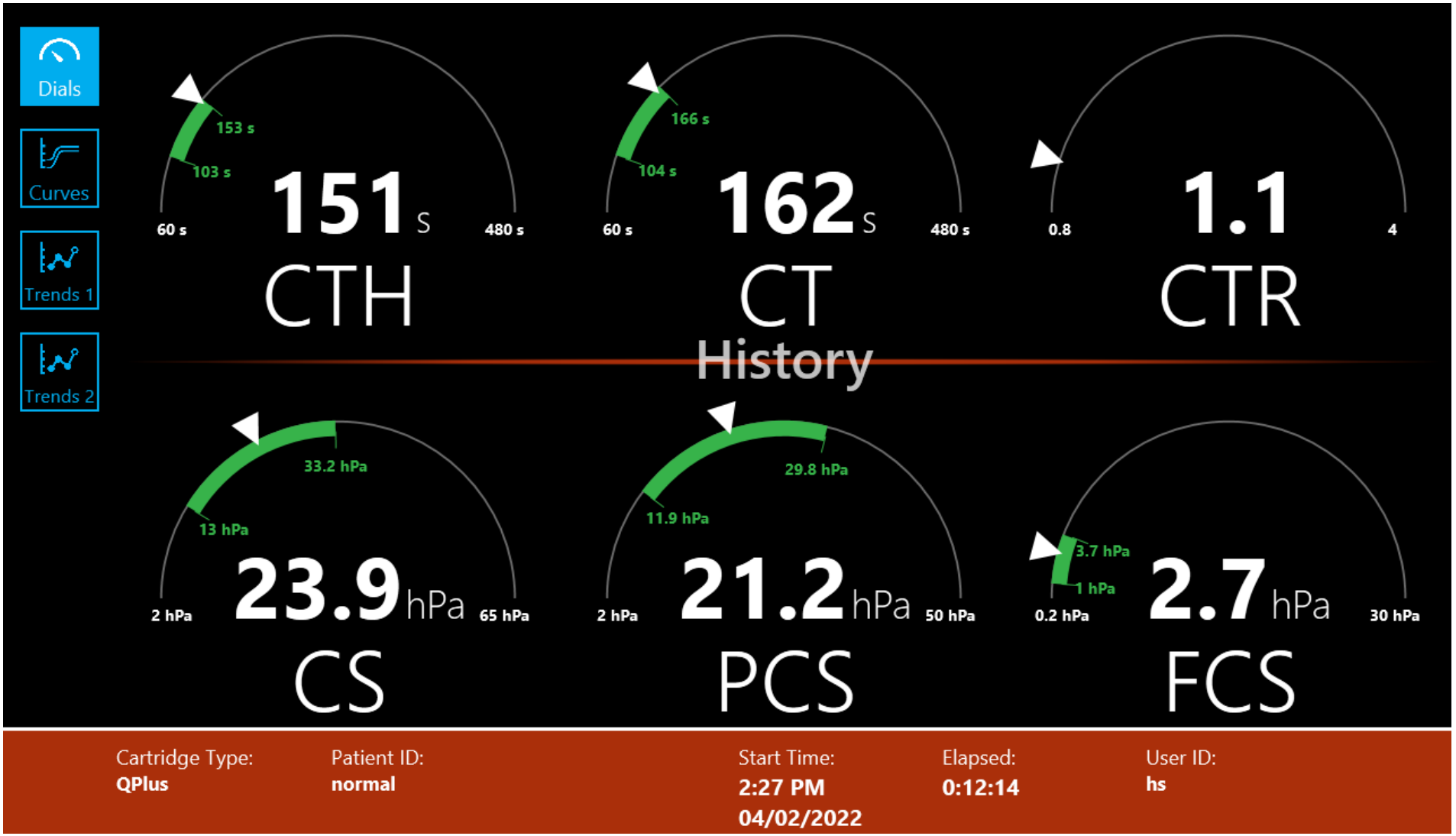
Sonorheometry [SEER]

- CTH: heparinase clot time
- CT: clot time
- CTR: clot time ratio
- CS: Clot stiffness
- PCS: platelets contribution
- FCS: fibrinogen contribution

Hemosonics Quantra Qplus Cartridge

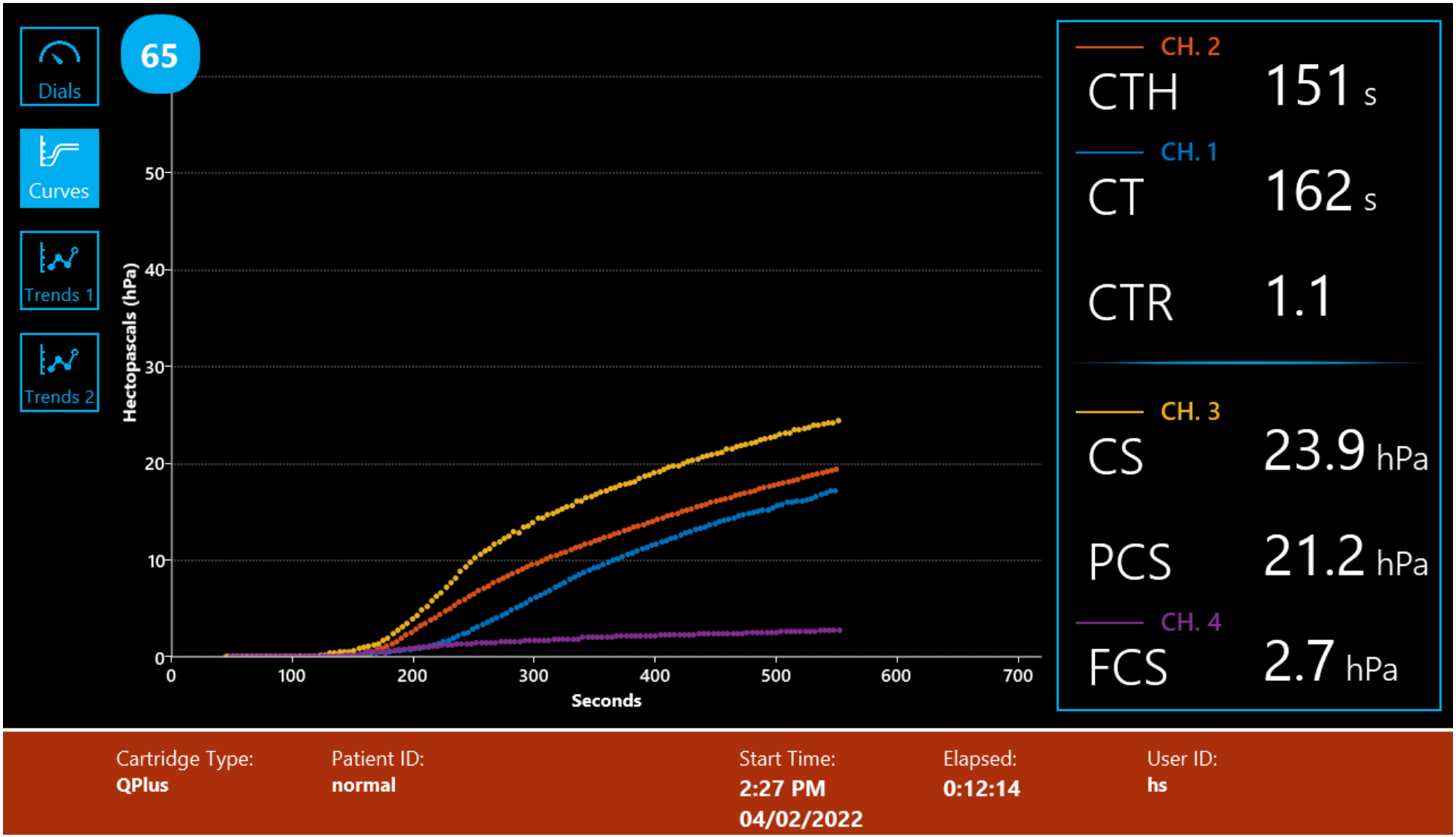
Parameter [Units]	Measurement
CT [s]	Intrinsic system clot time
CTH [s]	Intrinsic system clot time with heparinase neutralizer
CS [hPa]	Clot stiffness of WB, extrinsic activation [maximum amplitude]
FCS [hPa]	FBG contribution to clot stiffness
PCS [hPa, calculated]	PLT contribution to clot stiffness
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	

Quantra Qplus
Normal Result Numeric Screen



Thanks to Todd Allen, Clinical Development Director, Hemosonics, Inc.

Quantra Qplus
Normal Results Graphic Screen



Thanks to Todd Allen, Clinical Development Director, Hemosonics, Inc.

VET Assay Crosswalk

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

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

} Liver transplant, trauma, obstetrics

- Platelet mapping: TEG 5000 and 6S
  - Moderate complexity—requires laboratory scientist
  - Detect and monitor anti-PLT Rx, PLT dysfunction prior to surgery

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

VET Applications
Non-surgical Cardiology

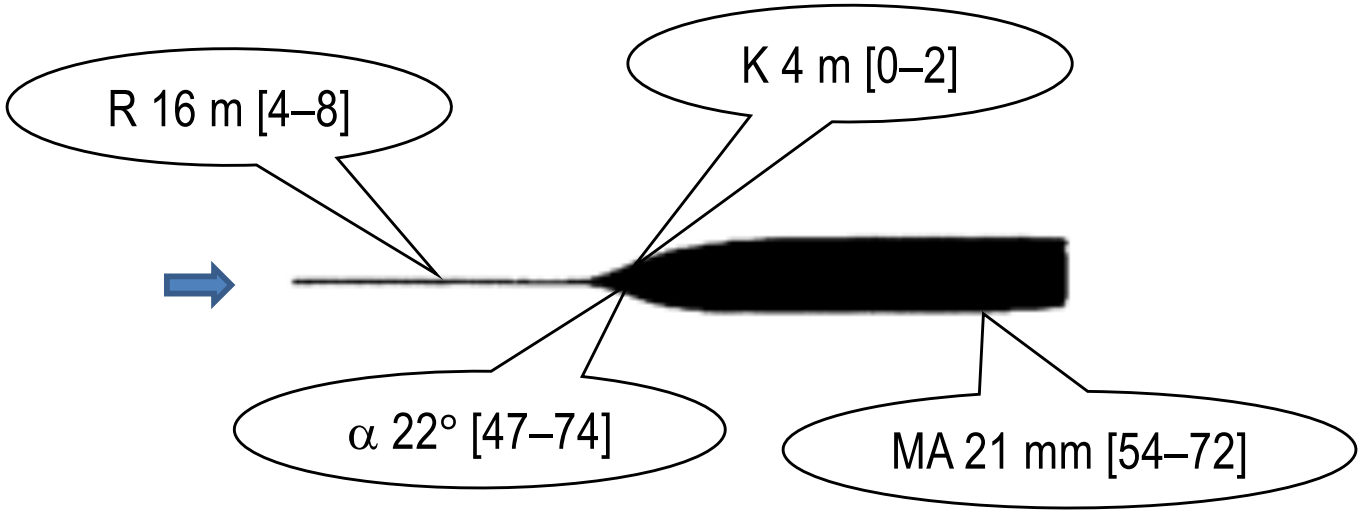
- Patient function monitoring when on antiplatelet therapy, such as GP IIb/IIIa antagonists [clopidogrel] or aspirin.
- VET is used in patients who appear to be "ASA resistant" as it permits *ex vivo* optimization of treatment
  - Raise ASA dosage, switch to clopidogrel, ticagrelor
- Platelet mapping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

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

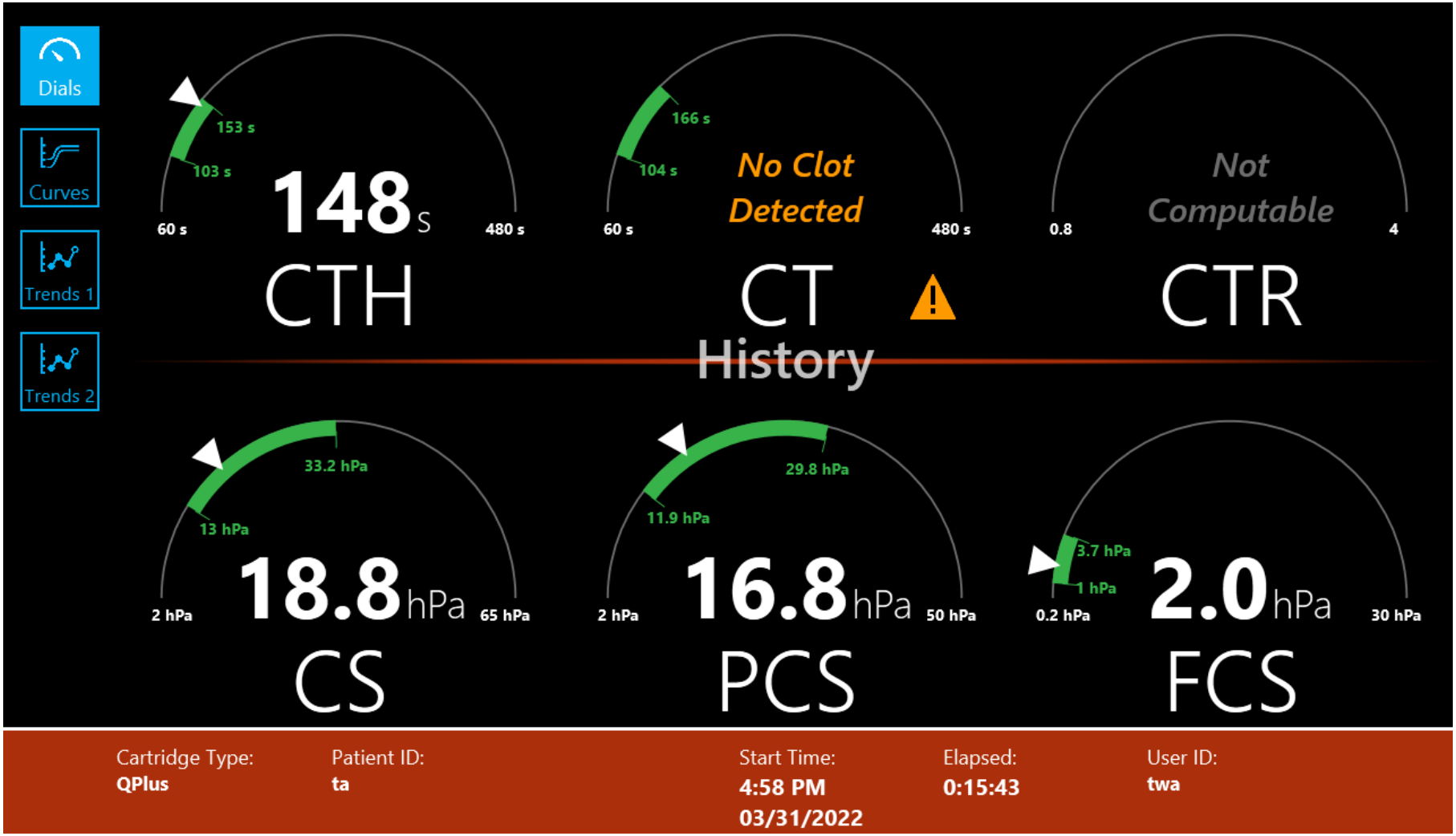
UFH Monitoring by TEG 5000

Kaolin, Ca^{++} [CK]

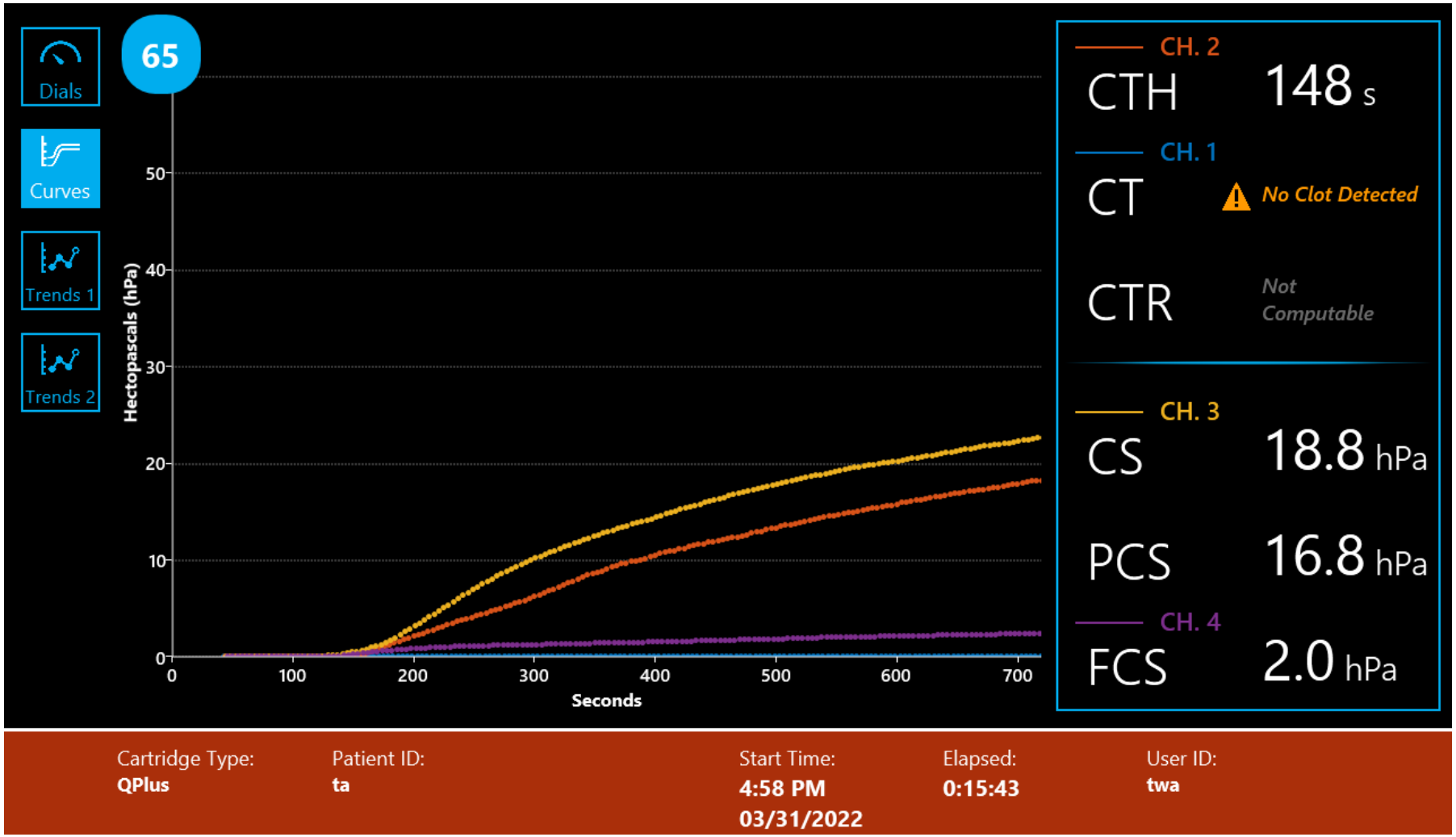


Kaolin, Ca^{++} + Heparinase [CH]

Quantra Qplus: UFH in CPB



Quantra Qplus: UFH in CPB Graphic Screen



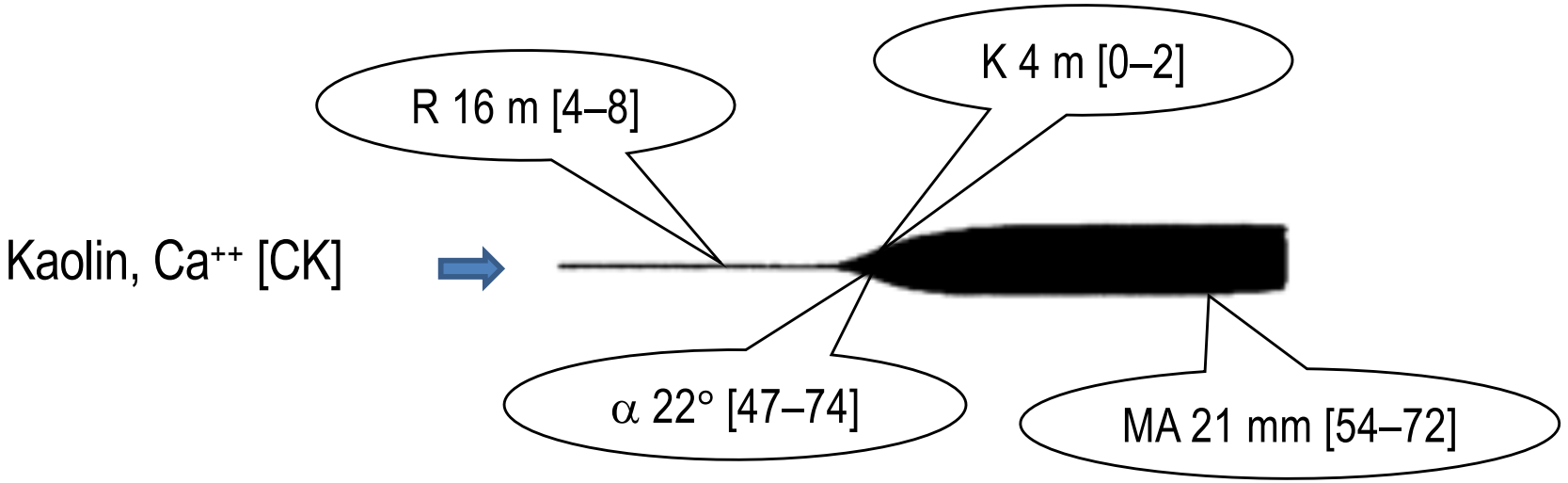
Thanks to Todd Allen, Clinical Development Director, Hemosonics, Inc.

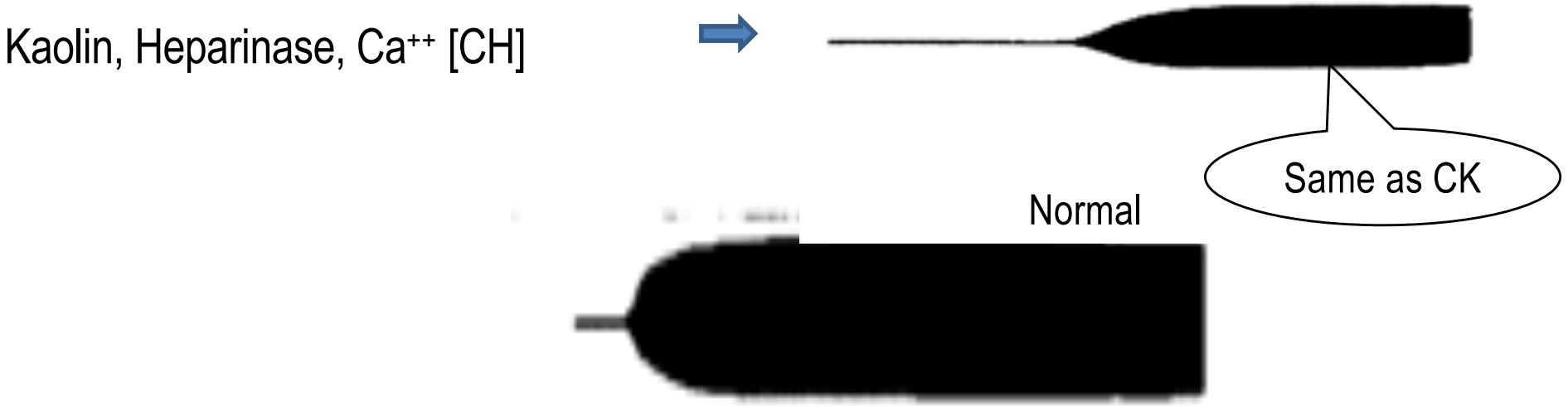
VET Applications: Liver

- Acute & chronic liver failure–coagulopathy, thrombocytopenia, platelet dysfunction
  - Most procoagulants produced in the liver
  - DIC is also characterized by thrombocytopenia and coagulopathy.
- During the an-hepatic phase of transplantation, tissue plasminogen activator [TPA] level from the diseased liver rises, contributing to hyperfibrinolysis.
- Serial tracings guide component therapy: tranexamic acid [TXA], PLT concentrate, plasma [not recommended], prothrombin complex concentrate [PCC. Kcentra®], FBG concentrate [FIBRYGA, RIASTAP].

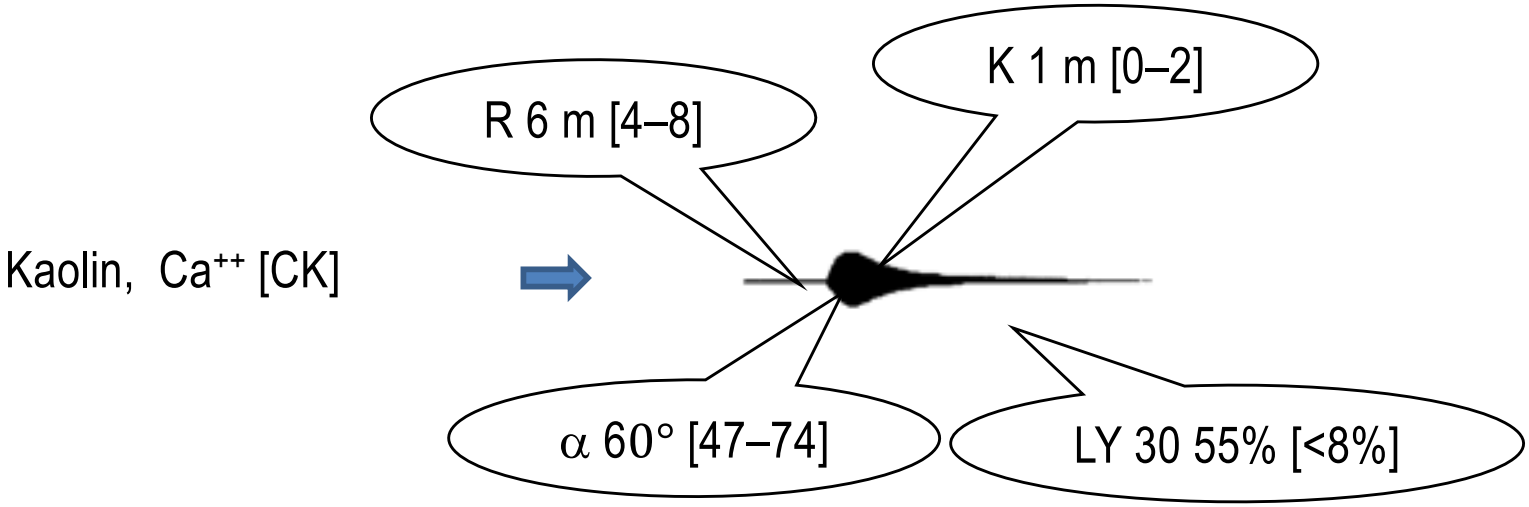
Trapani LM. Thromboelastography: current applications, future directions. Open Journal of Anesthesiology 2013; 3: 23–7.

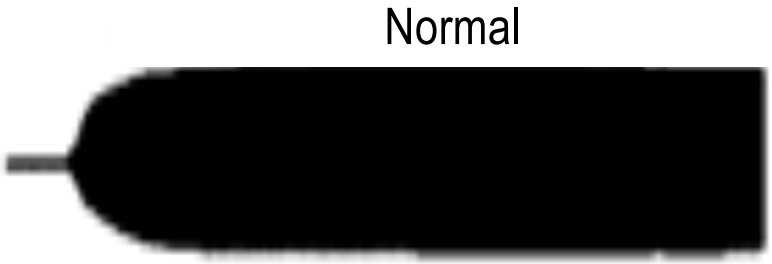
Liver Coagulopathy



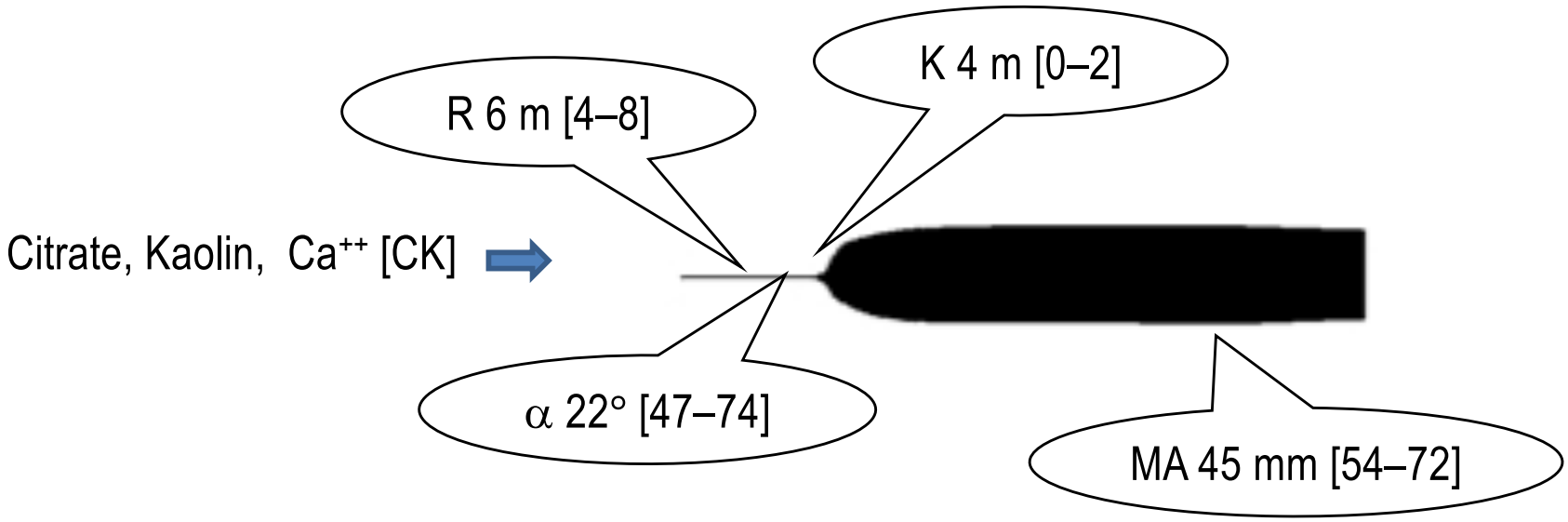


Liver Transplant: Hyperfibrinolysis





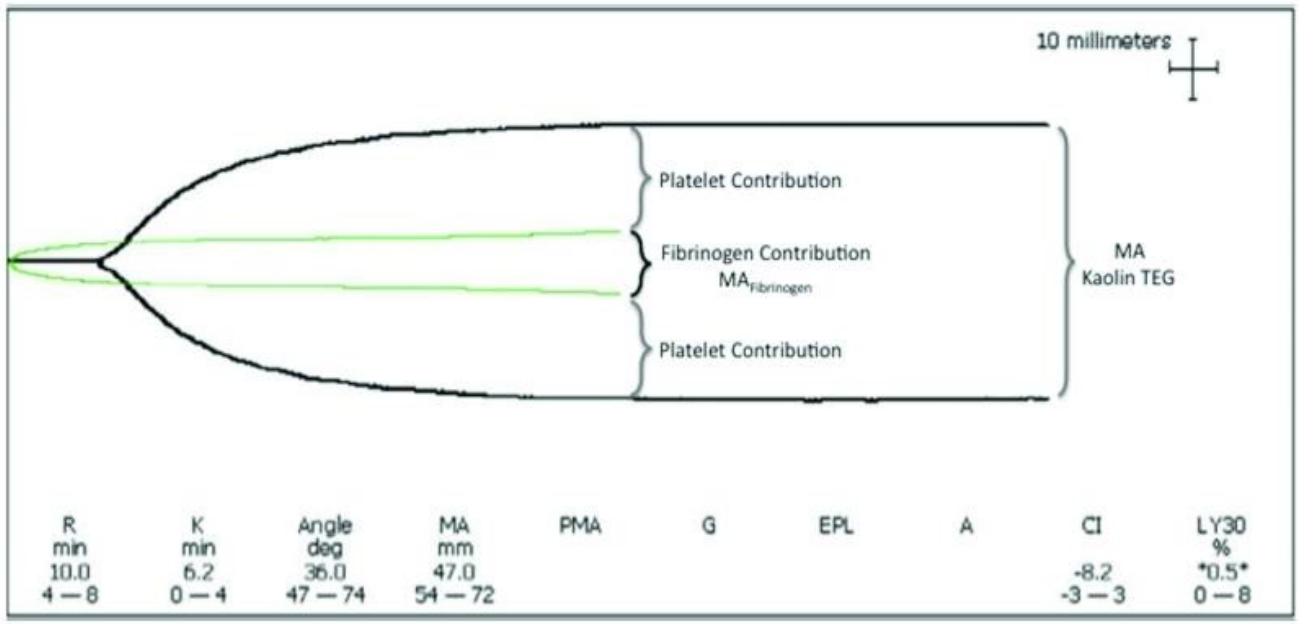
Thrombocytopenia, PLT Dysfunction, Anti-platelet Therapy



Normal

TEG Functional Fibrinogen [FF]

- [CK]: Mix 1 mL citrated WB in a Kaolin vial to provide PLT contribution.
- Transfer 340 µL to a 37°C TEG cup 20 µL 0.2 mol/L $CaCl_2$
- [CKA]: Mix 0.5 mL citrated WB in Kaolin/GPIIb/IIIa receptor antagonist vial.
- Transfer a 340 µL aliquot a 37°C TEG cup [20 µL 0.2 mol/L $CaCl_2$] for FBG.
- MA_{FBG} is converted to mg/dL FBG using a viscosity cal curve
- Correlation to von Clauss Fg is R^2=0.87, p<0.0001
- The contribution of FBG and PLTs to overall MA is determined by the equation:
  $MA = MA_{PLT} + MA_{FBG}$



Harr JN, Moore EE, Ghasabyan A, et al. Functional fibrinogen assay indicates that fibrinogen is critical in correcting abnormal clot strength following trauma. Shock. 2013; 39: 45–9.

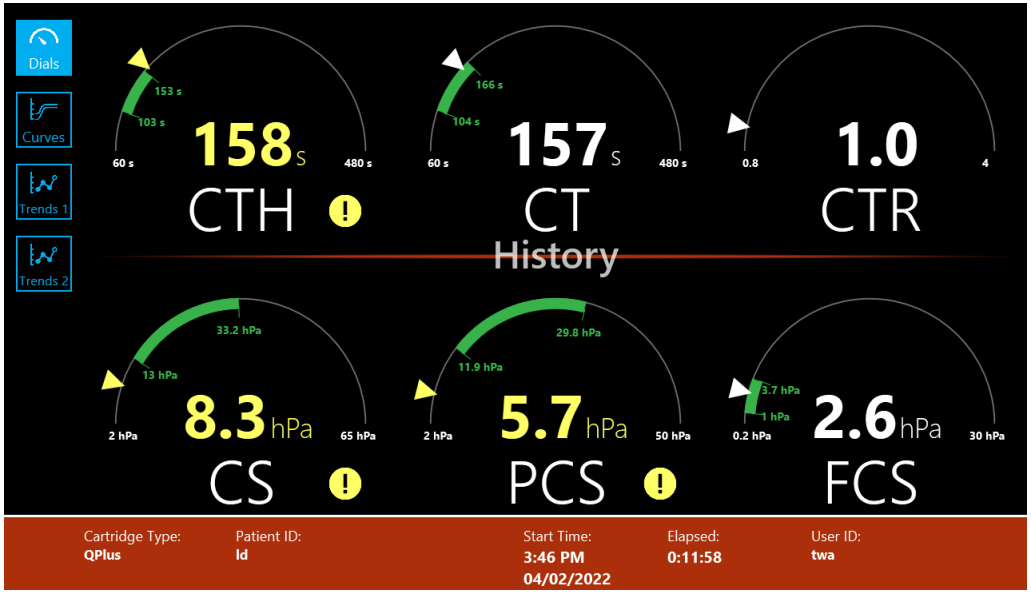
VET Applications: Obstetrics

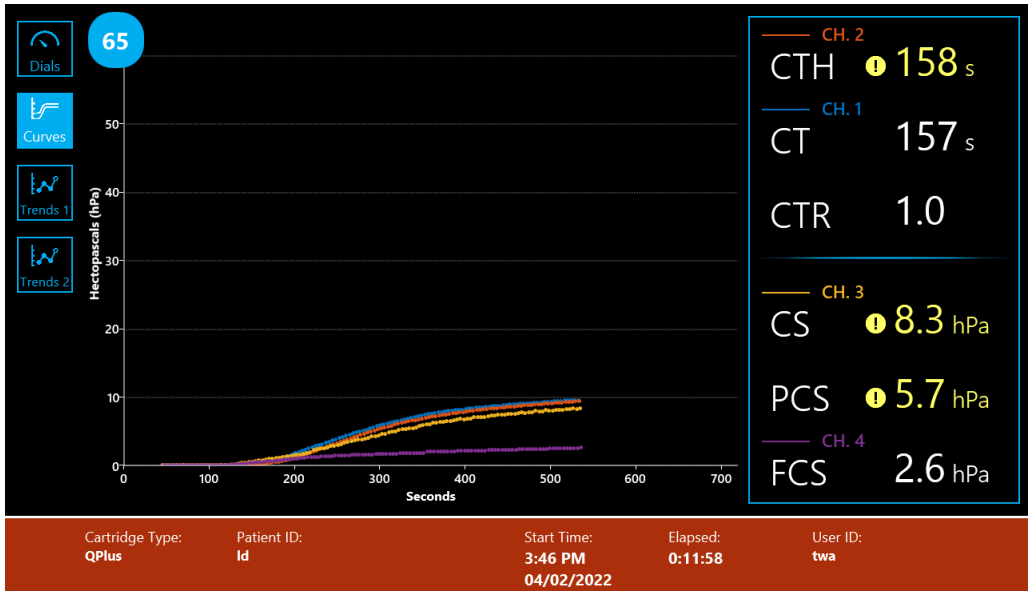
- VET differentiates the hypercoagulable state in pre-eclampsia from the coagulopathy and thrombocytopenia of HELLP syndrome.
  - Prenatal, postpartum
- VET may identify the coagulopathy in post-partum hemorrhage to guide therapy such as in VWD

The Fritsma Factor

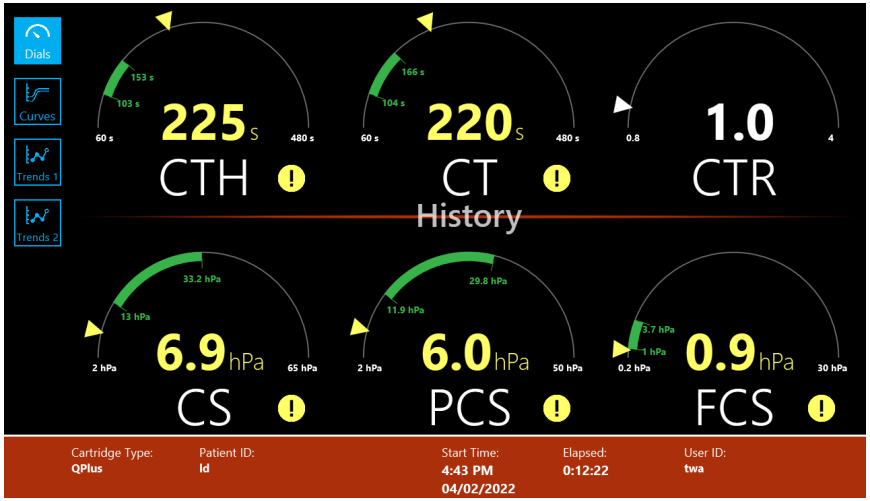
YOUR INTERACTIVE HEMOSTASIS RESOURCE

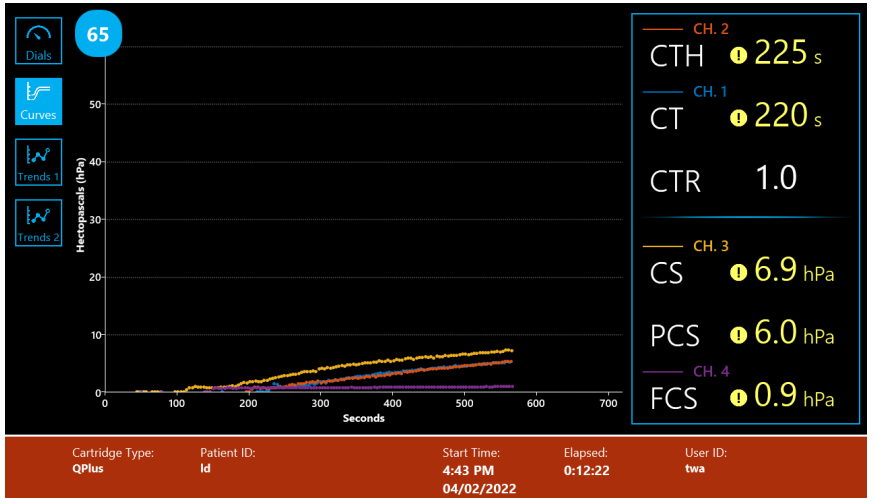
Quantra Q-plus Thrombocytopenia, Thrombocytopathy, Anti-platelet Therapy





Hemodilution

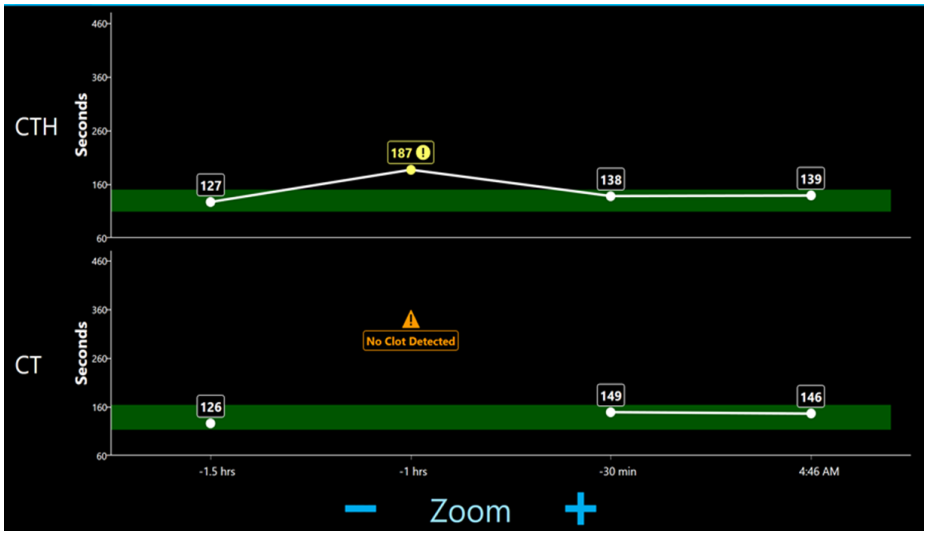




Quantra QPlus Trends Screens of Serial Results

- Results by parameter over time relative to their RIs [green bar].
  - CS, PCS, FCS above green bar indicate a hypercoagulable state; below the bar indicates hypocoagulable

CT, CTH above the green bar indicate slow clot initiation; below = faster



TEG 5000 Platelet Mapping [PM]

- TEG PM detects ASA or clopidogrel efficacy by activating the ADP receptor P_2Y_{12} and the eicosanoid TxA_2 pathways to produce the MA.
- Measuring % activation of either pathway requires 4 channels…
  1. Kaolin-induced TEG [CK] generates the $MA_{Thrombin}$ which estimates the fibrin and PLT contribution to the MA.
  2. Reptilase and FXIIIa activator [F] polymerizes and crosslinks fibrin W/O PLTs to isolate the fibrin component of the MA, MA_{Fibrin}
  3. Activator F plus ADP [MA_{ADP}] measures the PLT P_2Y_{12} receptor pathway, generates MA
  4. Activator F plus arachidonic acid [MA_{AA}] measures the PLT COX receptor pathway--MA
- This formula provides % PLT activation for either pathway:

$$\%\ Platelet\ Activation = \frac{MA_{AA}\ or\ MA_{ADP} - MA_{FIBRIN}}{MA_{THROMBIN} - MA_{FIBRIN}} * 100\,\%$$

George MJ, Burchfield J, MacFarlane B, et al. Multiplate and TEG platelet mapping in a population of severely injured trauma patients. Transfus Med. 2018; 28: 224–30.

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, Kjelgaard-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

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?

Bottom Line at the End [BLEAT]

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