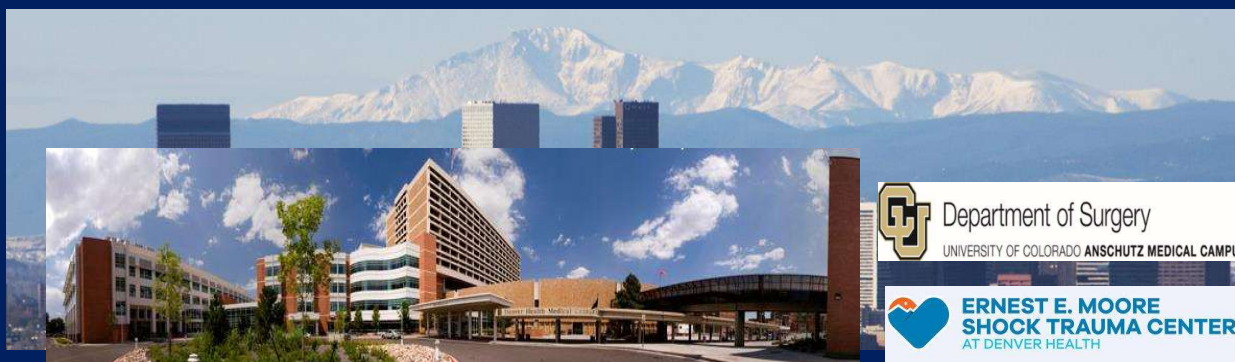


Hypocalcemia in Hemorrhagic Shock



EE Moore

Denver Health / University of Colorado Denver

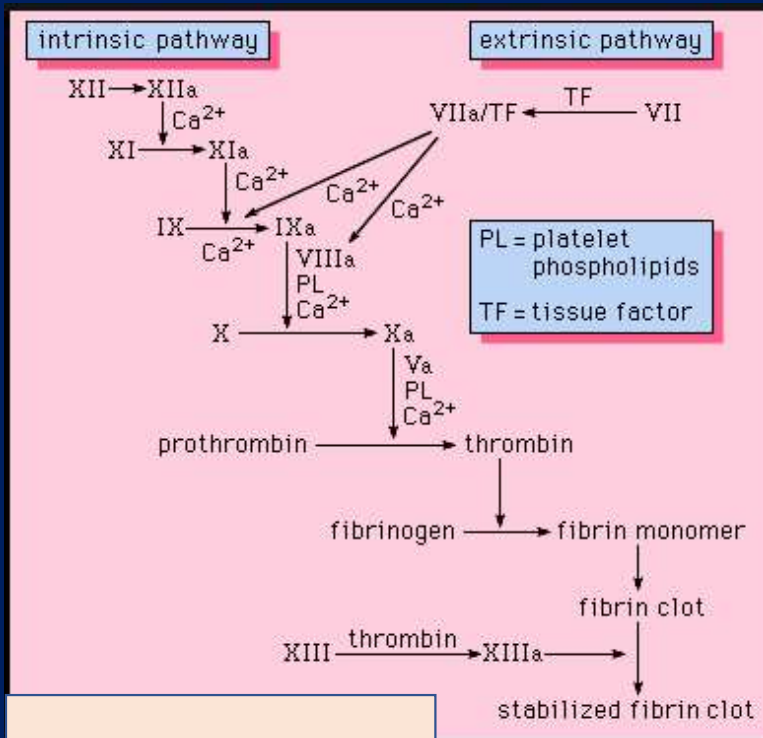
Research Support : Haemonetics, Instrumentation Laboratory, Hemosonics, Stago, Diapharma, Prytime, Humacyte & Genentech

Shared IP: Haemonetics; **Co-founder**: ThromboTherapeutics Inc

Federal Grants: NIH NIGMS RM1, T32; NIH NHBLI UMI; DOD



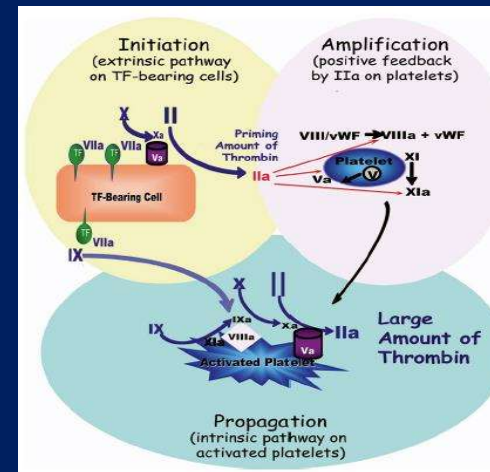
Role of Calcium in Coagulation



Review > *J Thromb Haemost.* 2009 Jul;7(7):1057-66. doi: 10.1111/j.1538-7836.2009.03411.x
 Epub 2009 Apr 24.

Calcium signaling in platelets

D Varga-Szabo¹, A Braun, B Nieswandt



DETERMINATION OF BLOOD COAGULABILITY.

[JULY 29, 1893.]

ON A METHOD OF DETERMINING THE CONDITION OF BLOOD COAGULABILITY FOR CLINICAL AND EXPERIMENTAL PURPOSES, AND ON THE EFFECT OF THE ADMINISTRATION OF CALCIUM SALTS IN HÆMOPHILIA AND ACTUAL OR THREATENED HÆMORRHAGE.

[PRELIMINARY COMMUNICATION.]

BY A. E. WRIGHT, M.D. DUBL.,

Professor of Pathology, Army Medical School, Netley.

It is evident that the foundations of a rational system of therapeutics in connection with the treatment of conditions of altered blood coagulability cannot even be laid until we are in possession of a method by which the necessary clinical data on blood coagulability can be collected. The method

- Potential value of citrate in blood transfusions in humans first reported in **1893 by Wright**
- In **1915**, sodium citrate was introduced as an anticoagulant independently by **Hustin in Belgium**, **Agote in Argentina**, and **Lewisohn in the USA**.

Citrate : Blood Storage in WWI

- **Oswald Robertson**, the “Father of Blood Banking”, transported group 4 (type O) blood preserved with **dextrose and citrate in glass jars placed in an “ice box”** (ammunition boxes with ice and sawdust)

JUNE 22, 1918]

TRANSFUSION WITH PRESERVED RED BLOOD CELLS.

THE BOSTON MEDICAL JOURNAL 691

TRANSFUSION WITH PRESERVED RED BLOOD CELLS.

BY
OSWALD H. ROBERTSON, CAPT. M.O.R.C., U.S.A.,
U.S. ARMY BARRACK HOSPITAL.

THERE is a definite need in front area medical work of a method for giving transfusions rapidly. At casualty clearing stations during the busy time of an attack, it is obviously impossible to perform transfusions by the usual methods in nearly all the cases in which transfusion is indicated. The difficulty of procuring sufficient blood under rush conditions, the time consumed in carrying out the transfusions, and the need of every available medical officer in the operating theatre, all tend to reduce the number of transfusions which can be given. The use of preserved human blood cells for transfusion suggested itself as a possible solution of certain of these difficulties.

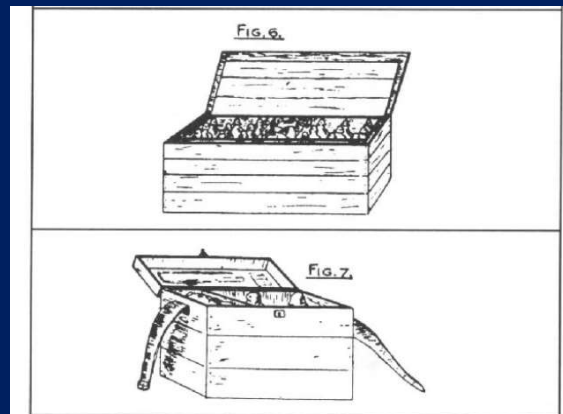


Fig. 2. Photograph of Captain Oswald Robertson, Boulogne, 1918. (O.H. Robertson's papers, American Philosophical Society, Philadelphia, PA.)

Hypocalcemia in Hemorrhagic Shock

> [Am J Physiol.](#) 1971 Apr;220(4):874-9. doi: 10.1152/ajplegacy.1971.220.4.874.

Plasma calcium concentration changes in hemorrhagic shock

G D Barry

Dog : Wiggers prep

the changes in plasma ionized calcium concentration observed in hemorrhagic hypotension and shock.

> [J Trauma.](#) 1976 Aug;16(08):633-8. doi: 10.1097/00005373-197608000-00007.

Calcium flux during hemorrhagic shock in baboons

D Trunkey, J Holcroft, M A Carpenter

This study shows that there are significant disturbances of Ca^{2+} and Mg^{2+} during resuscitation from hemorrhagic shock. These disturbances may in part explain cellular dysfunctions during shock,

When is Calcium Supplementation Warranted

- 1983-1985: The Detroit General group (Lucas, Ledgerwood et al) reported the beneficial role of **calcium supplementation during resuscitation from hemorrhagic shock**

> J Trauma. 1985 Jul;25(7):594-600. doi: 10.1097/00005373-198507000-00004.

The beneficial role of calcium supplementation during resuscitation from shock

R Denis, C E Lucas, A M Ledgerwood, J R Wallace, D E Grabow, C Harrigan, E J Dawe

PMID: 4009765 DOI: 10.1097/00005373-198507000-00004

- In the current ATLS Shock Chapter



CALCIUM ADMINISTRATION

Most patients receiving blood transfusions do not need calcium supplements.

> Crit Care Med. 2005 Sep;33(9):1946-52. doi: 10.1097/01.ccm.0000171840.01892.36.

Early hypocalcemia in severe trauma

Benoît Vivien ¹, Olivier Langeron, Eric Morell, Catherine Devilliers, Pierre A Carli, Pierre Coriat, Bruno Riou

Ca ++ 74 % < 1.1 mmol/L at arrival

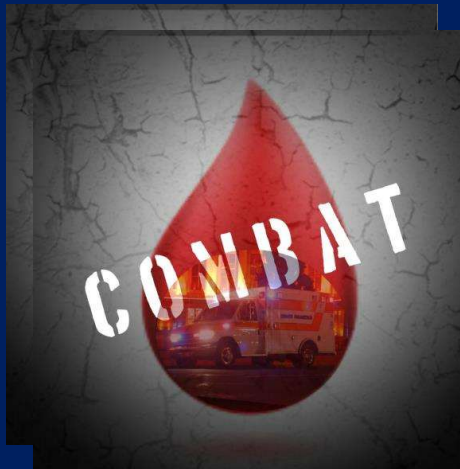
> Emerg Med J. 2016 Aug;33(8):569-72. doi: 10.1136/emered-2015-205096. Epub 2016 Feb 4.

Ionised calcium levels in major trauma patients who received blood in the Emergency Department

Stacey Webster ¹, Samuel Todd ², Julian Redhead ³, Chris Wright ³

Ca ++ 55 % < 1.1 mmol/L at arrival

ADMISSION IONIZED-CALCIUM IN TWO CIVILIAN RANDOMIZED CONTROLLED TRIALS OF PRE-HOSPITAL PLASMA FOR TRAUMATIC HEMORRHAGIC SHOCK



ERNEST E. MOORE
SHOCK TRAUMA CENTER
AT DENVER HEALTH



COMBAT : Secondary Endpoints

Secondary endpoints	Control N=60	Plasma N=65	
Variable	Median (IQR) or %	Median (IQR) or %	p-value
Arrival INR	1.15 (1.08-1.29)	1.27 (1.11-1.40)	0.10
INR >1.3	24%	43%	0.0298
BD >8 mEq/L	52%	55%	0.77
Lactate >5mmol/L	48%	51%	0.77

40 % Hypocalcemia; 36 % vs 53 %

Hypocalcemia is Associated with Impaired Coagulation

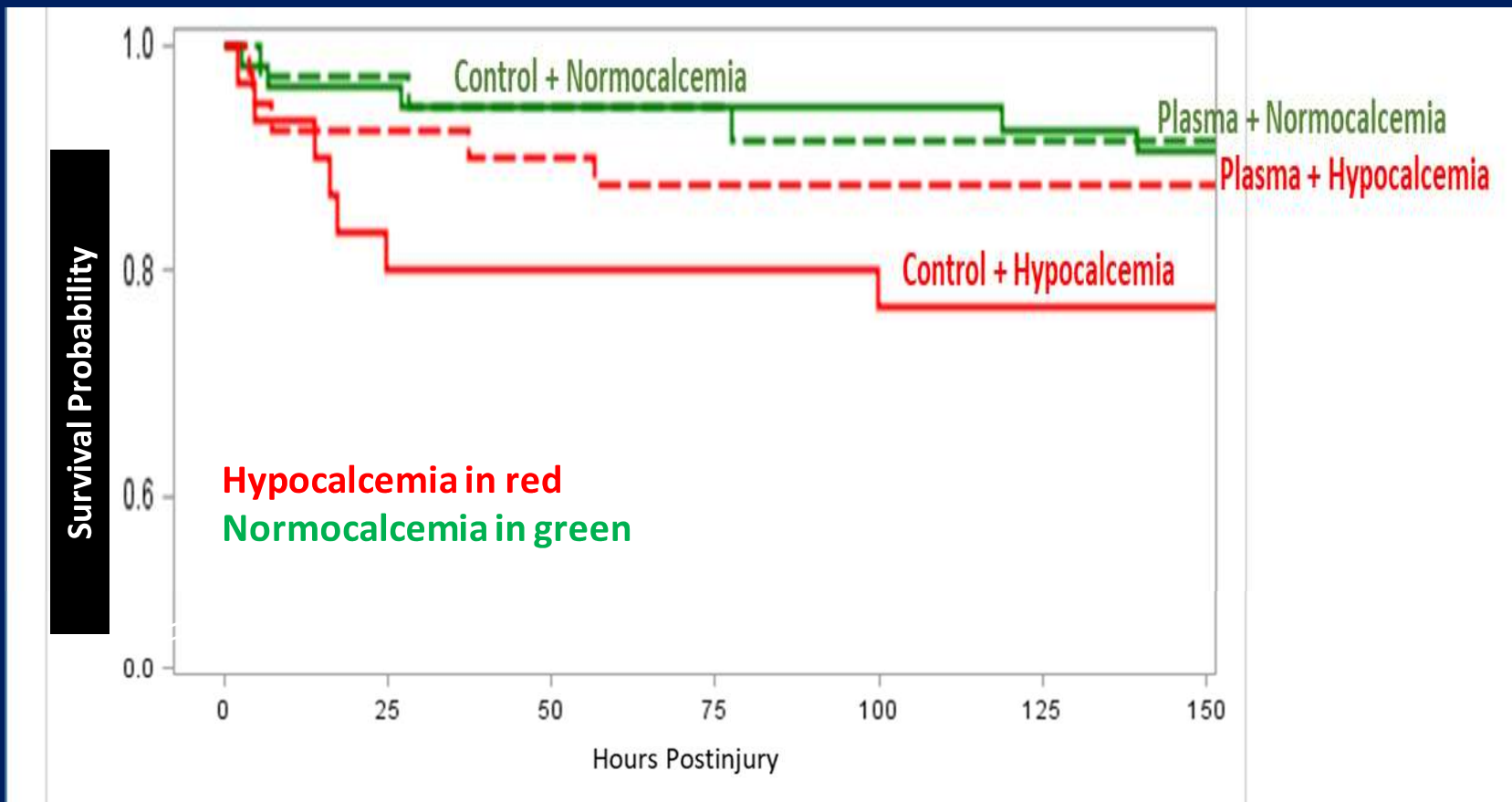
	NORMOCALCEMIA i-Ca >1.0mmol/L Median or %	HYPOCALCEMIA i-Ca ≤1.0mmol/L Median or %	p-value
INR	1.20	1.31	0.11
RAPID TEG -ACT	121	121	0.43
RAPID TEG-ANGLE	71	67	0.02
RAPID TEG-MA	58	54	0.005
RAPID TEG-LY30	0.70	0.45	0.69

Lower i-Ca Levels Associated with Higher Mortality

after Adjustment for Confounders

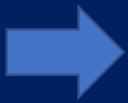
	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
First i-Calcium level	<.0001	0.527	0.488	0.570
Randomization group	0.2643	0.904	0.757	1.079
ISS	<.0001	1.004	1.004	1.004
Shock index	<.0001	1.000	1.000	1.000

Hypocalcemia: Reduced Survival in Plasma and Control Groups

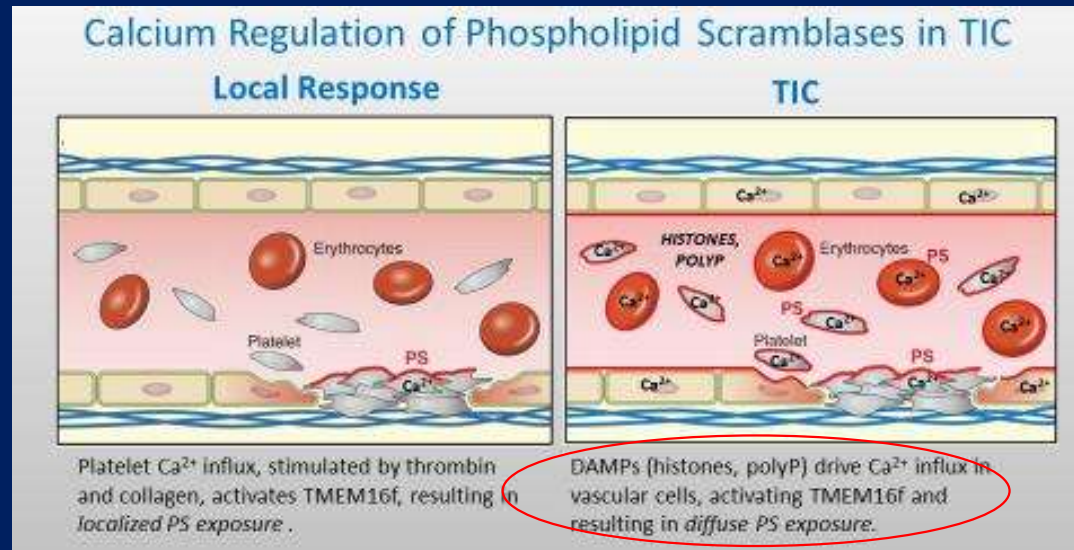


Mechanisms for Shock Induced Hypocalcemia

- Binding to citrate / hepatic clearance
- **Binding to exogenous albumin**
- Binding to lactate
- **Binding to phosphate**
- Magnesium elevated /depressed
- **Intracellular flux**



Trauma DAMPS Induce Calcium Influx



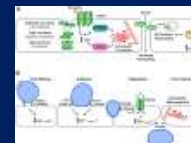
Bevers et al
Physiol Rev 2016

Review > Am J Pathol. 2020 Mar;190(3):535-542. doi: 10.1016/j.ajpath.2019.11.004.

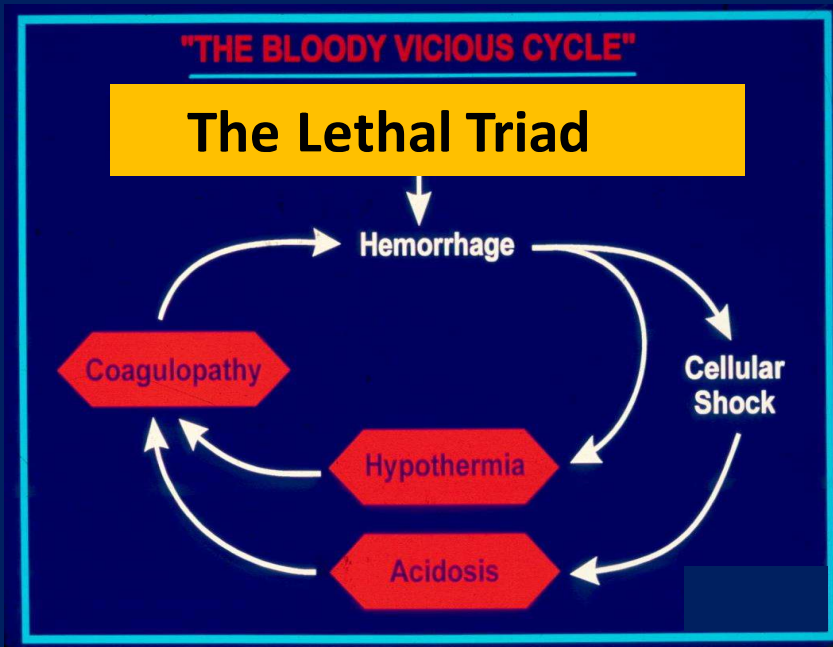
Epub 2019 Dec 19.

Endothelial Cell Calcium Signaling during Barrier Function and Inflammation

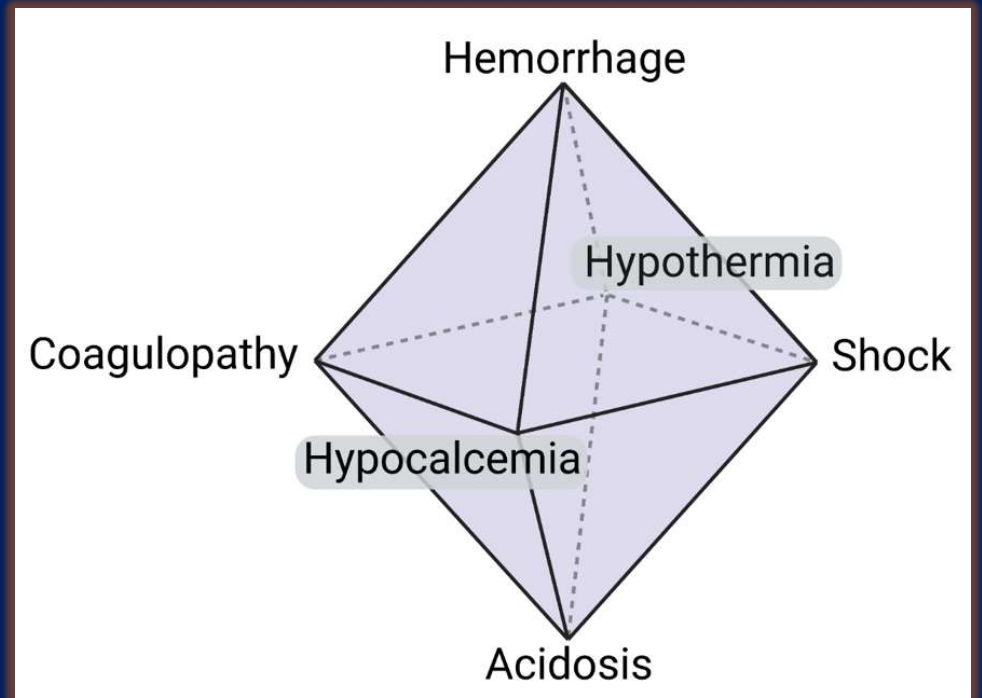
Prarthana J Dalal¹, William A Muller¹, David P Sullivan²



The Death Diamond

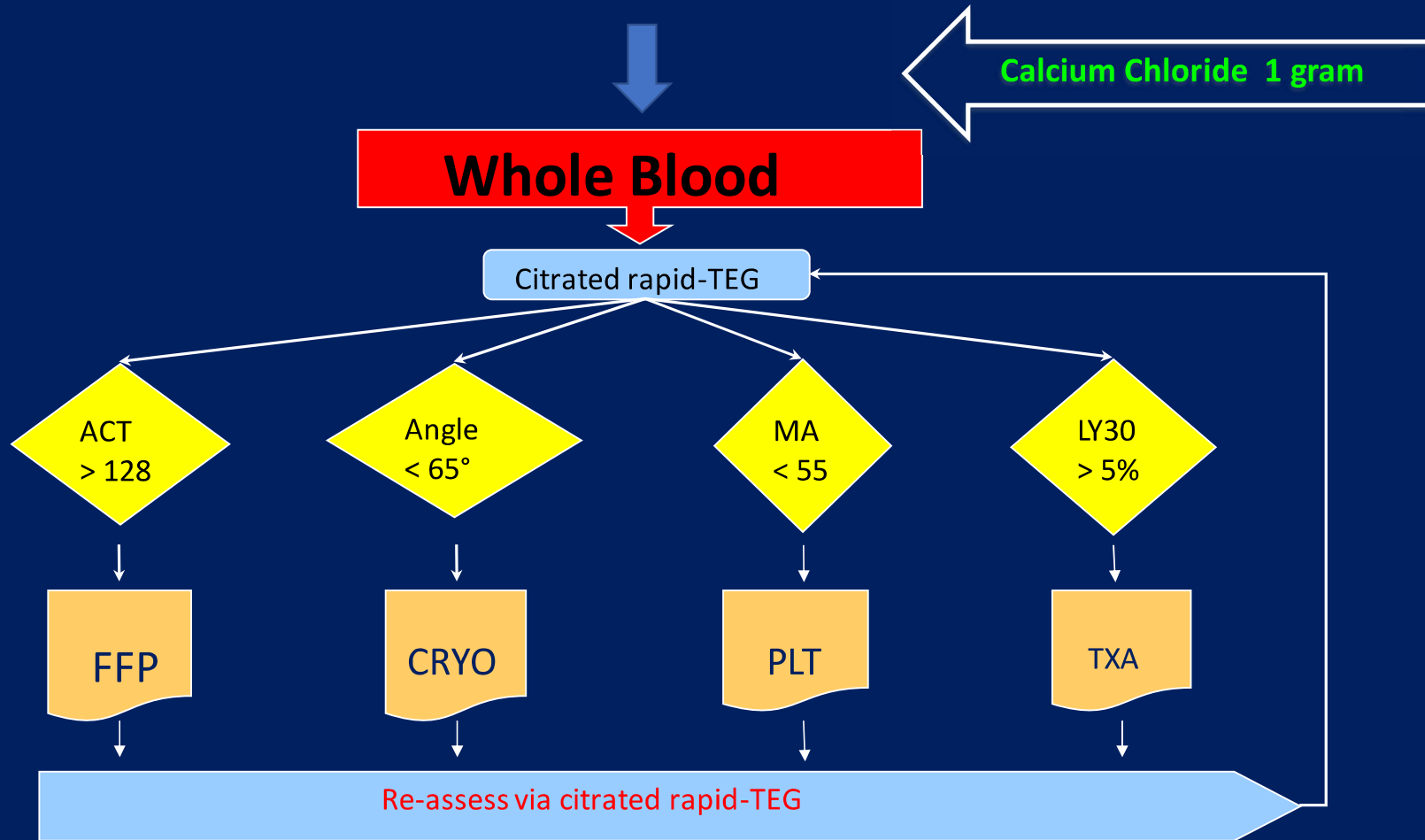


J Trauma 1982



Transfusion / THOR 2022

Massive Transfusion Protocol



FFP = fresh frozen plasma CRYO = cryoprecipitate
PLT = apheresis platelets TXA = tranexamic acid

Empiric Prehospital Calcium

Observational Study > Vox Sang. 2020 Feb;115(2):189-195. doi: 10.1111/vox.12875.

Epub 2019 Dec 17.

Hypocalcaemia and traumatic coagulopathy: an observational analysis

Mayank Vasudeva ^{1 2 3}, Joseph K Mathew ^{1 2 3 4}, Mark C Fitzgerald ^{1 2 3 4}, Zoe Cheung ^{1 2}, Biswadev Mitra ^{1 5 6}

Review > J Spec Oper Med. Winter 2021;21(4):126-137. doi: 10.55460/JYLU-4OZ8.

Fluid Resuscitation in Tactical Combat Casualty Care; TCCC Guidelines Change 21-01. 4 November 2021

Travis G Deaton, Jonathan D Auten, Richard Betzold, Frank K Butler Jr, Terence Byrne, Andrew P Cap, Benjamin Donham, Joseph J DuBose, Andrew D Fisher, James Hancock, Victor Jourdain, Ryan M Knight, Lanny F Littlejohn, Matthew J Martin, Kevin Toland, Brendon Drew

LITES Study : Prehospital Calcium

TO10-CAVALIER

Calcium and Vasopressin following Injury Early Resuscitation Trial

A multi-center, double blind, prehospital & in-hospital phase randomized trial

- 4-year study period, 3 years of enrollment
- Enrollment Goal: 1050
- Exception from Informed Consent (EFIC)
- Primary Outcome: 30-day mortality
- 11 Level I Trauma Centers

Prehospital Phase: Injured patients at risk of hemorrhagic shock

- Intervention: 10ml of 100mg/ml calcium gluconate
- Standard Care: 10 ml of saline placebo
- Randomization: 1:1 ratio of calcium gluconate or placebo

In-hospital Phase: Injured patients at risk of hemorrhagic shock requiring blood transfusion and early operative or interventional radiology procedures

- Intervention: Vasopressin infusion 0.04 U/min, initiated within three hours of randomization, given for 8 hours.
- Standard Care: Normal saline placebo infusion, initiated within three hours of randomization, given for 8 hours.
- Randomization: 1:1 ratio of vasopressin or placebo

Potential Adverse Impact of Calcium Loading

Review > [Adv Shock Res.](#) 1983;10:15-25.

Calcium entry blockers: potential applications in shock

M L Hess, L J Greenfield

> [J Appl Physiol \(1985\)](#). 2004 Oct;97(4):1470-6. doi: 10.1152/jappphysiol.01149.2003. Epub 2004 Jun 4.

Burn trauma alters calcium transporter protein expression in the heart

Cherry Ballard-Croft ¹, Deborah Carlson, David L Maass, Jureta W Horton

> [Circ Shock](#). 1992 Sep;38(1):14-21.

Altered cellular calcium regulation and hepatic glucose production during hemorrhagic shock

S R Maitra ¹, E R Geller, W Pan, P R Kennedy, L D Higgins

Conclusion:

Pre-emptive Calcium Administration for Shock

- Myocardial contractility
- Tissue perfusion
- Hemostasis

Strategies to Mitigate Endothelial Calcium Flux

- Calcium channel blockade
- TMEM16f inhibition

Thank you !!!

