THE OHIO STATE UNIVERSITY
COLLEGE OF MEDICINE

Effect of Sex on Hemostasis and Quality of Blood Products

Julia R Coleman MD MPH
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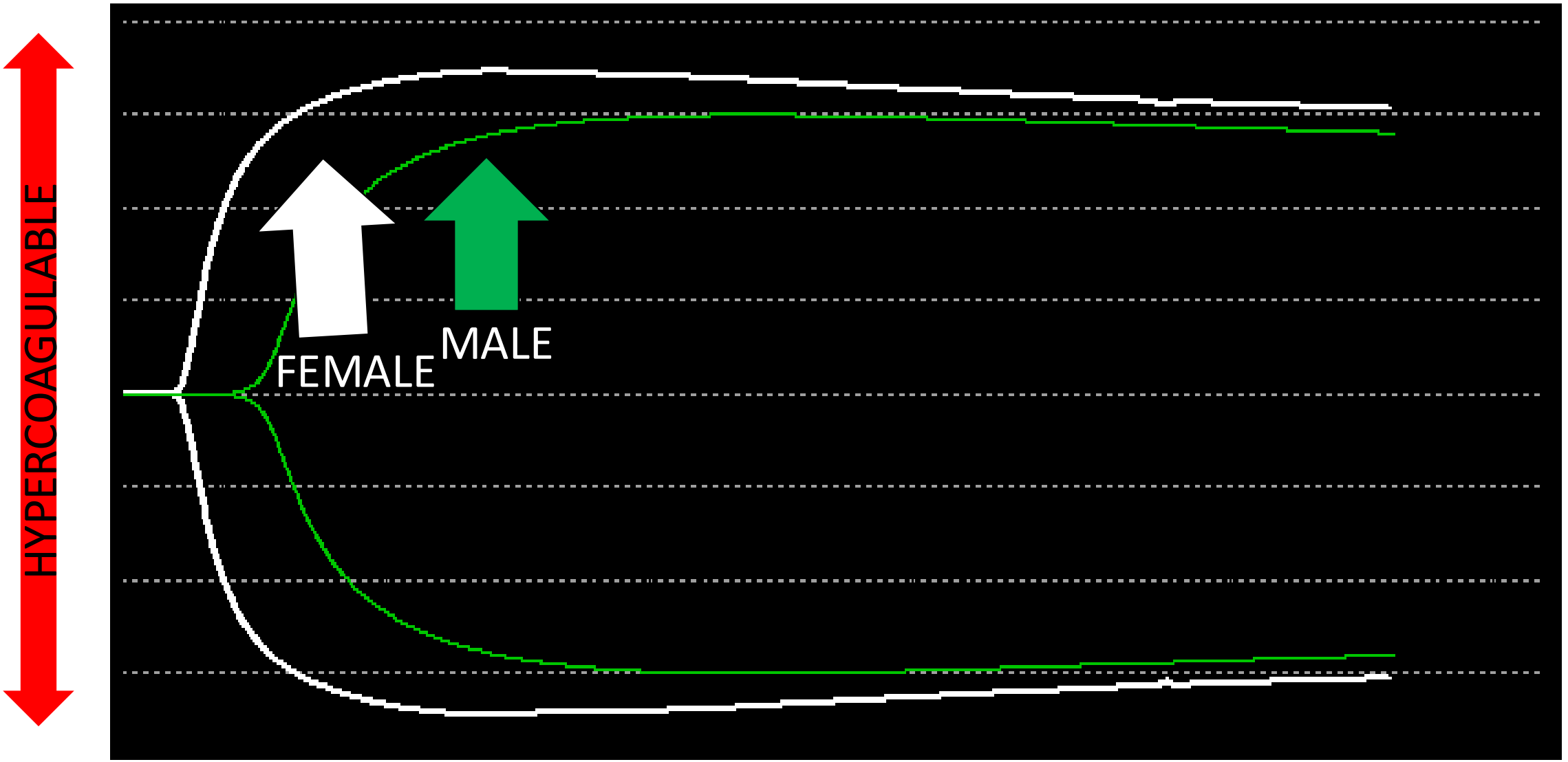
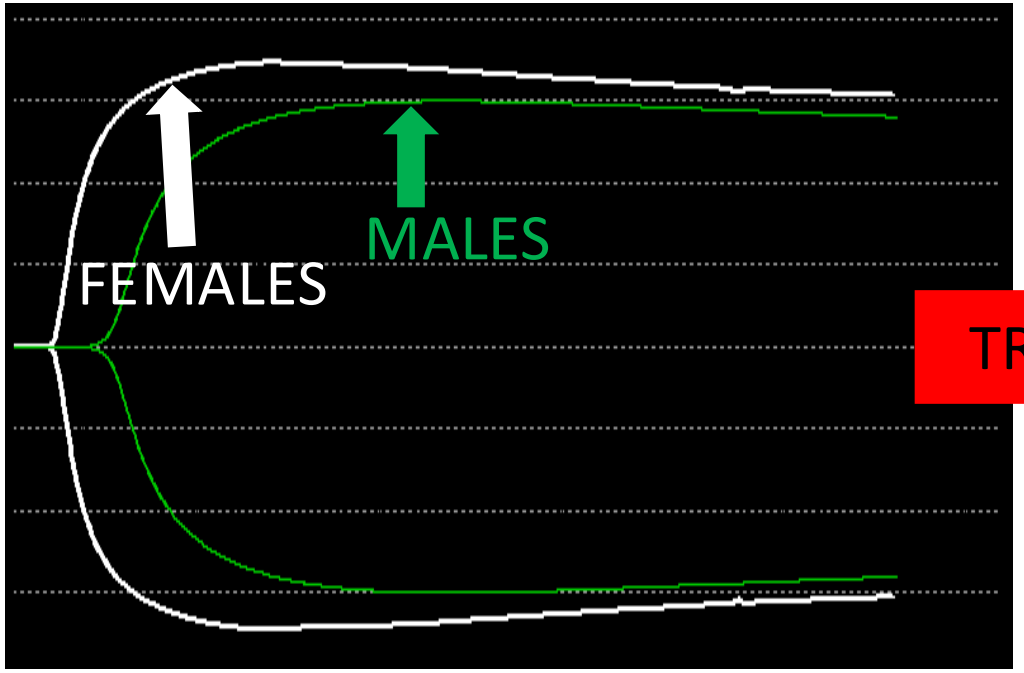


Journal of the American College of Surgeons
Volume 228, Issue 5, May 2019, Pages 760-768.e1

Original scientific article

Trauma Resuscitation Consideration: Sex Matters

Julia R. Coleman MD, MPH [a], Ernest E. Moore MD, FACS [a, d], Jason M. Samuels MD [a], Mitchell J. Cohen MD, FACS [d, e], Angela Sauaia MD, PhD [a], Joshua J. Sumislawski MD [a], Arsen Ghasabyan MPH [d], James G. Chandler [d], Anirban Banerjee PhD [a], Christopher C. Silliman MD, PhD [b, c], Erik D. Peltz DO, FACS [a]



TRAUMA

TRAUMA-INDUCED COAGULOPATHY

♀ **INCREASED SURVIVAL IN FEMALES**

♂ **DECREASED SURVIVAL IN MALES**

World J Surg (2008) 32:2185–2189
DOI 10.1007/s00268-008-9655-0

ORIGINAL SCIENTIFIC REPORTS

Outcome Analysis of Blood Product Transfusion in Trauma Patients: A Prospective, Risk-Adjusted Study

Grant V. Bochicchio · Lena Napolitano · Manjari Joshi · Walter Meyer · Thomas M. Scalea

ELSEVIER
Contents lists available at ScienceDirect
Heart & Lung
journal homepage: www.heartandlung.org

Injury severity, sex, and transfusion volume, but not transfusion cations after traumatic injury

M. Bush, PhD [b],

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

PA

Gender-Related Outcomes in Trauma

Gamal Mostafa, MD, Toan Huynh, MD, Ronald F. Sing, DO, William S. Miles, MD, H. James Norton, PhD, and Michael H. Thomason, MD

Mar;37(1):107-117. doi: 10.1016/j.anclin.2018.09.007.
Epub 2018 Nov 27.

Improved Survival Followi in Patients Who Have Undergone Trauma

Marianne E. Cinat, MD; William C. Wallace, MD; Frank Nastanski, MD; Justin West; Steven Sloan, MD; Jose Ocariz, MD; Samuel E. Wilson, MD

Gender Disparities in Trauma Care: How Sex Determines Treatment, Behavior, and Outcome

orecht [2], Kinjal N Sethuraman [3], Lena M Napolitano [4]

016/j.surg.2018.12.023. Epub 2019 Mar 12.

CLINICAL ASPECTS

INFLUENCE OF SEX AND AGE ON MOD AFTER MULTIPLE INJURIES

Frink, Michael*; Pape, Hans-Christoph†; van Griensven, Martijn‡; Krettek, Frank*

Author Information

Shock 27(2):p 151-156, February 2007. | DOI: 10.1097/01.shk.0000239767.647

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

Hypercoagulability Is Most Prevalent Early after Injury and in Female Patients

Martin A. Schreiber, MD, Jerome Differding, BS, Per Thorborg, MD, John C. Mayberry, MD, and Richard J. Mullins, MD

transfusion need after the PROPPR study

Marta L McCrum [1], Brian Leroux [2], Tingzhi Fang [2], Eileen Bulger [3], Sam Arbabi [3], Charles E Wade [4], Erin Fox [4], John B Holcomb [4], Bryce Robinson [3]; PROPPR Study Group

J Vasc Surg. 2023 Jan;77(1):56-62. doi: 10.1016/j.jvs.2022.07.178. Epub 2022 Aug 6.

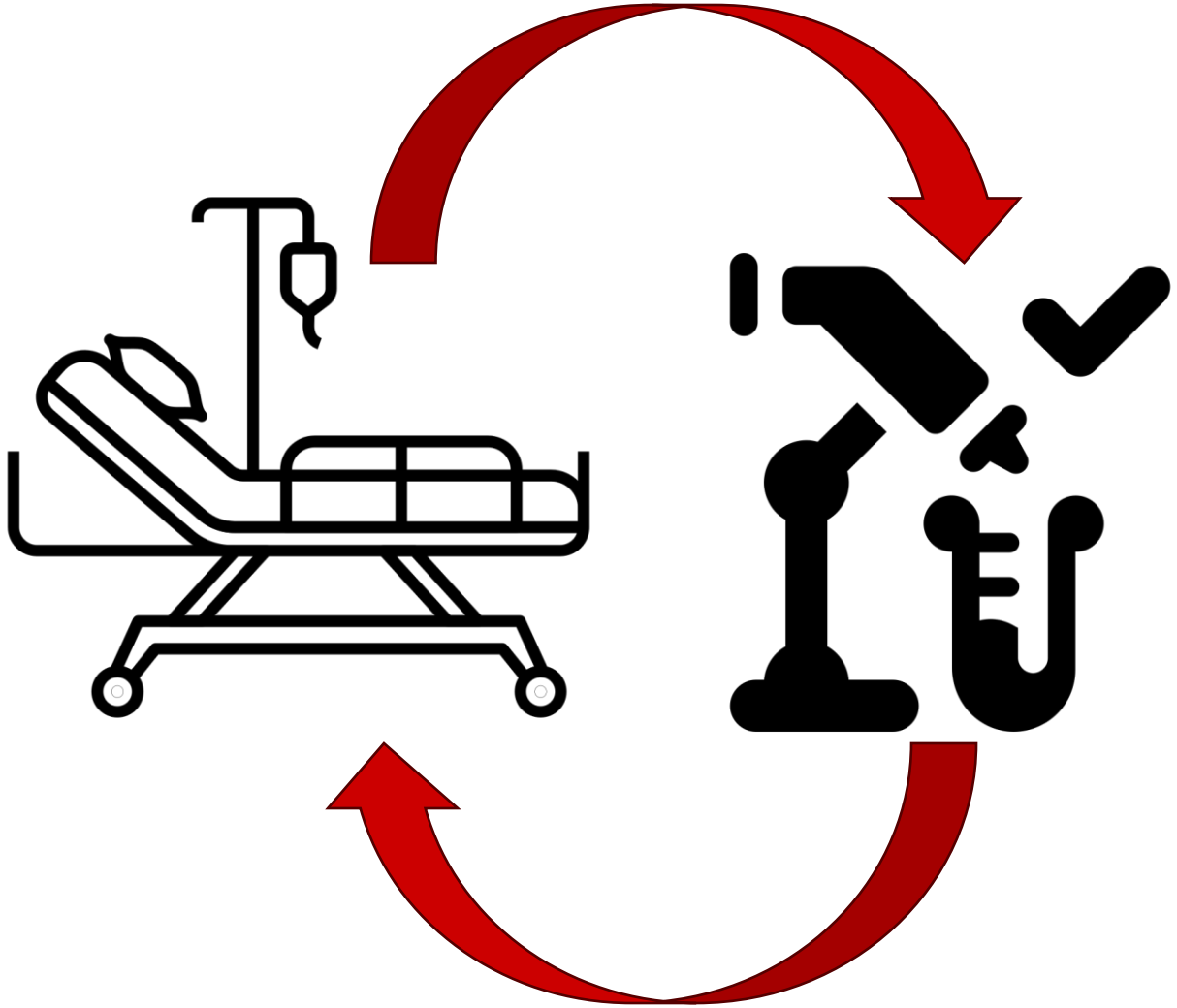
Female sex is independently associated with reduced inpatient mortality after endovascular repair of blunt thoracic aortic injury

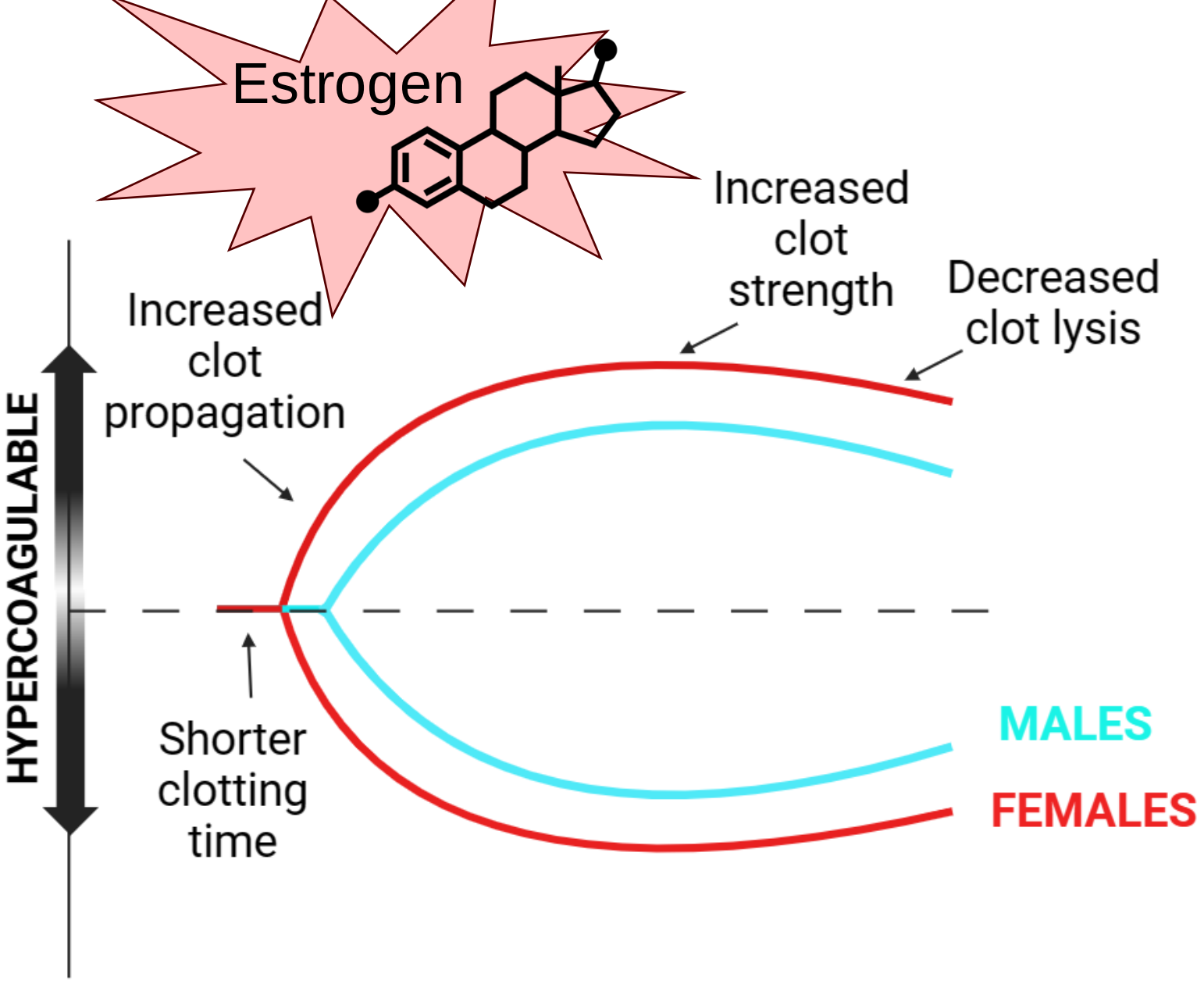
Vy Thuy Ho [1], Sabina Sorondo [2], Joseph D Forrester [3], Elizabeth L George [2], Kenneth Tran [2], Jason T Lee [2], Manuel Garcia-Toca [2], Jordan R Stern [2]

CellPress
Heliyon
journal homepage: www.cell.com/heliyon

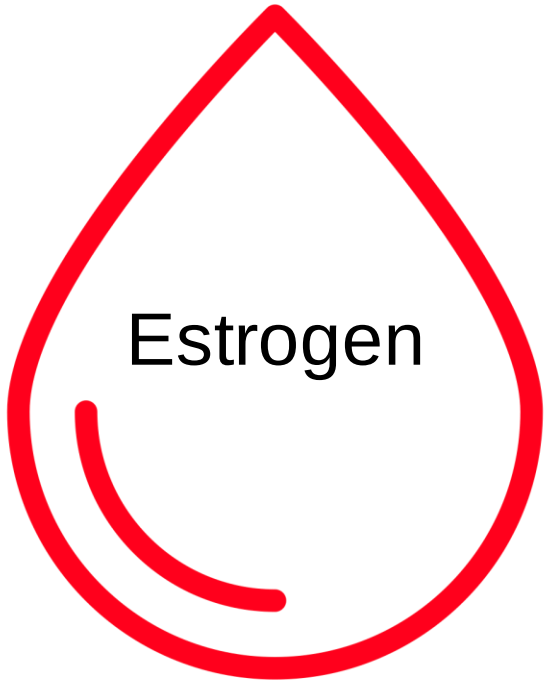
Age and sex differences in blood product transfusions and mortality in trauma patients at a level I trauma center

Linda Papa*, Lindsay Maguire, Josef G. Thundiyil, Jay G. Ladde, Susan A. Miller





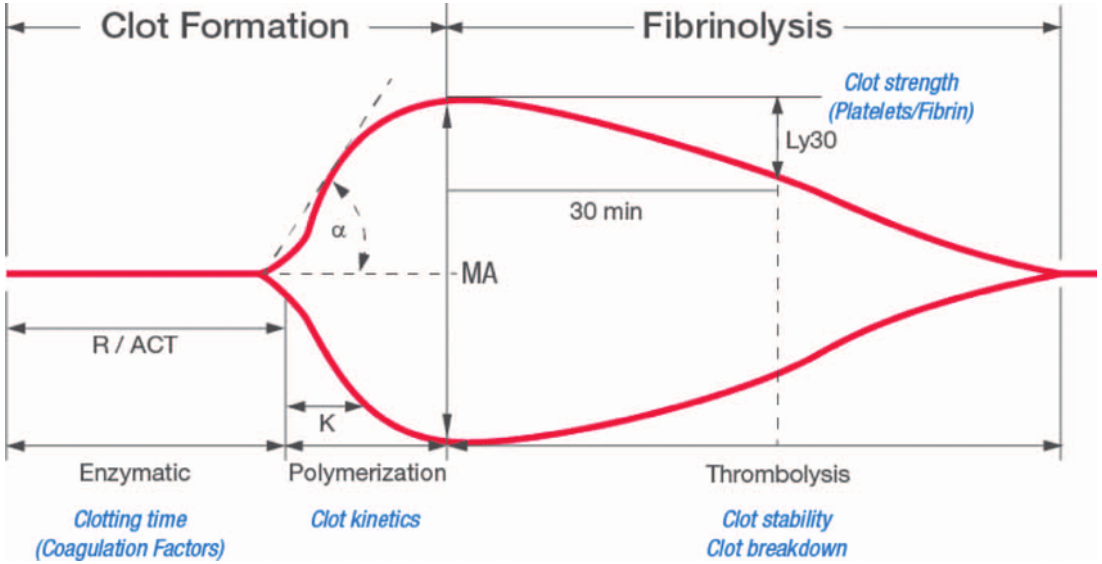
Methods

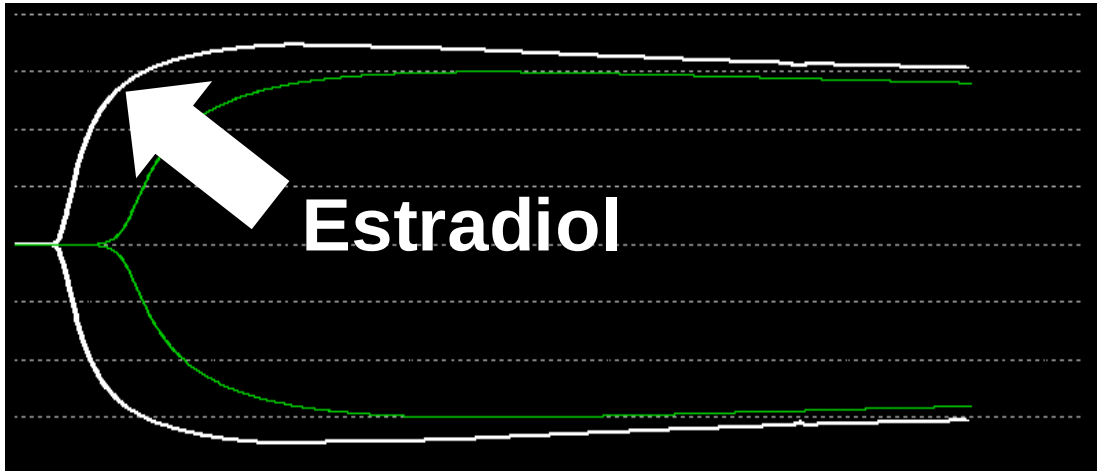


- Thrombelastography
- Whole blood thrombin generation
- Fibrin cross-linking
- Fluorescent fibrinogen density measurements
- Microfluidics modeling

Results: thrombelastography

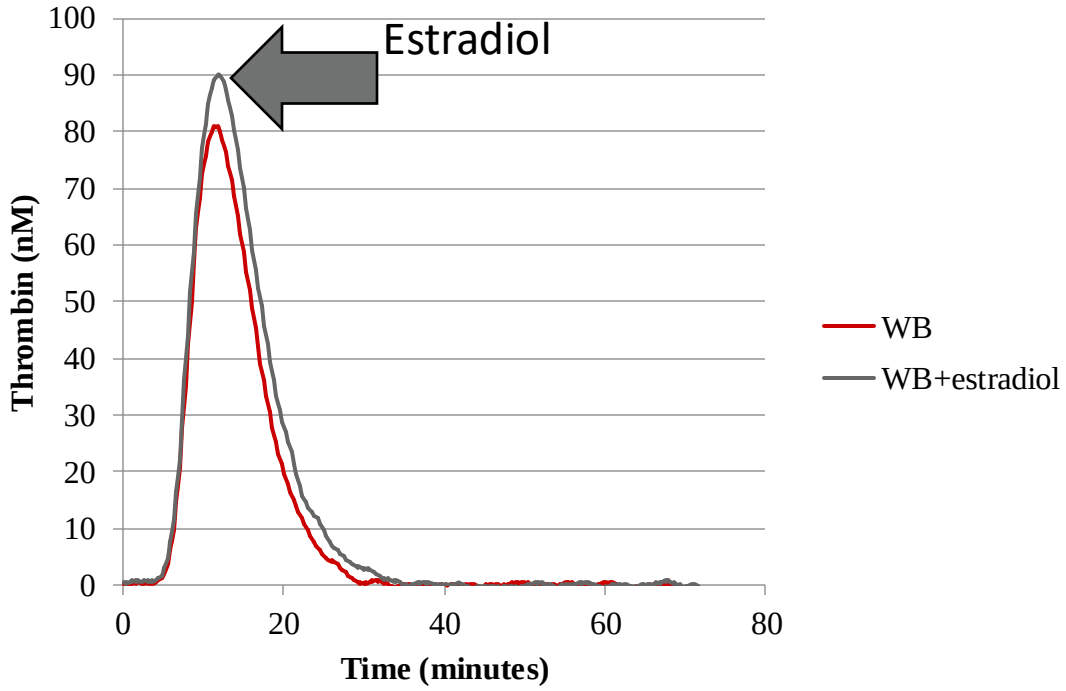
- *In vitro,* estradiol:
  - Shortens time to clot formation (reaction time)
  - Increases clot strength (MA)
  - Decreases fibrinolysis (LY30)
  - Increases functional fibrinogen (FLEV)
  - Increases platelet reactivity (ADP- and AA-provoked aggregation)





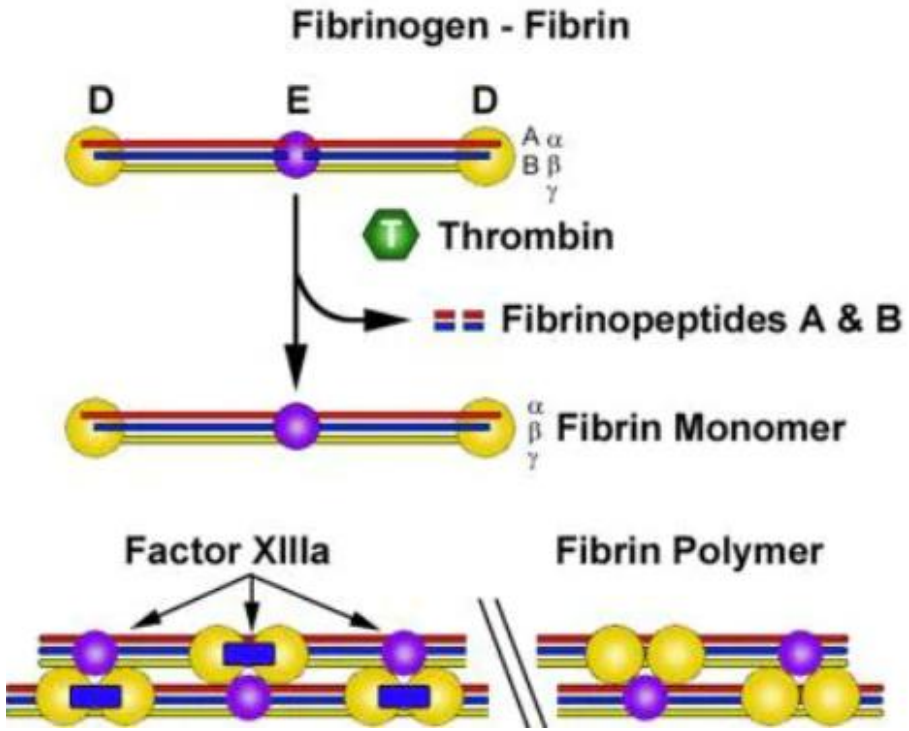
Results: thrombin generation

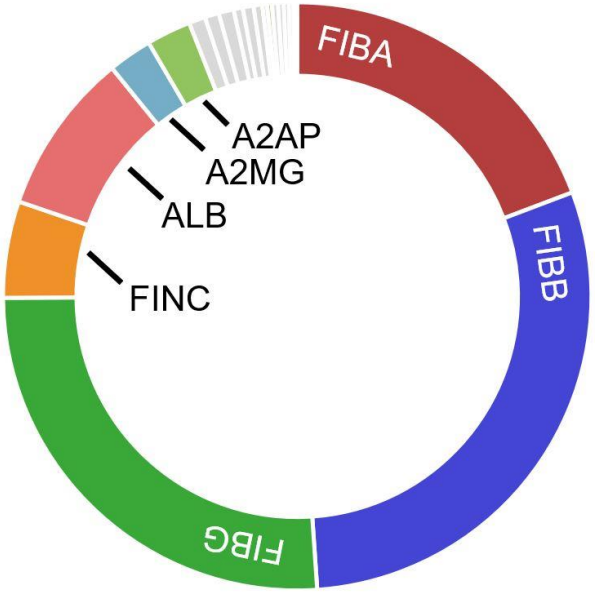
- Estradiol increases TG in females
  - Estradiol increased peak thrombin from 84.2 nM to 94.6 nM (p=0.03) in females, whereas it had no effect in males

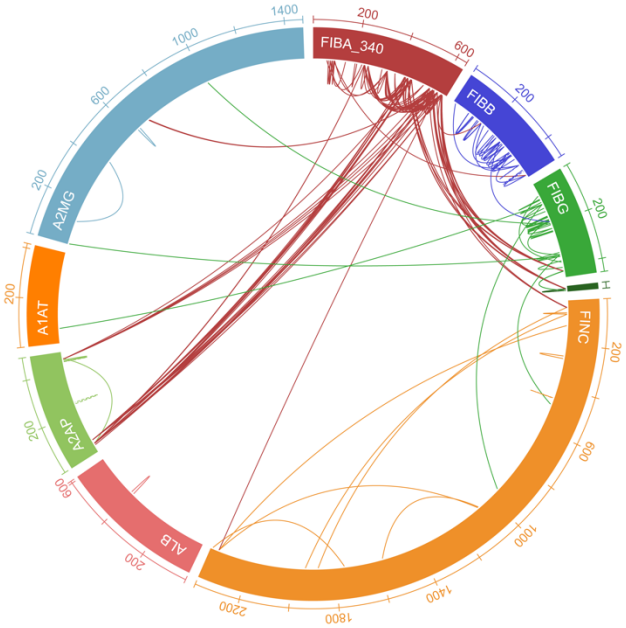


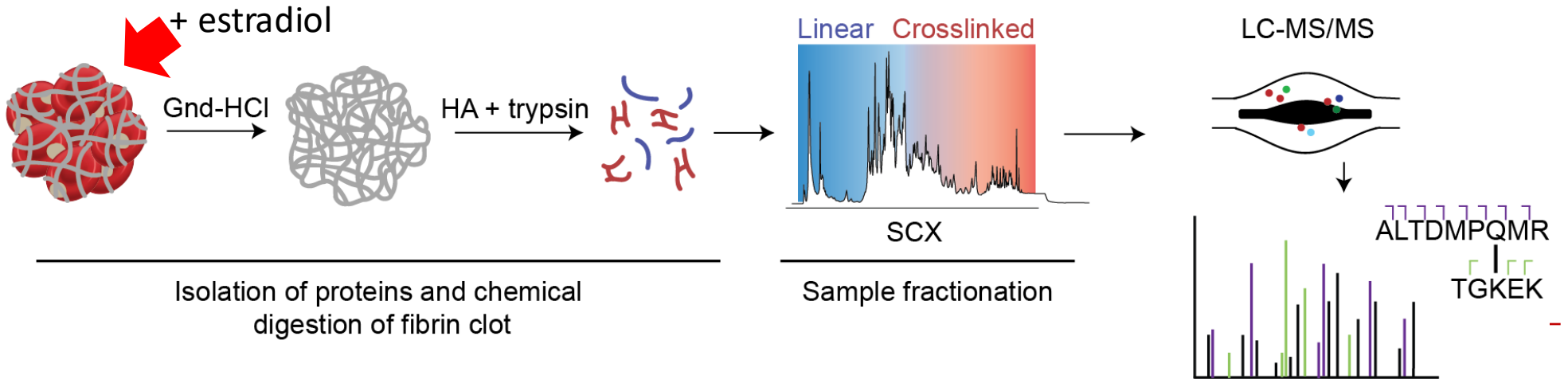
Results

Credits: Kirk Hansen, Lauren Schmidt



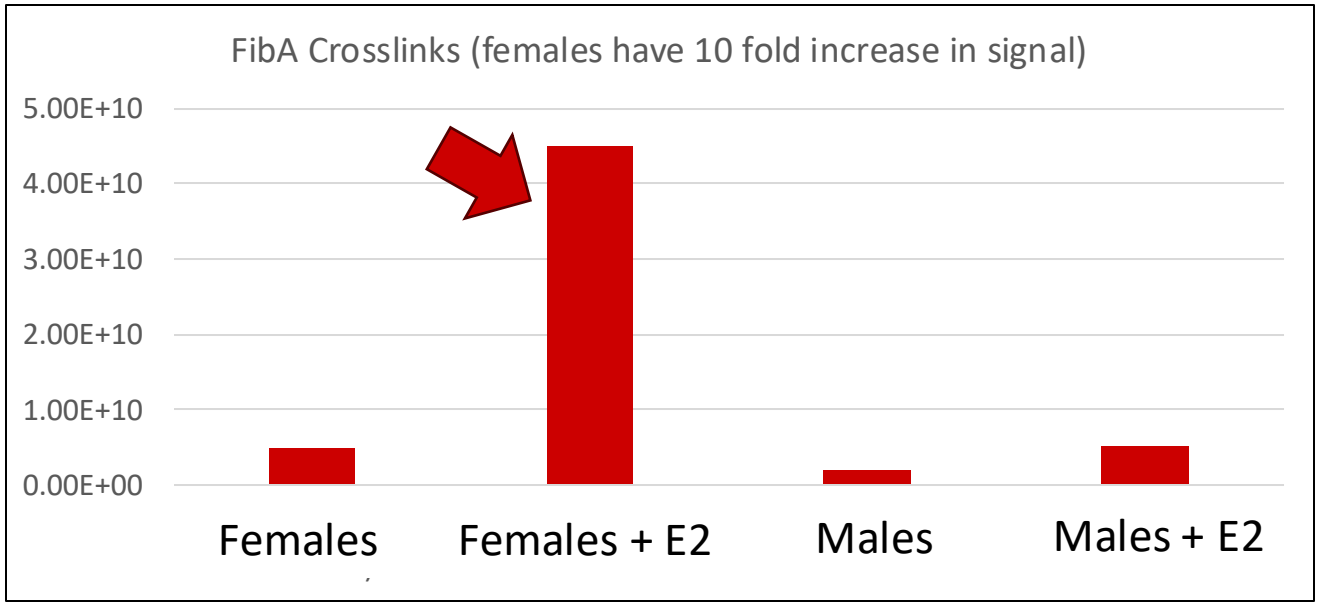




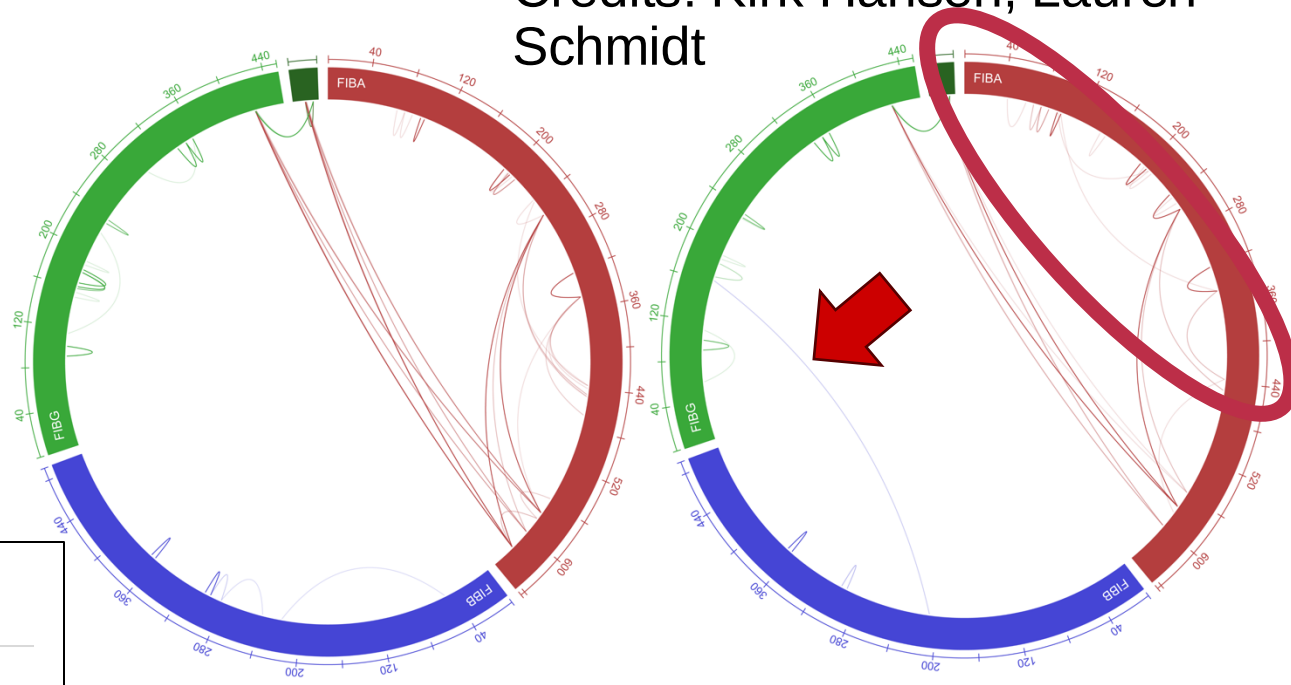


Results

- Estradiol:
  - Increases abundance of FXIII cross-links within fibrin chains in females



Credits: Kirk Hansen, Lauren Schmidt



Control

Estradiol

Credits: Kalev Freeman

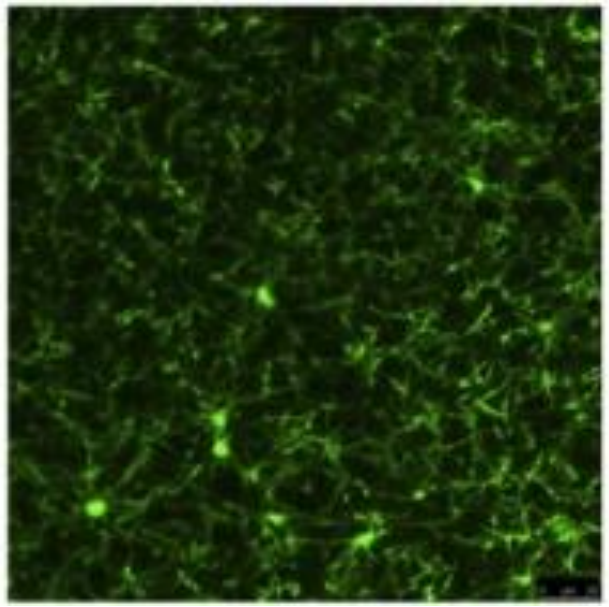
Results

- Added estradiol to plasma from healthy volunteers
- Monitored polymerization of fluorescent fibrinogen and response to plasmin under video confocal microscopy

Estradiol

Plasma

Fluorescent Fibrinogen



Time to fibrin formation

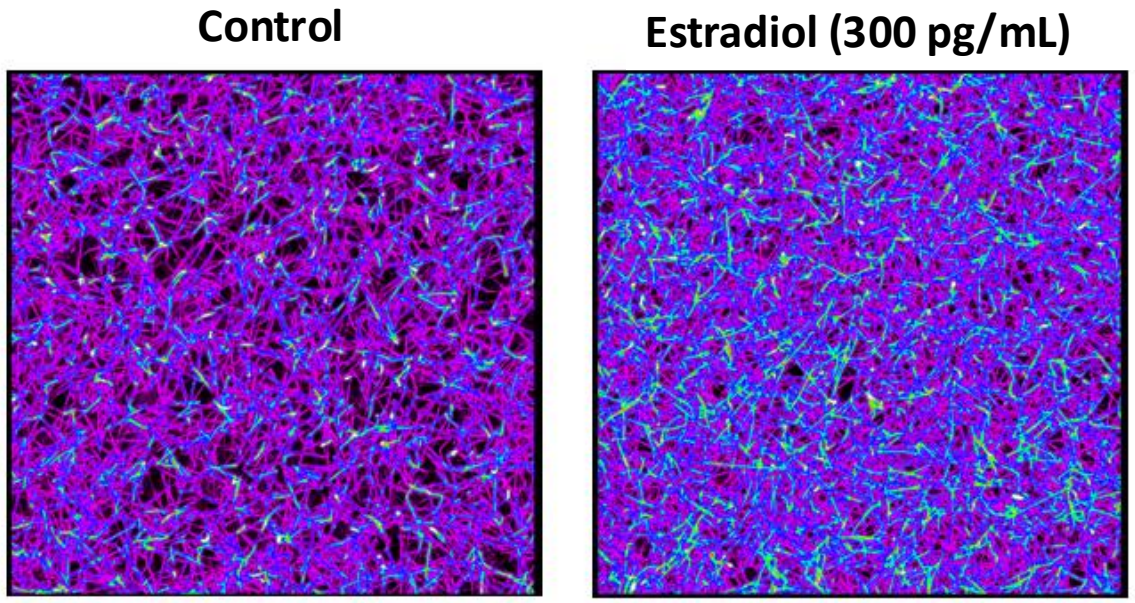
Time to fibrinolysis

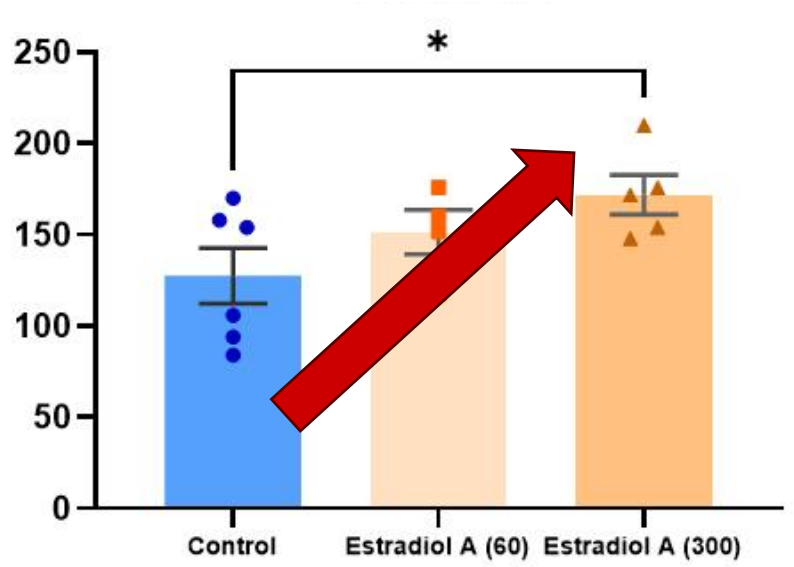
Clot resolvability index

Credits: Kalev Freeman

Results

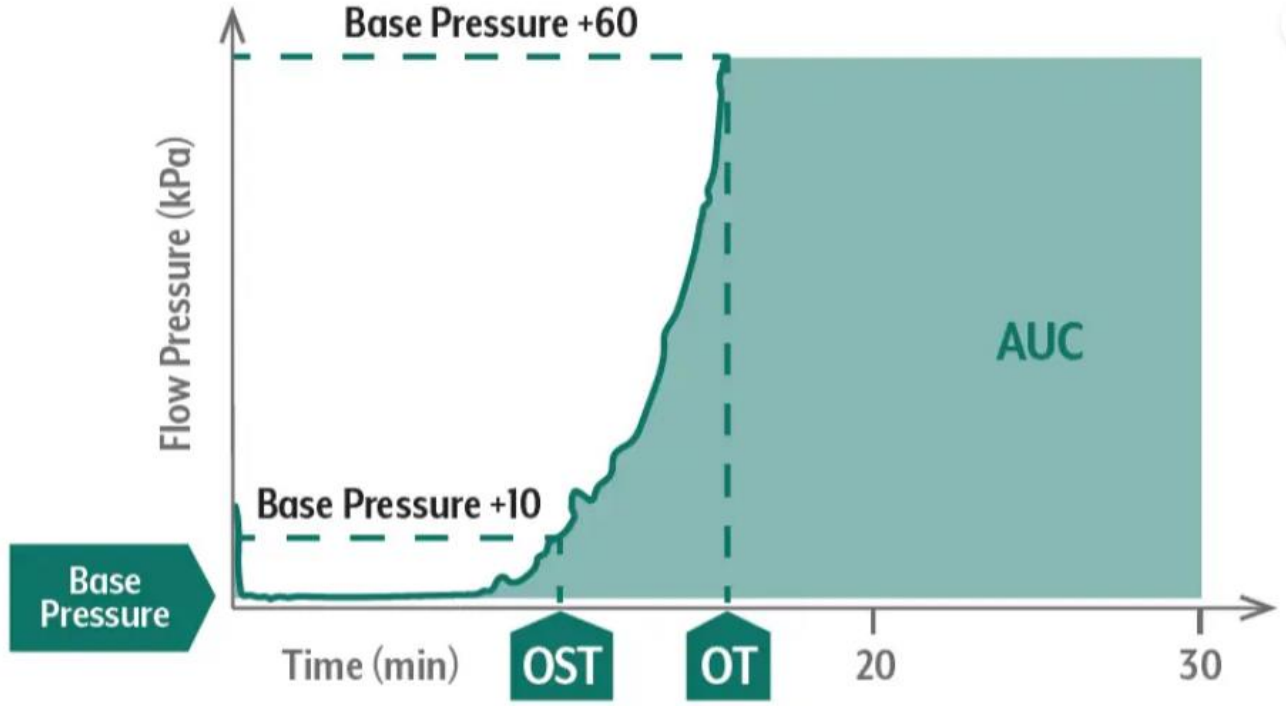
- Fiber resolvability significantly increased with estradiol concentration, signifying more highly structured and distinct fibrin fibers





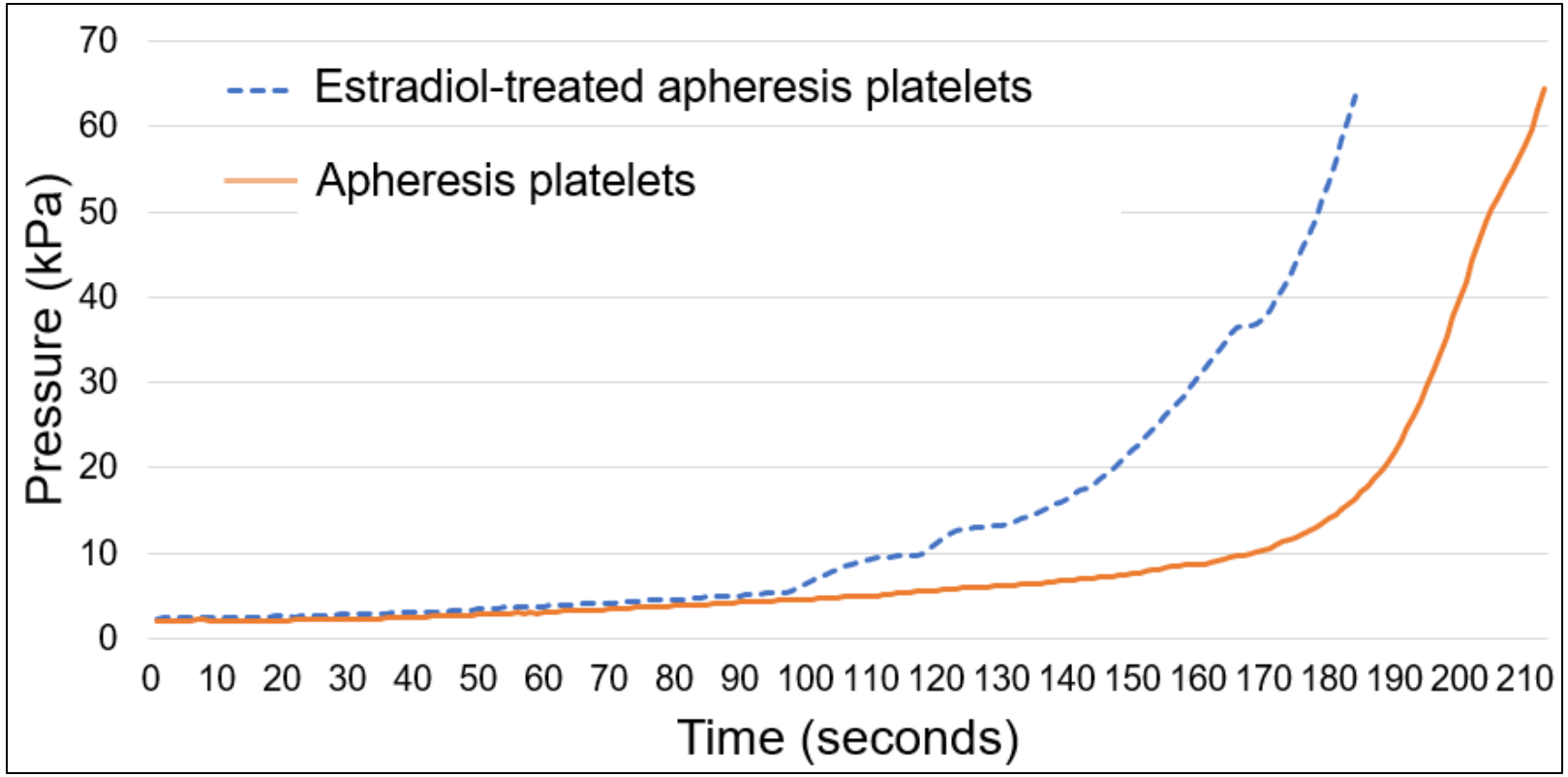
Effect of estradiol on platelets persists under flow conditions

- Apheresis platelets -> activation by collagen, tissue thromboplastin, calcium, *and* wall shear stress



Results

- Estradiol shortens time to occlusion and increases peak pressure of occlusion under flow conditions



Summary

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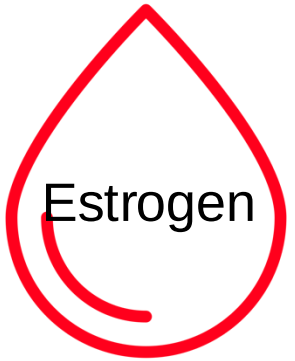
J Trauma Acute Care Surg. 2023 February 01; 94(2): 179–186. doi:10.1097/TA.0000000000003822.

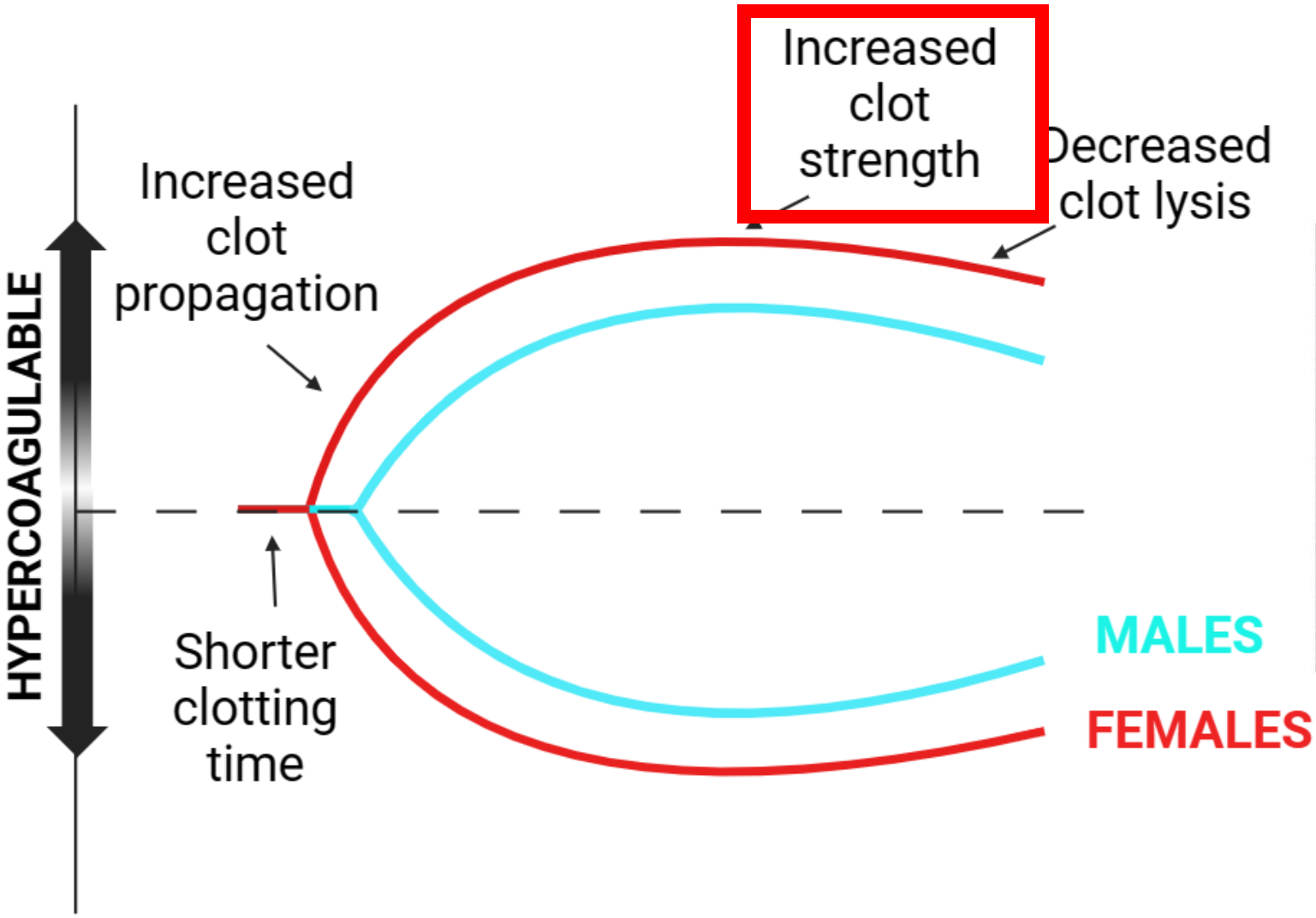
ESTRADIOL PROVOKES HYPERCOAGULABILITY AND AFFECTS FIBRIN BIOLOGY: A MECHANISTIC EXPLORATION OF SEX DIMORPHISMS IN COAGULATION

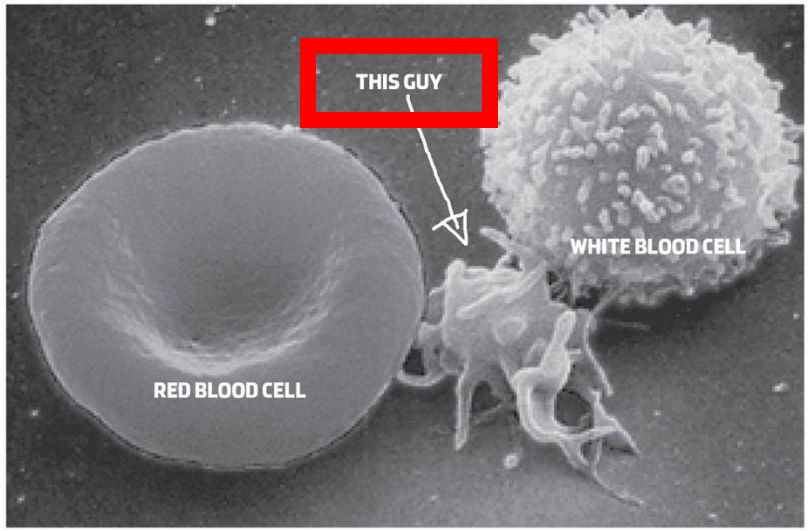
Julia R Coleman, MD MPH[1,*], Ernest E Moore, MD[2], Lauren Schmitt, BS[3], Kirk Hansen, PhD[3], Nathan Dow, BS[4], Kalev Freeman, MD PhD[4], Mitchell J Cohen, MD[5], Christopher C Silliman, MD PhD[6,7]

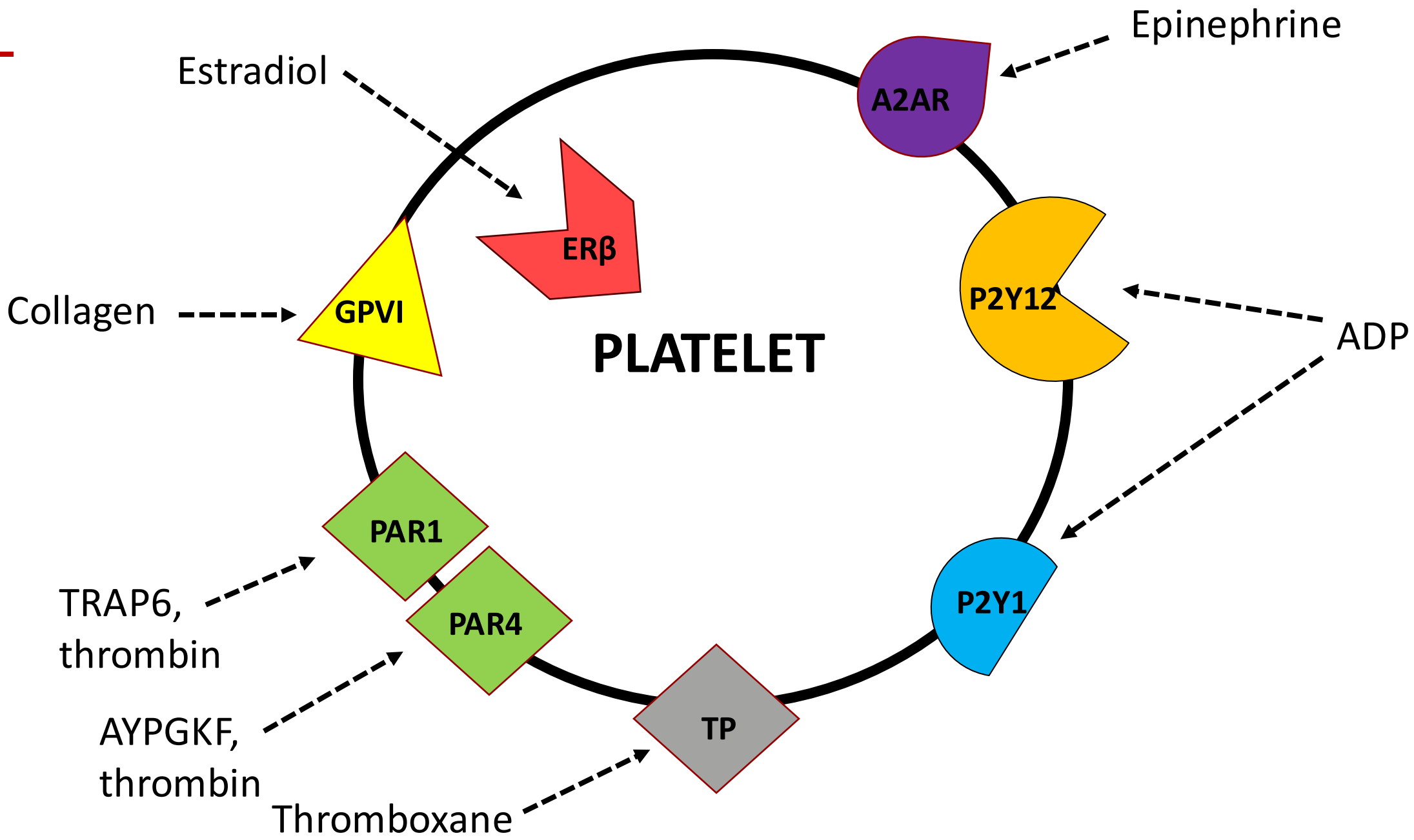


- Thrombelastography – provoked hypercoagulability
- Whole blood thrombin generation – increased peak thrombin
- Fibrin cross-linking – increased abundance of FXIII cross-links within fibrin chains
- Fluorescent fibrinogen density measurements – increased clot density
- Microfluidics modeling – shortened time to occlusion and increases peak pressure

Mechanism for sex dimorphisms in coagulation?







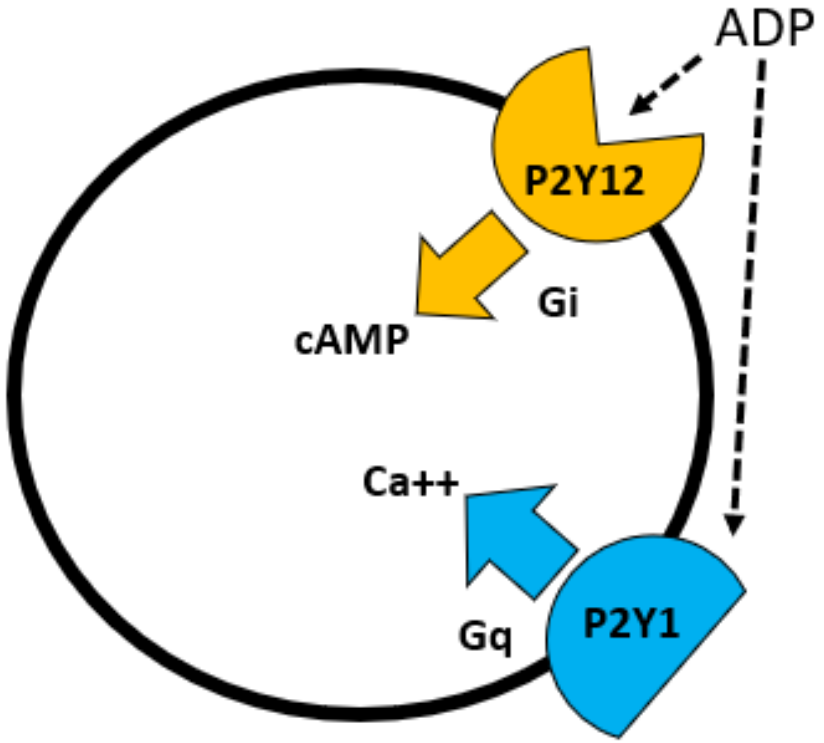
Hypothesis

- Platelets from females have increased response to stimuli compared to platelets from males

Methods

- Apheresis platelets, healthy volunteers (n=53)
  - Females:
    - premenopausal (≤54 yo)
    - post menopausal (>54 yo)
  - Males:
    - younger (≤54 yo)
    - older (>54 yo)

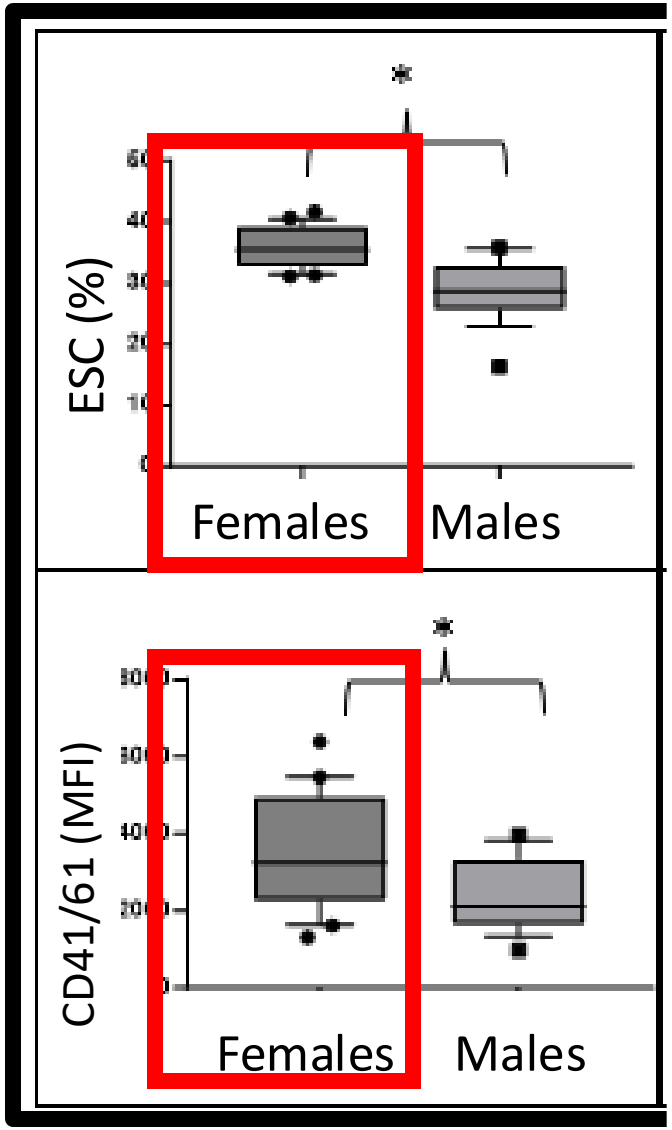
- ADP stimulation -> aggregation and flow cytometry (CD41/61)



Results

Aggregation

Flow cytometry



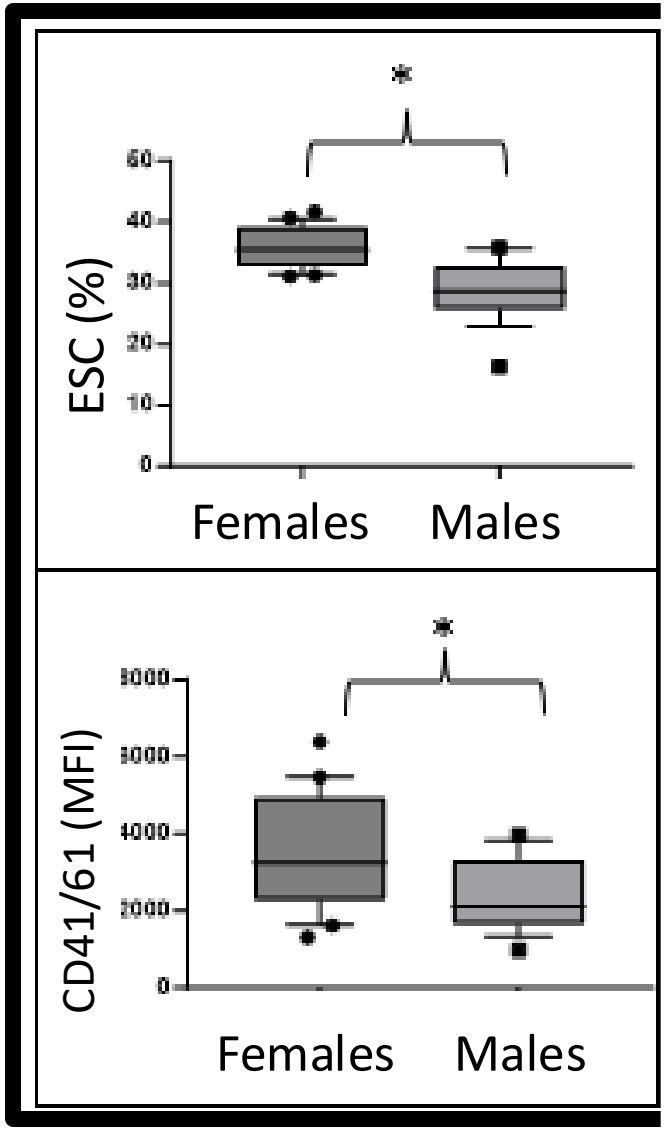
Hypothesis

- Estradiol increases platelet response to stimuli

Results

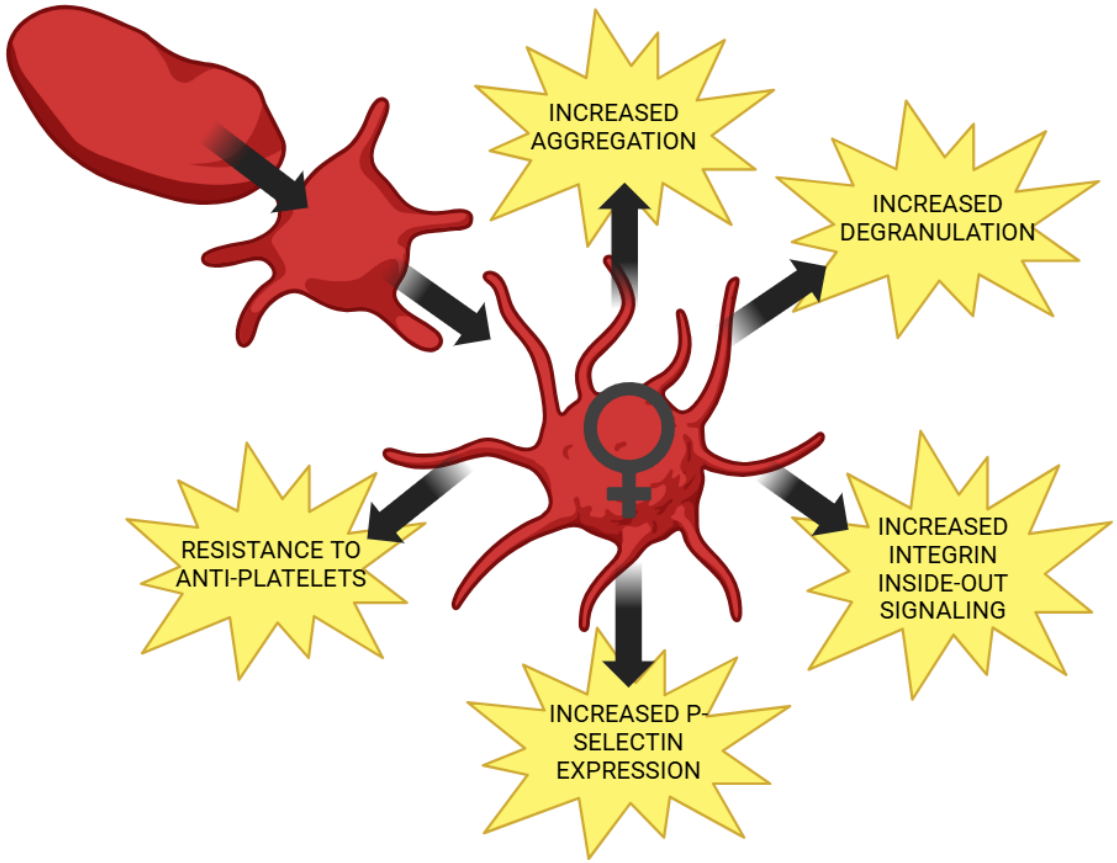
Aggregation

Flow cytometry



Summary

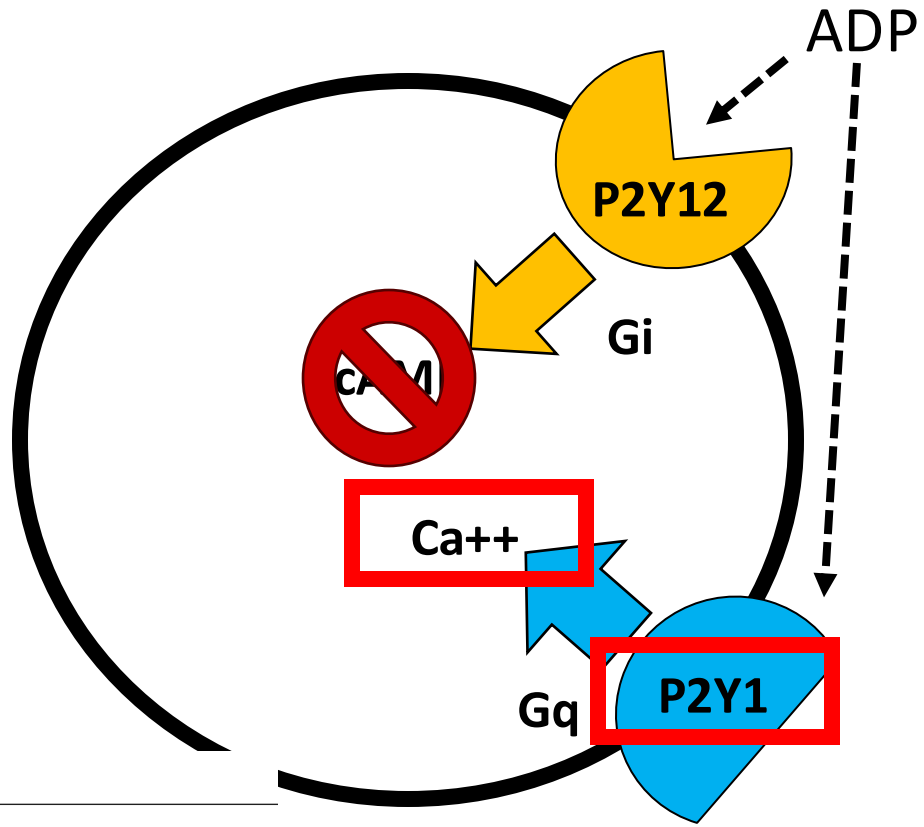
- Cellular response:
  - Platelets from females:
    - Increased extent shape change and activation with ADP as compared to males
- Hormonal effect:
  - Estradiol treatment -> “feminized” the male platelet response to ADP



J Trauma Acute Care Surg. 2019 November ; 87(5): 1052–1060. doi:10.1097/TA.0000000000002398.

Female Platelets Have Distinct Functional Activity Compared to Male Platelets: Implications in Transfusion Practice and Treatment of Trauma-Induced Coagulopathy

Julia R Coleman, MD MPH[1], Ernest E Moore, MD[2], Marguerite R Kelher, MS[1,3], Jason M Samuels, MD[1], Mitchell J Cohen, MD[2], Angela Sauaia, MD PhD[1], Anirban Banerjee, PhD[1], Christopher C Silliman, MD PhD[1,3], Erik Peltz, DO[1,*]



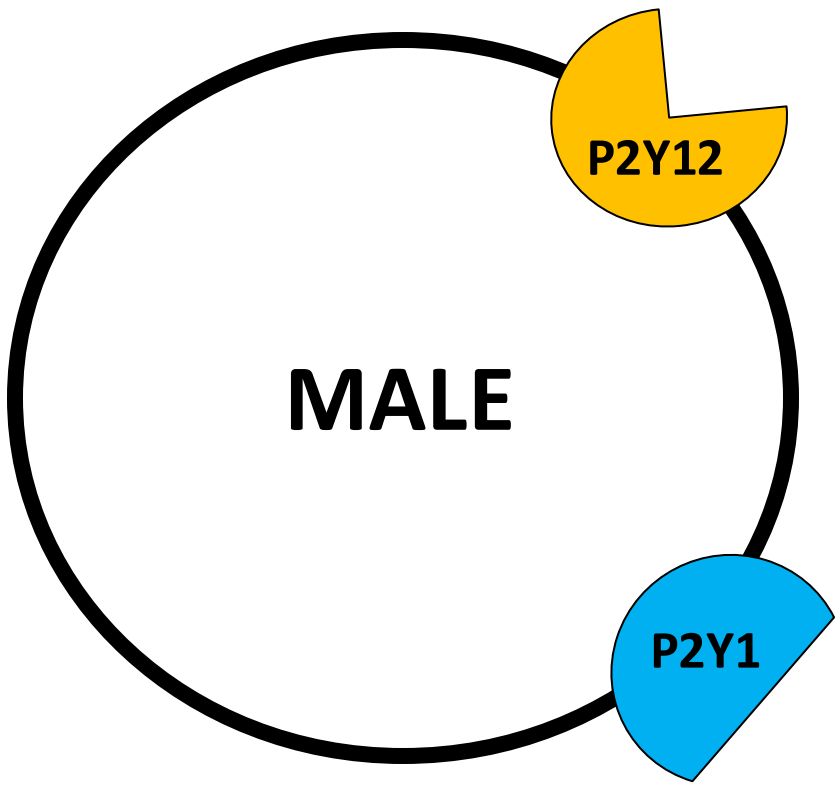
PLOS ONE

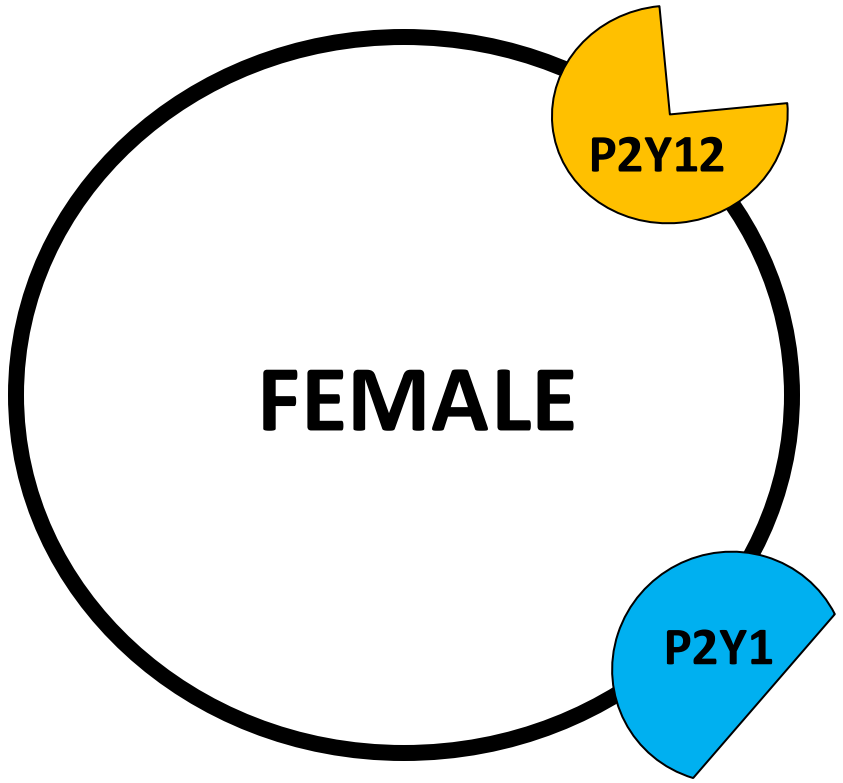
RESEARCH ARTICLE

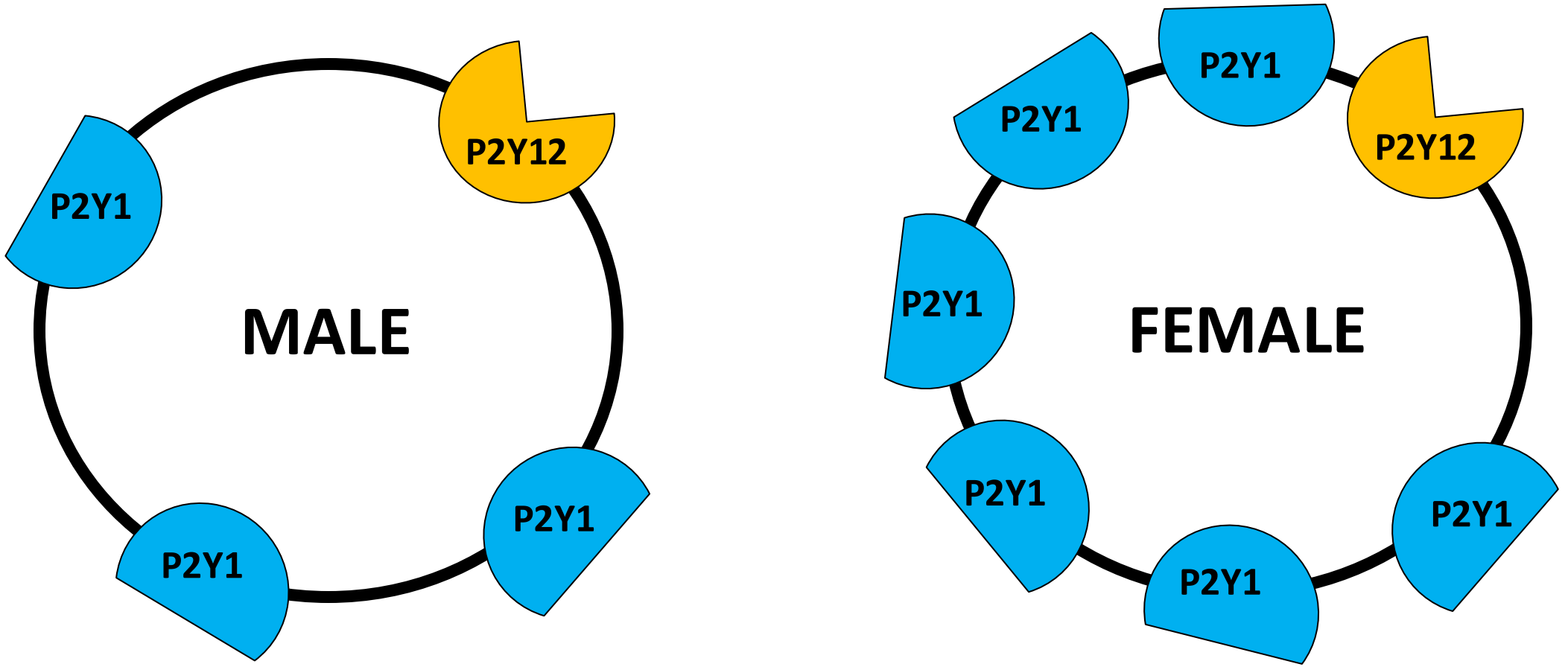
Gender-based differences in platelet function and platelet reactivity to $P2Y_{12}$ inhibitors

Marco Ranucci[1]*, Tommaso Aloisio[1], Umberto Di Dedda[1], Lorenzo Menicanti[2], Carlo de Vincentiis[2], Ekaterina Baryshnikova[1], for the Surgical and Clinical Outcome REsearch (SCORE) group[¶]

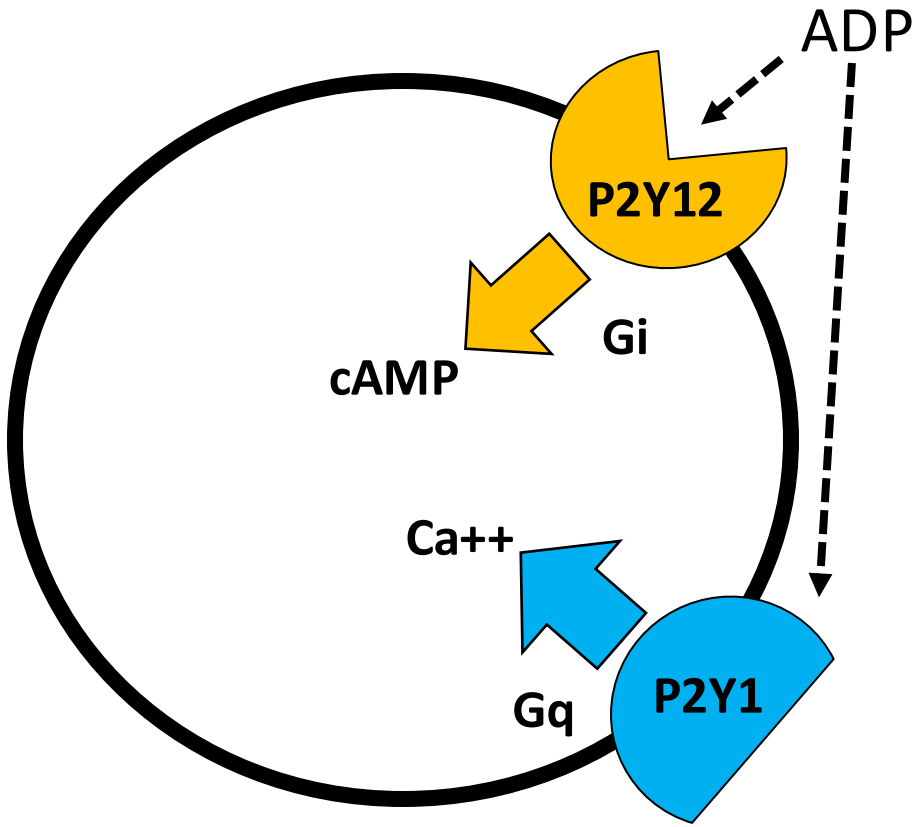
1 Department of Cardiothoracic, Vascular Anaesthesia and Intensive Care, IRCCS Policlinico San Donato, Milan, Italy, **2** Department of Cardiac Surgery, IRCCS Policlinico San Donato, Milan Italy

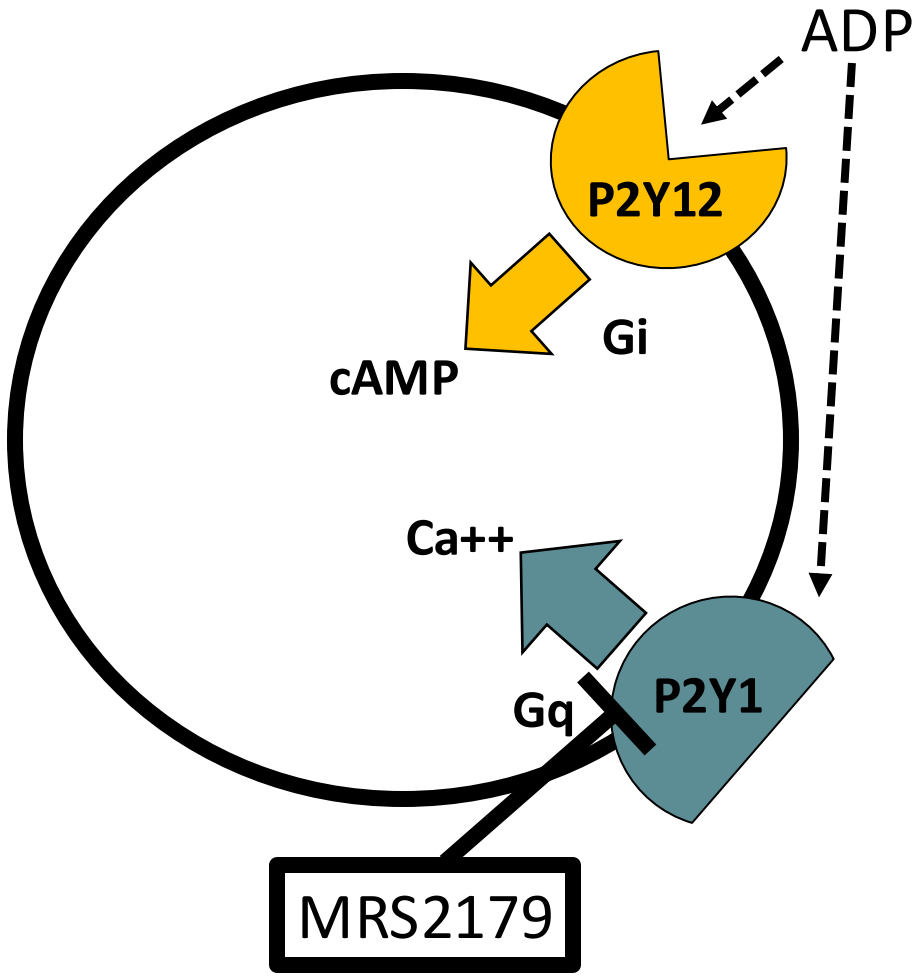

P2Y12
MALE
P2Y1

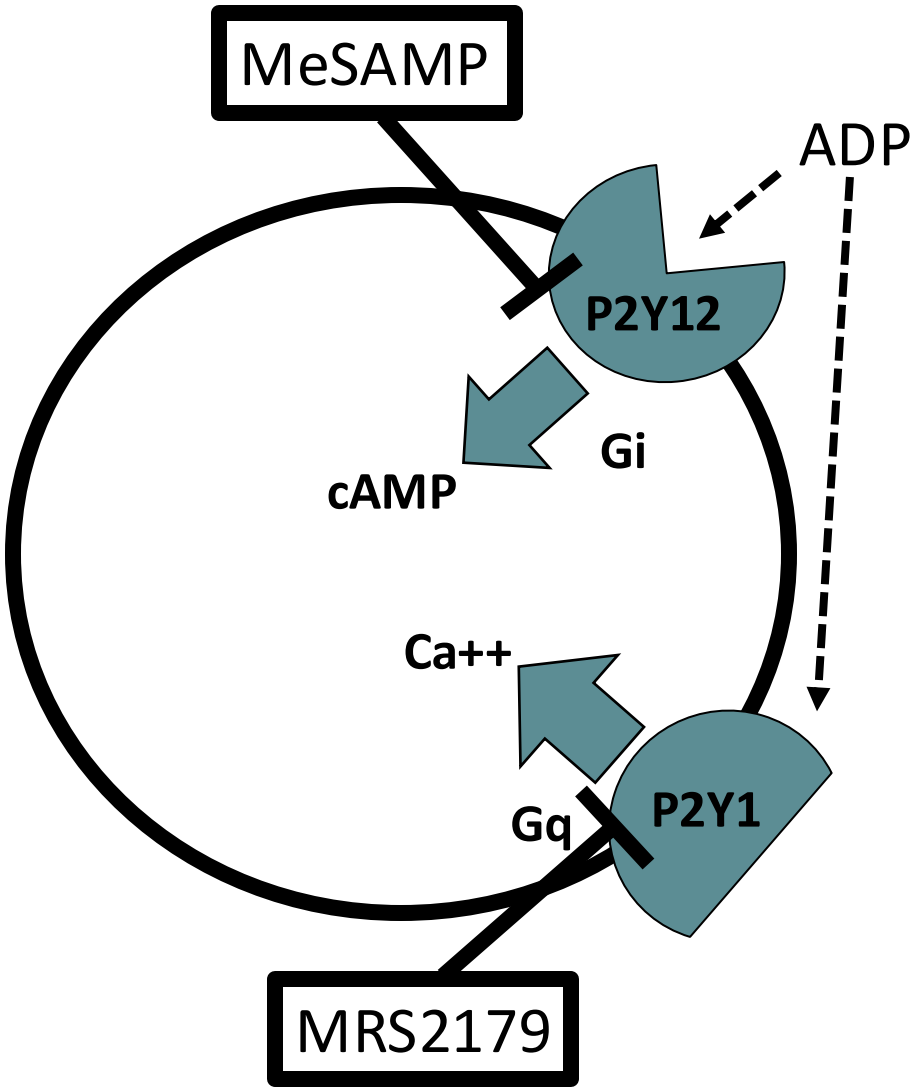

P2Y12
FEMALE
P2Y1



M: 25.6% (25.1-26.2) versus F: 91.5% (60.0-92.5), p=0.001


ADP
P2Y12
Gi
cAMP
Ca++
Gq
P2Y1


ADP
P2Y12
Gi
cAMP
Ca++
Gq
P2Y1
MRS2179


MeSAMP
ADP
P2Y12
Gi
cAMP
Ca++
P2Y1
Gq
MRS2179

Unpublished data

Effects of P2Y1 versus P2Y12 inhibition

MALE PLATELETS

	ADP	ADP + P2Y1 inhibitor	P value
Aggregation (%)	69.0 (54.3-73.7)	1.0 (0.3-1.7)	<0.0001
AUC	398 (386.3-427.1)	4.5 (2.5-3.6)	0.0008

FEMALE PLATELETS

	ADP	ADP + P2Y1 inhibitor	P value
Aggregation (%)	72.0 (57.3-86.7)	11.0 (8.5-13.7)	<0.0001
AUC	407.1 (368.2-409.8)	42.6 (32.7-45.1)	0.0008

Unpublished data

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	ADP	**ADP + P2Y12 inhibitor**	**P value**
Aggregation (%)	64.2 (59.3-69.1)	0.5 (0.1-1.2)	<0.0001
AUC	276.6 (236-302.0)	0.4 (0.2-0.9)	0.01

FEMALE PLATELETS

	ADP	ADP + P2Y1 inhibitor	P value
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AUC	407.1 (368.2-409.8)	42.6 (32.7-45.1)	0.0008
	ADP	**ADP + P2Y12 inhibitor**	**P value**
Aggregation (%)	67.0 (47.8-86.2)	21.6 (15.2-32.0)	0.02
AUC	306.0 (284-325.4)	71.0 (55.2-90.0)	0.01

Unpublished data

Effects of P2Y1 versus P2Y12 inhibition

MALE PLATELETS

	ADP	ADP + P2Y1 inhibitor	P value
Aggregation (%)	69.0 (54.3-73.7)	1.0 (0.3-1.7)	<0.0001
AUC	398 (386.3-427.1)	4.5 (2.5-3.6)	0.0008
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AUC	276.6 (236-302.0)	0.4 (0.2-0.9)	0.01

FEMALE PLATELETS

	ADP	ADP + P2Y1 inhibitor	P value
Aggregation (%)	72.0 (57.3-86.7)	11.0 (8.5-13.7)	<0.0001
AUC	407.1 (368.2-409.8)	42.6 (32.7-45.1)	0.0008
	ADP	**ADP + P2Y12 inhibitor**	**P value**
Aggregation (%)	67.0 (47.8-86.2)	21.6 (15.2-32.0)	0.02
AUC	306.0 (284-325.4)	71.0 (55.2-90.0)	0.01

Aggregation after isolated P2Y1 and P2Y12 receptor agonism is higher in females

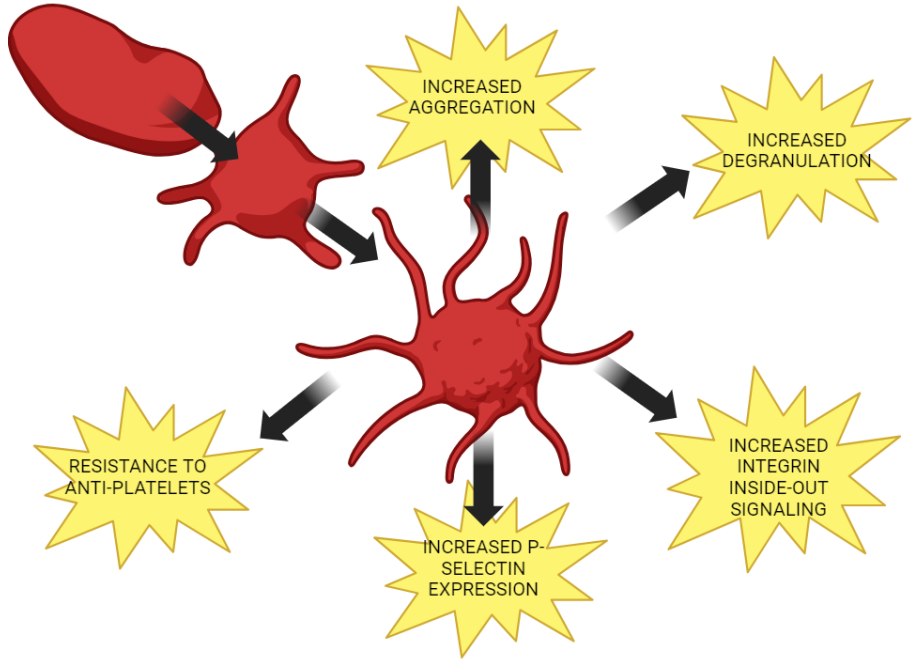
Interpretation of respective P2Y inhibition

- **Aggregation after isolated P2Y1 and P2Y12 receptor agonism is higher in females**
- **Female platelets are more resistant to P2Y1 and P2Y12 inhibition**
- **Female platelets have greater aggregation with P2Y1 (versus P2Y1) agonism**

Summary

- Cellular response:
  - Platelets from females:
    - Increased extent shape change and activation with ADP
  - Platelets from males:
    - Increased activation with platelet-activating factor

- Hormonal effect:
  - Estradiol treatment -> “feminized” the platelet from males response



J Trauma Acute Care Surg. 2019 November ; 87(5): 1052–1060. doi:10.1097/TA.0000000000002398.

Female Platelets Have Distinct Functional Activity Compared to Male Platelets: Implications in Transfusion Practice and Treatment of Trauma-Induced Coagulopathy

Julia R Coleman, MD MPH[1], Ernest E Moore, MD[2], Marguerite R Kelher, MS[1,3], Jason M Samuels, MD[1], Mitchell J Cohen, MD[2], Angela Sauaia, MD PhD[1], Anirban Banerjee, PhD[1], Christopher C Silliman, MD PhD[1,3], Erik Peltz, DO[1,*]

Mechanism?

Estrogen

Background

- Though anucleate cells, platelets are rich in RNA

- Nongenomic effects of estradiol
  - Evidence to suggest estradiol can change RNA translation in platelets

ESC European Society of Cardiology
Cardiovascular Research (2018) **114**, 645–655
doi:10.1093/cvr/cvy044

Non-genomic effects of nuclear receptors: insights from the anucleate platelet

Amanda J. Unsworth†, Gagan D. Flora†, and Jonathan M. Gibbins*

Am J Physiol Heart Circ Physiol 289: H1908–H1916, 2005.
First published June 17, 2005; doi:10.1152/ajpheart.01292.2004.

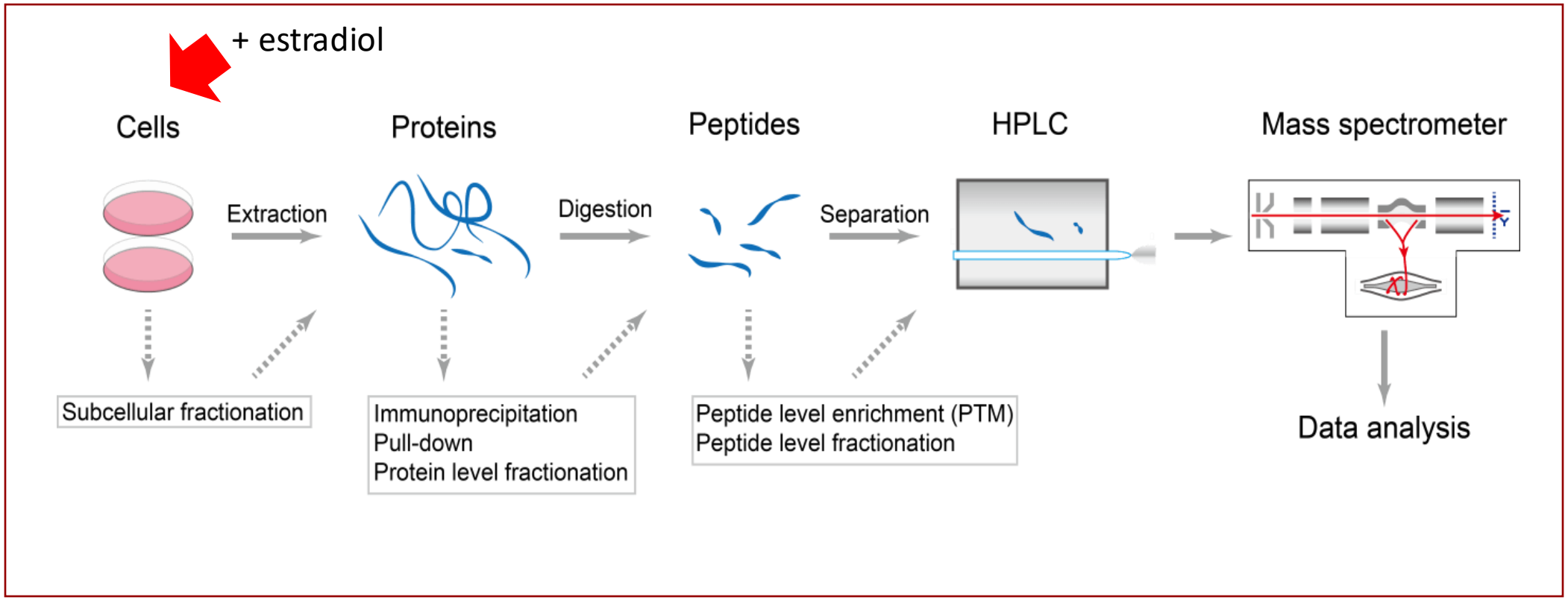
Estrogenic regulation of tissue factor and tissue factor pathway inhibitor in platelets

Muthuvel Jayachandran,[1] Antonio Sanzo,[1] Whyte G. Owen,[2,3] and Virginia M. Miller[1,4]

Methods

Credits: Kirk Hansen, Lauren Schmidt

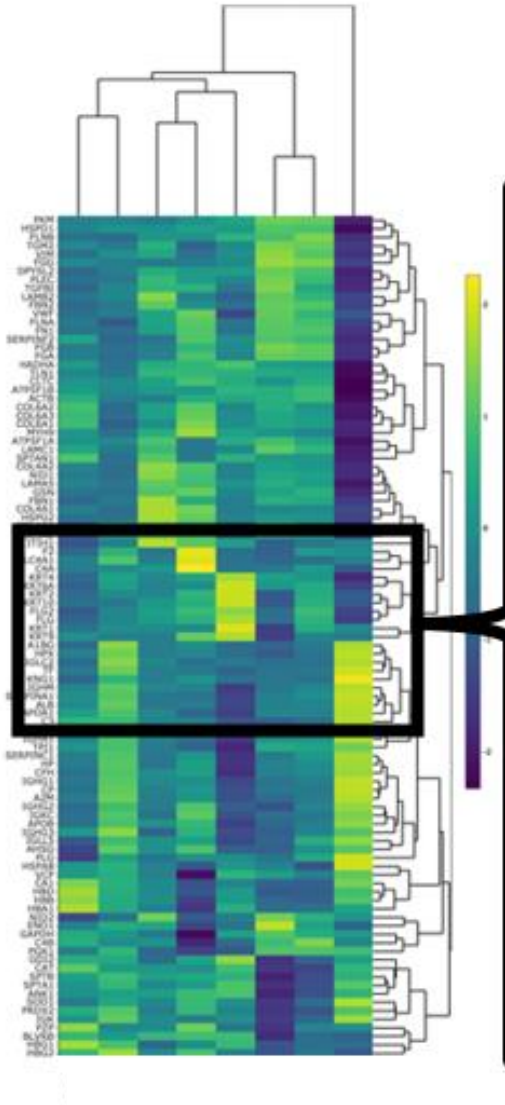
- Proteomics



Results

Credits: Kirk Hansen, Lauren Schmidt

- 411 proteins affected by estradiol!
- Estradiol associated with increases in several procoagulant and antifibrinolytic proteins, including:
  - Alpha-1 antitrypsin
  - Fibrinogen alpha chain
  - Myosin-0
  - Complement components
  - Apo-lipoprotein A
  - Coagulation factor IX
  - Multiple platelet glycoproteins
- Genomic effect of estrogen? Nongenomic effect?



Females

Protein	Control	+ Estradiol
Apolipoprotein A-I	160 (37–414)	1215 (329–1892
Apolipoprotein A-IV	20 (8–86)	87 (34–269)
Alpha-2-antiplasmin	15 (3–51)	67 (5–149)
Alpha-1-antitrypsin	628 (170–1060)	108 (59–252)
Fibrinogen gamma chain	683 (260–1642)	1395 (484–2380)
Complement factor H	206 (42–232)	36 (18–330)
Fibrinogen beta chain	360 (50–1530)	750 (179–2020)

Males

Protein	Control	+ Estradiol
Apolipoprotein A-I	21 (8–109)	76 (14–150)
Plasminogen	74 (26–196)	160 (81–248)
Vitamin K–dependent protein S	4 (1–14)	19 (5–37)
Plasma protease C1 inhibitor	16 (2–50)	20 (14–130)
Histone H1.3	37 (1–271)	89 (15–680)
Complement C1s subcomponent	1 (0.4–7)	12 (3–21)
Alpha-2-antiplasmin	5 (0.7–10)	18 (2–33)

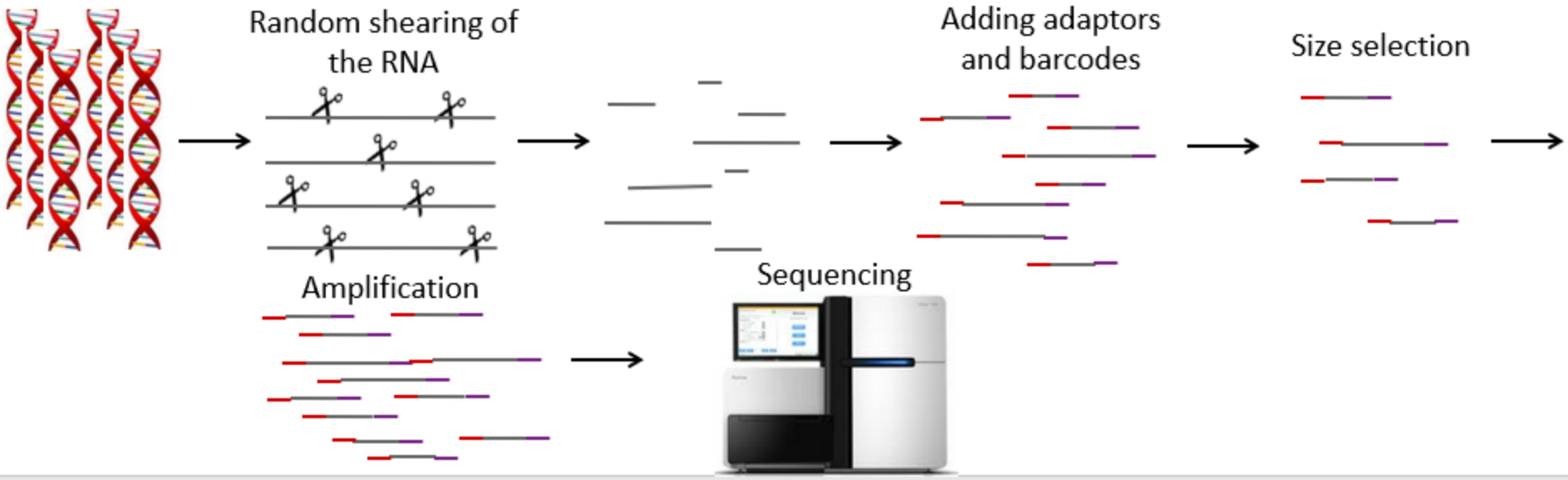
Hypothesis

- There are sex dimorphisms in platelet RNA profiles, conferring differential function and calcium signaling

Credits: Ken Jones

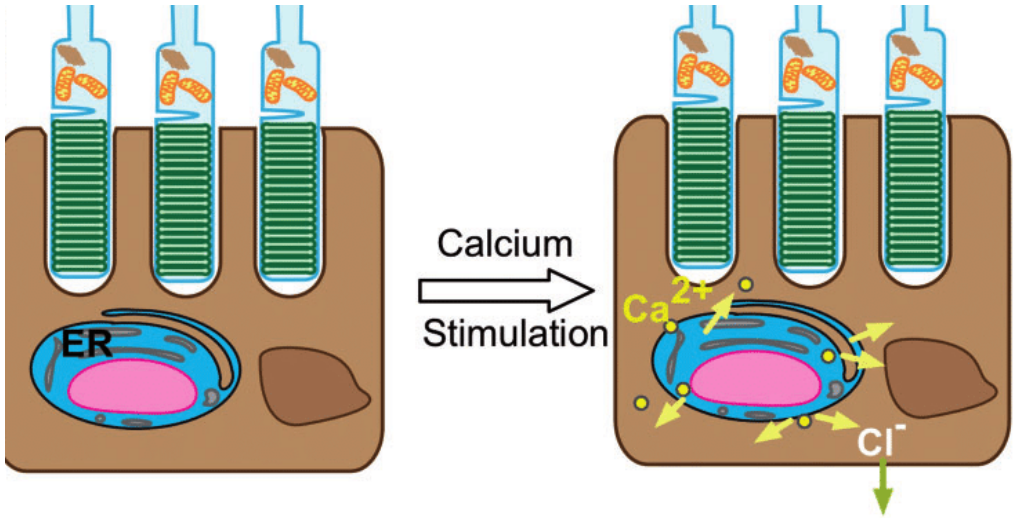
Methods

- Apheresis platelets were collected from healthy volunteers
- Fresh platelets were processed for RNA sequencing using Qiagen RNeasy miniprep kit and sequenced on the Illumina HiSeq2000 platform



Results

- 27 healthy volunteers (11 males, 16 females)
- Differences by sex in RNA sequences related to calcium signaling

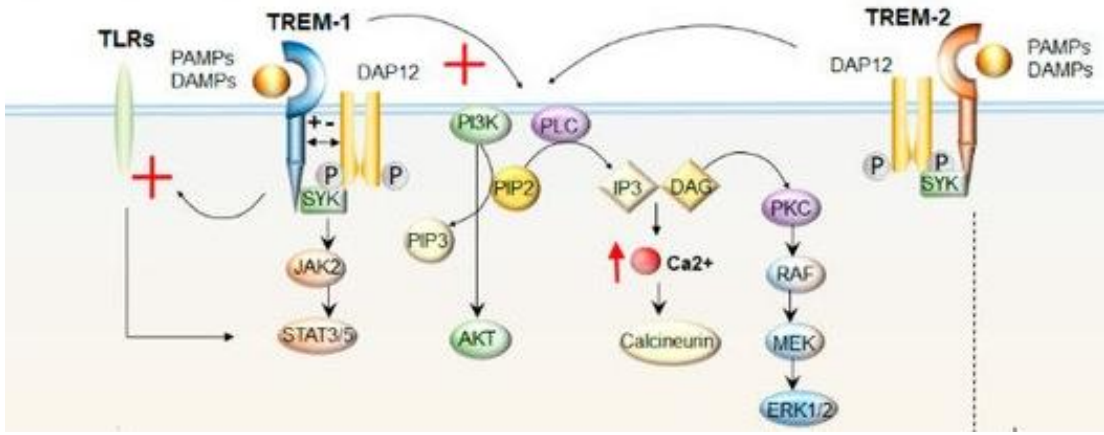


Best1 RNA: encodes proteins promoting intracellular calcium flux

- 1.38-fold higher in females versus males (225.32 versus 162.92, p=0.01)

Results

- 27 healthy volunteers (11 males, 16 females)
- Differences by sex in RNA sequences related to calcium signaling



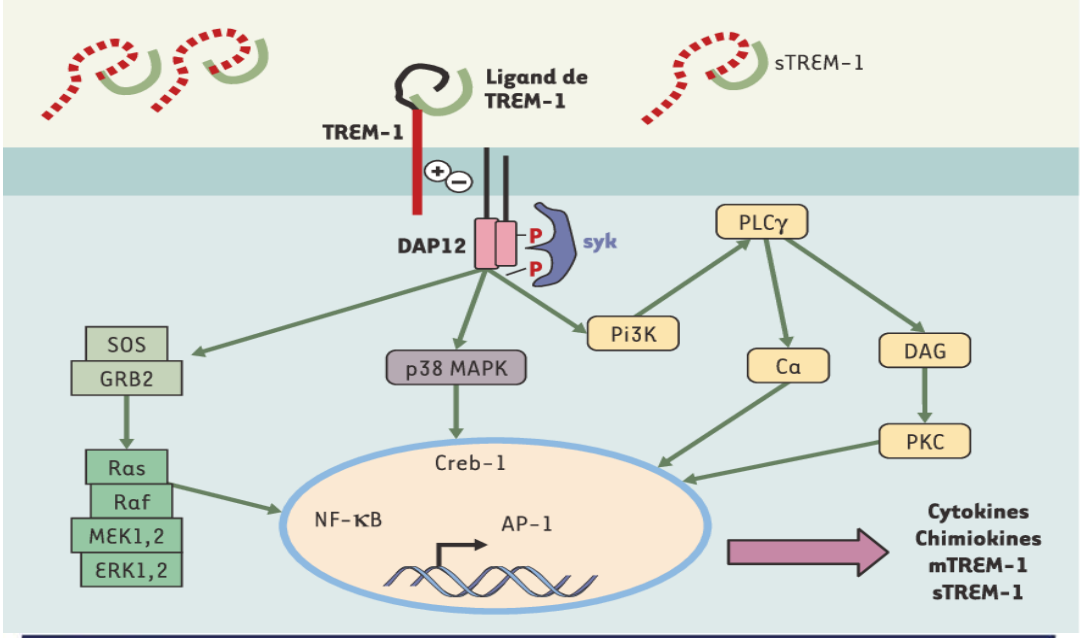
<u>TREM1 RNA:</u> encodes proteins that propagate platelet activation by enhancing calcium signaling

- 1.77-fold higher in females versus males (26.43 versus 14.91, p=0.007)

TREM1

- Triggering receptor expressed on myeloid cells (TREM) protein family

- TREM1 expressed in megakaryocytes and packaged into platelet alpha granules
  - Platelet activation
  - Binds fibrinogen
  - Cell adhesion and migration



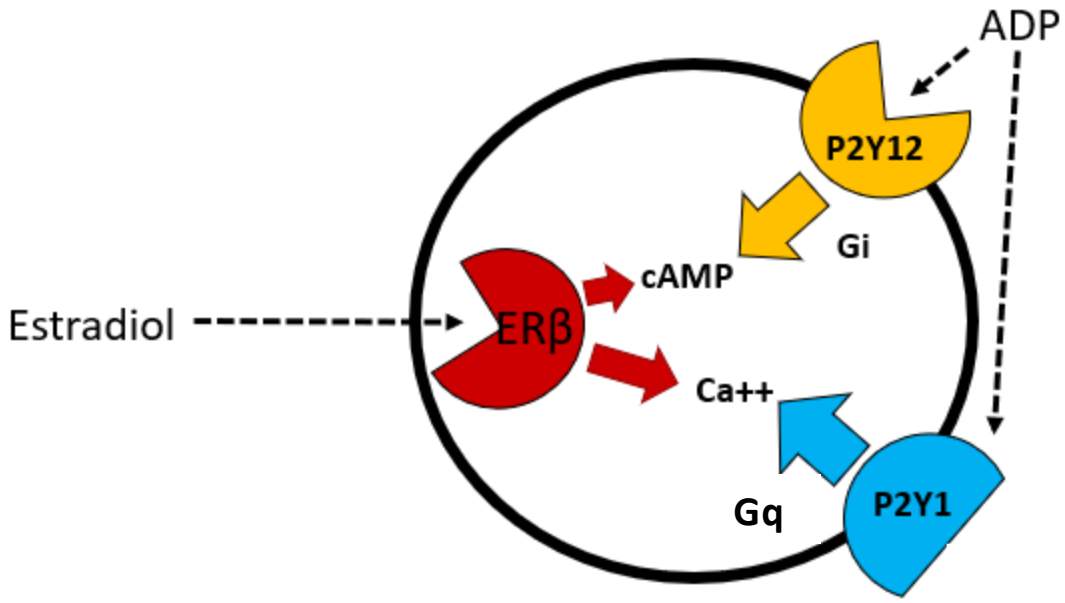
JCI The Journal of Clinical Investigation

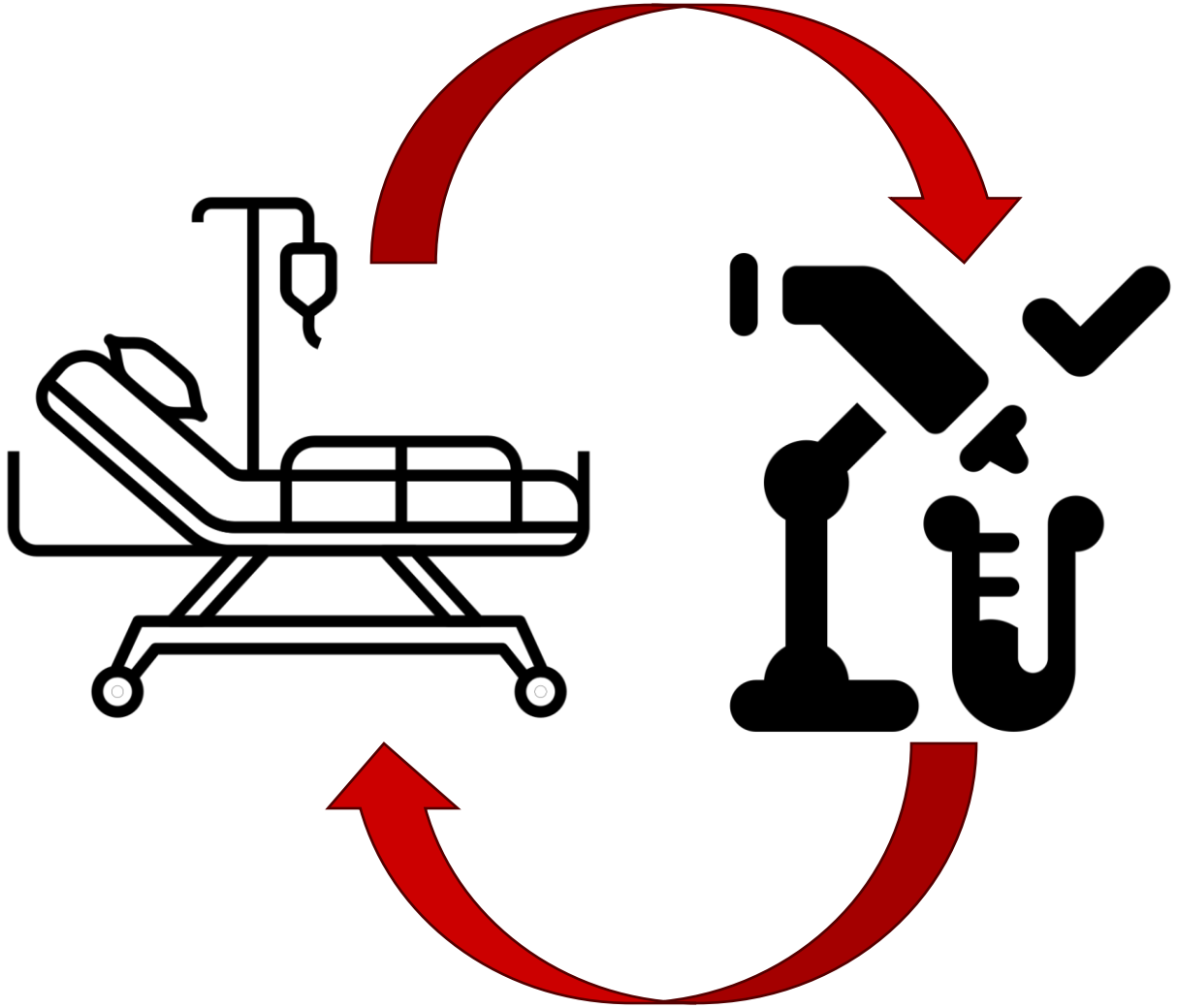
TREM-like transcript-1 protects against inflammation-associated hemorrhage by facilitating platelet aggregation in mice and humans

A. Valance Washington, ... , Pamela L. Schwartzberg, Daniel W. McVicar

Summary

- Sex dimorphisms exist in platelets, which are driven mechanistically by P2Y1 and P2Y12 receptor biology and distinct RNA and protein profiles
  - Can be affected by estradiol (through nongenomic action?)
  - Common pathway: src kinase





Clinical translation

- Do these data support sex-specific transfusion practices?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Donor Sex on Recipient Mortality in Transfusion

Michaël Chassé, M.D., Ph.D., Dean A. Fergusson, M.H.A., Ph.D., Alan Tinmouth, M.D., Jason P. Acker, M.B.A., Ph.D., Iris Perelman, M.Sc., Angie Tuttle, Shane W. English, M.D., Steven Hawken, Ph.D., Alan J. Forster, M.D., Nadine Shehata, M.D., Kednapa Thavorn, Ph.D., Kumanan Wilson, M.D., Nancy Cober, Heather Maddison, and Melanie Tokessy

- Multicenter, double-blind RCT of patients undergoing RBC transfusion
- 8719 patients randomized to receive RBCs from males or females, only 42% on surgical services
- No significant difference in survival between transfusions from female or male donors

Ann Surg. 2023 Jan 1;277(1):e170-e174. doi: 10.1097/SLA.0000000000004754. Epub 2021 Jan 22.

Association Between Blood Donor Demographics and Post-injury Multiple Organ Failure after Polytrauma

Francesco Amico [1 2], Jimmy T Efird [3], Gabrielle D Briggs [2], Natalie J Lott [4], Kate L King [1 2], Rena Hirani [5], Zsolt J Balogh [1 2]

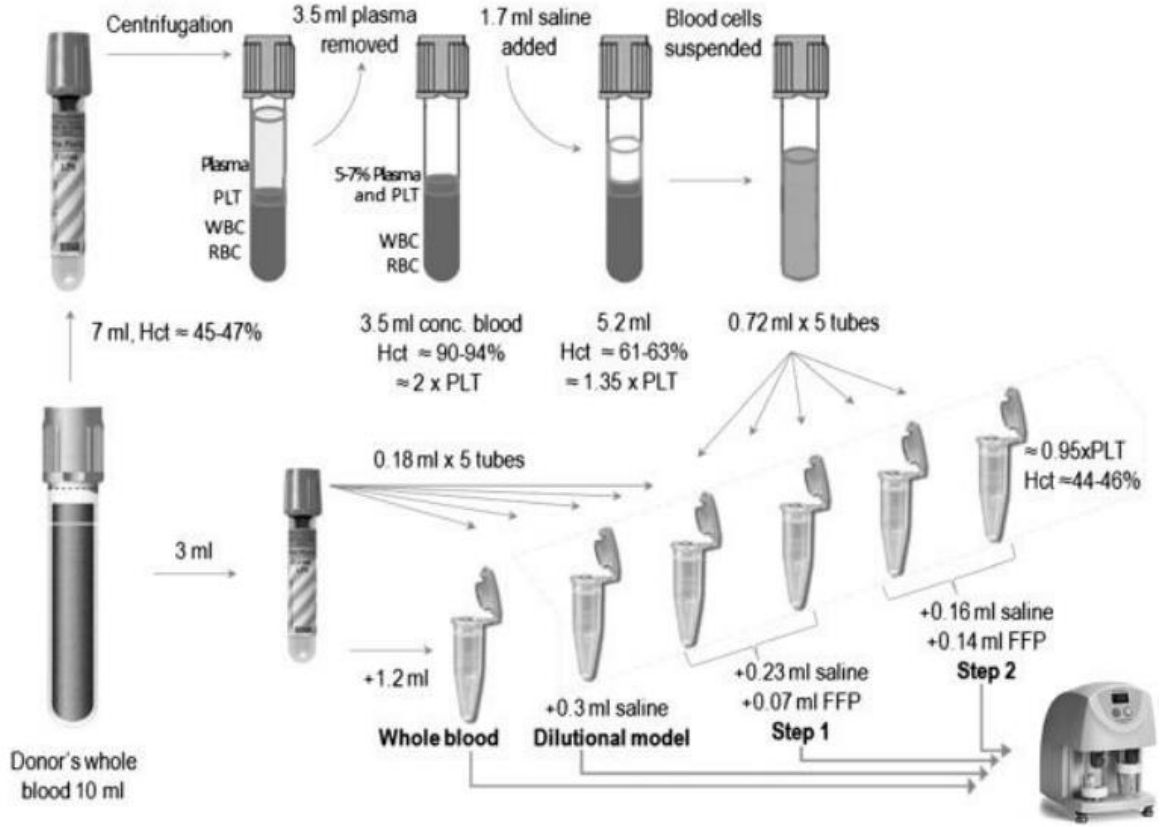
- Prospective study of 229 severely injured trauma patients admitted to the ICU and high risk for post-injury MOF at level-1 trauma center in Australia
- Role of blood donor demographics on transfusion recipients via log-linear analysis
- Donor-recipient sex mismatched red blood cell transfusions were more likely to be associated with MOF
- Fresh frozen plasma and cryoprecipitate recipients were more likely to experience MOF when transfused with a male (vs female) component

Hypothesis

- Blood products from female donors have increased hemostatic potential in an in vitro model of dilutional coagulopathy

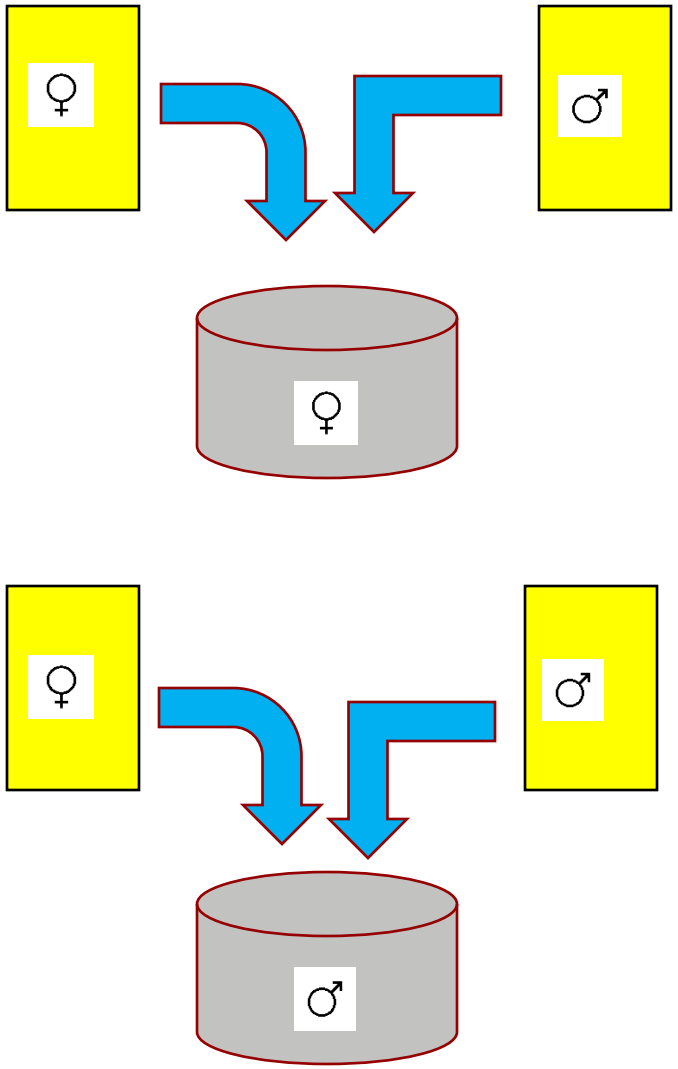
Methods

- Whole blood “recipients”, sex-specific donors (platelets, FBN)
- Sex concordant and discordant donors-recipients
- Dilutional coagulopathy model



Kostousov et. al, Thrombosis Research, 2012.

Sex concordant-discordant “transfusion” pairs

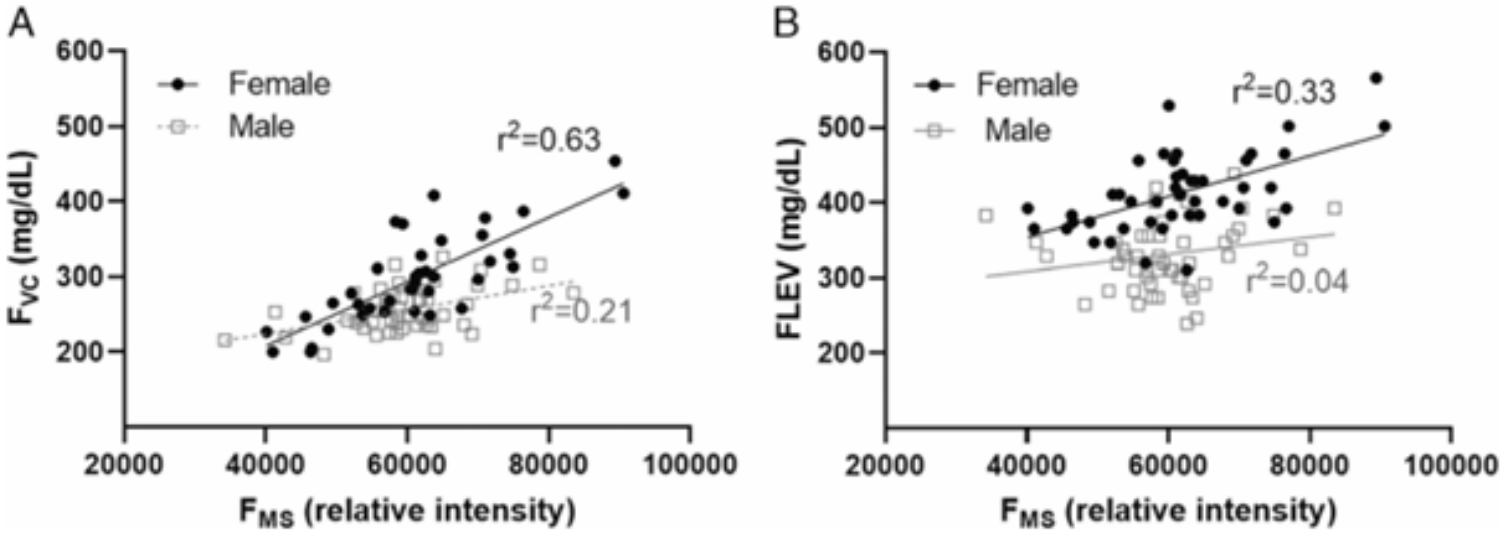


- Female platelets:
  - More hypercoagulable effect (greater decrease in r time [-8% vs 0%, p=0.02] than male platelets in male recipients)
- Female FBN:
  - More hypercoagulable effect (greater decrease in R [-9% vs -5%, p<0.05] than male FBN in male recipients, greater increase in angle in male recipients [23% vs. 14%, p=0.04] and F recipients [28% vs 20%, p=0.04])

Female fibrinogen compositional analysis

Credits: Kirk Hansen, Margot Debot

- Females have a stronger association between total and active fibrinogen than males



AAST PODIUM 2022

Platelet and cryoprecipitate transfusions from female donors improve coagulopathy in vitro

Margot DeBot, MD, Christopher Erickson, PhD, Marguerite Kelher, MS, Terry R. Schaid, Jr, MD, Ernest E. Moore, MD, Angela Sauaia, MD, PhD, Alexis Cralley, MD, Ian LaCroix, BS, Angelo D'Alessandro, PhD, Kirk Hansen, PhD, Mitchell J. Cohen, MD, Christopher C. Silliman, MD, PhD, *and* Julia Coleman, MD, *Aurora, Colorado*

Conclusions

- Female and male coagulation is not the same
  - Partially mediated by intrinsic differences in thrombin biology, fibrinogen and fibrinolysis, clot structure formation, platelet biology
  - Partially mediated by estrogen

- Implications for future practice:
  - Therapeutic sex-specific selection of blood products?
  - Role for therapeutic hormones?

Sex hormones as therapeutic adjuncts

Current Neuropharmacology, 2016, *14*, 641-653 641

Neuroprotection by Estrogen and Progesterone in Traumatic Brain Injury and Spinal Cord Injury

Evgeni Brotfai
and Moti Kleir

Received: 27 April 2022 | Revised: 13 June 2022 | Accepted: 19 June 2022
DOI: 10.1111/jne.13181

INVITED REVIEW

Journal of Neuroendocrinology WILEY

Therapeutic potential of progesterone in spinal cord injury-induced neuropat neuroinflammation and

Sol Ferreyra[1] | Susana González[1,]

Am J Transl Res 2017;9(9):3881-3895
www.ajtr.org /ISSN:1943-8141/AJTR0057123

Review A
Hormona

Parker E Ludwig[1]

Experimental Neurology 259 (2014) 28–37

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Review

Sex steroids and neuroprotection in spinal cord injury: A review of preclinical investigations

Stella Elkabes [a,*], Arnaud B. Nicot [b,c,d]

Ann Surg. 2000 Nov;232(5):673-9. doi: 10.1097/00000658-200011000-00009.

Estradiol administration after trauma-hemorrhage improves cardiovascular and hepatocellular functions in male animals

Y Mizushima [1], P Wang, D Jarrar, W G Cioffi, K I Bland, I H Chaudry

Ann Surg. 2000 Nov;232(5):673-9. doi: 10.1097/00000658-200011000-00009.

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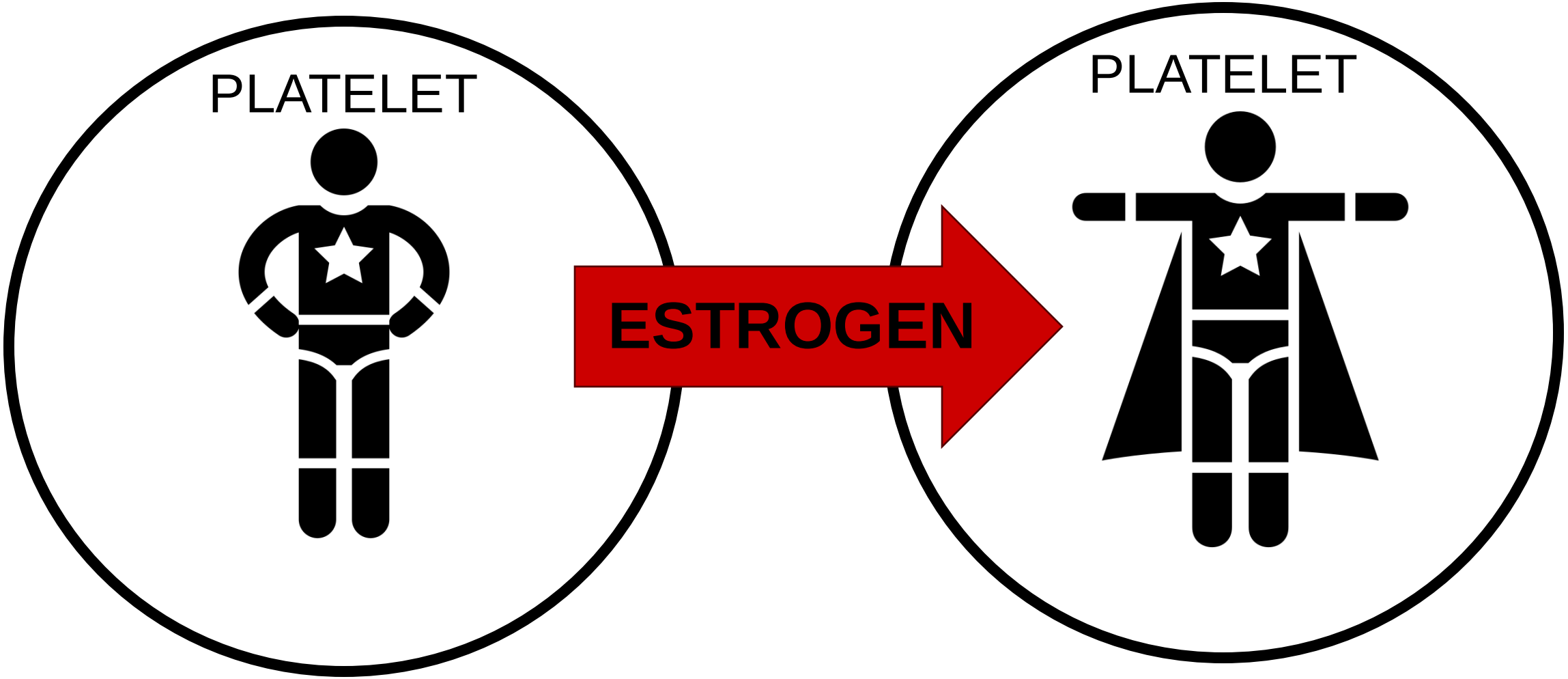
J Trauma Acute Care Surg. 2022 Jan 1;92(1):57-64. doi: 10.1097/TA.0000000000003434.

An estrogen (17α-ethinyl estradiol-3-sulfate) reduces mortality in a swine model of multiple injuries and hemorrhagic shock

Hossam Abdou [1], Jonathan J Morrison, Joseph Edwards, Neerav Patel, Eric Lang, Michael J Richmond, Noha Elansary, Mathangi Gopalakrishnan, Jonathan Berman, William J Hubbard, Thomas M Scalea, Irshad H Chaudry

“Primed” platelets??



Unpublished data

Estrogen dose response curve (incubation time 15 min)

	Control	100 nM estradiol	1 uM estradiol	10 uM estradiol	P value
Agg (%)	41.5 (29.3-56.0)	42.5 (29.4-63.6)	48.0 (30.2-67.6)	51.2 (27.6-50.2)	0.41
AUC	186.2 (127.6-290.3)	184.7 (105.6-245.1)	208.2 (107.8-265.3)	213.4 (126.1-261.1)	0.81

Increased aggregation? (p=NS)

Estrogen dose-time response curve

	Control	100 nM estradiol	1 uM estradiol	10 uM estradiol	P value
Agg (%)	41.5 (29.3-56.0)	42.5 (29.4-63.6)	48.0 (30.2-67.6)	51.2 (27.6-50.2)	0.41
AUC	186.2 (127.6-290.3)	184.7 (105.6-245.1)	208.2 (107.8-265.3)	213.4 (126.1-261.1)	0.81

100 nM estradiol	Control	15 minutes	1 hour	2 hours	P value
Agg (%)	32.0 (29.0-35.0)	32.0 (29.0-35.0)	40.0 (37.5-42.5)	36.2 (35.0-37.5)	0.004
AUC	135.4 (128.8-142.0)	109.4 (96.7-122.0)	176.8 (149.3-204.2)	152.9 (138.7-167.0)	0.06

Estrogen dose-time response curve

	Control	100 nM estradiol	1 uM estradiol	10 uM estradiol	P value
Agg (%)	41.5 (29.3-56.0)	42.5 (29.4-63.6)	48.0 (30.2-67.6)	51.2 (27.6-50.2)	0.41
AUC	186.2 (127.6-290.3)	184.7 (105.6-245.1)	208.2 (107.8-265.3)	213.4 (126.1-261.1)	0.81

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AUC	135.4 (128.8-142.0)	109.4 (96.7-122.0)	176.8 (149.3-204.2)	152.9 (138.7-167.0)	0.06

1 uM estradiol	Control	15 minutes	1 hour	2 hours	P value
Agg (%)	32.0 (29.0-25.0)	33.0 (29.5-36.5)	43.2 (36.5-50.0)	38.7 (35.0-42.5)	0.01
AUC	135.4 (128.8-142.0)	135.8 (126.1-145.5)	200.1 (148.6-251.6)	185.6 (145.3-225.8)	0.13

Unpublished data

Estrogen dose-time response curve: 10 uM, 1 hour!

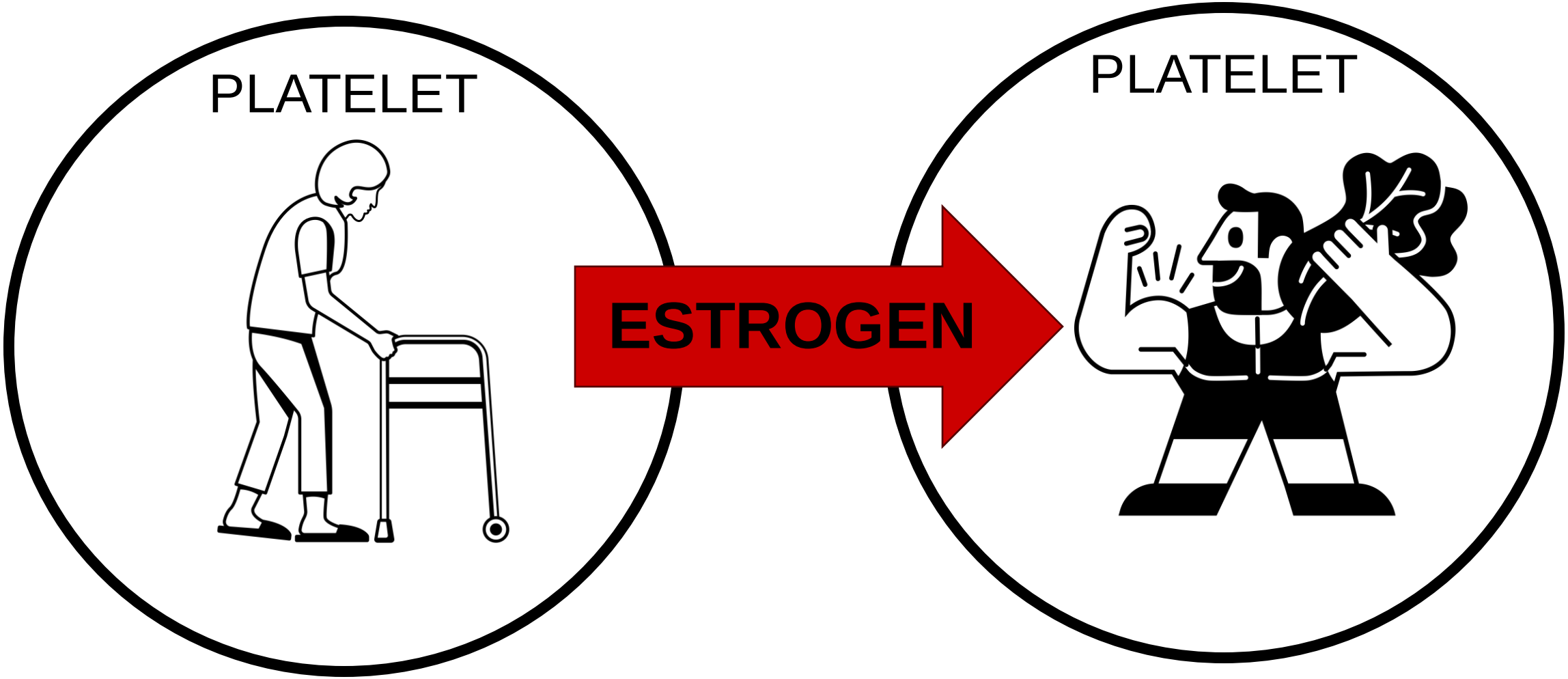
	Control	100 nM estradiol	1 uM estradiol	10 uM estradiol	P value
Agg (%)	41.5 (29.3-56.0)	42.5 (29.4-63.6)	48.0 (30.2-67.6)	51.2 (27.6-50.2)	0.41
AUC	186.2 (127.6-290.3)	184.7 (105.6-245.1)	208.2 (107.8-265.3)	213.4 (126.1-261.1)	0.81

100 nM estradiol	Control	15 minutes	1 hour	2 hours	P value
Agg (%)	32.0 (29.0-35.0)	32.0 (29.0-35.0)	40.0 (37.5-42.5)	36.2 (35.0-37.5)	0.004
AUC	135.4 (128.8-142.0)	109.4 (96.7-122.0)	176.8 (149.3-204.2)	152.9 (138.7-167.0)	0.06

1 uM estradiol	Control	15 minutes	1 hour	2 hours	P value
Agg (%)	32.0 (29.0-25.0)	33.0 (29.5-36.5)	43.2 (36.5-50.0)	38.7 (35.0-42.5)	0.01
AUC	135.4 (128.8-142.0)	135.8 (126.1-145.5)	200.1 (148.6-251.6)	185.6 (145.3-225.8)	0.13

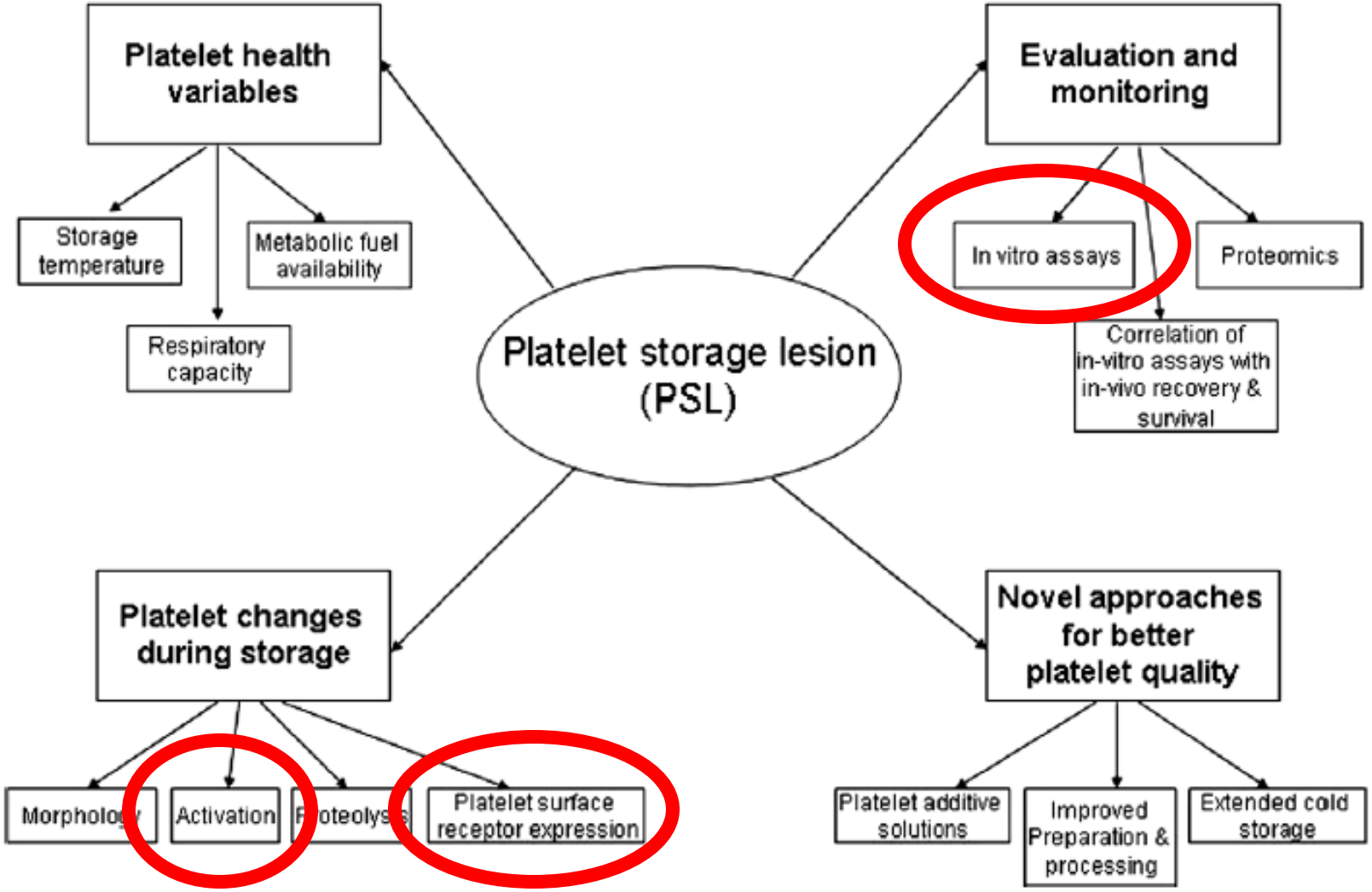
10 uM estradiol	Control	15 minutes	1 hour	2 hours	P value
Agg (%)	32.0 (29.0-35.0)	36.5 (33.5-39.5)	44.0 (39.0-45.0)	45.2 (38.0-52.5)	0.01
AUC	135.4 (128.8-142.0)	140.8 (135.8-145.8)	243.2 (169.1-317.2)	218.5 (170.9-266.1)	0.08

What about platelet longevity?



Shrivastava, *Transfusion and Apheresis Science*, 2009

Shelf life: storage lesions



Unpublished data

Shelf life: preserved aggregation in female platelets

Agg	Day 2
Males	45.0 (34.0-68.5)
Females	47.0 (38.9-52.0)

AUC	Day 2
Males	204.4 (140.5-358.2)
Females	226.7 (163.0-290.3)

Unpublished data

Shelf life: preserved aggregation in female platelets

Agg	Day 2	Day 3*
Males	45.0 (34.0-68.5)	28.0 (21.0-35.0)
Females	47.0 (38.9-52.0)	46.5 (41.0-52.0)

*p=0.001

AUC	Day 2	Day 3*
Males	204.4 (140.5-358.2)	142.0 (85.3-146.4)
Females	226.7 (163.0-290.3)	244.4 (198.5-290.3)

*p=0.001

Unpublished data

Shelf life: preserved aggregation in female platelets

Agg	Day 2	Day 3*	Day 4*
Males	45.0 (34.0-68.5)	28.0 (21.0-35.0)	29.0 (28.0-31.0)
Females	47.0 (38.9-52.0)	46.5 (41.0-52.0)	42.5 (37.0-48.0)
		*p=0.001	*p=0.001

AUC	Day 2	Day 3*	Day 4
Males	204.4 (140.5-358.2)	142.0 (85.3-146.4)	146.4 (128.8-237.1)
Females	226.7 (163.0-290.3)	244.4 (198.5-290.3)	179.3 (128.1-230.4)
		*p=0.001	

Unpublished data

Shelf life: preserved aggregation in female platelets

Agg	Day 2	Day 3*	Day 4*	Day 5
Males	45.0 (34.0-68.5)	28.0 (21.0-35.0)	29.0 (28.0-31.0)	29.5 (24.0-80.0)
Females	47.0 (38.9-52.0)	46.5 (41.0-52.0)	42.5 (37.0-48.0)	57.0 (46.0-68.0)
		*p=0.001	*p=0.001	

AUC	Day 2	Day 3*	Day 4	Day 5*
Males	204.4 (140.5-358.2)	142.0 (85.3-146.4)	146.4 (128.8-237.1)	123.8 (117.0-203.6)
Females	226.7 (163.0-290.3)	244.4 (198.5-290.3)	179.3 (128.1-230.4)	255.6 (245.4-275.8)
		*p=0.001		*p=0.001

Unpublished data

Shelf life: increased storage lesion accumulation in male platelets

P-selectin (CD62p)	Day 2
Males	44.9 (41.8-48.0)
Females	52.2 (47.3-73.5)

Unpublished data

Shelf life: increased storage lesion accumulation in male platelets

P-selectin (CD62p)	Day 2	Day 3*
Males	44.9 (41.8-48.0)	55.1 (47.3-62.9)
Females	52.2 (47.3-73.5)	31.8 (18.1-46.7)

*p=0.01

Unpublished data

Shelf life: increased storage lesion accumulation in male platelets

P-selectin (CD62p)	Day 2	Day 3*	Day 4*
Males	44.9 (41.8-48.0)	55.1 (47.3-62.9)	63.3 (52.2-74.4)
Females	52.2 (47.3-73.5)	31.8 (18.1-46.7)	32.4 (13.4-50.0)
		*p=0.01	*p=0.01

Unpublished data

Shelf life: increased storage lesion accumulation in male platelets

P-selectin (CD62p)	Day 2	Day 3*	Day 4*	Day 5
Males	44.9 (41.8-48.0)	55.1 (47.3-62.9)	63.3 (52.2-74.4)	74.8 (66.6-83.1)
Females	52.2 (47.3-73.5)	31.8 (18.1-46.7)	32.4 (13.4-50.0)	26.5 (20.8-53.0)
		*p=0.01	*p=0.01	*p=0.001

› Blood Transfus. 2021 May;19(3):216-223. doi: 10.2450/2020.0145-20. Epub 2020 Oct 14.

The impact of donor sex and age on stored platelet metabolism and post-transfusion recovery

Angelo D'Alessandro [1 2], Davide Stefanoni [1], Sherrill J Slichter [3 4], Xiaoyun Fu [4], James C Zimring [5]

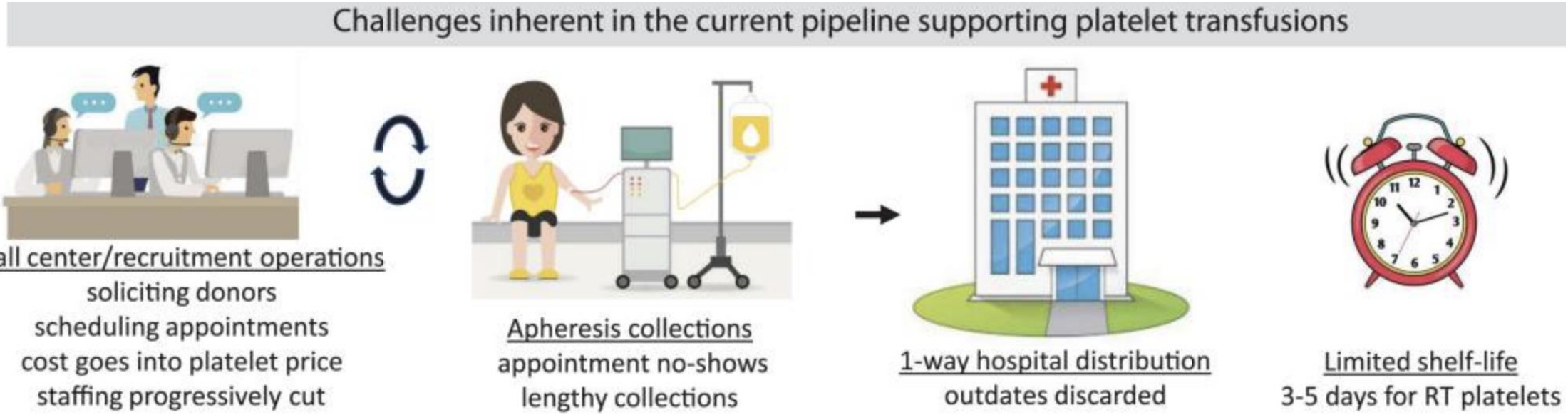
Clinical Trial › J Proteomics. 2015 Jan 1:112:190-209. doi: 10.1016/j.jprot.2014.08.016. Epub 2014 Sep 6.

Proteomics of apheresis platelet supernatants during routine storage: Gender-related differences

Monika Dzieciatkowska [1], Angelo D'Alessandro [1], Timothy A Burke [2], Marguerite R Kelher [2], Ernest E Moore [3], Anirban Banerjee [4], Christopher C Silliman [5], Bernadette F West [2], Kirk C Hansen [6]

Blood shortage crises

- Every 2 seconds, someone in the US needs a blood transfusion
- Only 3% of eligible US population donate blood per year
  - Globally 33% of blood donations are given by women



- 2.2 million platelet transfusions are performed annually

Blood shortage crises

Home > About Us > News and Events > Press Release >
Red Cross national blood inventory plummets 25% in July —declares emergency blood shortage

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transfusion.org
TRANSFUSION

DISASTER PREPAREDNESS

U.S. cities will not meet blood product resuscitation standards during major mass casualty incidents: Results of a THOR-AABB working party prospective analysis

Jeremy W. Cannon, Noah M. Igra, P. Dayand Borge, Andrew P. Cap, Dana Devine, Heidi Doughty, Zhi Geng, Jessica F. Guzman, Paul M. Ness, Donald H. Jenkins, Srijana Rajbhandary, Daniela Schmulevich, James R. Stubbs, Douglas J. Wiebe, Mark H. Yazer, Philip C. Spinella ... See fewer authors

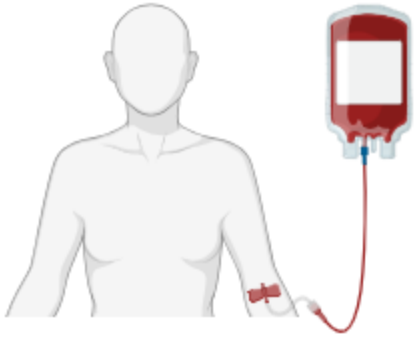
If female platelets are better and for longer, is estradiol the answer to platelet shortage crises???

Conclusions

Female are relatively hypercoagulable compared to males, conferring benefit in trauma-induced coagulopathy.

MECHANISTIC INVESTIGATION

CLINICAL TRANSLATION



Implications for donor sex-specific transfusion and treatment of blood products with estrogen pre-transfusion

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THE OHIO STATE UNIVERSITY
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QUESTIONS?

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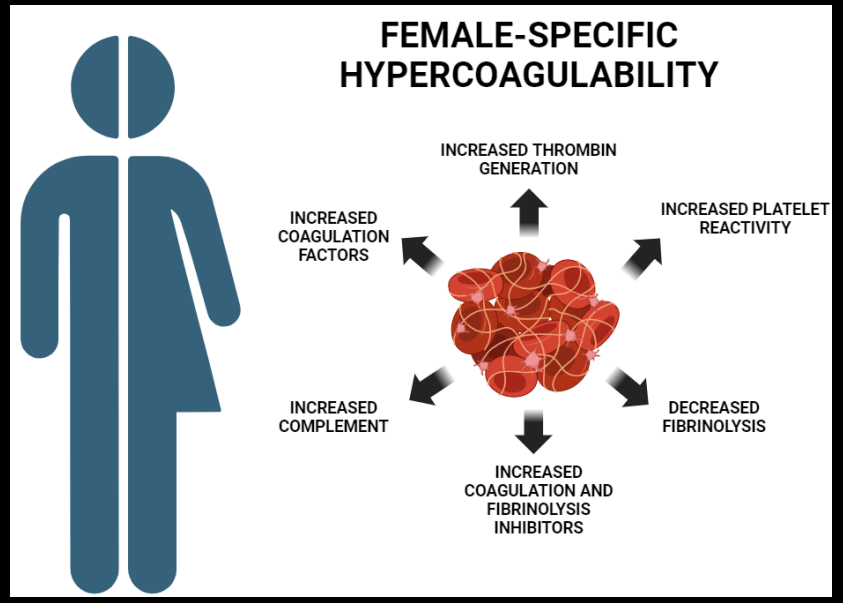
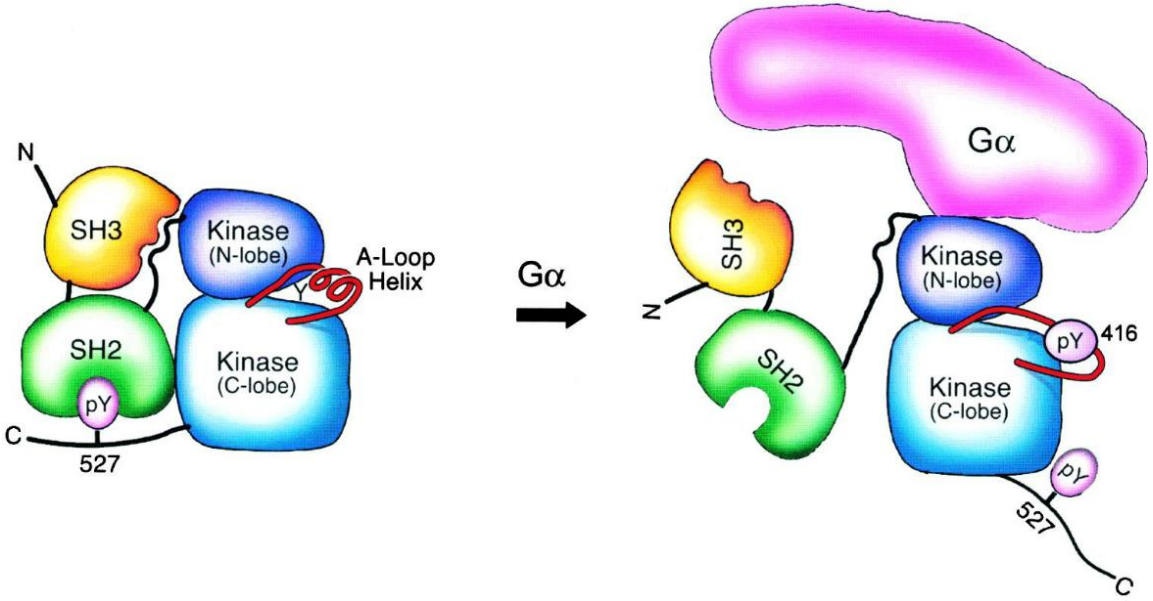


Please reach out for collaboration opportunities!

Src kinase

- SFKs: contribute to signaling via G protein–coupled receptors (PAR-1 and PAR-4, P2Y) that synergize with primary activation signals to maximally activate platelets



- SFKs also initiate inhibitory pathways ITIM–containing receptors, lipid and protein-tyrosine phosphatases that attenuate platelet activation,-limiting thrombus size

Src kinase

- Src kinase inhibition (PPI) decreases platelet aggregation

	Control	**PPI**	**P value**
Aggregation (%)	58.0 (50-68.5)	16.0 (5.0-39.0)	0.001
AUC	321.1 (225.0-358.2)	82.0 (54.1-139.0)	0.001

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AUC	321.1 (225.0-358.2)	82.0 (54.1-139.0)	0.001
MALES			
Aggregation (%)	54.0 (50.0-58.0)	22.0 (5.0-39.0)	0.003
AUC	273.1 (225.0-321.1)	110.5 (82.0-139.0)	<0.0001

Src kinase

- Src kinase inhibition (PPI) decreases platelet aggregation in sex-specific manner?

	Control	PPI	P value
Aggregation (%)	58.0 (50-68.5)	16.0 (5.0-39.0)	0.001
AUC	321.1 (225.0-358.2)	82.0 (54.1-139.0)	0.001
MALES			
Aggregation (%)	54.0 (50.0-58.0)	22.0 (5.0-39.0)	0.003
AUC	273.1 (225.0-321.1)	110.5 (82.0-139.0)	<0.0001
FEMALES			
Aggregation (%)	71.5 (58.0-85.0)	34.5 (30.0-39.0)	0.04
AUC	276.1 (231.0-321.1)	166.0 (139.0-193.0)	0.07