Culture générale
Hémostase
et
Chirurgie Cardiaque pédiatrique

DIU de Réanimation des Cardiopathies Congénitales
2020
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Introduction

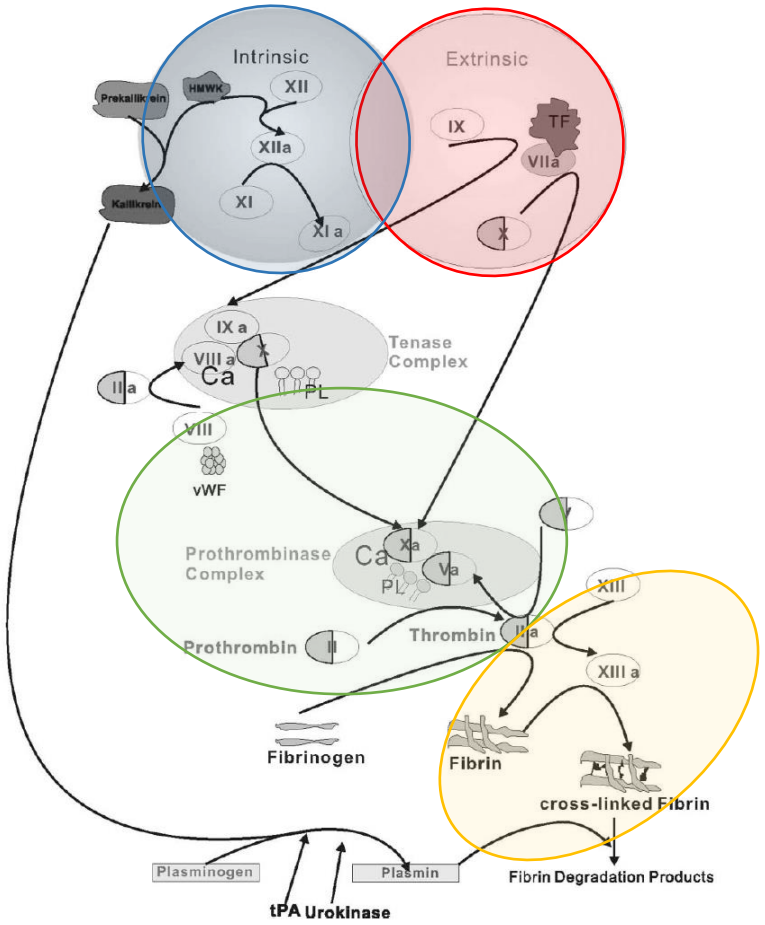
- Chirurgie cardiaque pédiatrique et assistances circulatoires implique la confrontation au double risque thrombotique et hémorragique.

- Les buts de ce cours est de donner des éléments de réflexions sur la prise en charge de l'hémorragie et de la thrombose dans le contexte de correction chirurgicale des cardiopathies congénitales en incluant les assistances de courte (type ECMO) et de moyenne durée (type VAD).
- Il demeure en effet un très large champ de recherche dans ce domaine, concernant plus particulièrement
    1. La physiologie de l'hémostase.
    2. La recherche d'un anticoagulant idéal.
    3. L'évaluation biologique de l'hémostase.
    4. L'existence d'un lien entre la conduite du traitement anticoagulant et la survenue des évènements hémorragiques et thrombotiques.

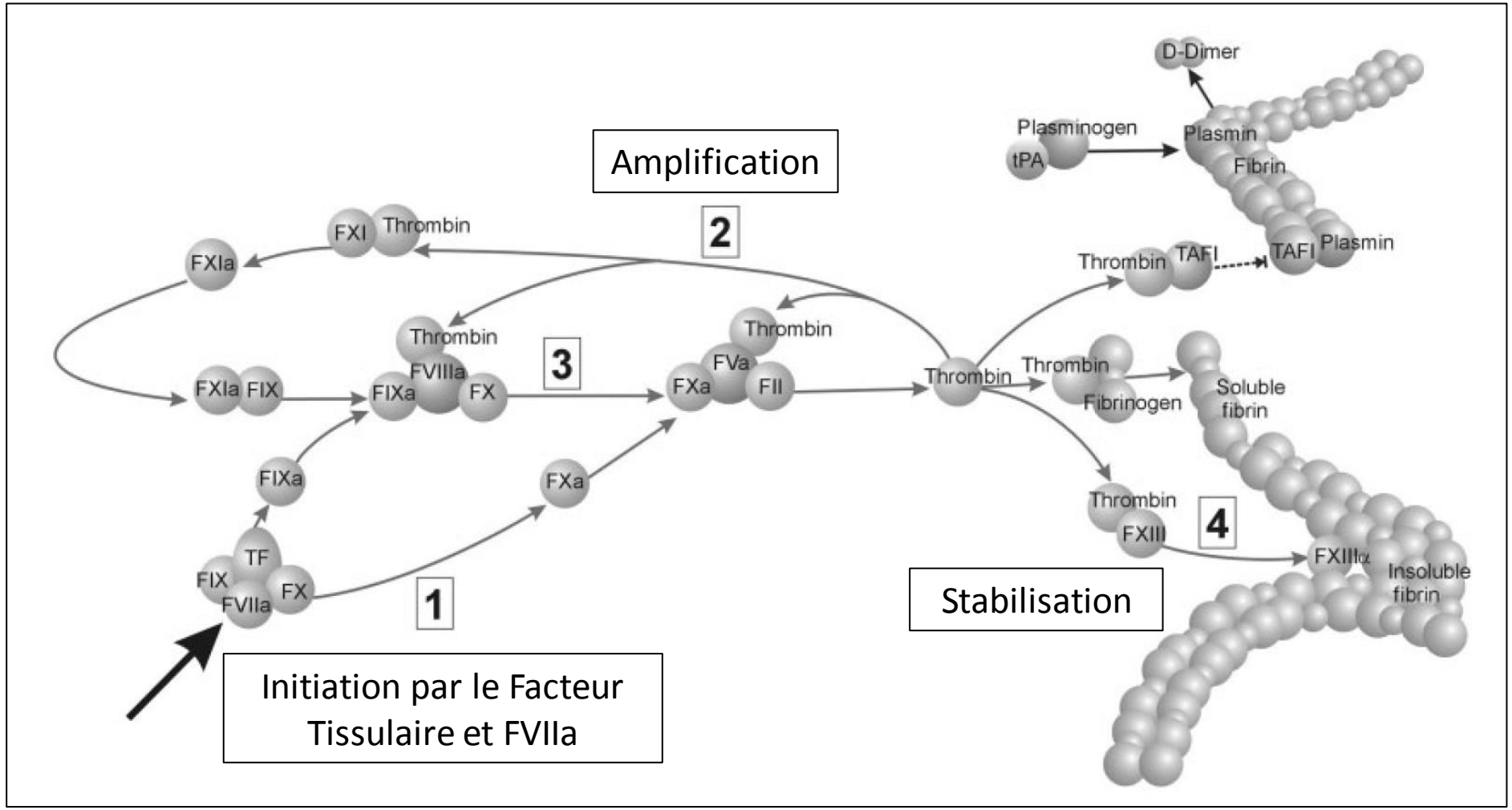
Un bref rappel physiologique

- Davies EW, Ratnoff. **Waterfall sequence for intrinsic blood clotting**. *Science*. 1964;145:1310-1312.
- Macfarlane RG. **An enzyme cascade in the blood clotting mechanism, and its function as a biochemical amplifier**. *Nature*. 1964;202:498-499.

- Une voie extrinsèque induite par une lésion tissulaire (facteur tissulaire).
- Le rôle de la voie intinsèque (système contact) en situation physiologique est moins claire mais prend une dimension essentielle quand le sang se trouve en contact avec des surfaces artificielles.
- Ces deux voies convergent pour forme le complexe prothrombinase (Ca^{2+}-V_a-X_a-PL).
- Formation de thrombine.
- $FXIII_a$ stabilisant le caillot de fibrine
- Phase de fibrinolyse



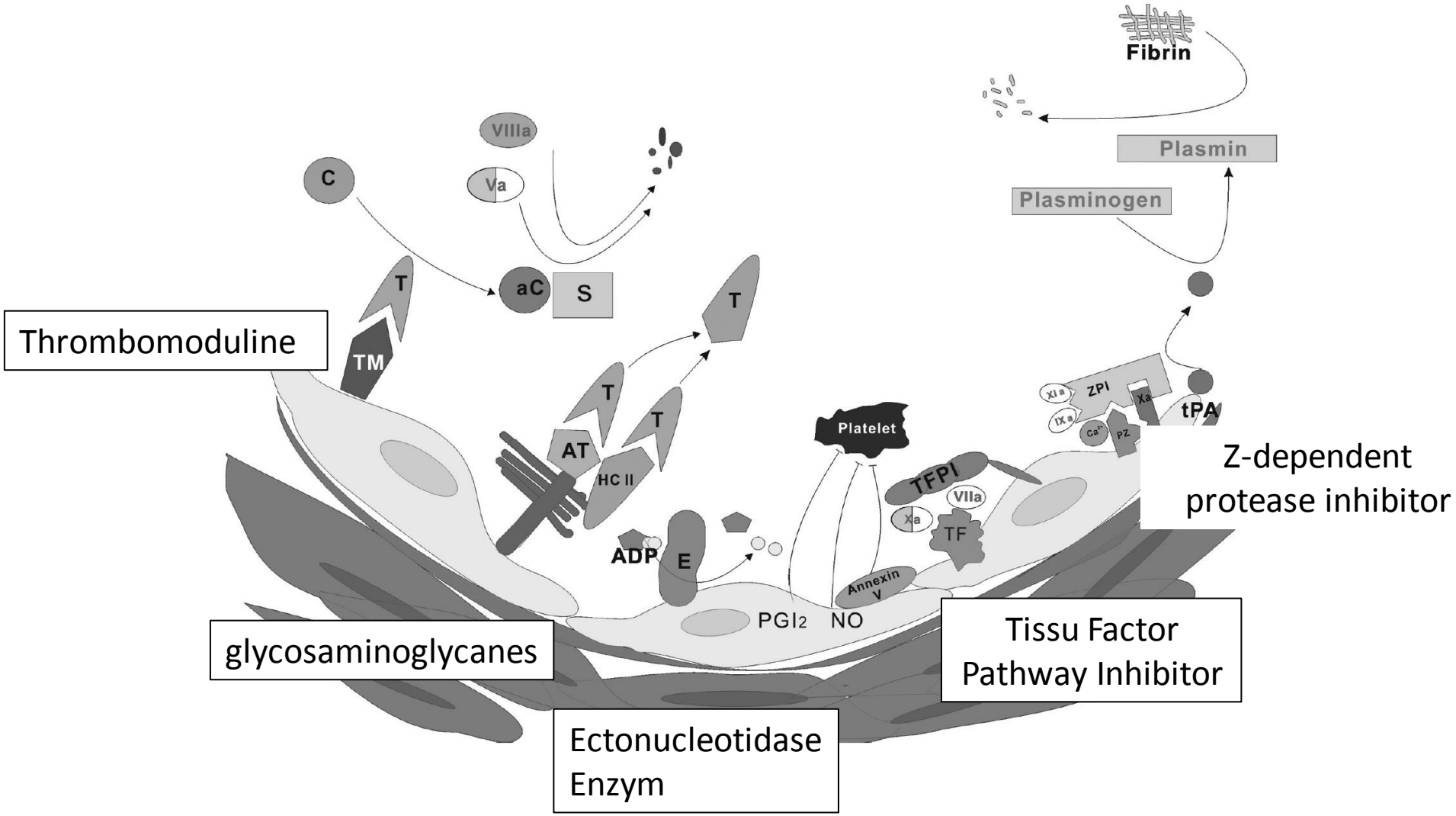
Nouveau model de l'hémostase



Les plaquettes sont activés par deux voies indépendantes

1. L'expression du Facteur tissulaire aboutit, in fine, a la formation des premières molécules de thrombine ➔ activation plaquettaire. Ce mécanisme ne nécessite pas de lésion endothéliale.
2. L'exposition du sous endothélium entraine une interaction activatrice entre le vWf, et les plaquettes.
3. L'expression ADP activent les plaquettes en se fixant sur les récepteurs P2Y1 et P2Y12 des plaquettes. Celles-ci peuvent se fixer sur les structures sous endothéliales par l'intermédiare de la fibrine et le vWf.

L'Endothélium…
Un traitement de surface naturel



Thrombomoduline

Z-dependent protease inhibitor

glycosaminoglycanes

Tissu Factor Pathway Inhibitor

Ectonucleotidase Enzym

Anesthésie
Chirurgie
CEC

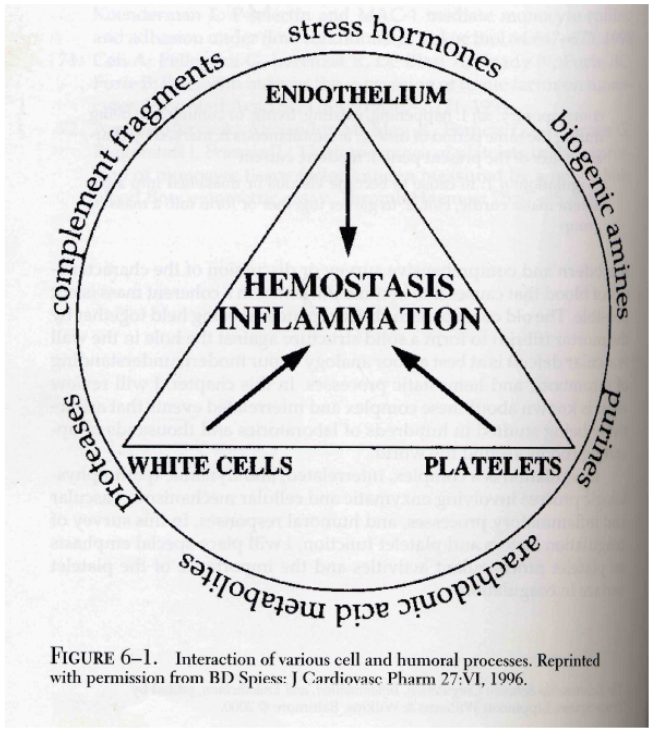


FIGURE 6–1. Interaction of various cell and humoral processes. Reprinted with permission from BD Spiess: J Cardiovasc Pharm 27:VI, 1996.

Activation de la coagulation
Activation de la fibrinolyse
Activation de l'endothélium

Dilution et consommation des facteurs coagulation/anticoagulation: déficit acquis (AT…)

Dilution et Activation/consommation des plaquettes

Relation coagulation/inflammation

Inflammation & hémostase

Inflammation pro coagulante

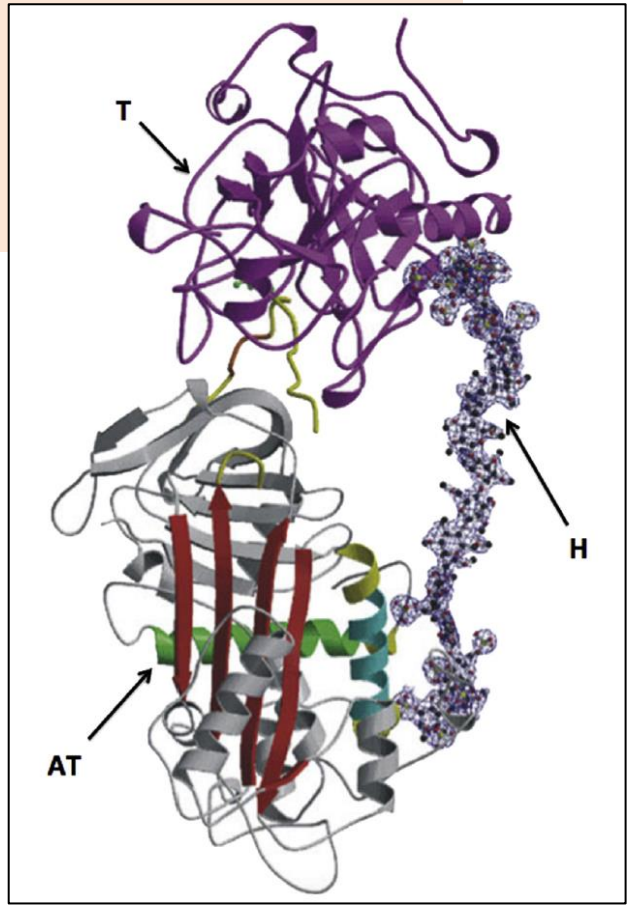
- IL6 => Facteurs tissulaire => Activation coagulation
- F 4P <= activation plaquettaire
- Down regulation des inhibiteurs physiologiques de la coagulation (prot C, AT et TFPI)

Coagulation pro inflammatoire

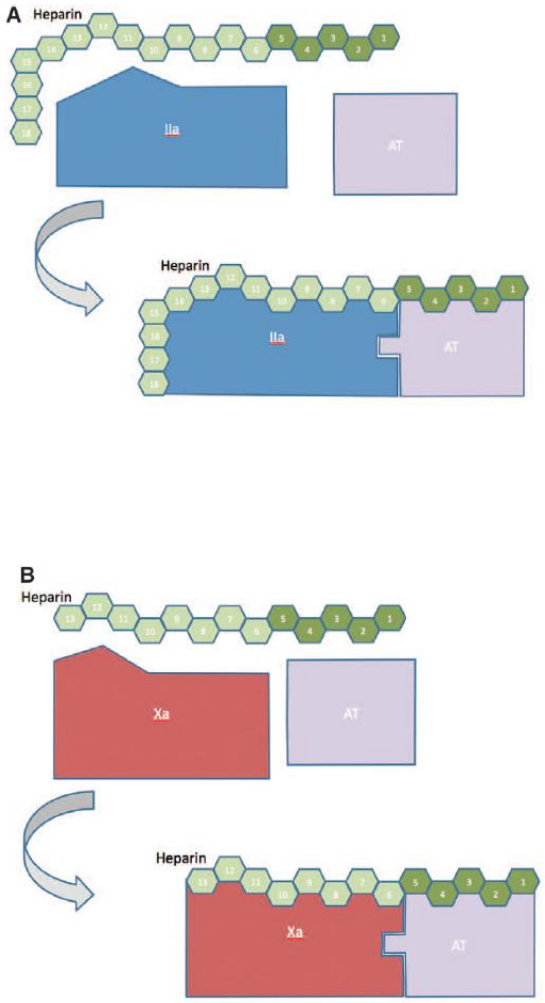
- Facteurs (protéases) => PAR => macrophages (ICAM)
  neutrophiles (TNF, IL-1)
- Plaquettes activées => IL-1, ligand CD40 & F4P

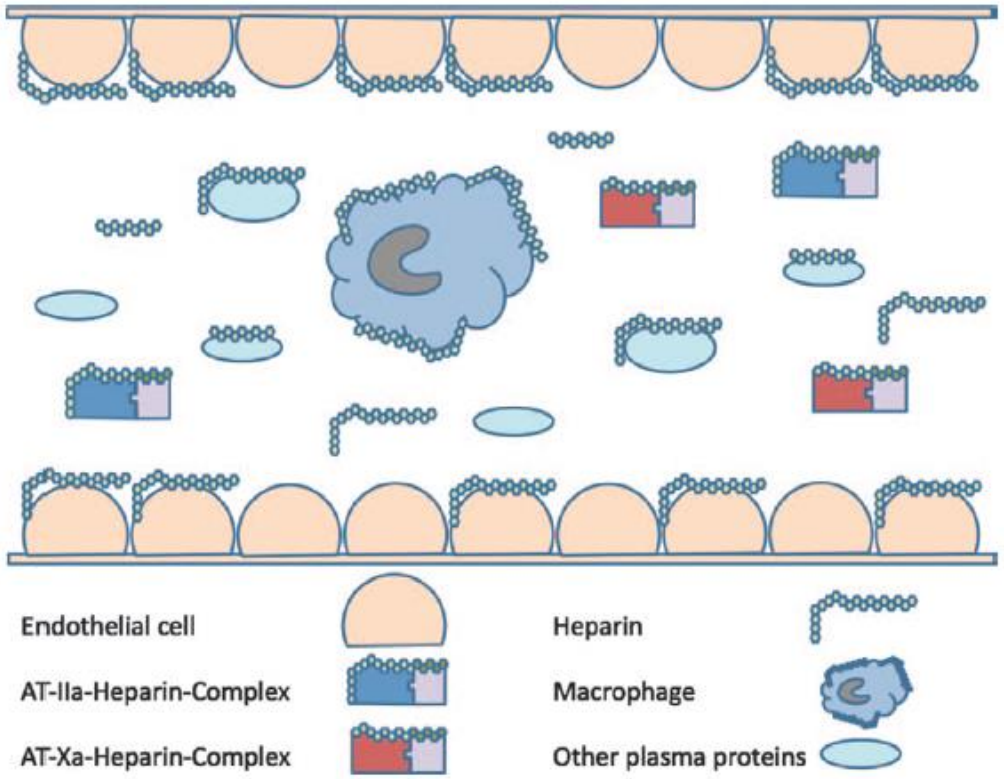
Un anticoagulant de référence **l'héparine…**

et son cofacteur, l'antithrombine



Un anticoagulant de référence **l'héparine…**





Low paediatric thrombin generation is caused by an attenuation of prothrombin conversion

What is known about this topic?

- Coagulation factor levels and their activity are different at young age (developmental haemostasis).
- The outcome of haemostatic tests is different in children and treatment strategies have to be tailored to children's needs.
- Children hardly ever suffer from thrombosis, suggesting that they are in a favourable coagulation state.

What does this paper add?

- Thrombin generation is reduced at young age due to a reduction of prothrombin conversion.
- The amount of prothrombin converted during TG is reduced due to lower plasma prothrombin levels and the activity of the prothrombinase complex is less.
- α_2Macroglobulin plays a more important role in the inhibition of thrombin in children than adults.

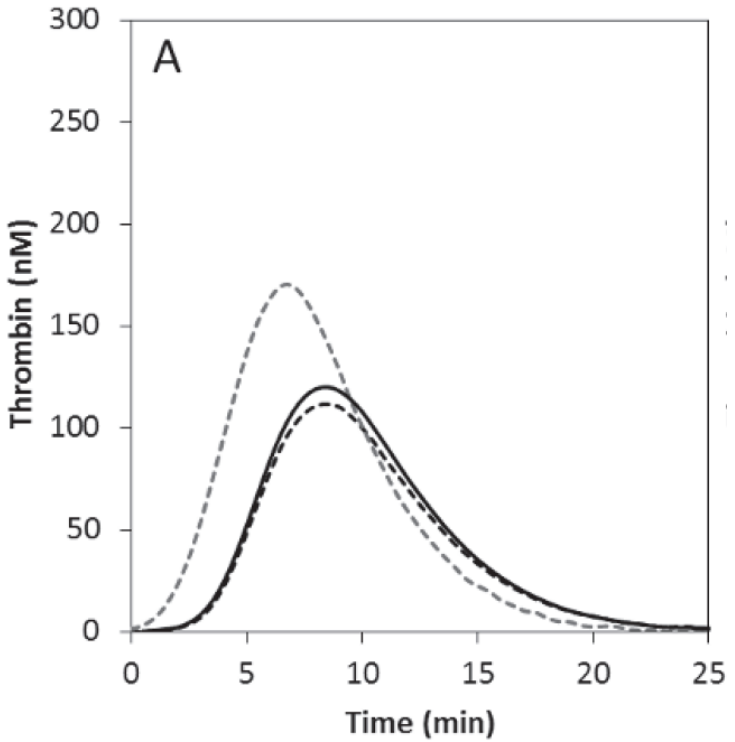


Figure 4: *In silico* experimentation of thrombin generation curves in children after normalisation of α_2M levels, prothrombin conversion or both. A-B) Mean of individual TG curves in children at real (dashed black line) and normalised α_2M levels (continuous black line) compared to the mean individual TG curve in adults (dashed gray line) measured at 1 pM TF (A) and 5 pM TF (B). C-D) Mean of individual TG curves in children at real (dashed black line) and normalised prothrombin conversion (continuous

An Evaluation of the Effects of a Standard Heparin Dose on Thrombin Inhibition During Cardiopulmonary Bypass in Neonates

Nina A. Guzzetta, (Anesth Analg 2005;100:1276–82)

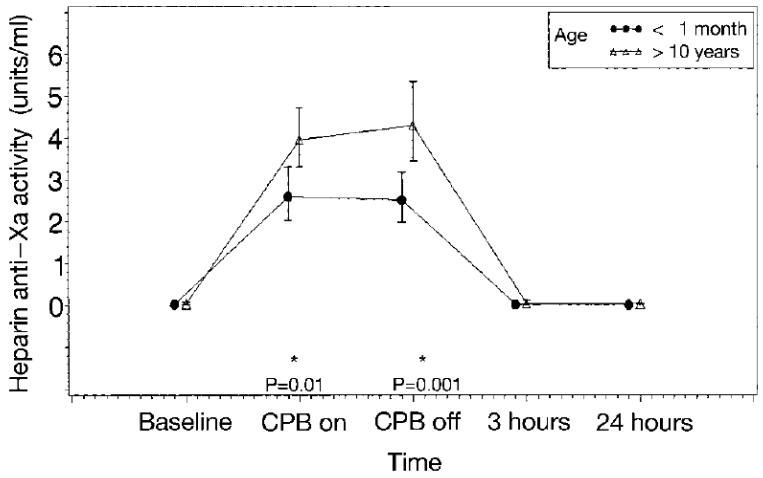


Figure 1. Intergroup comparison of heparin anti-Xa activity (mean and 95% confidence intervals). CPB, cardiopulmonary bypass.

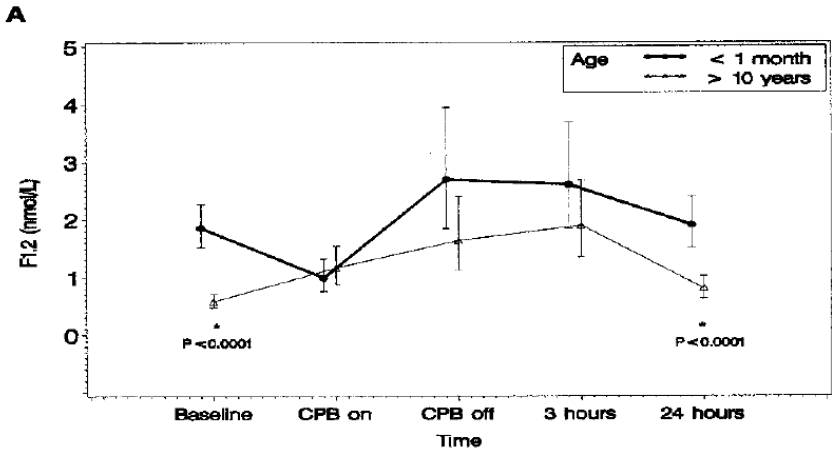


Figure 2. Intergroup comparisons of prothrombin fragment 1.2 (F 1.2) and fibrinopeptide A (FPA) values (mean and 95% confidence intervals). CPB, cardiopulmonary bypass.

standard heparin doses used for neonatal CPB are inadequate to appropriately suppress thrombin generation and activity. Formation of thrombin in neonates during CPB is significant in the face of decreased heparin anti-Xa activity after standard weight-based heparin doses. Although conversion of fibrinogen to

A Comparison of Heparin Management Strategies in Infants Undergoing Cardiopulmonary Bypass

Nina A. Guzzetta (Anesth Analg 2008;106:419–25)

Table 2. Heparin Dosing

	Control group	Intervention group	*P*
Initial heparin dose (U/kg)	400	425 ± 130	0.5
Heparin to CPB prime (U)	1000	1562 ± 470	0.001
Additional heparin on CPB (U/kg)	—	347 ± 218	<0.001
Total heparin dose (U/kg)	597 ± 22	1080 ± 392	<0.001

Values expressed as mean ± SD.

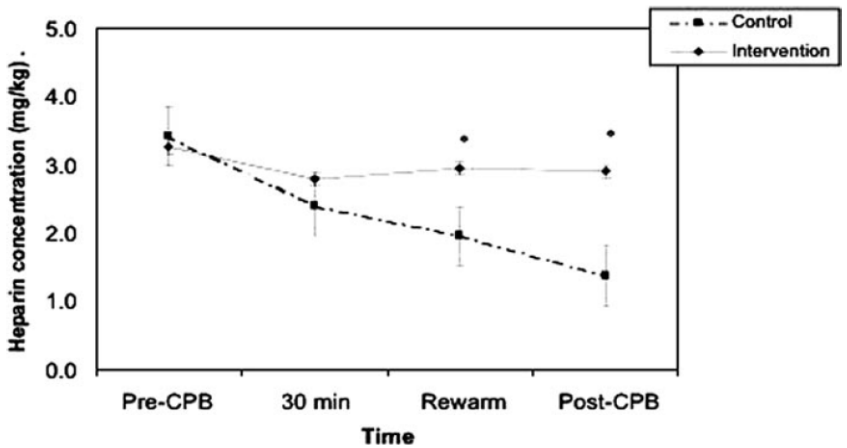


Figure 1. Heparin concentrations during CPB as measured by the Hepcon HMS. *$P < 0.01$ vs. control. Values expressed as mean ± SD.

tocol. According to our data, heparin levels achieved by a standard weight-based protocol, while initially adequate, begin to decrease at the start of rewarming. Small supplemental heparin boluses directed by the Hepcon HMS maintained a more constant heparin concentration throughout the duration of CPB and, consequently, were associated with decreased levels of thrombin generation. Unfortunately, the measure-

Clinical Measures of Heparin's Effect and Thrombin Inhibitor Levels in Pediatric Patients with Congenital Heart Disease

Nina A. Guzzetta (Anesth Analg 2006;103:1131–8)

Table 4. Thrombin Inhibitor Values

Age group	N	ATIII (% activity)	% of adult value	HCII (U/ml)	% of adult value	α2M (mg/dL)	% of adult value
<1 mo	20	74 ± 17*	78.9	0.65 ± 0.35†	73.9	232 ± 50‡	85.5
1–3 mo	19	89 ± 14	95.4	0.81 ± 0.22	92.0	334 ± 86	123.0
3–6 mo	20	91 ± 12	97.3	0.82 ± 0.19	93.2	322 ± 55	118.8
6–12 mo	19	100 ± 10	106.4	0.88 ± 0.22	100.0	338 ± 46	124.4
12–24 mo	20	98 ± 20	105.0	0.96 ± 0.30	109.1	320 ± 45	117.8
>10 yr	20	94 ± 16	100.0	0.88 ± 0.25	100.0	271 ± 59	100.0

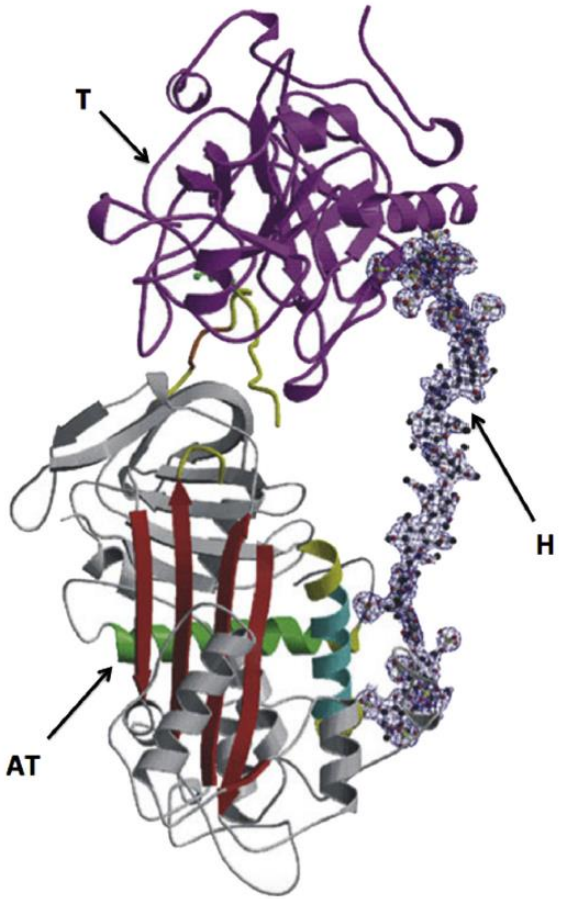
Values expressed as mean ± SD.

* $P < 0.003$ vs all other groups; † $P < 0.003$ vs 12–24 mo; ‡ $P < 0.003$ vs 1–3 mo, 3–6 mo, 6–12 mo, and 12–24 mo.

In summary, our investigation demonstrates that kaolin-ACTs of heparin's effect in children with CHD show less variable results than coagulation tests activated by celite. Our data also reveal that neonates with CHD are distinct from healthy neonates and from older pediatric patients with CHD, in that neonates with CHD may be deficient in all three of the major thrombin inhibitors. Although deficiencies in thrombin inhibitor levels may help explain the recent findings of excess thrombin formation in neonates

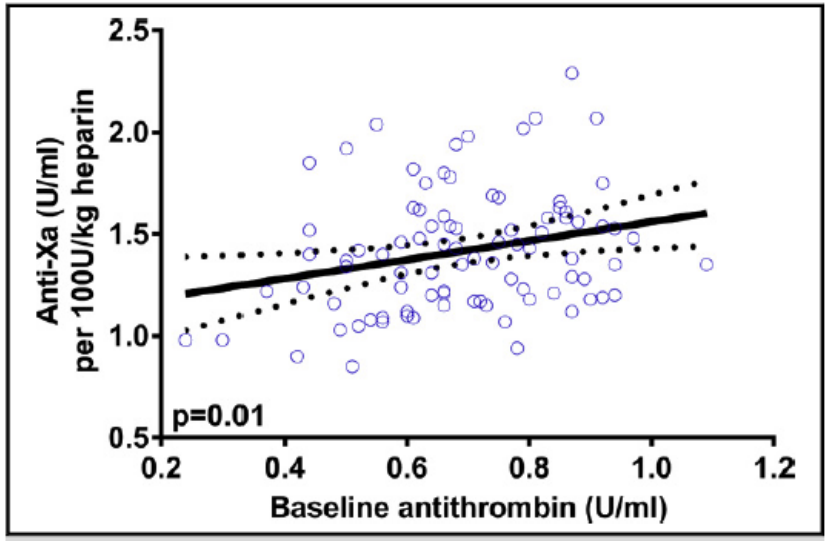
Antithrombin levels during pediatric cardiopulmonary bypass: Key to changing a decades-old paradigm for anticoagulation?

Dean B. Andropoulos, MD, MHCM,[a,b,c] and Charles D. Fraser, Jr, MD[b,d,e]



Challenges with heparin-based anticoagulation during cardiopulmonary bypass in children: Impact of low antithrombin activity

Manlhiot (J Thorac Cardiovasc Surg 2016;151:444-50)



Low preoperative blood antithrombin activity is associated with decreased heparin response.

Central Message

Low blood antithrombin is associated with lower heparin efficacy and a lower ability to suppress thrombin generation during neonatal cardiac surgery.

ANESTHESIOLOGY

Fresh Frozen Plasma *versus* Crystalloid Priming of Cardiopulmonary Bypass Circuit in Pediatric Surgery

A Randomized Clinical Trial

Audrey Dieu, M.D., Maria Rosal Martins, M.D., Stephane Eeckhoudt, Ph.D., Amine Matta, M.D., David Kahn, M.D., Céline Khalifa, M.D., Jean Rubay, M.D., Ph.D., Alain Poncelet, M.D., Ph.D., Astrid Haenecour, M.D., Emilien Derycke, M.D., Dominique Thiry, C.C.P., André Gregoire, C.C.P., Mona Momeni, M.D., Ph.D.

Anesthesiology 2020; 132:95–106

Table 6. Data of the Patients Analyzed on a Per-Protocol Basis

Variable	FFP (N = 28)	Crystalloid (N = 28)	*P* Value	Difference (95% CI)
N total allogeneic blood products (erythrocytes, FFP, platelets; priming not included)*	0 (0, 1)	0 (0, 2)	0.313	0 (0 to 0)
Patients transfused with any product (priming not included), no. (%)*	7 (25.0)	10 (35.7)	0.383	1.7‡ (0.5 to 5.3)
Chest drain blood loss 6 h postoperative, ml · kg^{-1}*	6.9 (5.1, 9.4)	5.7 (3.7, 8.4)	0.225	1.2 (−0.7 to 3.0)
Total volume erythrocytes transfused (ml · kg^{-1} (priming not included)†	8.8 (0, 17.2)	10.9 (0, 17.8)	0.641	0 (−6.8 to 4.4)
Total volume FFP transfused (ml · kg^{-1}) (priming not included)†	0 (0, 0)	0 (0, 3.2)	0.173	0 (0 to 0)
Total volume platelets transfused, ml · kg^{-1}†	0 (0, 0)	0 (0, 0)	0.231	0 (0 to 0)
N total allogeneic blood products including priming (erythrocytes, FFP, platelets)	2 (2, 2)	1 (1, 3)	0.001	
Total volume FFP transfused (priming included), ml · kg^{-1}	15.0 (15.0, 15.0)	0 (0, 3.2)	< 0.001	
Total N packed erythrocytes (priming not included)	0 (0, 1)	0 (0, 1)	0.709	
Total N FFP (priming not included)	0 (0, 0)	0 (0, 0)	0.263	
Total N platelet concentrates	0 (0, 0)	0 (0, 0)	0.124	
Patients receiving fibrinogen, no. (%)	0	1 (3.5)	0.999	

The continuous variables are expressed as medians (25th percentile, 75th percentile).

*Primary endpoint. †Secondary endpoint. ‡Odds ratio.

FFP, fresh frozen plasma.

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Fresh frozen plasma is often used to prime the cardiopulmonary bypass circuit for pediatric cardiac surgical patients to help offset dilutional coagulopathy that might result in increased perioperative bleeding and allogeneic blood transfusion
- Prior randomized trials of crystalloid *versus* fresh frozen plasma prime have reported conflicting results, but the vast majority of these studies were not blinded

What This Article Tells Us That Is New

- In this double-blind randomized controlled trial of patients undergoing pediatric cardiac surgery with cardiopulomonary bypass, postoperative bleeding and the need for allogeneic blood products does not differ significantly between patients for whom the cardiopulmonary bypass circuit was primed with crystalloid *versus* fresh frozen plasma

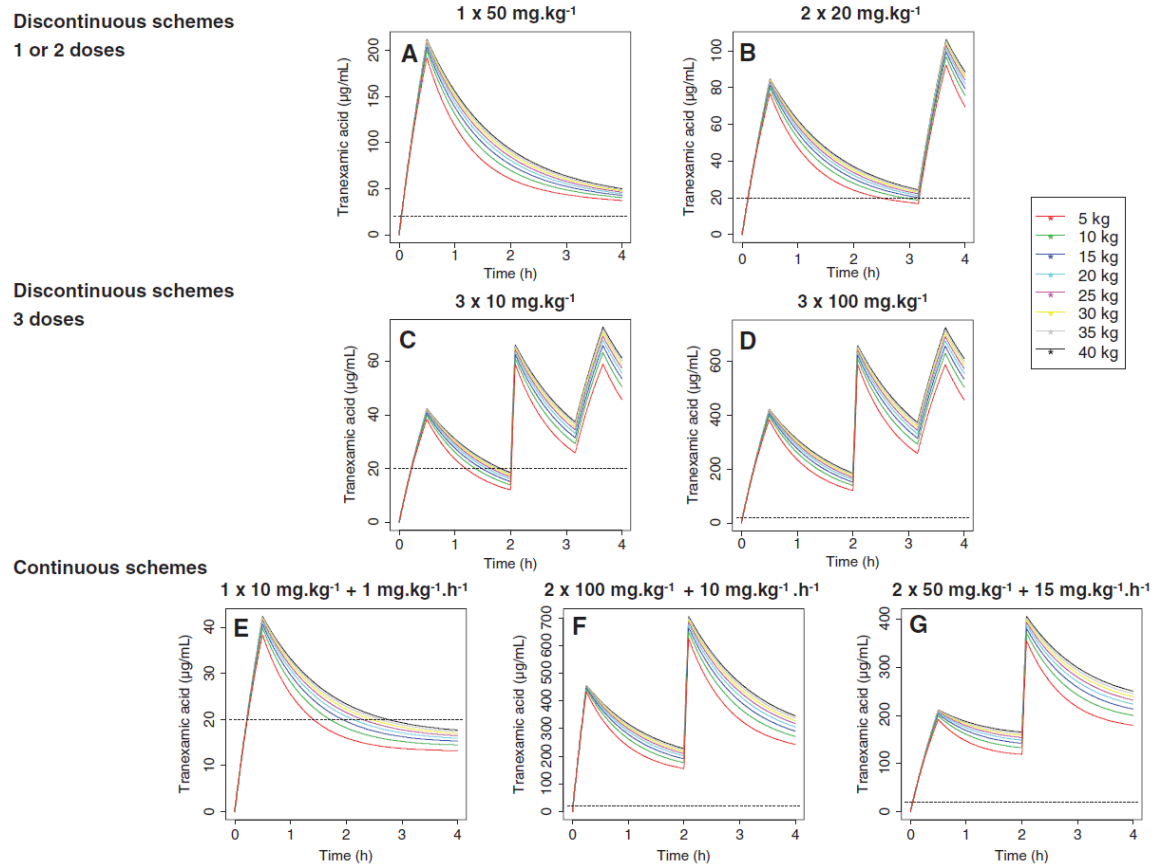


Fig. 4. Simulated concentrations of tranexamic acid obtained with the dosing schemes described previously in the literature, for children with a body weight between 5 and 40 kg. We assumed that the total duration of the surgical procedure was 4 h, that there was 2 h between the first bolus dose and the cardiopulmonary bypass (CPB) initiation, that the CPB duration was 70 min, and that the continuous infusion (when present) was started immediately after the end of the bolus dose and maintained until the end of the procedure. Unless stated otherwise, we considered that all the discontinuous doses were given over 30 min, except the doses into the CPB prime volume over 5 min. Discontinuous schemes were a 50-mg/kg bolus (*A*),[7,11,14] two 20-mg/kg doses (*B*),[7] or three 10- (*C*) or 100-mg/kg (*D*) doses (with one into the CPB prime volume).[6–8] Continuous schemes were a 10-mg/kg bolus followed with a 1-mg·kg^{-1}·h^{-1} infusion (*E*),[7] a 100-mg/kg bolus given over 15 min followed by a 10-mg·kg^{-1}·h^{-1} infusion and another 100 mg/kg dose in the CPB prime volume (*F*),[9] and a 50-mg/kg bolus followed by a 15-mg·kg^{-1}·h^{-1} infusion and another 50-mg/kg dose in the CPB prime volume (*G*).[10] The *gray horizontal lines* in each plot represent the threshold target concentration of 20 µg/ml.

Acide Tranexamic

Grande hétérogénéïté ente les equipes:
A Marseille: 15 mg/kg en1h à l'induction puis 10mg/kg/h pendant la chirurgie

A Practical Tranexamic Acid Dosing Scheme Based on Population Pharmacokinetics in Children Undergoing Cardiac Surgery

Stanislas Grassin-Delyle, Pharm.D., Ph.D.,* Roland Couturier, M.D.,† Emuri Abe, Pharm.D.,‡ Jean Claude Alvarez, Pharm.D., Ph.D.,§ Philippe Devillier, M.D., Ph.D.,‖ Saïk Urien, M.D., Ph.D.#

Comment définir une hémorragie postopératoire significative?

First Author	Year	Type	Age	n	Definition	Incidence (%)
Pekelharing[14]	2014	Prospective	< 18	107	≥ 5 mL/kg/hr in first 4 hours	21.4
Moganasundram[9]	2010	Prospective	< 5 years	50	> 10 mL/kg in first 4 hours	38
Faraoni[35]	2015	Retrospective	≤ 16 years	150	> 10% EBV in first 6 hours	23
Savon[20]	2014	Retrospective	≤ 16 years	182		28.9
Timpa[18]	2016	Prospective	< 18 years	161	>10 mL/kg in the first CICU hour	26
Niebler[10]	2012	Prospective	< 18 years	60	> 6 mL/kg/hr for ≥ 2 consecutive hours in 6 hours	31.7
Niles[12]	2008	Retrospective	< 18 years	328	> 4 mL/kg/hr for ≥ 2 consecutive hours in 7 hours	NA
Tobias[22]	2004	Retrospective	< 18 years	17	≥ 12 mL/kg for the first 3 postoperative hours	NA
Razon[16]	2005	Prospective	≤ 19 years	5	> 8 mL/kg for any 1 hour > 4 mL/kg/hr for ≥ 3 consecutive hours	NA
Agarwal[5]	2015	Retrospective	< 18 years	253	> 10 mL/kg in 1st hour *OR* > 5 mL/kg for 3 consecutive hours in 12 hours	42
Guay[36]	1996	Review	NA	NA	> 10% EBV in any 1 hour *OR* > 5% EBV for 3 consecutive hours in 24 hours	NA
Oliver[37]	2005	Textbook	< 18 years			
Singh[17]	2012	Retrospective	< 15 years	20		
Tirosh-Wagner[19]	2011	Prospective	≤ 10 years	15	> 20% EBV in 24 hours	NA
Hoda[7]	2016	Retrospective	< 18 years	82	> 4 mL/kg/hr average for 24 hours	0
Pychynska-Pokorska[15]	2004	Prospective	< 5 years	8	Children ≤ 5kg: ≥ 10 mL/kg/hr Children ≥ 5kg: ≥ 2 mL/kg/hr	NA
Williams[11]	1999	Prospective	< 18 years	494	≥ 20% EBV in hours 0-2 *OR* ≥ 20% EBV in hours 2-6 *OR* ≥ 30% EBV in hours 7-12	19
Brenner[6]	2015	Retrospective		91		28.5
Guzzetta[3]	2015	Retrospective	≤ 30 days	167	Top 25th percentile for CTO in 24 hours	25
Wolf[4]	2014	Retrospective	< 1 year	1071	Top 25th percentile for CTO in 12 hours	25
Kylasam[8]	2009	Retrospective	≤ 90 mo	25	Required re-exploration for bleeding	2.5

Validation of a definition of excessive postoperative bleeding in infants undergoing cardiac surgery with cardiopulmonary bypass

Rachel S. Bercovitz, MD, MS, Allison C. Shewmake, MD, Debra K. Newman, PhD, Robert A. Niebler, MD, John P. Scott, Eckehard Stuth, MD, Pippa M. Simpson, PhD, Ke Yan, PhD, Ronald K. Woods, MD, PhD

The Journal of Thoracic and Cardiovascular Surgery

infants and neonates. **Results:** Excessive bleeding was defined as ≥ 7 mL/kg/hr for ≥ 2 consecutive hours in the first 12 postoperative hours and/or ≥ 84 mL/kg total for the first 24 postoperative hours and/or surgical re-exploration for bleeding or cardiac tamponade physiology in the first 24 postoperative hours. Excessive bleeding was associated with longer length of hospital stay, increased 30-day readmission rate, and increased transfusions in the postoperative period. **Conclusions:** The proposed standard definition of excessive bleeding

Demographics n=124	Patients without Bleeding (n=93)	Patients with bleeding (n=31)	Risk Ratio	*P*
Weight (kg)	4.2 (2.4 – 8.7)	3.1 (2.2 – 7.5)		< 0.0001
Age (days)	49 (0 – 180)	8 (0 – 146)		0.0002
STAT Score				
1	13 (14.0)	2 (6.4)		0.0117
2	20 (21.5)	2 (6.4)		
3	15 (16.1)	5 (16.1)		
4	31 (33.3)	8 (25.8)		
5	11 (11.8)	13 (41.9)		
Minimum Temperature (°C)	28.0 (17.0 – 37.0)	18 (16.7 – 32)		0.0024
DHCA (yes)	28 (30.1)	19 (61.3)	2 (1.3 – 3.1)	0.0027
Intraoperative FVIIa	5 (5.4)	6 (19.4)	3.6 (1.1 – 11)	0.0278
Prime				
Whole blood	61 (65.6)	11 (35.5)		0.0068
RBCs + plasma	31 (33.3)	19 (61.3)		
Other	1 (1.1)	1 (3.2)		
Delayed chest closure	37 (39.8)	26 (83.9)	2.1 (1.5 – 2.9)	< 0.0001
Single ventricle physiology	34 (36.6)	20 (64.5)	1.8 (1.2 – 2.6)	0.0113
Cyanotic heart disease (pre)	61 (65.6)	27 (87.1)	1.3 (1.1 – 1.7)	0.0234

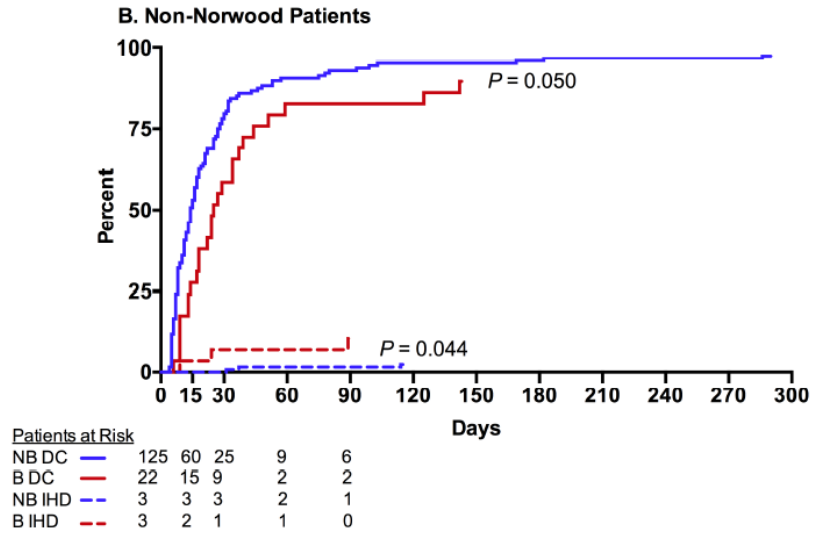


Figure 2. Time to discharge or in-hospital death in patients with (red) and without (blue line) excessive bleeding undergoing either a Norwood procedure (A) or another surgery (B). Patients were divided based Supplement Materials 3 for the 95th% CI on days 15, 30, 60, and 90. *NB,* no bleeding; *B*, bleeding; *DC*, discharged; *IHD*, in-hospital death.

Facteurs corrélés au saignement

- **Age, hématocrite préop, hémodilution**
- Chirurgie complexe, ACHP
- consommation +++

chez les plus petits : hypothermie, hte post CEC

chez les grands : polyglobulie (cyanosés), sternotomie redux , durée de CEC, saignement

- Dans le sténoses aortiques adultes, activité du VWF diminuée car diminution des multimères de HPM : restauration après la chirurgie

Récupération sang activé: tPA pendant la CEC : **risque potentiel de fibrinolyse postop CEC**

- Fibrinolyse jusque à 6 h après la chirurgie

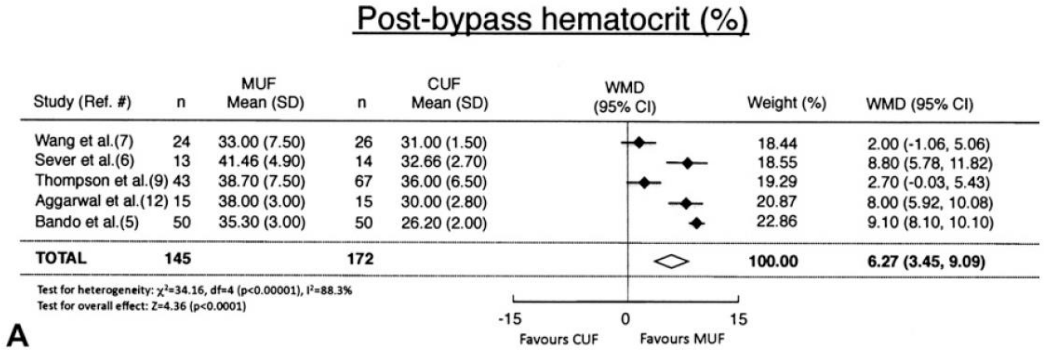
Ignjatovic V, Pediatr Cardiol. 2012

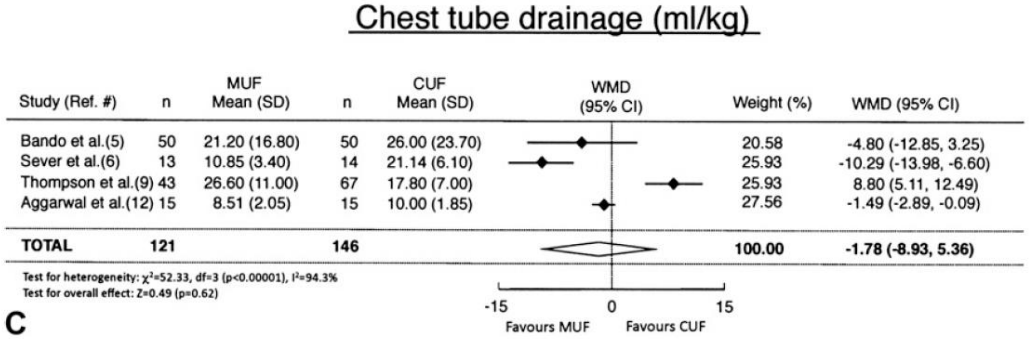
Ultrafiltration

Deux effets
- Hémoconcentration
- Anti inflammatoire

Modified versus conventional ultrafiltration in pediatric cardiac surgery: A meta-analysis of randomized controlled trials comparing clinical outcome parameters

J Thorac Cardiovasc Surg 2011;142:861-7





La prédiction du saignement est-elle possible?

- Profiter de la CEC pour optimiser les conditions de charge.
- L'obtention de l'hémostase est un sujet cruciale:
  - ➢ Hémostase chirurgicale: prolène – colle biologique – pansement hémostatique.
  - ➢ Hémostase biologique: Fondamentale pour créer les conditions du succès –
    - PH / T° / Hb / Ca^{2+}
    - Etude de l'hémostase au laboratoire – Point Of Care – PVI /CUP/ Cplx Prothrombinique/Fibrinogène/$fVII_a$

Excessive Postoperative Bleeding and Outcomes in Neonates Undergoing Cardiopulmonary Bypass

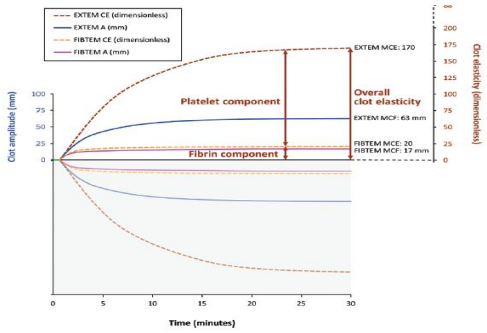
Anesth Analg 2014 Nina A. Guzzetta,

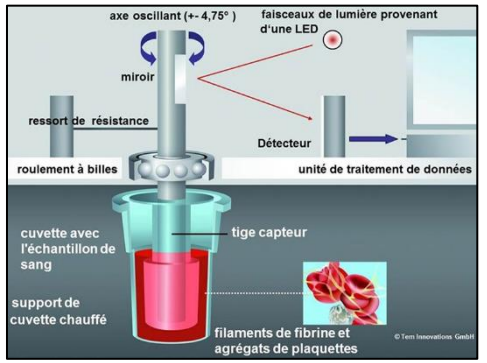
Table 6. Outcome Data Based on Bleeding Quartile and Adjusted Relative Risk

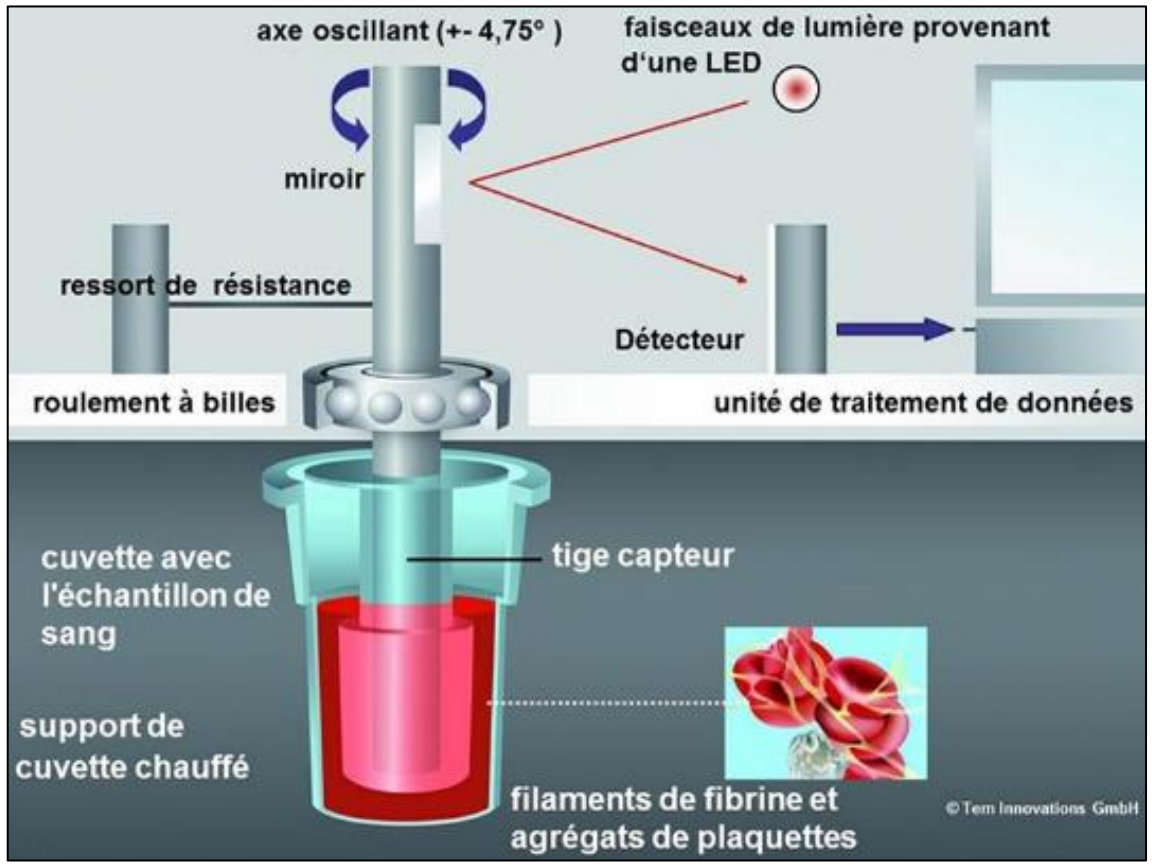
	CTO ≤75% (*n* = 124)	CTO >75% (*n* = 42)			
	Total (%)	Total (%)	RR[a]	95% CI	*P*
Renal dysfunction[b]	21 (17)	11 (26)	1.18	0.54–2.18	0.64
Dialysis	1 (1)	6 (14)	12.0	1.50–54.69	0.02
Thrombosis	9 (7)	4 (10)	0.82	0.17–2.87	0.78
ECMO	3 (2)	11 (26)	9.95	3.07–28.47	0.0008
In-hospital mortality	6 (5)	8 (19)	3.01	0.99–7.70	0.052

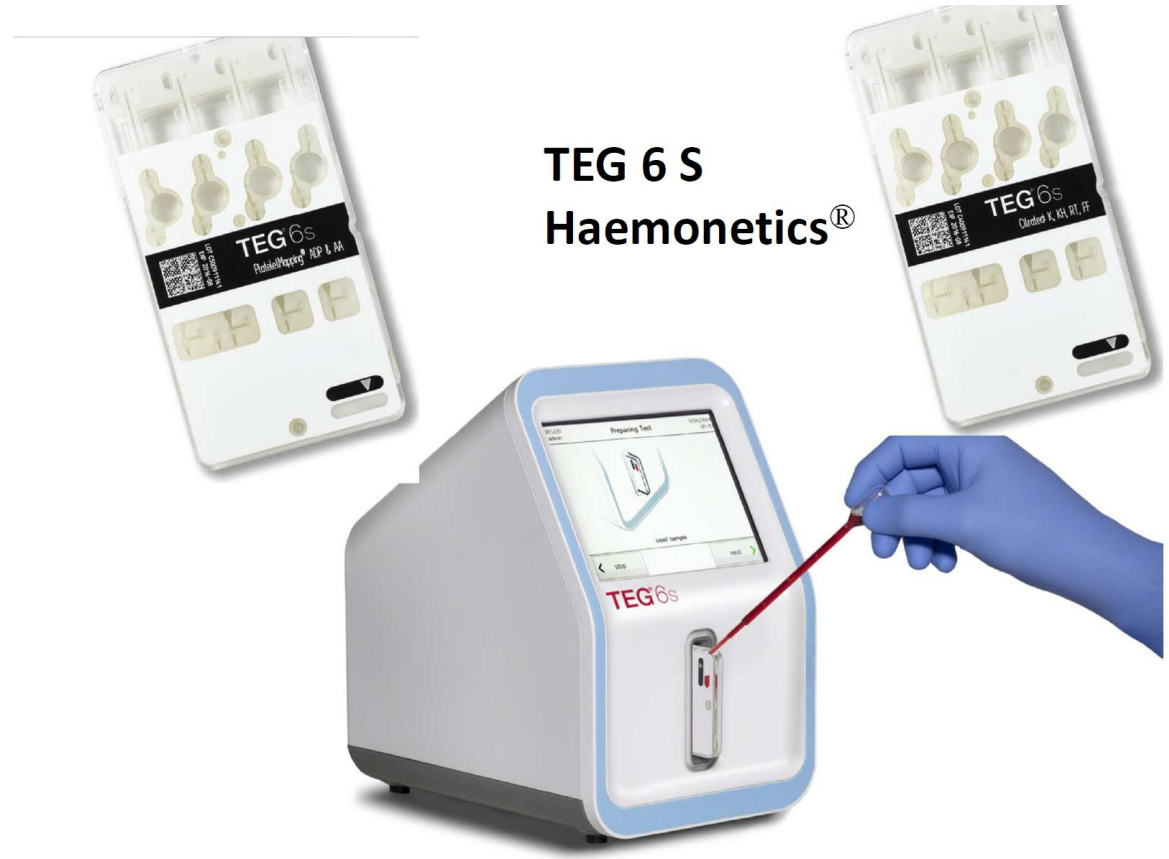
Thromboelastometry-guided intraoperative haemostatic management reduces bleeding and red cell transfusion after paediatric cardiac surgery

British Journal of Anaesthesia. 1 janv 2015;114(1):91-102.






axe oscillant (+- 4,75°)
faisceaux de lumière provenant d'une LED
miroir
ressort de résistance
Détecteur
roulement à billes
unité de traitement de données
cuvette avec l'échantillon de sang
tige capteur
support de cuvette chauffé
filaments de fibrine et agrégats de plaquettes
© Tem Innovations GmbH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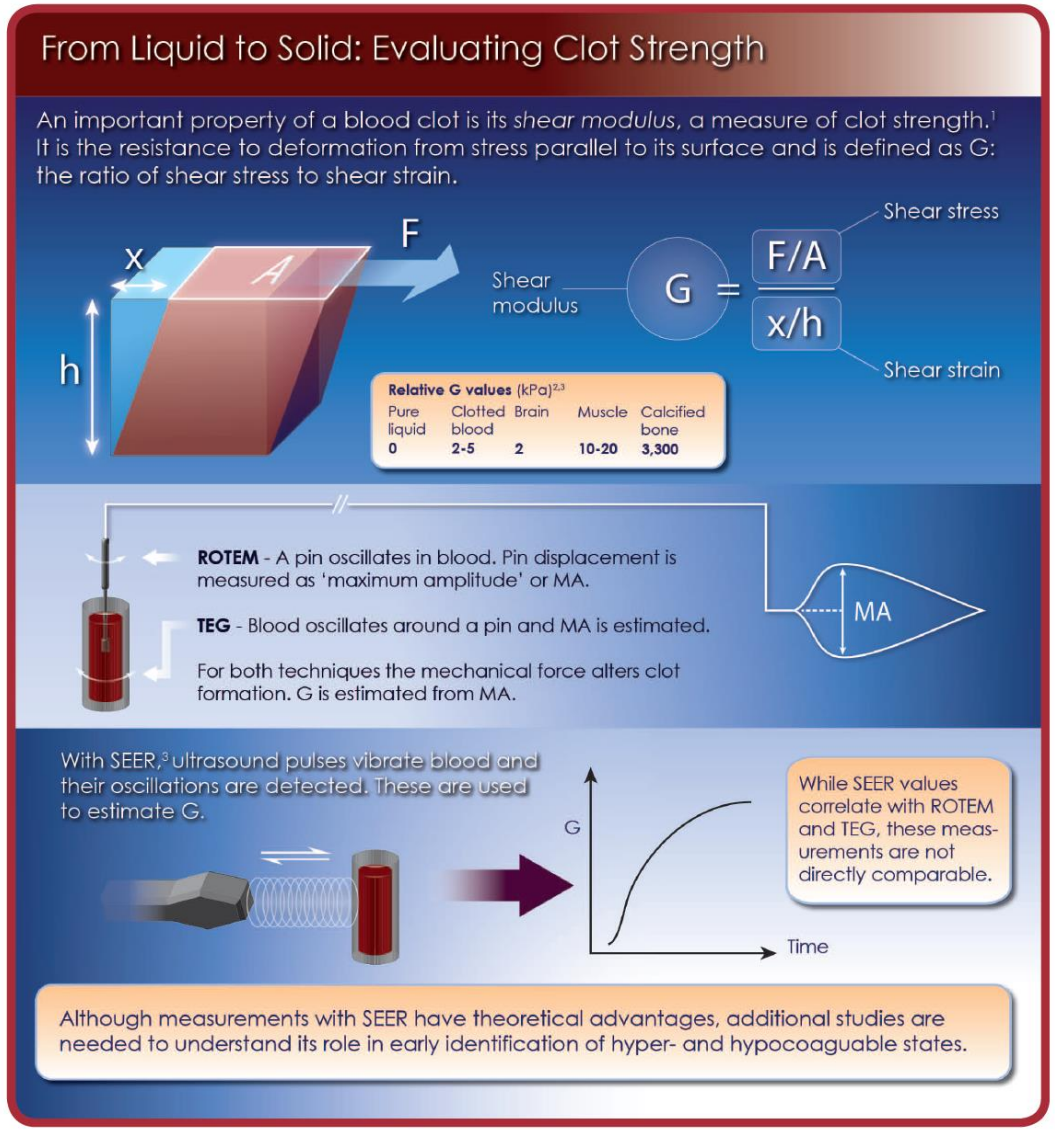


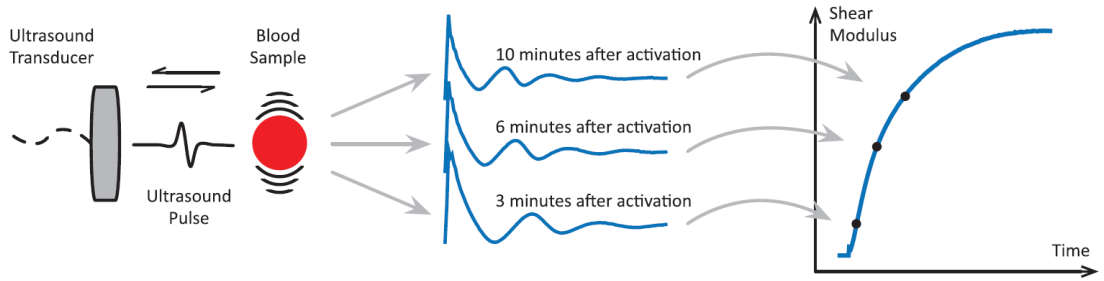
A Comparison of a New Ultrasound-Based Whole Blood Viscoelastic Test (SEER Sonorheometry) Versus Thromboelastography in Cardiac Surgery

Penny S. Reynolds, PhD, Paul Middleton, MD, Harry McCarthy, CCP, Bruce D. Spiess, MD, FAHA

Data Acquisition
An ultrasound pulse is sent into the blood sample to generate a shear wave, causing the sample to resonate.

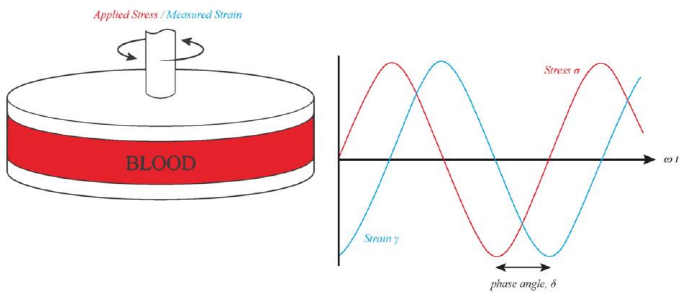
Displacement Estimation
As the clot vibrates during resonance, ultrasound "tracking" pulses are used to estimate the sample motion.

Shear Modulus Estimation
The shear modulus of the sample at a specific time point is calculated by analyzing the sample motion pattern.



A new structural biomarker that quantifies and predicts changes in clot strength and quality in a model of progressive haemodilution

Matthew J. Lawrence [a,b], Sendhil Kumar [c], Karl Hawkins [b], Stuart Boden [d], Harvey Rutt [d], Gavin Mills [a], Ahmed Sabra [a,b], Roger H.K. Morris [e], Simon J. Davidson [f], Nafieseh Badiei [g], Martin R. Brown [g], Phylip R. Williams [g], Phillip A. Evans [a,b,c,*]



ig. 1. Haemorheological analysis of whole blood. A representation of a small amplitude oscillatory shear measurement being carried out on a blood sample between two testing surfaces ı a rheometer. Representing the stress and strain waveforms (red and blue respectively); where the phase angle, δ, is a measure of viscoelastic response to imposed stress.

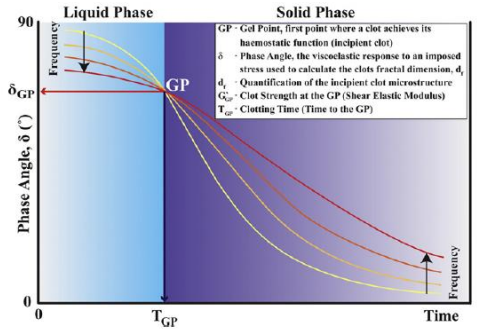
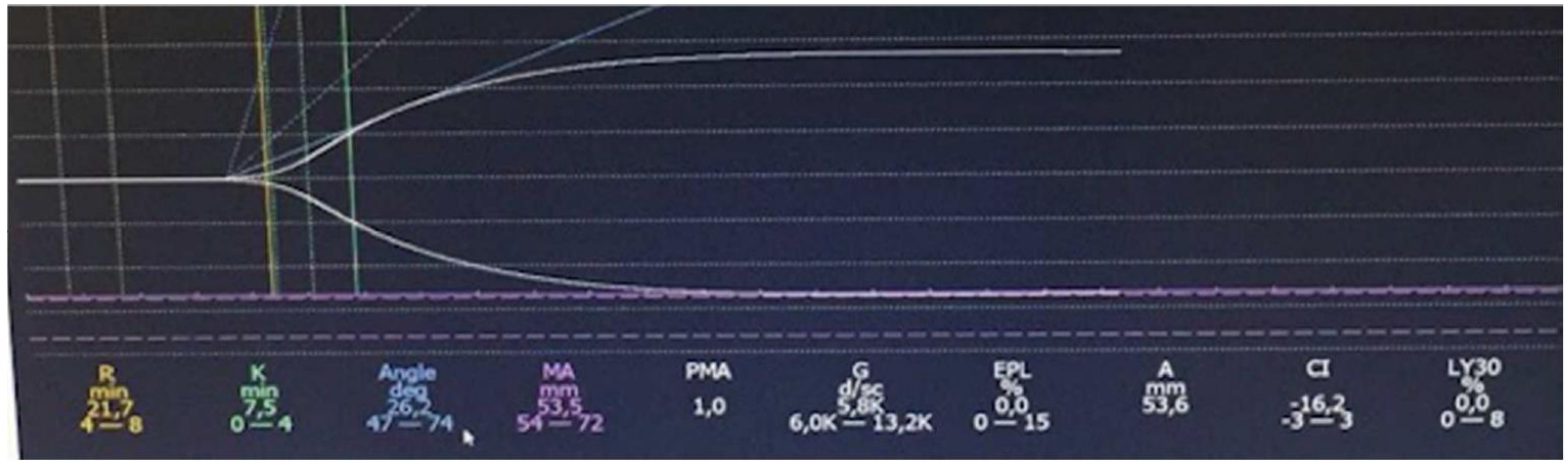
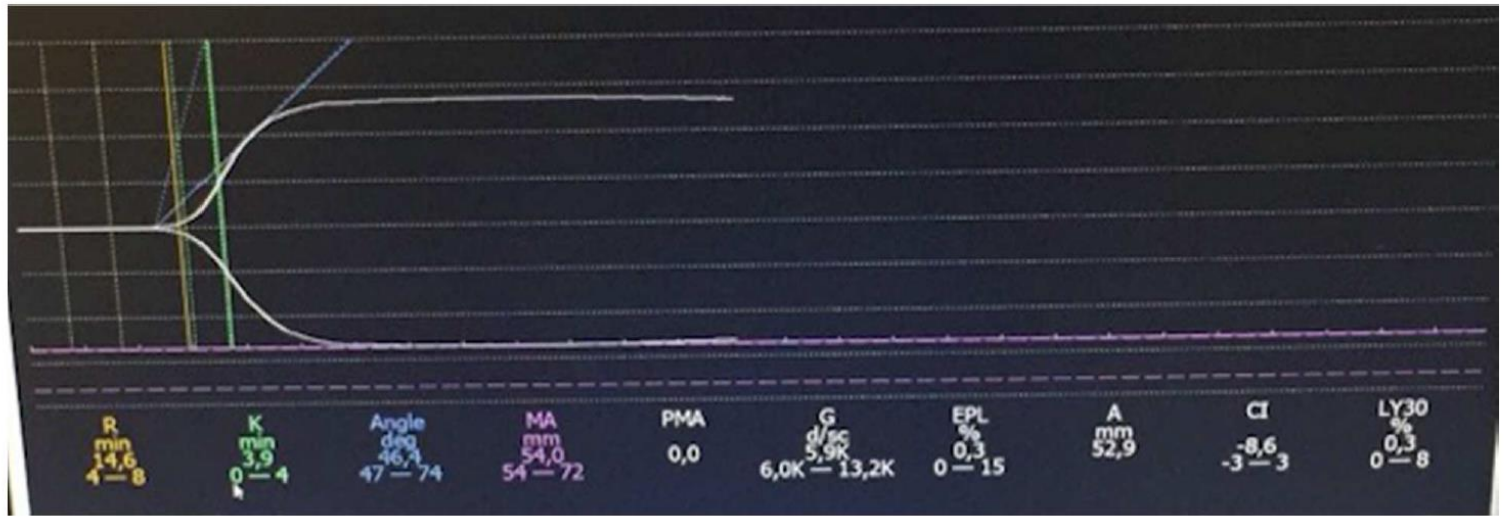


Fig. 2. –GP Trace: Fig. 2 provides a typical representation of a GP curve showing the change in phase angle for the different testing frequencies with respect to time. The initial response is characteristic of a viscoelastic liquid, where Fig. 2 shows the measurement of the phase angle, δ, with respect to time (δ being a measure of the viscoelastic response to imposed stress). The frequency dependence of δ decreases as clotting proceeds and δ becomes frequency independent as the incipient clot is established at the GP. Thereafter the frequency dependence is characteristic of a viscoelastic solid. The structural property of the incipient clot (in terms of its fractal dimension, d_f) is derived from the frequency independent value of δ.

TEG KAOLIN

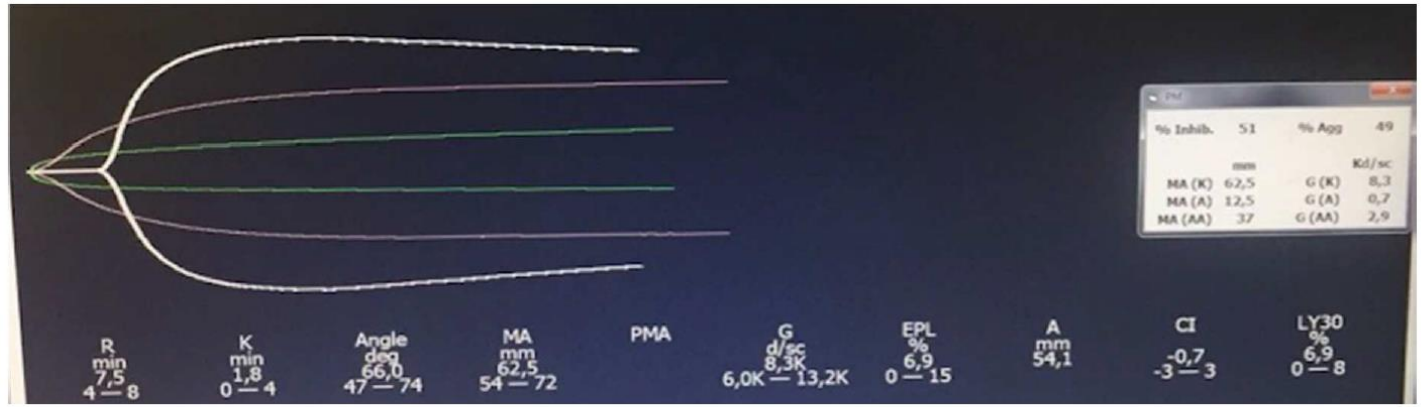




TEG KH

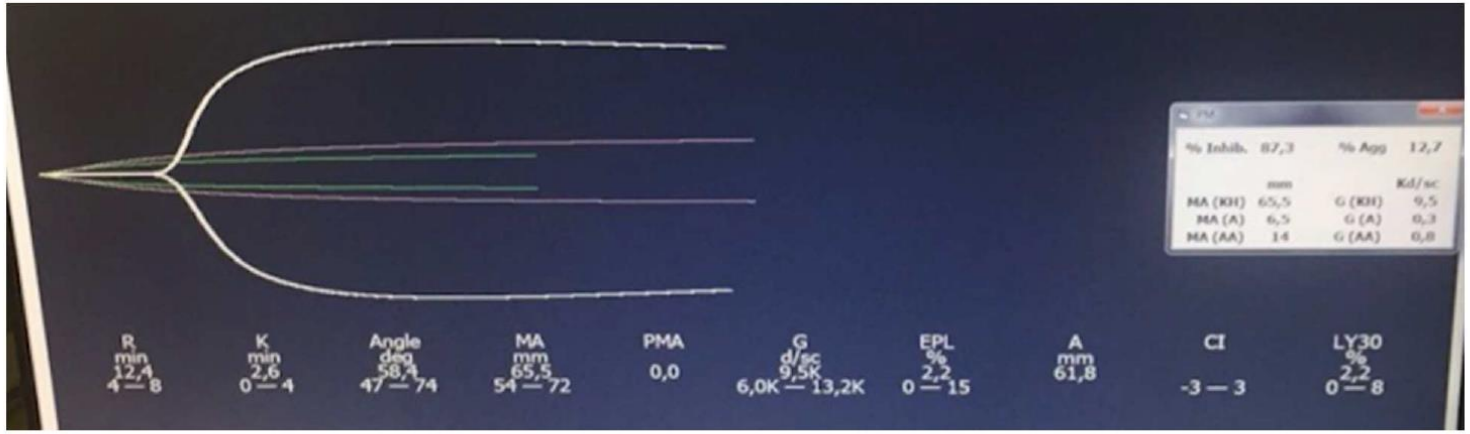
% inhib AA

Aspirine 2 mg/Kg



% inhib AA

Aspirine 3 mg/Kg



ANESTHESIOLOGY

Fresh Frozen Plasma *versus* Crystalloid Priming of Cardiopulmonary Bypass Circuit in Pediatric Surgery

A Randomized Clinical Trial

Audrey Dieu, M.D., Maria Rosal Martins, M.D., Stephane Eeckhoudt, Ph.D., Amine Matta, M.D., David Kahn, M.D., Céline Khalifa, M.D., Jean Rubay, M.D., Ph.D., Alain Poncelet, M.D., Ph.D., Astrid Haenecour, M.D., Emilien Derycke, M.D., Dominique Thiry, C.C.P., André Gregoire, C.C.P., Mona Momeni, M.D., Ph.D.

Anesthesiology 2020; 132:95–106

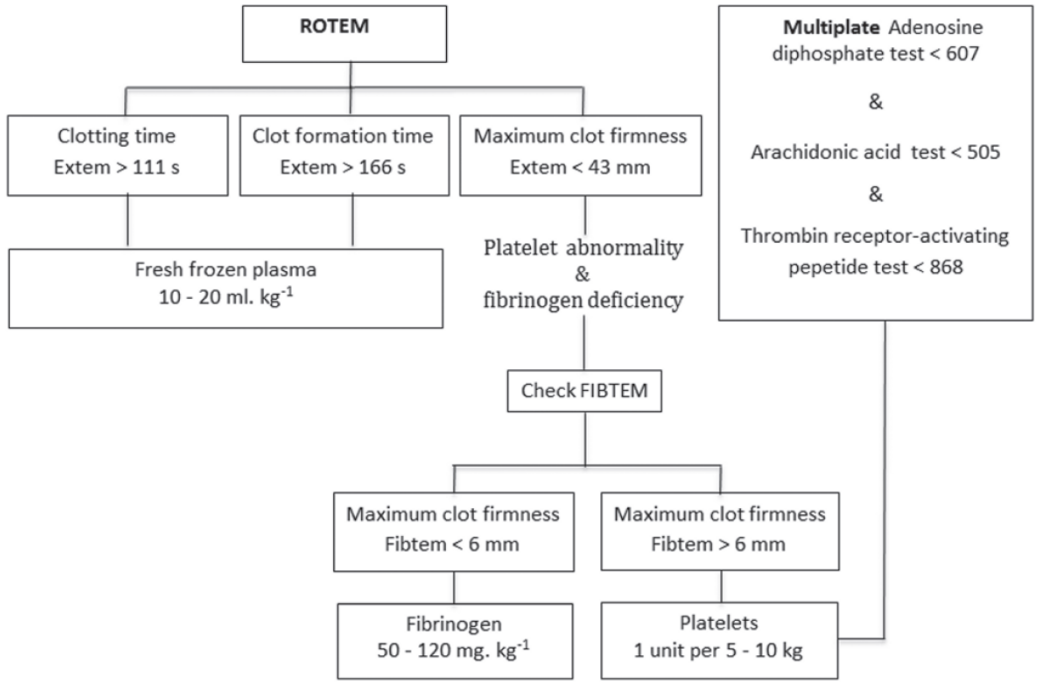
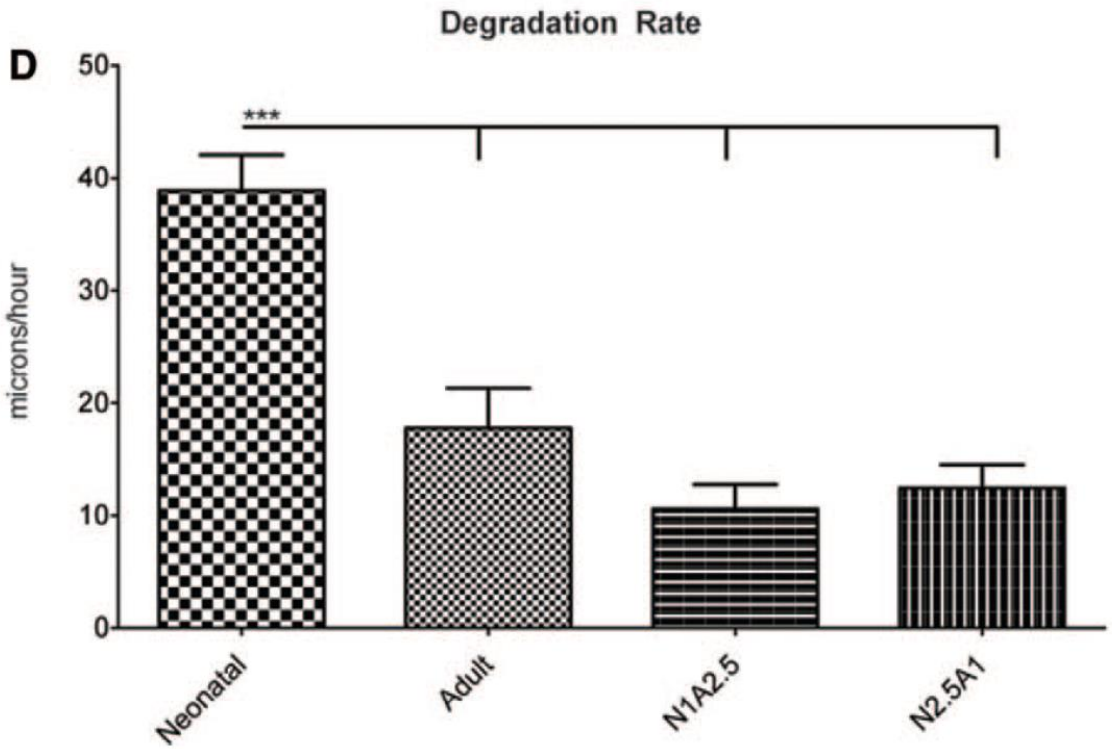


Fig. 1. Point-of-care test guided algorithm for transfusion of hemostatic factors in case of clinical bleeding.

Fibrin Network Changes in Neonates after Cardiopulmonary Bypass

Ashley C. Brown, Ph.D., Riley H. Hannan, B.S., Lucas H. Timmins, Ph.D., Janet D. Fernandez, C.C.R.C., Thomas H. Barker, Ph.D., Nina A. Guzzetta, M.D., F.A.A.P.

(Anesthesiology 2016; 124:1021-31)



What We Already Know about This Topic

- Bleeding after cardiac surgery is particularly common and problematic in neonates
- Fetal fibrinogen, present until 1 yr of age, is dysfunctional compared with adult fibrinogen and may contribute to bleeding after cardiopulmonary bypass

What This Article Tells Us That Is New

- Clots formed from blood samples collected from 10 neonates after cardiopulmonary bypass were more porous than clots formed from samples collected before surgery
- Clots formed from purified fibrinogen from neonates alone or mixed with adult fibrinogen were less dense than adult clots, suggesting that transfusion of adult fibrinogen may be less effective in neonates than in adults

gen. We also demonstrate that, similar to adults, increasing thrombin concentration promotes the formation of a more robust fibrin network. Thus, it is possible that procoagulant therapies designed to augment thrombin generation could potentially assist clinicians in achieving hemostasis in neonates after major surgery. Further translational studies into

Optimizing Thrombin Generation with 4-Factor Prothrombin Complex Concentrates in Neonatal Plasma After Cardiopulmonary Bypass

Sarah W. Franklin, BA,* Fania Szlam, MMSc,* Janet D. Fernandez, RRT, CCRC,† Traci Leong, PhD,‡ Kenichi A. Tanaka, MD, MSc,§ and Nina A. Guzzetta, MD, FAAP*‖

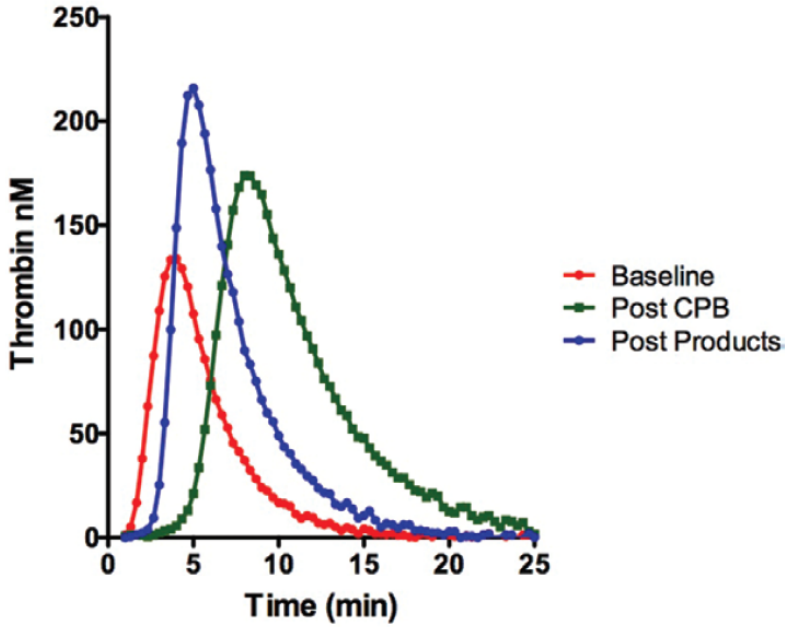


Figure 1. Example of thrombin generation curves before cardiopulmonary bypass (CPB), after CPB, and after administration of a standard transfusion protocol consisting of a quarter of a platelet apheresis unit (approximately 20 mL·kg^{-1}) and 3 units of cryoprecipitate.

Table 4. Thrombin Generation After CPB with the Addition of 4F-PCC

	Lag Time (min)		Peak (nM)		Rate (nM min^{-1})	
	Median (range)	*P*	Median (range)	*P*	Median (range)	*P*
Post-CPB	2.9 (2.0–5.7)	—	173.9 (88.1–195)	—	68.7 (31.5–117)	—
Kcentra 0.1 IU·mL^{-1}	2.9 (1.7–5.3)	0.008	212.1 (144.6–234.2)	0.0002	85.4 (37.9–125.3)	0.0002
Kcentra 0.3 IU·mL^{-1}	2.9 (1.7–4.5)	0.028	273.5 (230.4–827.7)	0.0002	122 (61.5–183.7)	0.0002
FEIBA 0.1 IU·mL^{-1}	2.6 (1.7–4.2)	0.002	208.8 (137.8–249.2)	0.0002	79.8 (36.2–134.4)	0.0002
FEIBA 0.3 IU·mL^{-1}	2.3 (1.3–3.7)	0.001	272.7 (205.6–307.6)	0.0002	126.3 (57.4–162.1)	0.0002

Values expressed as median (range). *P* value relative to thrombin generation post-CPB without 4F-PCC.
CPB = cardiopulmonary bypass; 4F-PCC = four-factor prothrombin complex concentrate; FEIBA = factor 8 inhibitor bypassing activity.

CONCLUSIONS: After CPB, thrombin generation in neonatal plasma was augmented by the addition of 4F-PCCs. The peak amount and rate of thrombin generation were enhanced in all conditions, whereas the lag time was shortened more with FEIBA. Our findings suggest that the use of 4F-PCCs containing activated FVII may be an effective adjunct to the initial transfusion of platelets and cryoprecipitate to augment coagulation and control bleeding in neonates after CPB. (Anesth Analg 2016;122:935–42)

Recombinant activated factor VII in neonatal cardiac surgery

Andrea S. Christoff[a,*], David S. Winlaw[b,c,d], Julie Curtin[d,e], Elizabeth H. Barnes[f] and Jonathan R. Egan[a,c,d]

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[b] Cardiothoracic Surgery Department, The Children's Hospital at Westmead, Sydney, Australia
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Received 4 September 2018; received in revised form 10 December 2018; accepted 21 December 2019

Key question

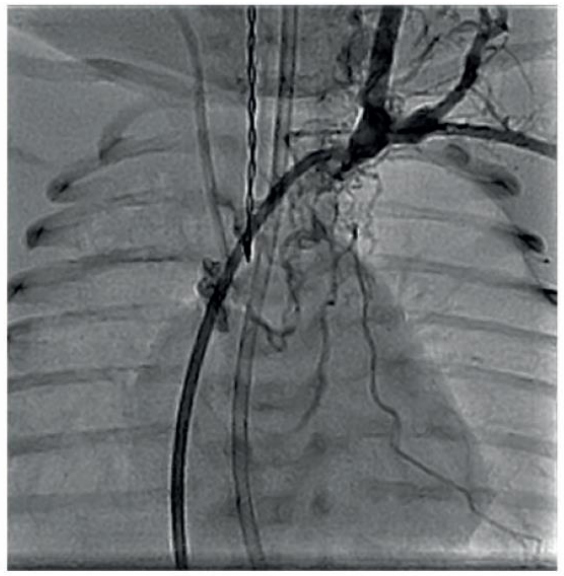
Is rVIIa associated with thrombus formation in neonates after repair of complex congenital heart lesions?

Key finding

The use of rVIIa was associated with increased mortality and thrombus formation after adjusting for severity of illness.

Take-home message

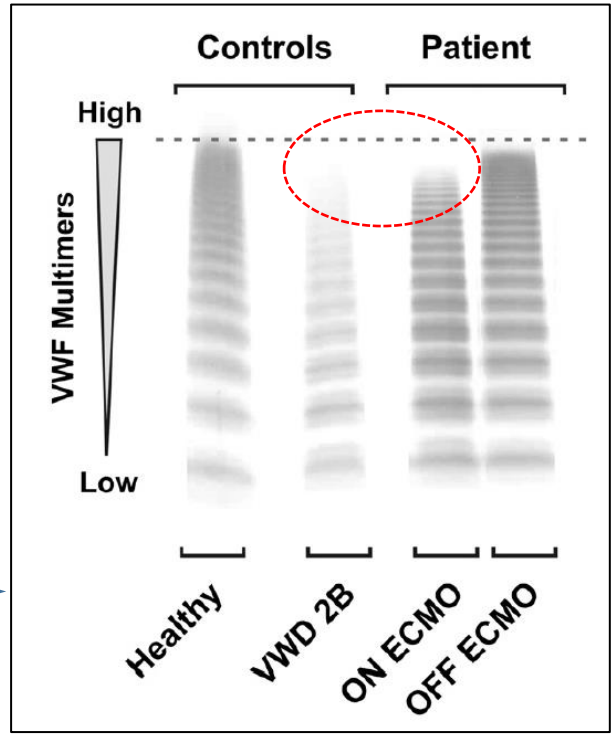
The use of rVIIa was associated with an increased risk of thrombus formation and should be used with caution in neonates.



Conséquences hémostatiques d’une assistance

Mécanisme expliquant les Phénomènes Hémorragiques

- Thrombocytopénie:
  - Complication très classique au cours de l'ECMO qui curieusement est assez peu décrite dans les études.
  - La physiopathologie conjugue des causes inhérentes au patient et à la machine d'assistance.
  - Seuils transfusionels assez variable.
- CIVD:
  - Maladie primitive
  - Rôle important des interactions
  - Difficulté diagnostic
- Hyperfibrinolyse:
  - Activation de la fibrinolyse.
  - Phénomène secondaire à un processus thrombotique.
- Maladie de von Willebrand acquise
- Hémolyse



Méchanisme expliquant les Phénomènes Thrombotiques

- Contact du sang avec les surfaces artificielles.
- Inflammation médiée par le complément.
- ECMO ≈ CEC de très longue durée.
- Très rarement TIH chez l'enfant.

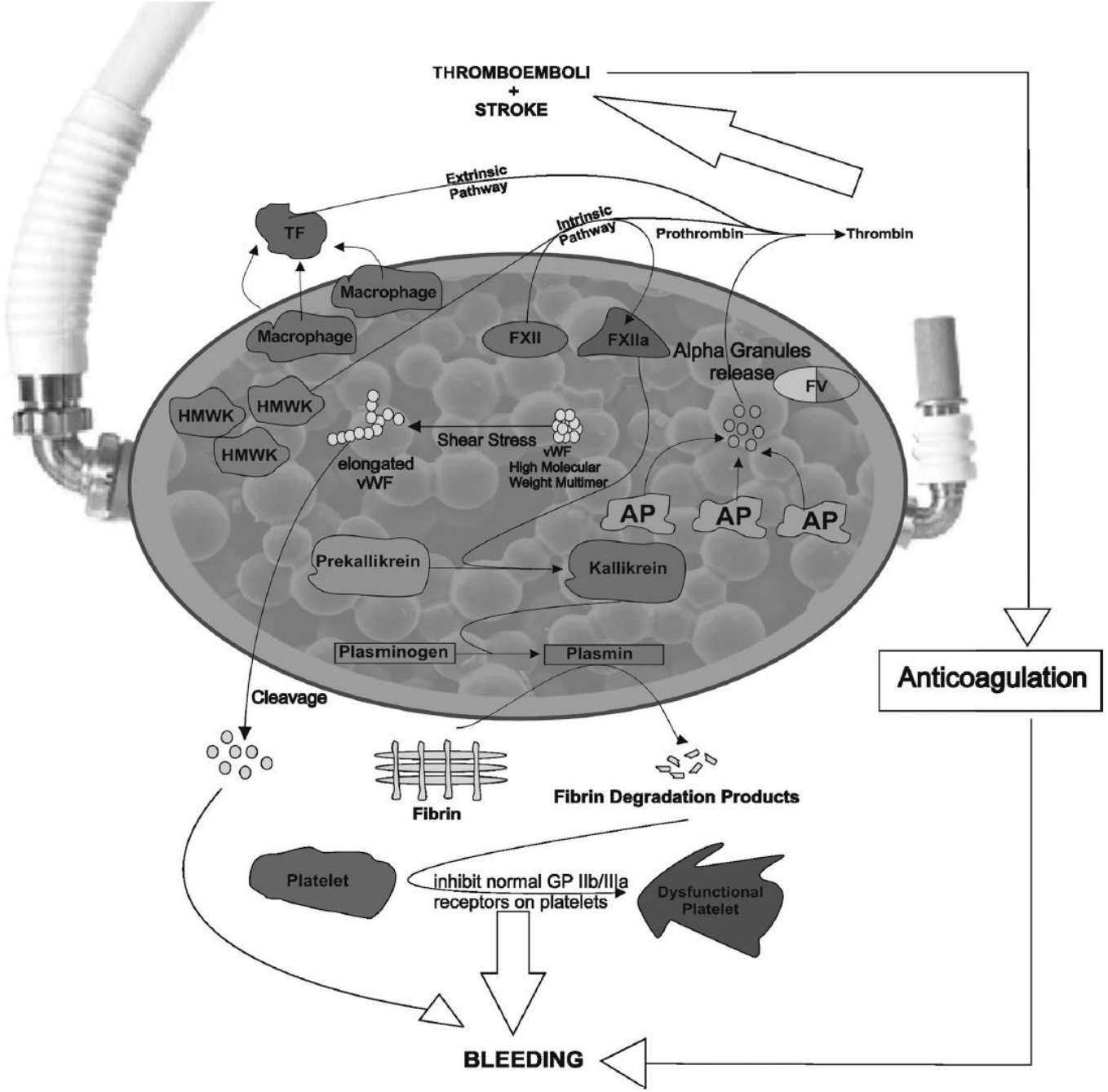
Complications in patients requiring ECMO for respiratory support adapted from ELSO registry data 2014 (this includes both VV and VA ECMO)

	Pediatric (1 mo–18 y)	Survived (%)	Adult (>18 y)	Survived (%)
Total nos. 1986-2013	6270	57	5278	56
Complication	Reported (%)	Survived[a] (%)	Reported (%)	Survived[a] (%)
Clots: oxygenator	10.4	51	12.9	55
Clots: bridge	4.0	55	1.6	56
Clots: bladder	5.6	54	1.7	57
Clots: other	11.6	54	2.7	44
CNS: infarction	4.0	34	2.0	30
CNS: hemorrhage	6.1	22	3.9	20
GI hemorrhage	4.0	27	5.6	34
Cannula site bleeding	17.5	53	15.1	51
Surgical site bleeding	13.4	46	13.6	43
Hemolysis (PfHg > 0.5 g/L)	9.8	44	6	37
DIC	5.4	27	3.3	27
Cardiac tamponade	1.9	43	2.3	48
Pulmonary hemorrhage	8.2	31	7.4	37

Total numbers are cumulative ECMO runs.
Abbreviations: CNS, central nervous system; GI, gastrointestinal.
[a] Survived = survival to discharge or transfer based on number of runs. Percentage survival describes patients with that complication who survived. Because patients who died may have had more than one complication, numbers will not total 100%.

Physiologie appliquée au VAD

- Adsorbtion du Kininogène de HPM sur le titanium du VAD ➔ activation de la voie intrinsèque.
- Macrophages et monocytes expriment du facteur tissulaire ➔ activation de la voie extrinsèque.
- Activation plaquettaire avec libérattion de facteurV ➔ amplification des phénomènes thrombotiques.
- Activation de la fibrinolyse par le système Kallikreine.
- Les produits de dégradation de la fibrine ➔ fixation R G2b3a.
- Déficit vWf



Quelles sont les implications de ces phénomène thrombotiques et hémorragiques?

Association of Bleeding and Thrombosis With Outcome in Extracorporeal Life Support*

Pediatric Critical Care Medicine | February 2015 • Volume 16 • Number 2

Période recrutement2005-2011

TABLE 2. Characteristics of the Study Cohort ($n = 2,036$)

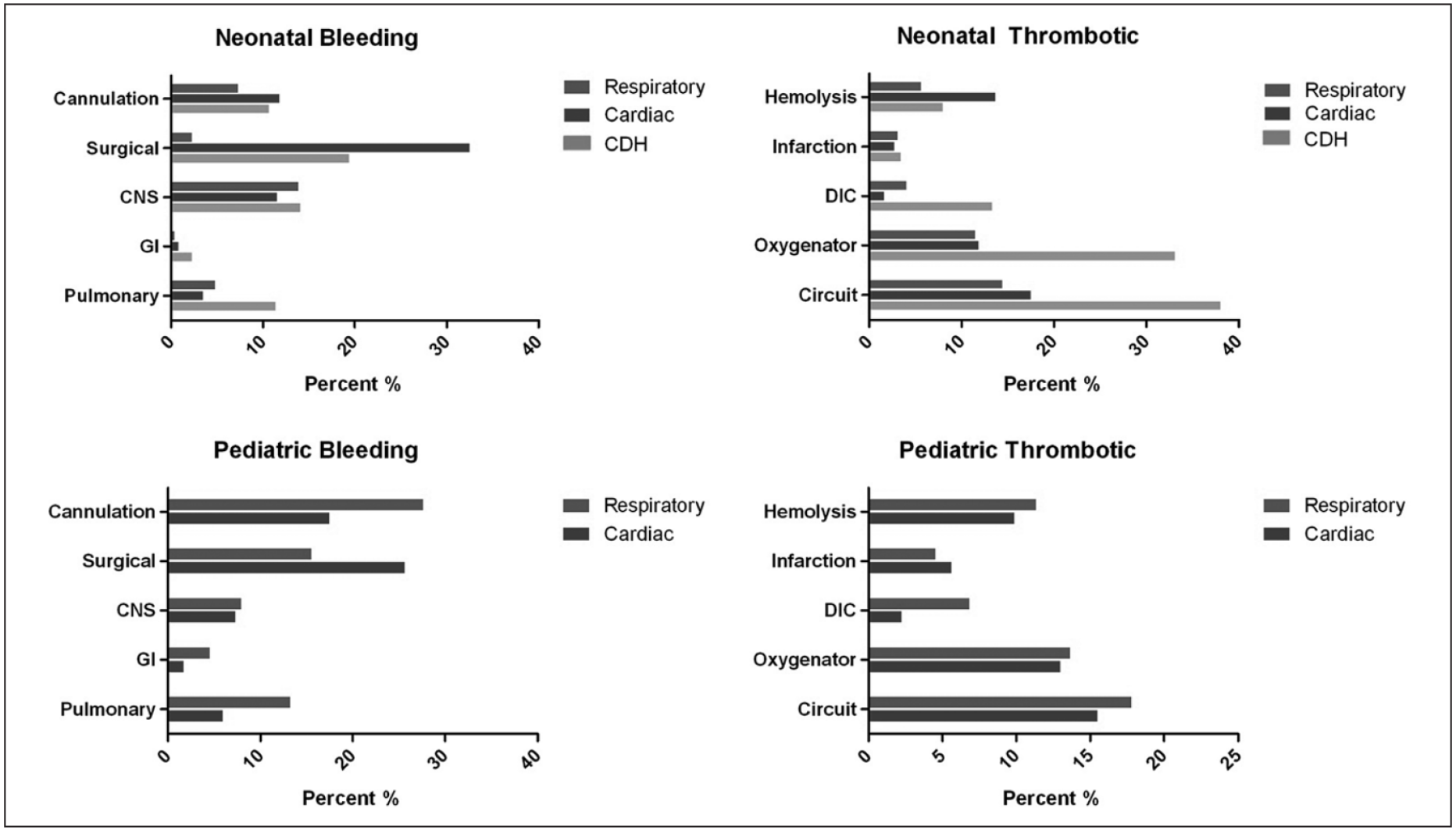
Variable	Percent (%)[a]	*n*
Neonatal (non-CDH)	56	1,001
Indication for extracorporeal life support		
Respiratory	39	784
Neonates	66	520
Pediatric	34	264
Cardiac	36	727
Neonates	51	372
Pediatric	49	355
Extracorporeal cardiopulmonary resuscitation	13	262
Neonatal	42	109
Pediatric	58	153
CDH	13	263

TABLE 1. List of Extracorporeal Life Support Organization Mechanical and Patient-Related Complications[a]

Patient-related	Mechanical
Thrombotic	**Clots: oxygenator**
Intracranial infarction (US or CT)	**Clots: bridge**
Hemorrhagic	**Clots: bladder**
Intracranial hemorrhage (US or CT)	**Clots: hemofilter**
Gastrointestinal hemorrhage	**Clots: other**
Cannulation site bleeding	
Surgical site bleeding	
Hemolysis (plasma hemoglobin > 50 mg/dL)	
Disseminated intravascular coagulation	
Pulmonary hemorrhage	

Association of Bleeding and Thrombosis With Outcome in Extracorporeal Life Support*

Pediatric Critical Care Medicine February 2015 • Volume 16 • Number 2



Association of Bleeding and Thrombosis With Outcome in Extracorporeal Life Support*

Pediatric Critical Care Medicine February 2015 • Volume 16 • Number 2

- Survie globale 49%(NN 40% ; Ped 57%)
- Evts hémorragiques 23% des cas.
- Survie annuelle stable durant la période de recrutement.
- Evènements hémorragiques significativement corrélés a une diminution de survie de 33% dans la cohortes néonatale et de 32% dans le groupe pédiatrique.
- L'association de plusieurs complications hémorragiques diminue la surviede façon significative.

TABLE 4. Frequency[a] of Complications During Extracorporeal Life Support for Cardiac Support and Relative Risk of Survival[a] (Excludes Cases of Congenital Diaphragmatic Hernia)

	Bleeding				
Variable	*n*	% (*n*)	% Survival	Survival RR[b]	95% CI
Neonatal					
	0	57 (211)	49	1.00	–
	1	28 (103)	35	0.80	0.59–1.07
	2+	16 (58)	19	0.45	0.26–0.77
				$p < 0.001$[a]	
Pediatric					
	0	56 (200)	69	1.00	–
	1	31 (109)	42	0.66	0.52–0.83
	2+	13 (46)	43	0.73	0.52–1.02
				$p = 0.003$[a]	

Association of Bleeding and Thrombosis With Outcome in Extracorporeal Life Support*

Pediatric Critical Care Medicine February 2015 • Volume 16 • Number 2

- Evts thrombotiques dans 33% des cas.
- Diminution équivalente de la survie ≈ 30% dans les deux groupes de patients.
- L'augmentation du nombre de complication thrombotique chez un même patient diminue la survie.

TABLE 4. Frequency[a] of Complications During Extracorporeal Life Support for Cardiac Support and Relative Risk of Survival[a] (Excludes Cases of Congenital Diaphragmatic Hernia)

Thrombosis				
n	% (*n*)	% Survival	Survival RR[b]	95% CI
0	68 (251)	49	1.00	–
1	20 (75)	21	0.51	0.32–0.81
2	8 (29)	31	0.78	0.45–1.35
3+	5 (17)	12	0.36	0.09–1.35
			$p = 0.014$[a]	
0	67 (239)	67	1.00	–
1	20 (70)	41	0.67	0.50–0.89
2	10 (35)	31	0.57	0.34–0.93
3+	3 (11)	27	0.58	0.23–1.47
			$p = 0.002$[a]	

Factors Associated with Bleeding and Thrombosis in Children Receiving Extracorporeal Membrane Oxygenation

Heidi J. Dalton[1] American Journal of Respiratory and Critical Care Medicine Volume 196 Number 6 2017

- 1ere étude prospective consacrée à l'ECMO.
- Buts de l'étude:
  - Incidence des évènements thrombotiques et hémorragiques.
  - Identifier les facteurs associés à ces évènements.
  - Evaluer leur impact sur le pronostic du patient.
- **514 patients < 19 ans** (centres US majeurs)
  - Survie globale à 54,9%.
  - 27,5 évènements hémorragiques % jours ECMO.
  - 11 évènements thrombotiques % jours ECMO.

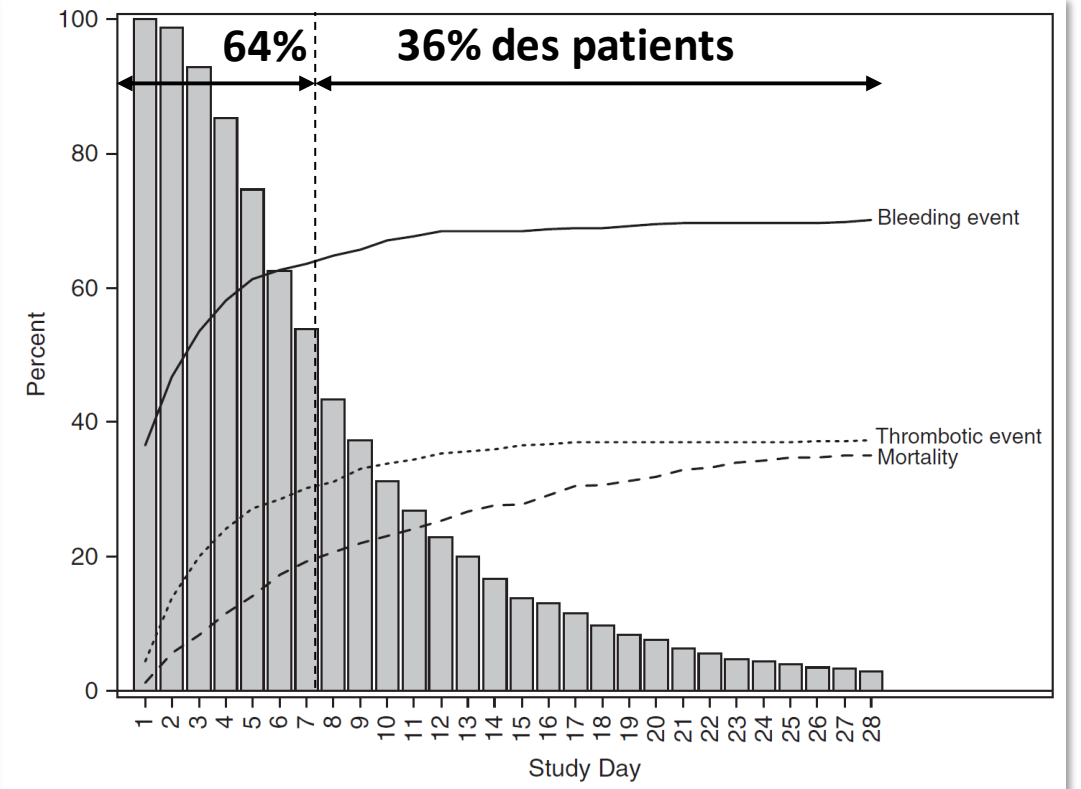


Figure 1. The cumulative percent of patients who have suffered mortality, bleeding events, or thrombotic events by day of extracorporeal membrane oxygenation support. The histogram shows the percent of patients who remain on extracorporeal membrane oxygenation support as the duration of support increases.

Risque de décès de 1-3% par jour d'ECMO

Factors Associated with Bleeding and Thrombosis in Children Receiving Extracorporeal Membrane Oxygenation

Heidi J. Dalton[1] American Journal of Respiratory and Critical Care Medicine Volume 196 Number 6 2017

Nouveaux évènements hémorragiques pour 100 jours d'assistance par âge et indication d'ECMO

	Respiratory		Cardiac		ECPR		
	Neonatal (1,724 d)	Pediatric (1,123 d)	Neonatal (583 d)	Pediatric (771 d)	Neonatal (153 d)	Pediatric (306 d)	Overall (4,660 d)
Bleeding events, n (%)	282 (16.4)	335 (29.8)	218 (37.4)	297 (38.5)	51 (33.3)	100 (32.7)	1283 (27.5)
Surgical site bleeding, n (%)	84 (4.9)	90 (8.0)	105 (18.0)	116 (15.0)	28 (18.3)	31 (10.1)	454 (9.7)
Chest tube bleeding, n (%)	75 (4.4)	127 (11.3)	139 (23.8)	185 (24.0)	34 (22.2)	62 (20.3)	622 (13.3)
ml/kg, median (IQR)	0.0 (0.0–1.8)	0.0 (0.0–1.3)	17.3 (0.0–48.8)	7.4 (0.0–33.5)	16.7 (3.2–42.4)	0.9 (0.0–15.4)	0.0 (0.0–13.2)
Cannula site bleeding, n (%)	85 (4.9)	124 (11.0)	46 (7.9)	94 (12.2)	13 (8.5)	35 (11.4)	397 (8.5)
Pulmonary hemorrhage, n (%)	33 (1.9)	66 (5.9)	6 (1.0)	26 (3.4)	5 (3.3)	8 (2.6)	144 (3.1)
Gastrointestinal bleeding, n (%)	15 (0.9)	49 (4.4)	1 (0.2)	4 (0.5)	1 (0.7)	11 (3.6)	81 (1.7)
Genitourinary bleeding, n (%)	13 (0.8)	26 (2.3)	2 (0.3)	6 (0.8)	0 (0.0)	3 (1.0)	50 (1.1)
Intracranial bleeding, n (%)	57 (3.3)	16 (1.4)	25 (4.3)	13 (1.7)	6 (3.9)	5 (1.6)	122 (2.6)
Laboratory sample bleeding, n (%)	483 (28.0)	203 (18.1)	145 (24.9)	180 (23.3)	41 (26.8)	73 (23.9)	1125 (24.1)
ml/kg, median (IQR)	9.0 (6.3–11.6)	1.4 (0.6–3.2)	7.1 (4.2–10.3)	2.7 (1.0–5.5)	7.6 (3.7–9.6)	2.4 (1.4–4.5)	6.0 (2.1–9.7)
Only laboratory sample bleeding, n (%)	349 (20.2)	137 (12.2)	63 (10.8)	79 (10.2)	19 (12.4)	32 (10.5)	679 (14.6)

- Evènements hémorragique chez 70,2% des patients…
- …dont 16% d'AVC hémorragique.
- …soit 27,5 evts hémorragiques %j ECMO.
- Rôle joué par les bilans…
- …qui sont la seul cause d'une transfusion dans 42.2% des cas.

Factors Associated with Bleeding and Thrombosis in Children Receiving Extracorporeal Membrane Oxygenation

Heidi J. Dalton[1] American Journal of Respiratory and Critical Care Medicine Volume 196 Number 6 2017

- Forte association entre la ***durée de l'assistance*** et la survenue de complications hémorragiques.
- Les facteurs prédictifs d'hémorragie sont:
  - ***« Cardiac » ECMO.***
  - ***« ECPR » ECMO.***
  - ***ECMO en salle d'opération sur non seuvrabilité de la CEC.***
- Assez grandes variations d'incidence entre les ***centres***!
- Impératif d'homogénéisation des pratiques.

Table 7. Multivariate Model for Daily Bleeding Event

	Adjusted Relative Risk (95% CI)	*P* Value
Age, yr	1.04 (1.02–1.05)	<0.001
Patient placed on ECMO directly from CPB		<0.001
No	Reference	
Yes	1.76 (1.45–2.13)	
Primary ECMO indication		0.002
Cardiac	1.34 (1.11–1.63)	
ECPR	1.52 (1.16–1.98)	
Respiratory	Reference	
Patient has MAS		0.002
No	Reference	
Yes	0.54 (0.34–0.84)	
Organ Failure Index on day of ECMO initiation		0.013
1	1.00 (0.65–1.53)	
2	Reference	
3	1.28 (1.08–1.51)	
4–5	1.47 (1.09–1.97)	
Clinical site		<0.001
A	1.53 (1.24–1.90)	
B	0.58 (0.35–0.95)	
C	0.44 (0.33–0.58)	
D	0.77 (0.59–1.01)	
E	Reference	
F	0.86 (0.64–1.16)	
G	1.21 (0.84–1.73)	
H	0.90 (0.66–1.21)	

Definition of abbreviations: CI = confidence interval; CPB = cardiopulmonary bypass; ECMO = extracorporeal membrane oxygenation; ECPR = extracorporeal cardiopulmonary resuscitation; MAS = meconium aspiration syndrome.

Factors Associated with Bleeding and Thrombosis in Children Receiving Extracorporeal Membrane Oxygenation

Heidi J. Dalton[1] American Journal of Respiratory and Critical Care Medicine Volume 196 Number 6 2017

Nouveaux évènements thrombotiques pour 100 jours d'assistance par âge et indication d'ECMO

	Respiratory		Cardiac		ECPR		
	Neonatal (1,724 d)	Pediatric (1,123 d)	Neonatal (583 d)	Pediatric (771 d)	Neonatal (153 d)	Pediatric (306 d)	Overall (4,660 d)
Thrombotic events, n (%)	154 (8.9)	104 (9.3)	66 (11.3)	122 (15.8)	17 (11.1)	48 (15.7)	511 (11.0)
Patient-related thromboses, n (%)	27 (1.6)	39 (3.5)	33 (5.7)	75 (9.7)	7 (4.6)	29 (9.5)	210 (4.5)
Intracranial infarction, n (%)	17 (1.0)	17 (1.5)	5 (0.9)	15 (1.9)	0 (0.0)	17 (5.6)	71 (1.5)
Limb ischemia, n (%)	2 (0.1)	15 (1.3)	21 (3.6)	26 (3.4)	0 (0.0)	10 (3.3)	74 (1.6)
Intracardiac clot, n (%)	0 (0.0)	1 (0.1)	0 (0.0)	25 (3.2)	0 (0.0)	0 (0.0)	26 (0.6)
Aortopulmonary shunt clot, n (%)	1 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Pulmonary embolus, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.8)	0 (0.0)	0 (0.0)	6 (0.1)
Other, n (%)	7 (0.4)	18 (1.6)	5 (0.9)	10 (1.3)	7 (4.6)	2 (0.7)	49 (1.1)
Circuit-related thromboses (requiring change-out), n (%)	129 (7.5)	70 (6.2)	36 (6.2)	55 (7.1)	12 (7.8)	22 (7.2)	324 (7.0)
Entire circuit, n (%)	51 (3.0)	20 (1.8)	8 (1.4)	12 (1.6)	3 (2.0)	7 (2.3)	101 (2.2)
Oxygenator, n (%)	8 (0.5)	10 (0.9)	9 (1.5)	17 (2.2)	4 (2.6)	4 (1.3)	52 (1.1)
Bladder, n (%)	16 (0.9)	5 (0.4)	3 (0.5)	6 (0.8)	2 (1.3)	0 (0.0)	32 (0.7)
CVVH, n (%)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.1)
Tubing, n (%)	7 (0.4)	14 (1.2)	2 (0.3)	1 (0.1)	1 (0.7)	0 (0.0)	25 (0.5)
Arterial cannula, n (%)	1 (0.1)	3 (0.3)	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	6 (0.1)
Bridge, n (%)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.7)	0 (0.0)	3 (0.1)
Hemofilter, n (%)	19 (1.1)	4 (0.4)	4 (0.7)	0 (0.0)	2 (1.3)	2 (0.7)	31 (0.7)
Pump head, n (%)	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.3)	5 (0.1)
Venous cannula, n (%)	1 (0.1)	3 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)
Other, n (%)	32 (1.9)	20 (1.8)	11 (1.9)	22 (2.9)	2 (1.3)	9 (2.9)	96 (2.1)
Hemolysis, n (%)	275 (16.0)	145 (12.9)	108 (18.5)	78 (10.1)	24 (15.7)	35 (11.4)	665 (14.3)

Factors Associated with Bleeding and Thrombosis in Children Receiving Extracorporeal Membrane Oxygenation

Heidi J. Dalton[1] American Journal of Respiratory and Critical Care Medicine Volume 196 Number 6 2017

Outcome…

- Survie globale de la cohorte est de 54,9%, variable bien sur en fonction de l'indication, mais pas fonction de l'âge ni du site ECMO.
- Les évènements hémorragiques et thrombotiques sont associés à une statut clinique altéré à la sortie de réanimation *(Patient Overall Performance Category score; Pediatric Cerebral Performance Category score).*
- Rôle statistique important des mort cérébrales dans cette association.
- La survenue d'une hémolyse ne semble pas avoir d'impact sur l'état clinique à la sortie de réanimation.
- En analyse multivariée, les évènements hémorragiques sont associés à une sur-mortalité *(Hazard Ratio = 1,75).*

	Bleeding Event		
	No (*n* = 153)	Yes (*n* = 361)	*P* Value
Total FSS at hospital discharge			0.323*
n	101	181	
Mean (SD)	8.7 (2.95)	9.1 (3.11)	
Minimum, maximum	6.0, 24.0	6.0, 21.0	
Median (IQR)	8.0 (6.0–10.0)	8.0 (7.0–10.0)	
POPC score at hospital discharge, n (%)			<0.001*
1 (good)	21 (13.7)	31 (8.6)	
2 (mild disability)	46 (30.1)	82 (22.7)	
3 (moderate disability)	29 (19.0)	49 (13.6)	
4 (severe disability)	5 (3.3)	19 (5.3)	
5 (Coma/vegetative)	0 (0)	0 (0)	
6 (brain death)	52 (34.0)	180 (49.9)	
PCPC score at hospital discharge, n (%)			<0.001*
1 (normal)	56 (36.6)	89 (24.7)	
2 (mild disability)	33 (21.6)	64 (17.7)	
3 (moderate disability)	10 (6.5)	17 (4.7%)	
4 (severe disability)	2 (1.3)	11 (3.0)	
5 (Coma/vegetative)	0 (0)	0 (0)	
6 (brain death)	52 (34.0)	180 (49.9)	

Definition of abbreviations: FSS = Functional Status Scale; IQR = interquartile range; PCPC = Pediatric Cerebral Performance Category; POPC = Pediatric Overall Performance Category.
FSS is only measured on survivors, whereas POPC and PCPC include death as the worst possible score.
**P* values are based on the Wilcoxon rank-sum test.

La conduite de l'anticoagulation

Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: an international survey

Melania M. Bembea — *Pediatr Crit Care Med.* 2013 February

Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: an international survey

Melania M. Bembea

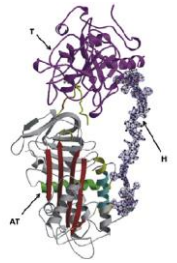
Pediatr Crit Care Med. 2013 February

- 121 centres / 187 qui sont affilliés à l'ELSO.
- 67% sont des centres pédiatriques.
- Tous les centres ont l'HNF comme anticoagulant en première intention.

What is the minimum UFH infusion rate allowed by your protocol? (n=115 respondents)	0 U/kg/h[a]	35 (30%)
	1–10 U/kg/h	62 (54%)
	11–25 U/kg/h	18 (16%)
	>25 U/kg/h	0
What is the maximum UFH infusion rate allowed by your protocol? (n=115 respondents)	No upper limit	83 (72%)
	50–75 U/kg/h	21 (18%)
	76–100 U/kg/h	8 (7%)
	101–125 U/kg/h[b]	3 (3%)
In the last six months, have you used non-UFH anticoagulation? (n=117 respondents)	Yes	10 (8%)
	No	107 (90%)
What non-UFH anticoagulation do/can you use in your ICU? (n=107 respondents)	Argatroban	48 (45%)
	Bivalirudin	10 (9%)
	Lepirudin	6 (6%)
	We never use any other pharmacologic anticoagulation besides UFH	50 (47%)
	Other	0

Antithrombin levels during pediatric cardiopulmonary bypass: Key to changing a decades-old paradigm for anticoagulation?

Dean B. Andropoulos, MD, MHCM,[a,b,c] and Charles D. Fraser, Jr, MD[b,d,e]



- « Cofacteur » de l'héparine.
- Une fois liée à l'héparine, les pouvoirs antithrombinique sont multiplié par 2000-4000.
- Antithrombine du nouveau né = 60% de l'activité observée chez un adulte.

Administration of Antithrombin Concentrate in Infants and Children on Extracorporeal Life Support Improves Anticoagulation Efficacy ASAIOJ 2014

RYERSON *ET AL.*

- La perfusion d'antithrombine permet de diminuer les doses d'héparine et augmente le niveau d'antiXa.
- Absence d'effet adverse (notamment hémorragique).

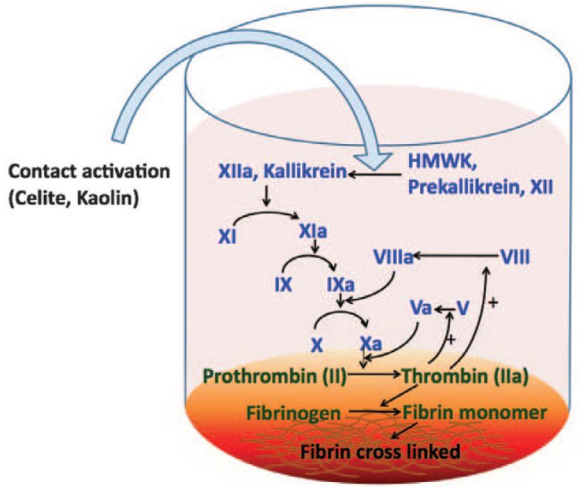
Monitorage de l’anticoagulation

Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: an international survey

Melania M. Bembea

Pediatr Crit Care Med. 2013 February

ACT



ACT goal (sec) (n=116 respondents)	Minimum ACT goal, mean (SD)	183 (13), range 140–220
	Maximum ACT goal, mean (SD)	210 (15), range 170–240
	We do not follow ACT (n=3 respondents)	

Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: an international survey

Melania M. Bembea | *Pediatr Crit Care Med.* 2013 February

Anti-factor Xa measurements (n=115 respondents)	Routinely	46 (40%)
	Occasionally	29 (25%)
	Never	40 (35%)
Anti-factor Xa monitoring frequency (n=66 respondents)	Every 1–8 h	15 (23%)
	Every 9–12 h	12 (18%)
	Every 13–24 h	27 (41%)
	Only as needed	12 (18%)

Anti-Factor Xa Assay Is a Superior Correlate of Heparin Dose Than Activated Partial Thromboplastin Time or Activated Clotting Time in Pediatric Extracorporeal Membrane Oxygenation*

Anna Liveris | Pediatric Critical Care Medicine | 2014

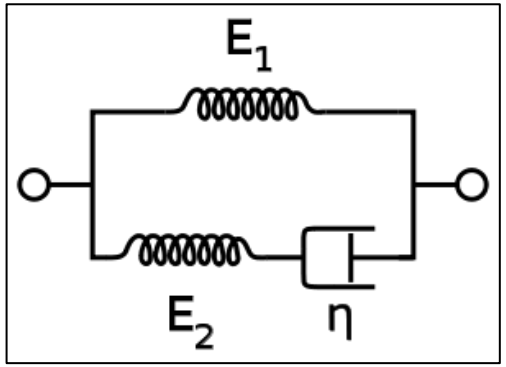
Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: an international survey

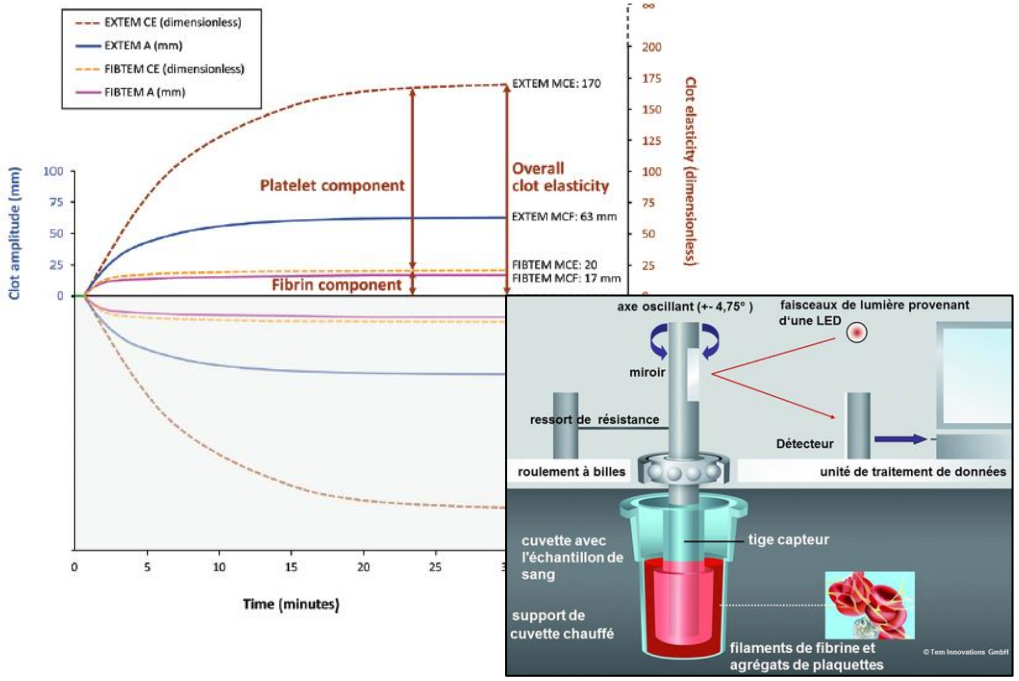
Melania M. Bembea

Pediatr Crit Care Med. 2013 February

TEG measurements (n=116 respondents)	Routinely	21 (18%)
	Occasionally	29 (25%)
	Never	66 (57%)

- Méthode viscoélastométrique de formation du caillot.
- Sur sang total.
- En situation de « no flow » (donc la plus thrombogène).





Prospective Observational Study of Hemostatic Alterations During Adult Extracorporeal Membrane Oxygenation (ECMO) Using Point-of-Care Thromboelastometry and Platelet Aggregometry

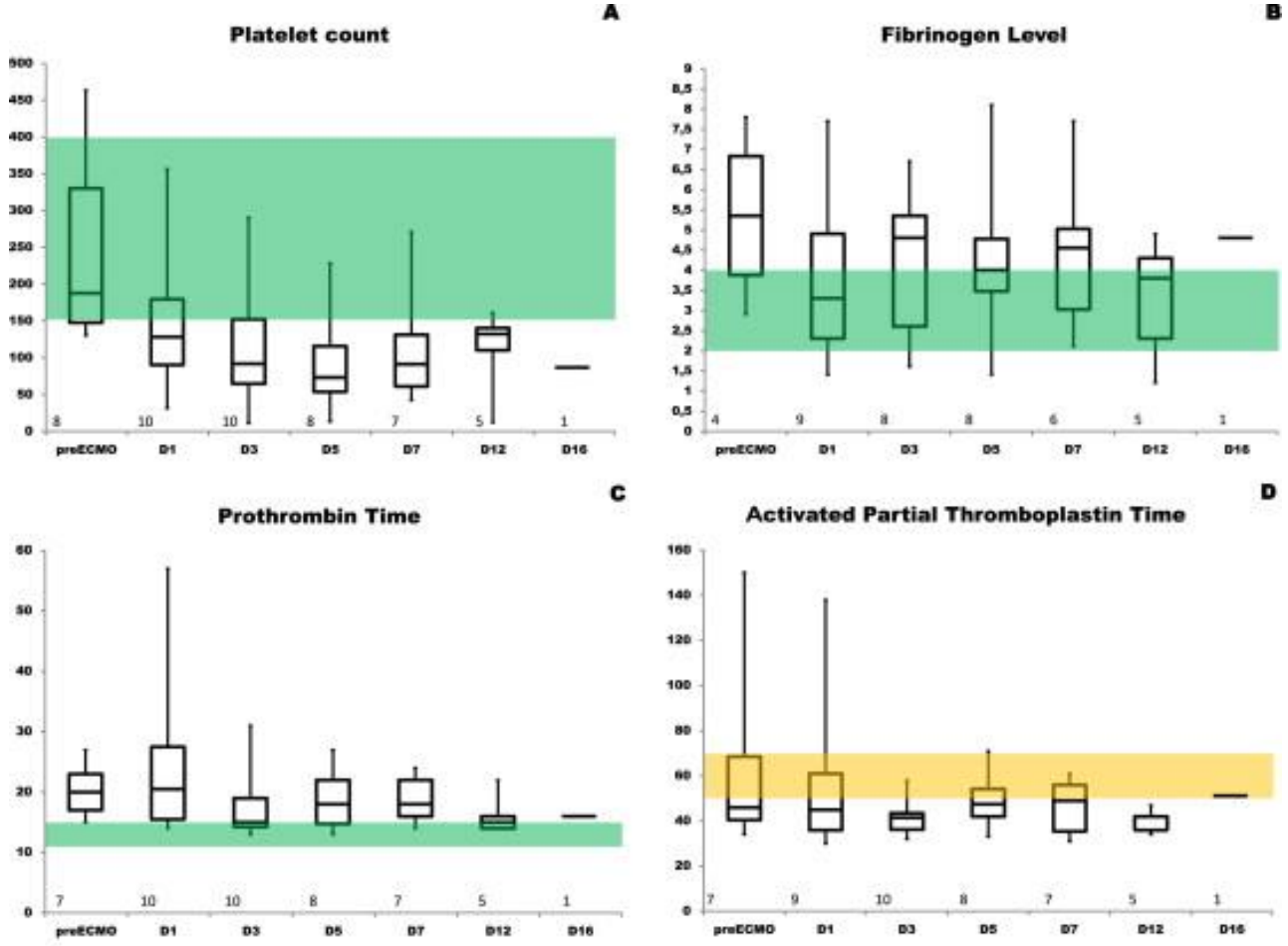
NAIR ET AL

Journal of Cardiothoracic and Vascular Anesthesia, Vol 29, No 2 (April), 2015: pp 288–296

- 10 ECMO adultes ➔ 110 jours ECMO.
- 7 ECMO VA / 3 ECMO VV.
- 6 survivants.

- Objectifs d'anticoagulation:
  - APTT 1,5 – 2 X Normal

- Etude observationnelle
  - Thromboélastométrie
  - Multiaggrégométrie

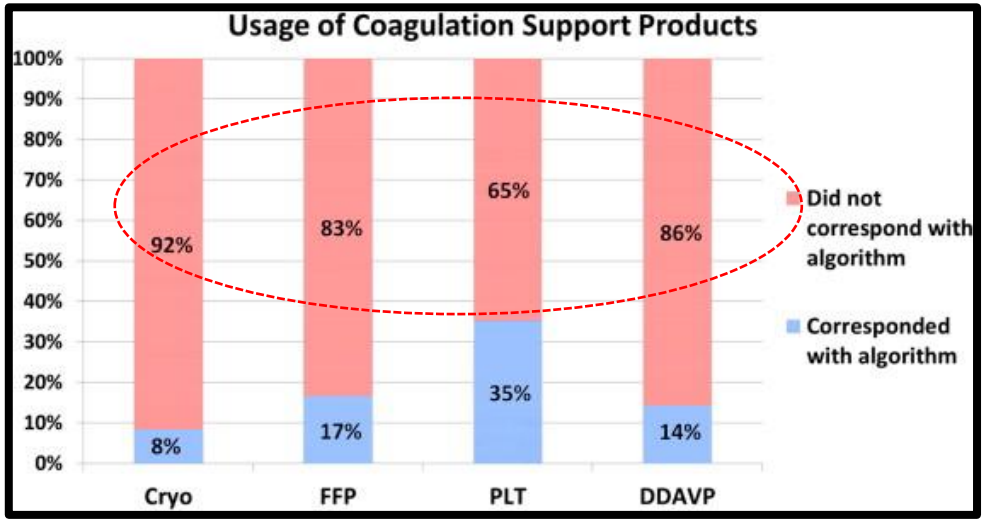


Prospective Observational Study of Hemostatic Alterations During Adult Extracorporeal Membrane Oxygenation (ECMO) Using Point-of-Care Thromboelastometry and Platelet Aggregometry

NAIR ET AL

Journal of Cardiothoracic and Vascular Anesthesia, Vol 29, No 2 (April), 2015: pp 288–296

- Analyse des options thérapeutiques en réponse à une hémorragie portant sur la conduite de l'héparinothérapie et la transfusion de produits hémostatiques.
- Comparaison « fictive » avec un protocole validé guidé par le TEG.



Cette étude suggère que les réponses thérapeutiques à une hémorragie selon le protocol théorique thromboélastométrie ne correspond qu'assez rarement à la décision prise par le clinicien avec le protocole traditionnel.

Jeune Fille de16 ans

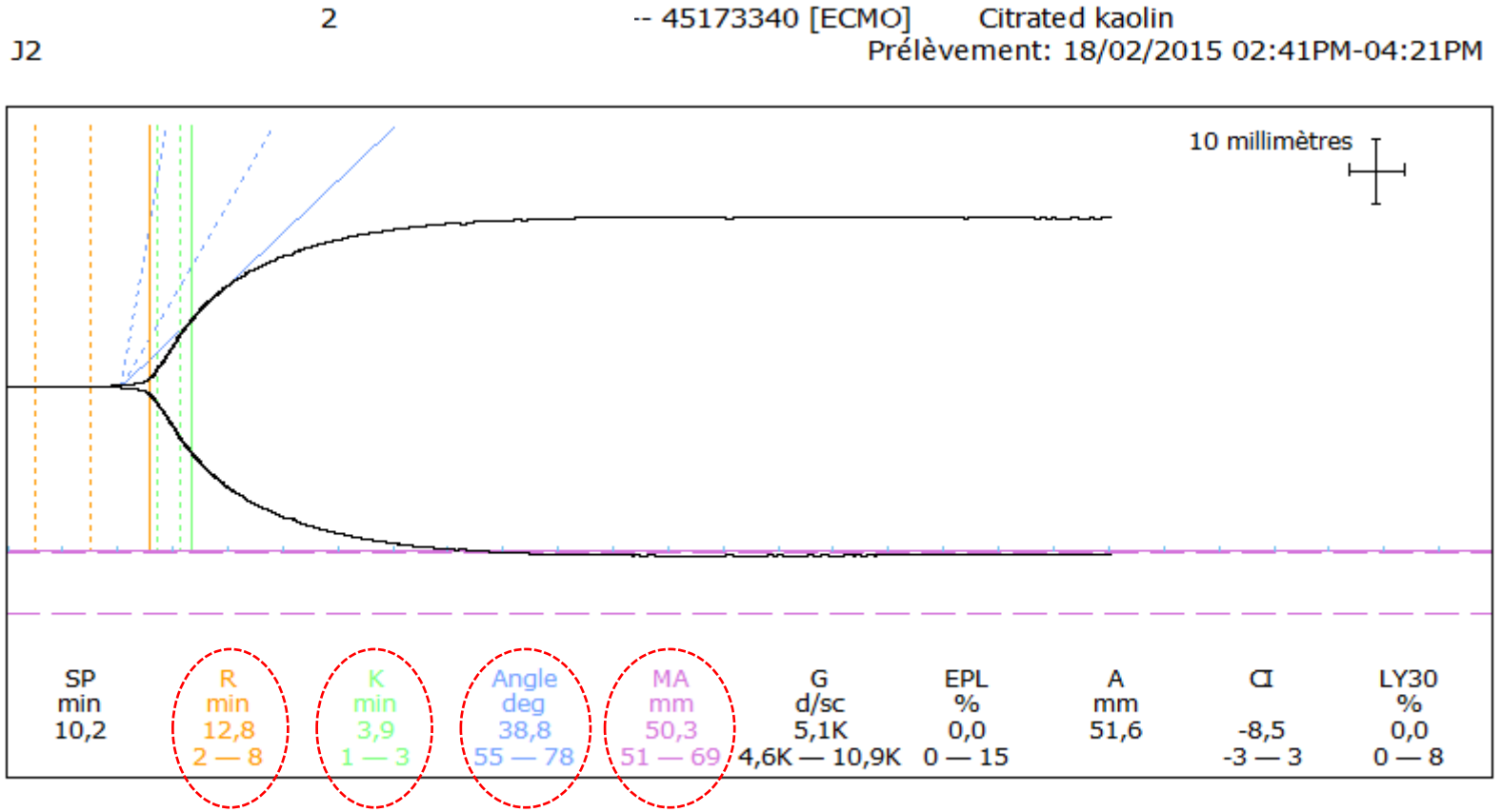
- Myocardite (qui senrévelera être une grippe)
- Dégradation très rapide de la situation
- ECMO ECLS
- Pas de no flow
- Low flow 45 mn en cumulé
- Canulation fémoro-fémorale gauche

Bilan de coagulation de 22h
Hémorragie modérée au site d'insertion des canules
Hémorragie sphère ORL
HNF 550 UI/Kg/j

- APTT > 150
- Activité anti Xa = 0.5
- Plaquettes = 80 000
- TP=37%

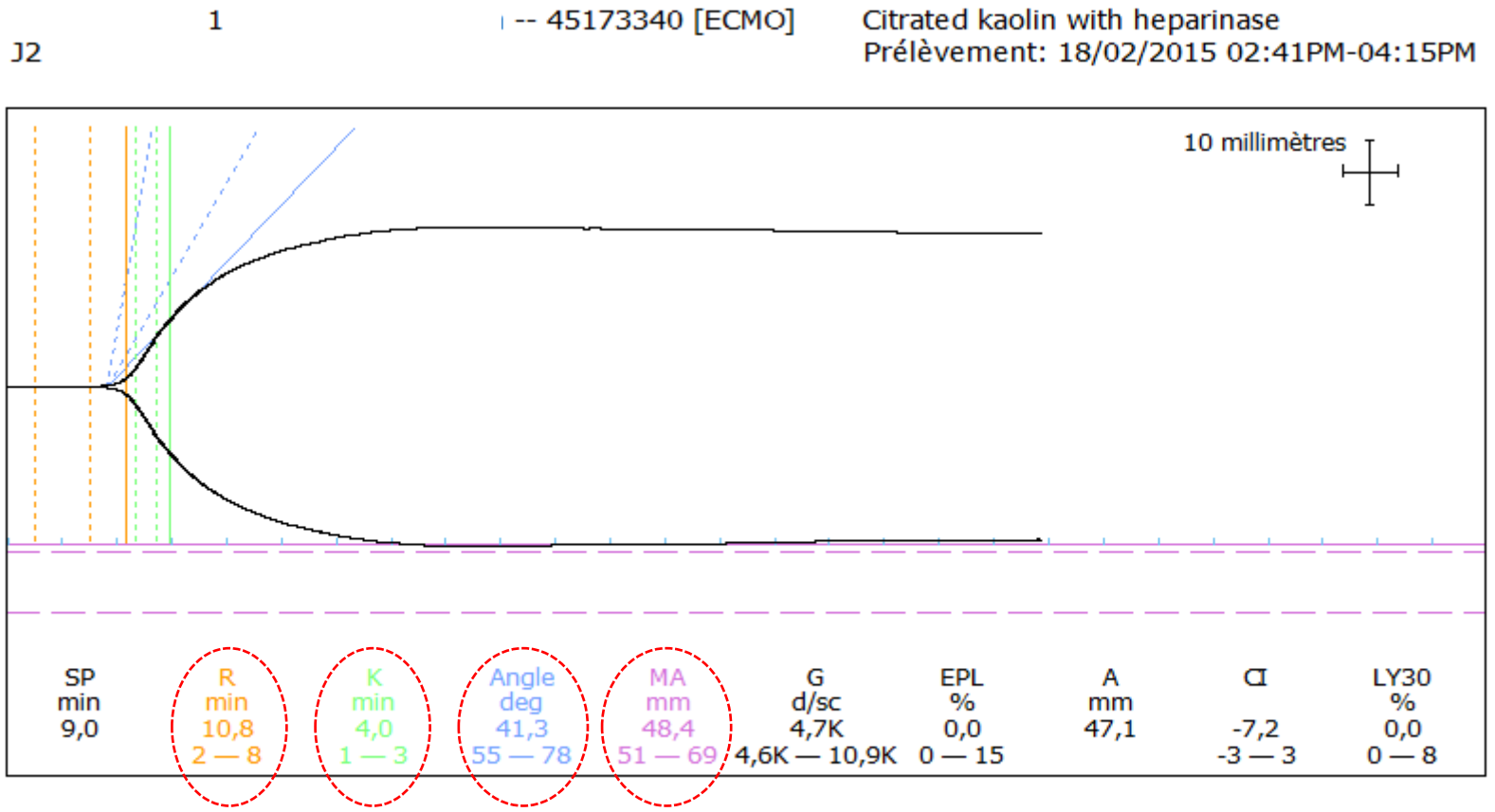
Quel est votre conduite vis-à-vis de l'héparine ?

Prélèvement de 14h du sang total alors que la patiente est sous héparine



On pourrait interpréter toutes ces anomalies de la coag comme un effet de l'héparine…mais

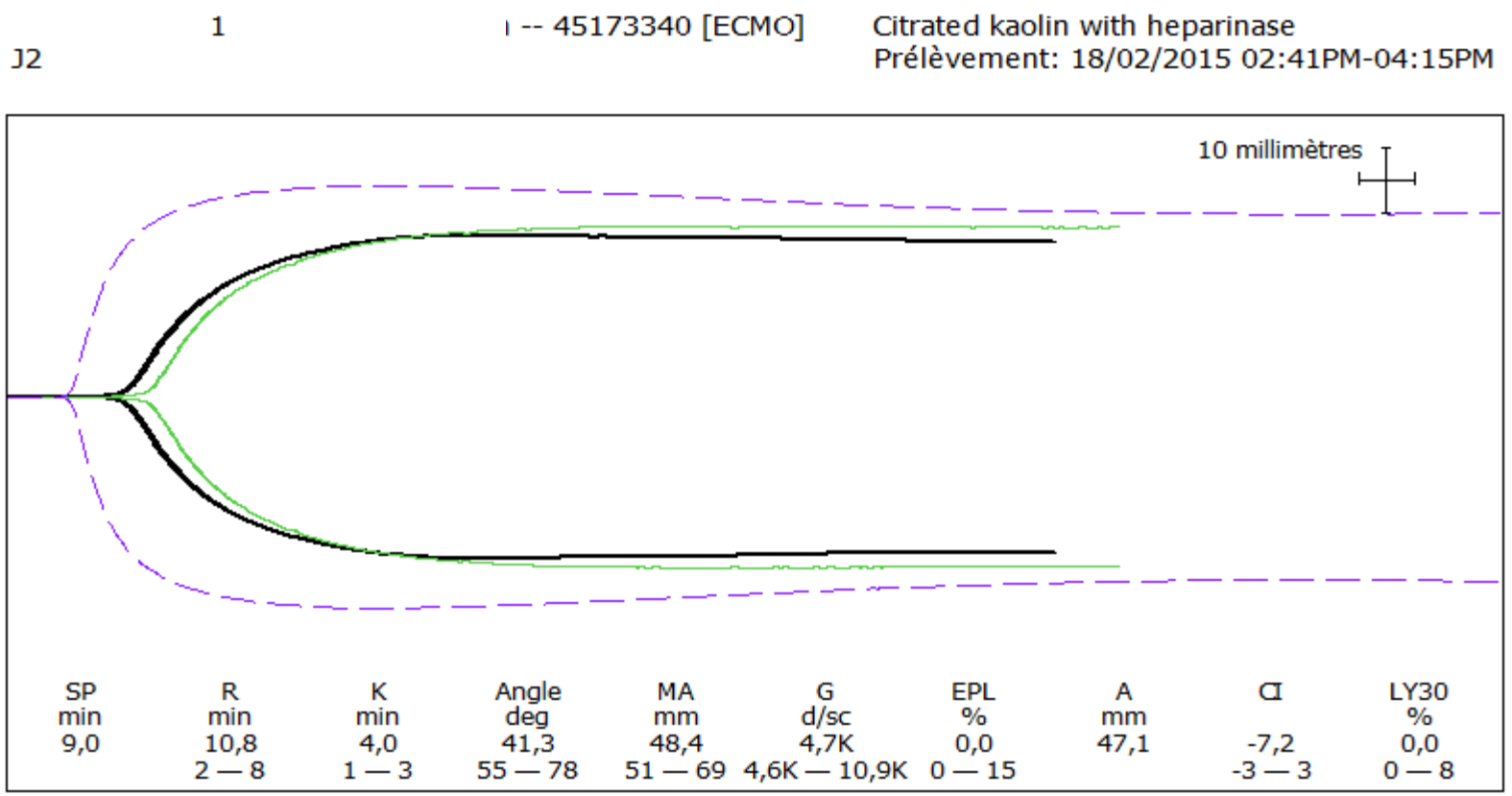
Le même prélèvement avec antagonisation de l'héparine…



Ça ressemble beaucoup au prélèvement précédent
conclusion le malade n'est absolument pas anti coagulé!!!!

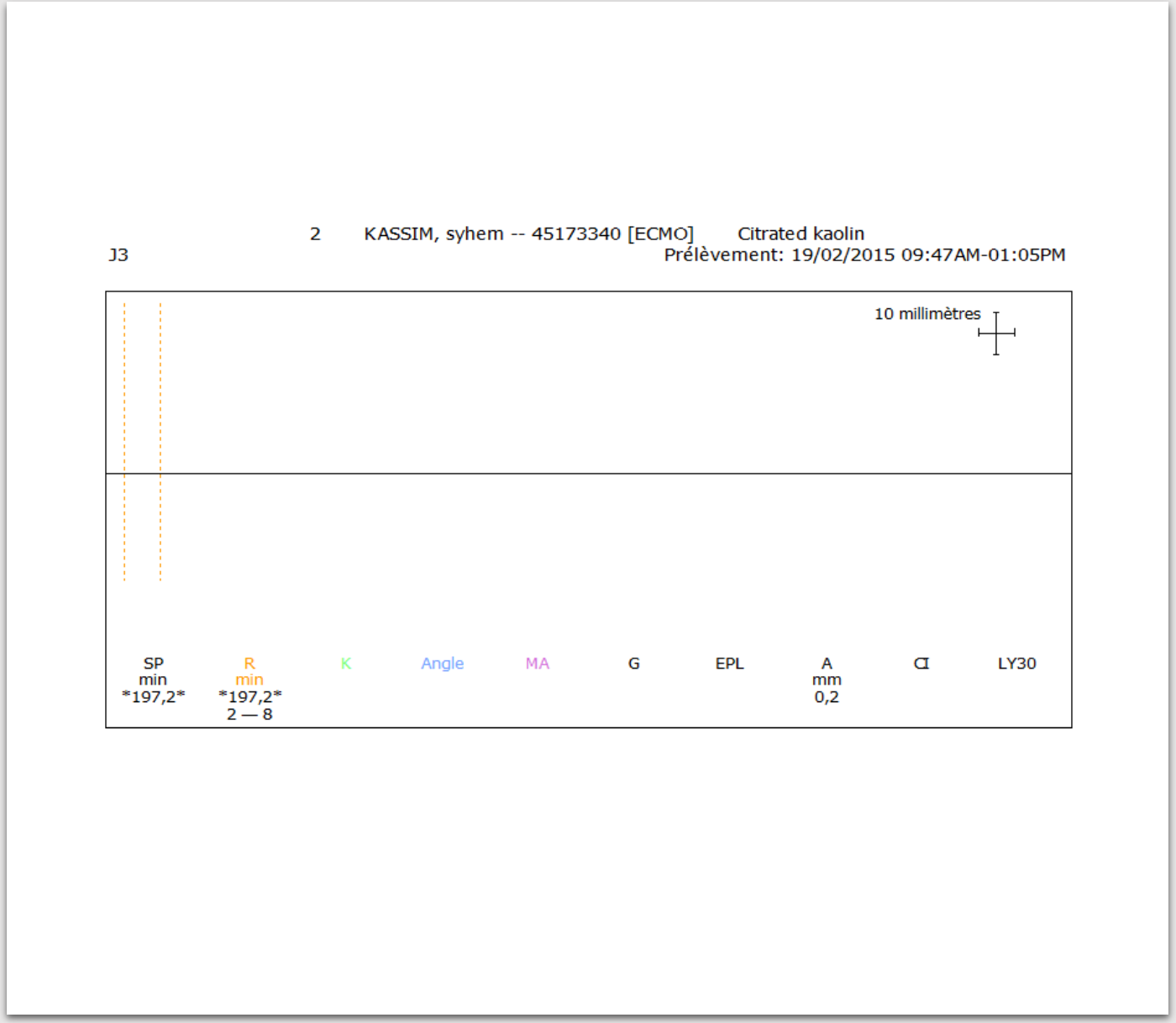
AT3= 15%!!!!!

Une autre façon de le montrer…

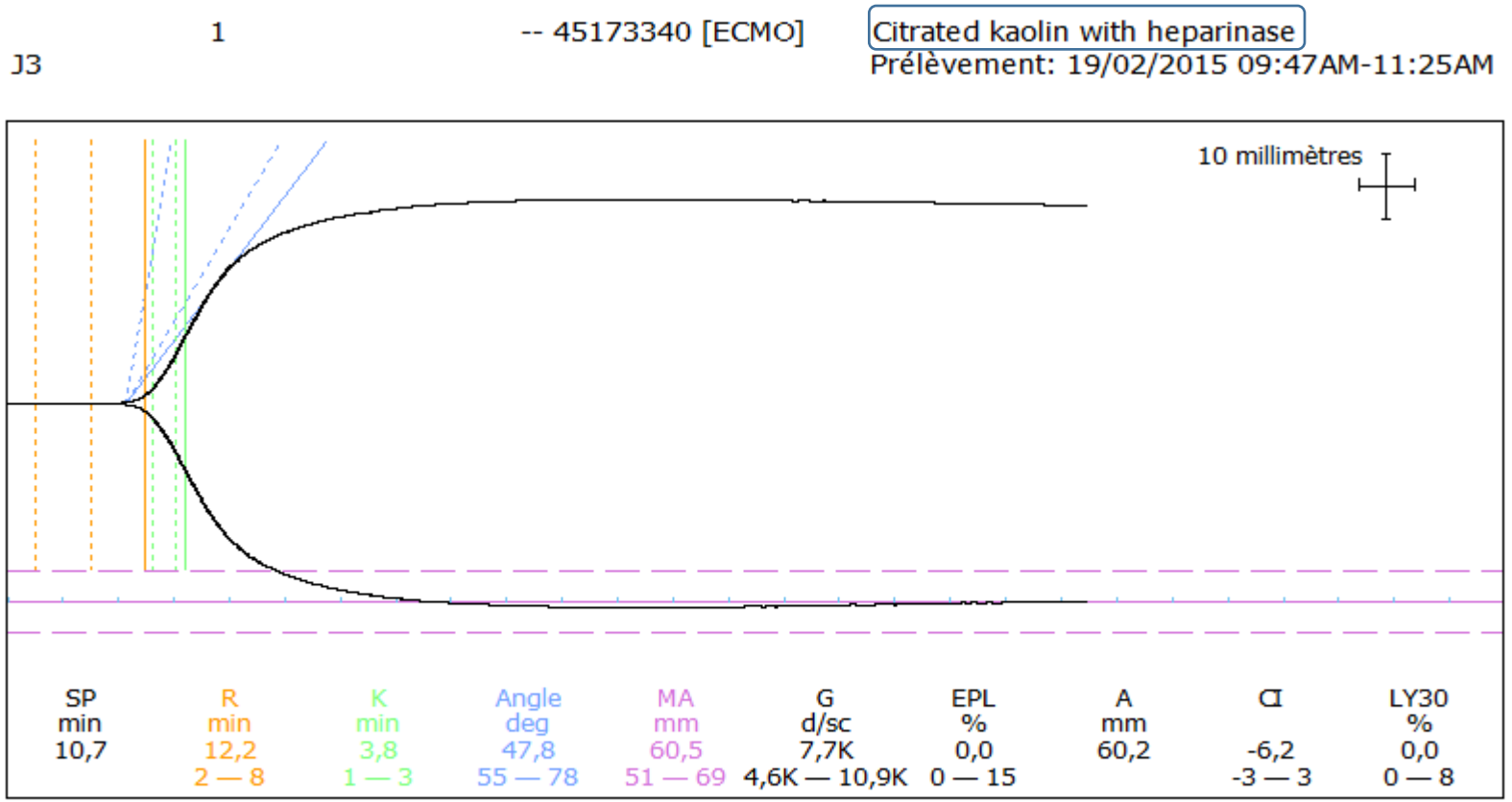


ECMO J3 ; Vidange d'un épanchement péricardique + rajout d'une canule cervicale
Persistance des phénomènes hémorragiques locaux sans critères de gravité

- TCA >150
- Activité anti Xa = 0,7
- Plaquettes = 135 000
- TP=37%
- Anti thrombine: 85%

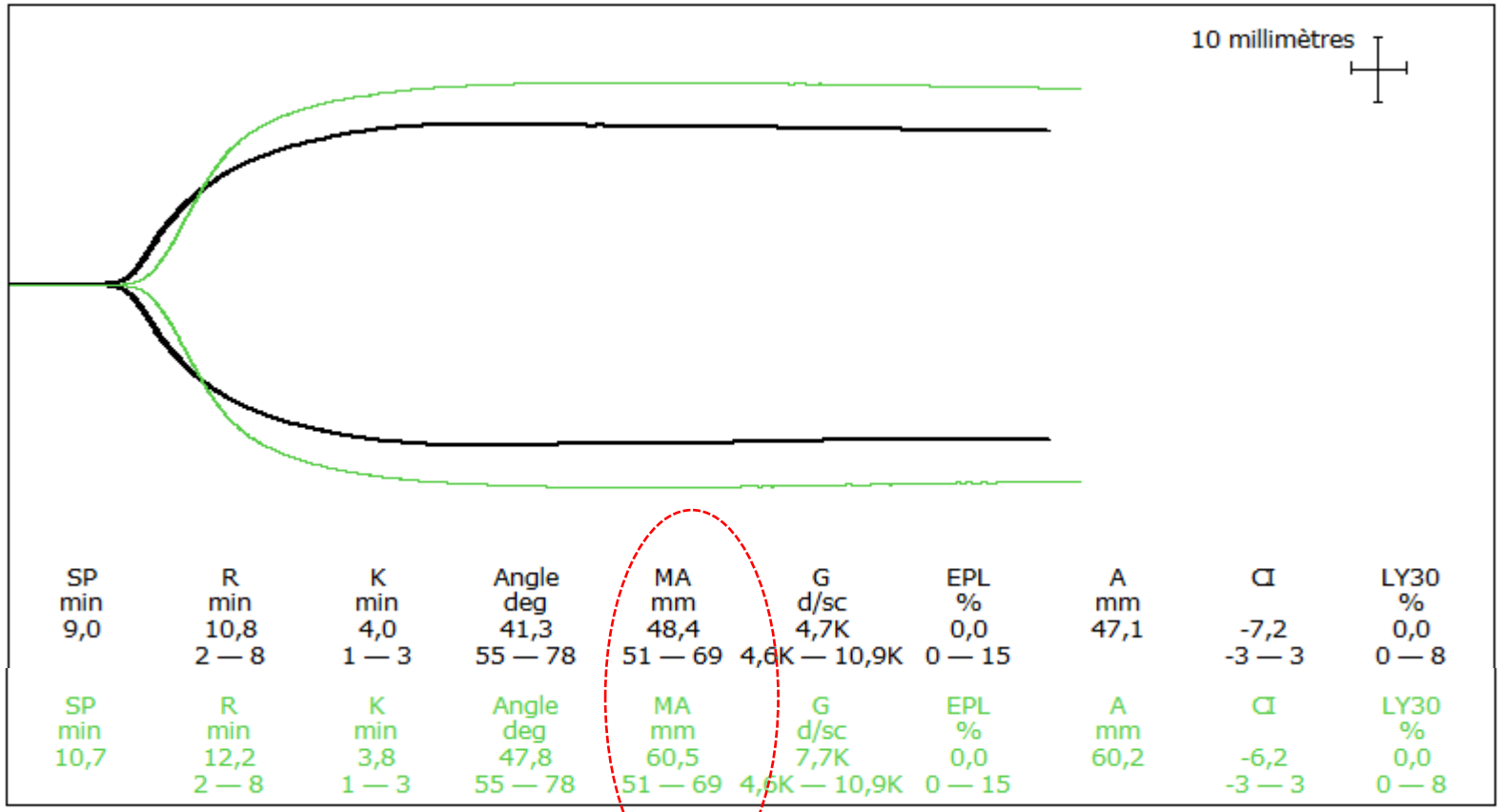


Une coagulation sous héparine qui est un peu mieux qu'hier



Une autre façon de le montrer

J3	1	-- 45173340 [ECMO]	Citrated kaolin with heparinase Prélèvement: 19/02/2015 09:47AM-11:25AM
J2	1	-- 45173340 [ECMO]	Citrated kaolin with heparinase Prélèvement: 18/02/2015 02:41PM-04:15PM

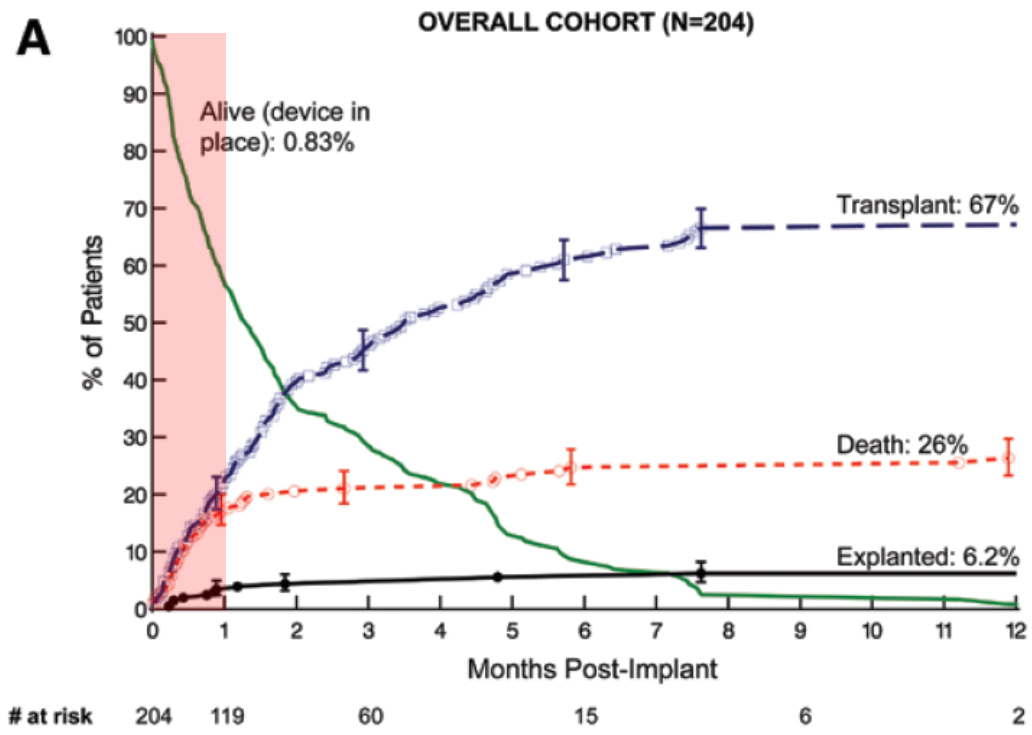


Le cas particulier des VAD

Berlin Heart EXCOR Pediatric Ventricular Assist Device for Bridge to Heart Transplantation in US Children

Circulation. 2013;127:1702-1711

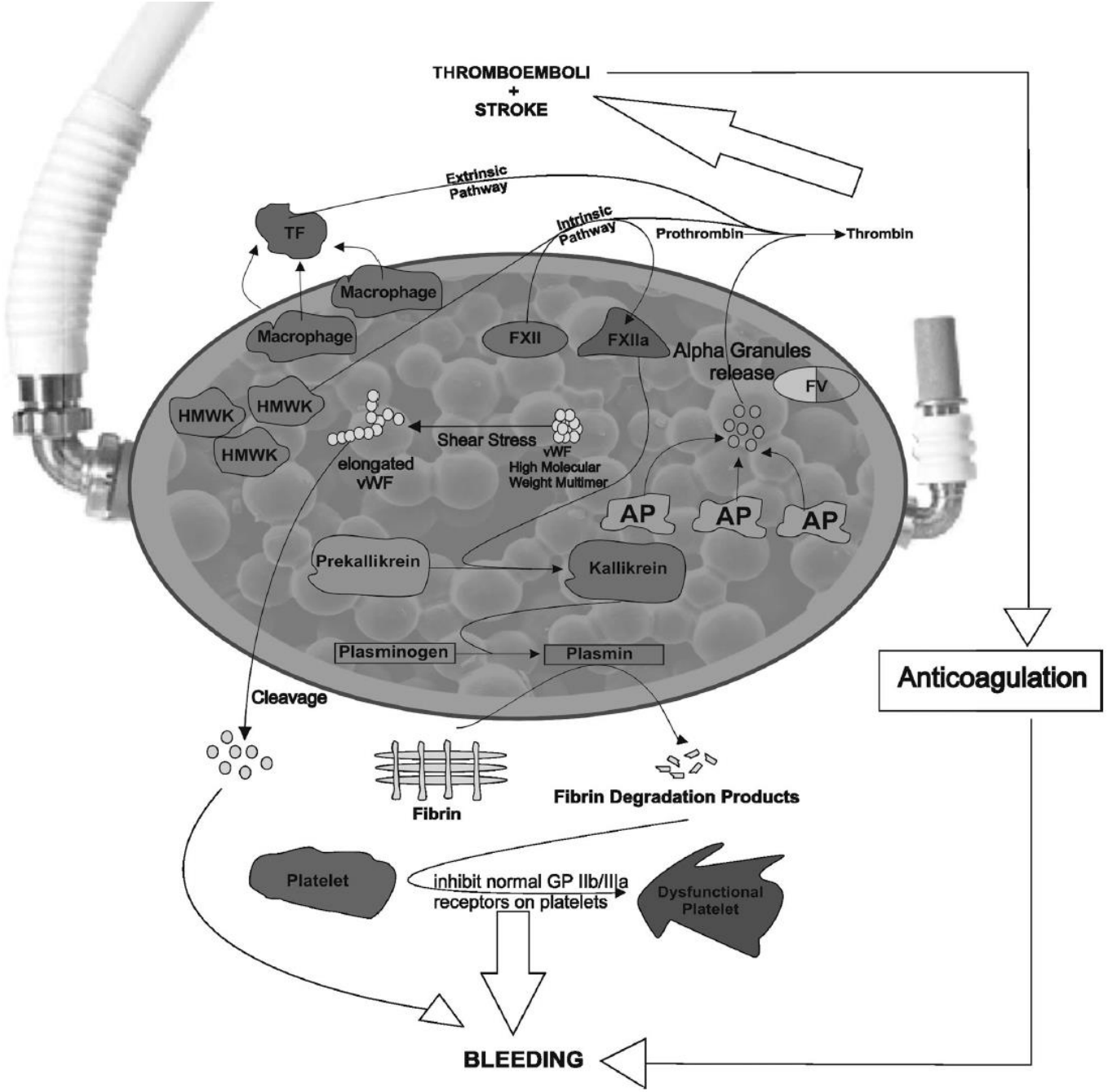
- Les complicationds neurologiques sont la principale cause de morbi-mortalité.
- 73 évènements sur 59 patients
- 89% sont des accidents ischémiques.
- 12% sont des accidents hémorragiques.
- 75% surviennet dans les 28 premiers jours (50% dans les 14 premiers jours)



Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Physiologie appliquée au VAD

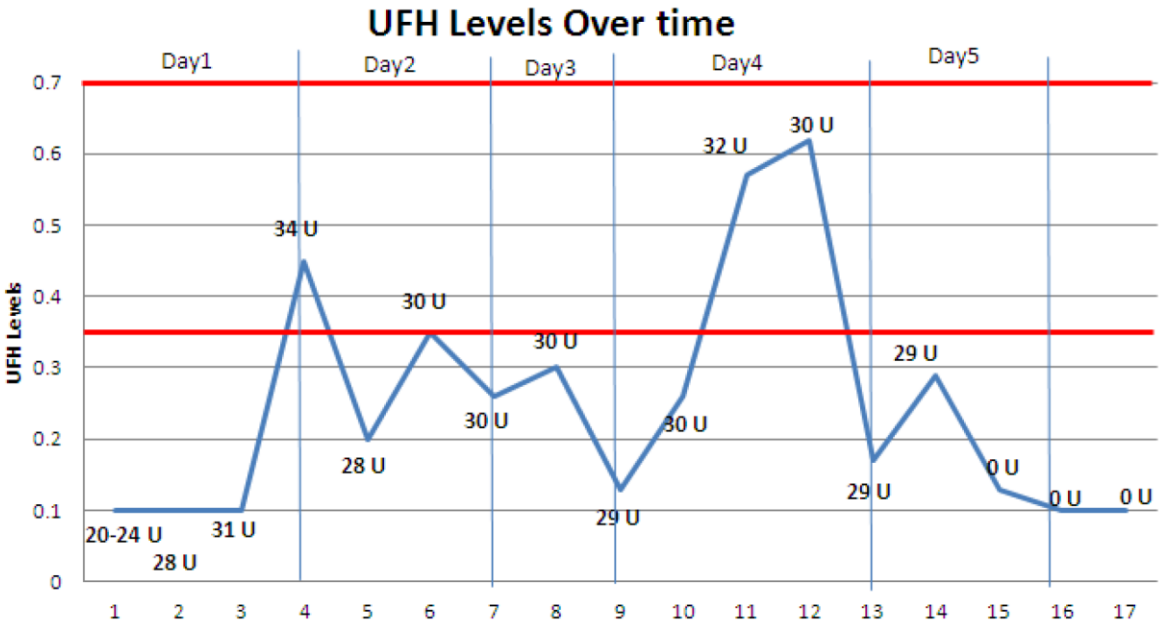
- Adsorbtion du Kininogène de HPM sur le titanium du VAD ➔ activation de la voie intrinsèque.
- Macrophages et monocytes expriment du facteur tissulaire ➔ activation de la voie extrinsèque.
- Activation plaquettaire avec libérattion de facteurV ➔ amplification des phénomènes thrombotiques.
- Activation de la fibrinolyse par le système Kallikreine.
- Les produits de dégradation de la fibrine ➔ fixation R G2b3a.
- Déficit vWf



Pourquoi avons-nous tant de difficulté à maitriser l'hémostase dans ce contexte??

Non respect du protocole d'anticoagulation?

- Atteinte retardée des objectifs d'anticoagulation.
- Patient rarement en fenêtre thérapeutique ou, en tout cas insuffisamment.
- Prélèvements contaminés par de l'héparine, ne reflétant pas le vrai statu hémostatique.



Pourquoi avons-nous tant de difficulté à maitriser l'hémostase dans ce contexte??

Le protocole est il adapté?

Center	aPTT or anti-Xa	Target range	Highest range
IDE trial	aPTT	0.35-0.5	--
Boston Children Hospital	Anti-Xa	0.35-0.5	0.5-0.7
Stanford	Anti-Xa	0.35-0.5	--
St Louis	Anti-Xa	0.35-0.5 (<3 mos) 0.35-0.7 (>3 mos)	--
Texas Children's	Anti-Xa	0.35-0.7	0.7-1
Mount Sinai, NY	Anti-Xa and aPTT	0.35-0.5 65-80	--
Edmonton, Stollery	Anti-Xa	0.35-0.5	--
Freeman, Newcastle	Anti-Xa	0.35-0.7	0.7-1
Zurich, University Children	Anti-Xa	0.35-0.7	0.8
German Heart Center	aPTT	60-80	--

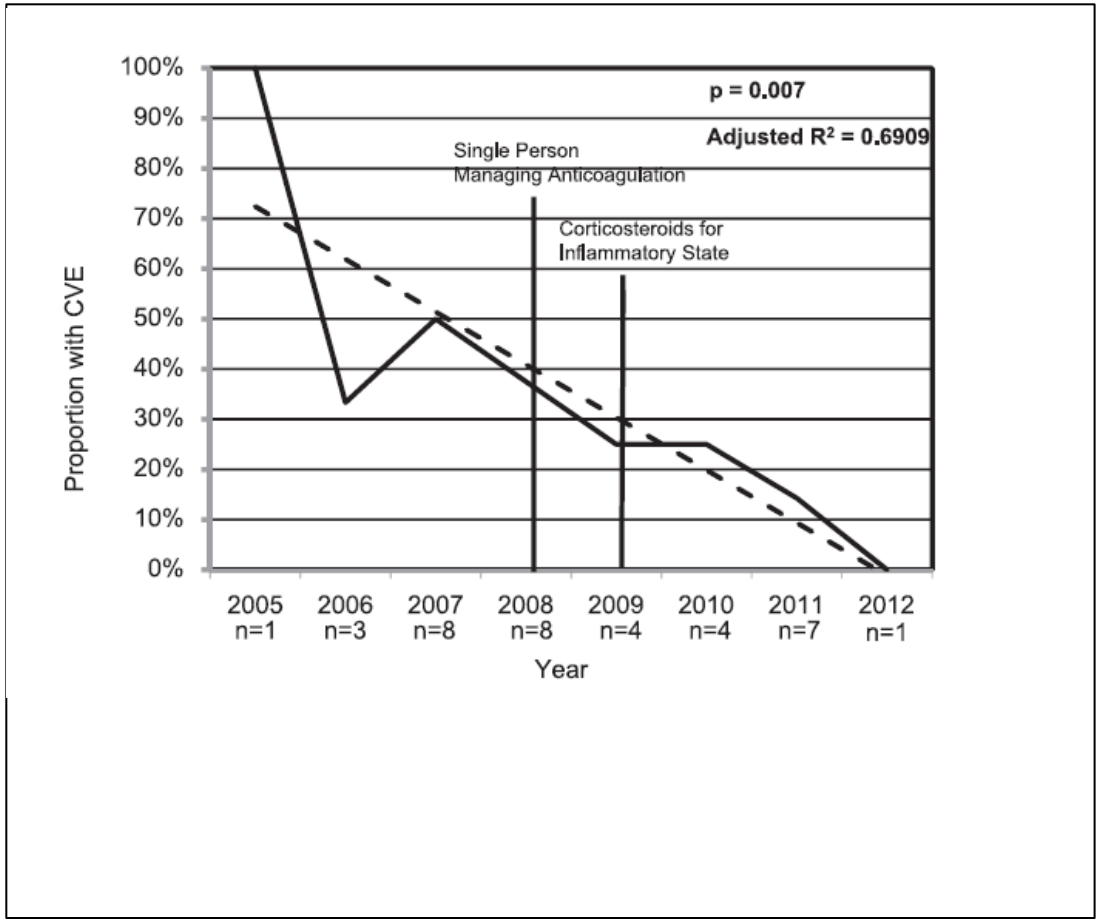
Center	Criteria for AP	1st AP Dose range	2nd AP Dose range	3rd AP
IDE trial	Plt>40 000 TEG ADP <70%	Dipyridimol 1mg/kg QID	ASA 0.5mg/kg BID	Based on TEG (Clopidogrel)
Boston Children Hospital	Same IDE	ASA 1 mg/kg BID	Dipyridamol	Based on TEG
Stanford	3-5 days Bleeding	ASA max 30mg/kg/day	Dipyridamol	Clopidogrel
St Louis	Plt >50 000 TEG AA<70	ASA 0.5 mg/kg BID (max 5 mg/kg/d)	Dipyridamol (optional)	--
Texas Children's	~3-5 days	ASA ~4 mg/kg/day	Dipyridamol	--
Mount Sinai, NY	~3-5 days	ASA 0.5 mg/kg BID (max 5 mg/kg/day)	Dipyridamole max 6g/kg/day	Based on PFA-100
Edmonton, Stollery	24-48hrs, TEG	ASA 0.5 mg/kg BID	Dipyridamole	Based on TEG
Freeman, Newcastle	>48 hrs, min bleed	IV Dipyridamol 0.5mg/kg ggt	ASA 1mg/kg BID	Based on TEG (Clopidogrel)
Zurich	Same as IDE	ASA 0.5 mg/kg BID	Dipyridamol	Based on TEG
German Heart Center	1 wk, wires out	ASA 1mg/kg/day (max 5 mg/kg/day)	Clopidogrel	--

Incremental Reduction in the Incidence of Stroke in Children Supported With the Berlin EXCOR Ventricular Assist Device

Jonathan W. Byrnes

(Ann Thorac Surg 2013;96:1727–33)

- Importance d'une équipe référente qui manage la conduite du traitement anticoagulant et antiaggrégant.
- Idéalement en lien avec le laboratoire d'hémostase.



Platelet testing to guide aspirin dose adjustment in pediatric patients after cardiac surgery

Sirisha Emani, PhD **The Journal of Thoracic and Cardiovascular Surgery • Volume 154, Number 5**

Results: Suboptimal platelet response to aspirin was detected in 64 of 430 patients (15%) and thrombosis was detected in 11 patients (2.6%). Lack of aspirin responsiveness on initial testing was a significant risk factor for thrombosis ($P < .001$) independent of age, weight, diagnosis, and initial aspirin dose. Dose escalation based on aspirin testing was performed in 40 of 64 patients, and significantly lower rate of thrombosis was observed in patients who underwent dose escalation compared with those without dose escalation (0/40 vs 9/24, $P < .001$). By multivariable analysis, the only significant independent risk factor for thrombosis was failure to increase aspirin dose after initial unresponsiveness ($P < .001$).

The Verify Now device allows automated testing of aspirin responsiveness in pediatric patients.

Merci de votre attention