Management de l'hémostase, des pertes sanguines et de la transfusion en CCP

DIU de Réanimation des Cardiopathies Congénitales

Paris, le 11 janvier 2017

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Anesthésie
Chirurgie
CEC

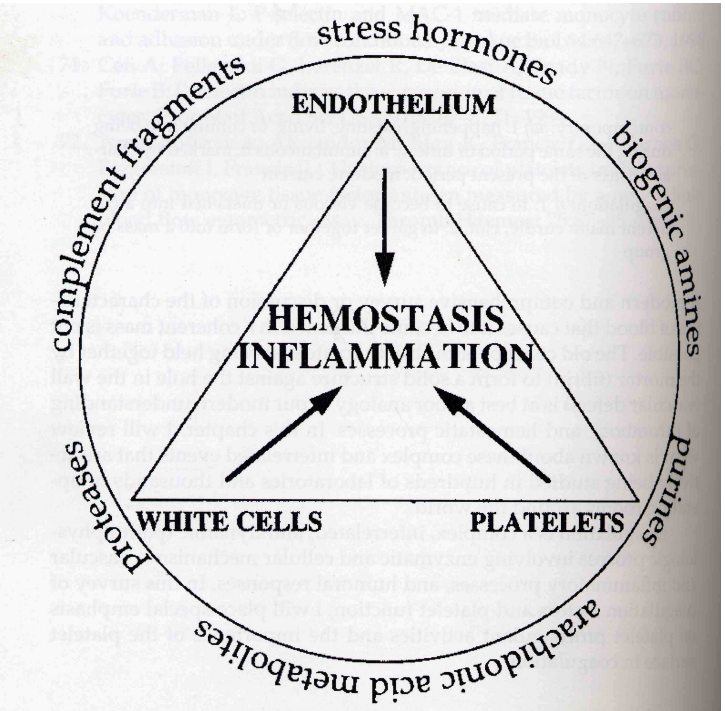


FIGURE 6–1. Interaction of various cell and humoral processes. Reprinted with permission from BD Spiess: J Cardiovasc Pharm 27:VI, 1996.

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)

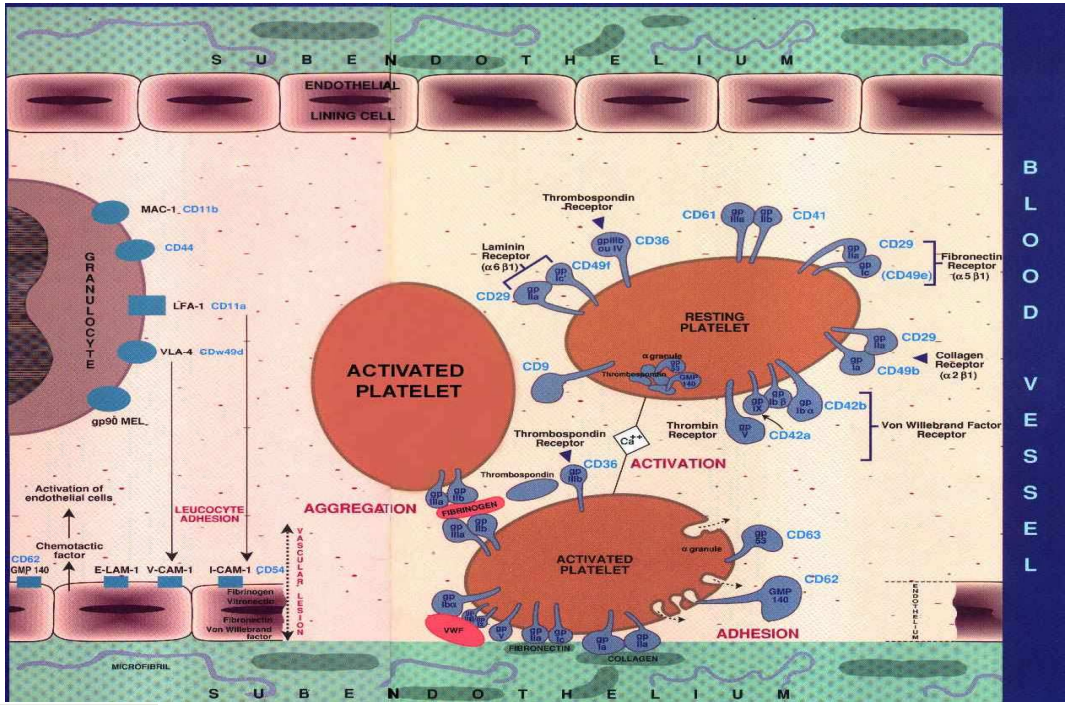
Coagulation pro inflammatoire

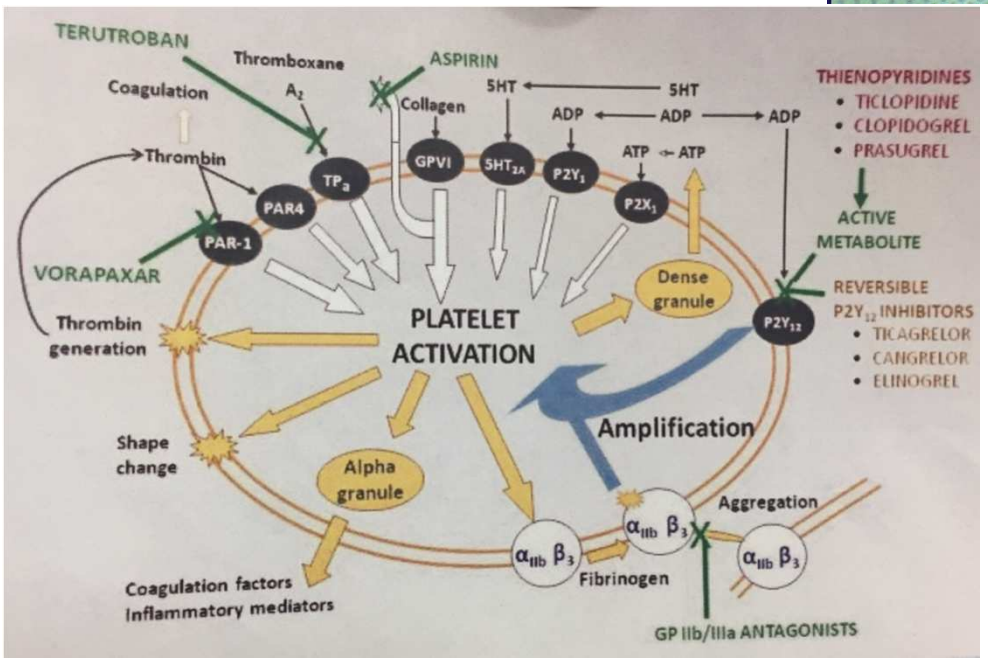
➢ Facteurs (protéases) => PAR => macrophages (ICAM)

neutrophiles (TNF, IL-1)

➢ Plaquettes activées => IL-1, ligand CD40 & F4P

Coagulation pro inflammatoire





Etat des lieux

- Hémostase-inflammation liées à l'age
- Hétérogénéité des études pédiatriques
- Données rares et contradictoires : AT
- CEC, ECMO, VAD : utilisation de matériel non biologique
- Sd hémorragiques devenus <u>très rares</u> malgré la complexité des réparations….

Données contradictoires :
AT et CEC

EDITORIAL: CONGENITAL

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

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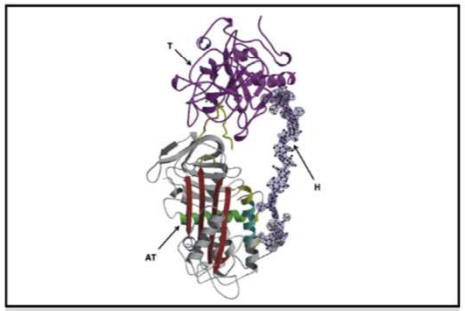
http://dx.doi.org/10.1016/j.jtcvs.2015.10.042



Thrombin-antithrombin-heparin binding.

Central Message

Lower antithrombin levels during infant bypass are associated with lower heparin efficacy and increased thrombin generation.

In 1959, Drs Arthur Keats, Denton Cooley, and Janet Telford from Texas Children's Hospital and Baylor College of Medicine published their landmark article in *The Jour-*

Données contradictoires : AT et ECMO

Antithrombin Administration in Extracorporeal Membrane Oxygenation Patients: Putting the Cart Before the Horse*

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in anticoagulation practices internationally, with a wide range of medications, monitoring tests, and institutional protocols being used (3).

In recent years, administration of antithrombin has become popular in many ECMO centers (4), predicated on the untested theory that, because many critically ill children have acquired antithrombin deficiency (and young infants have naturally lower antithrombin levels), providing more substrate for heparin to bind to will facilitate a reduction in heparin requirements and provide more effective anticoagulation (5). In most cases, this therapy involves increasing antithrombin to supraphysiologic levels. Data supporting this practice are sparse. The reduction in heparin requirements following antithrombin administration is highly variable (5–8) and studies of children on ECMO have thus far not shown any beneficial effect of antithrombin on clinical outcomes, including bleeding, blood product administration, ECMO circuit changes, length of stay, or mortality (7, 8). Furthermore, antithrombin is used to facilitate achievement of therapeutic target ranges for UFH that have never been proven

ECMO patients should pause for reflection. First, the theory that antithrombin administration helps by reducing heparin requirements was always suspect. In one study of over 600 children on ECMO, *increased* heparin dosing was independently associated with improved survival (13). Second, there was no sensible attempt to prospectively evaluate the safety or efficacy of antithrombin administration in ECMO patients before the practice became widespread, despite the medication's high cost and despite it being associated with increased bleeding in other groups of pediatric patients (11).

*See also p. 1170.

Key Words: anticoagulation; extracorporeal life support; neonatal; pediatric

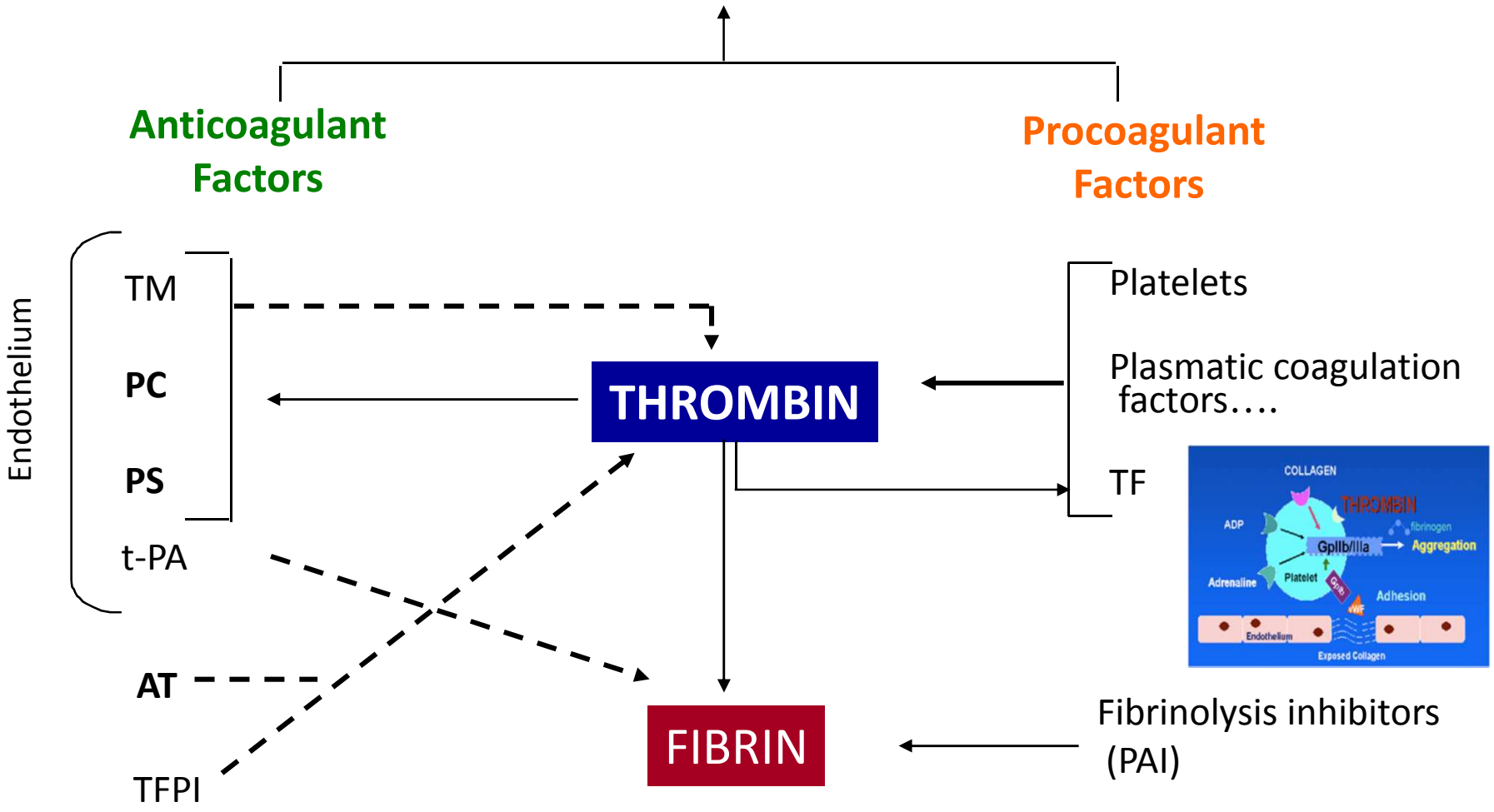
Dr. MacLaren disclosed off-label use of antithrombin. Dr. Monagle disclosed off-label use of unfractionated heparin (not approved for use in children) and antithrombin (not approved for use during ECMO in children).

DOI: 10.1097/PCC.0000000000000988

Third, exogenous antithrombin therapy is associated with a change in circulating antithrombin isoforms in children, and our knowledge of physiology would suggest that this change is significant (14). Finally, we now have a report linking anti-

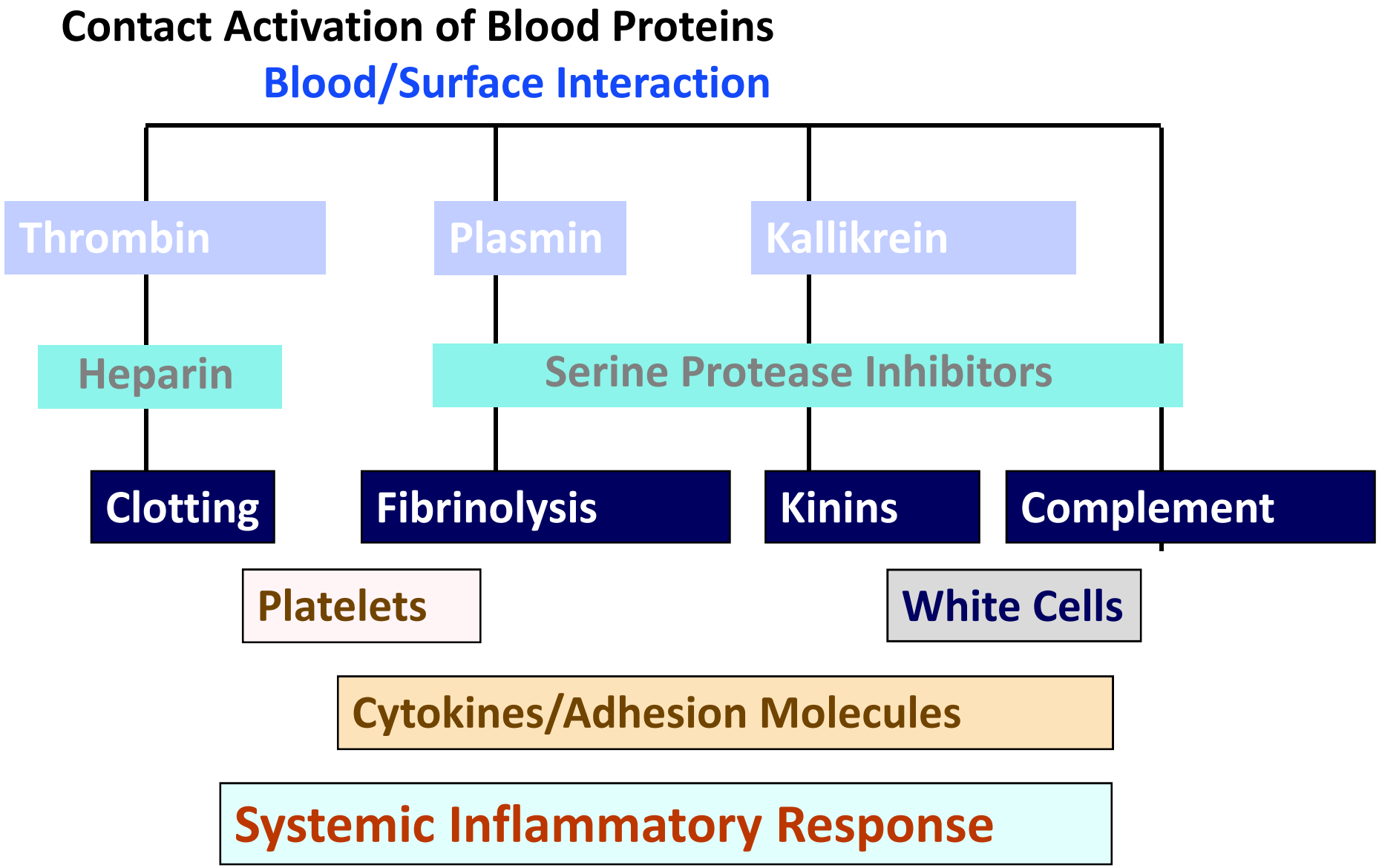
analysis of the Extracorporeal Life Support Organization Registry. *Pediatr Crit Care Med* 2015; 16:276–288
2. Werho DK, Pasquali SK, Yu S, et al; ELSO Member Centers: Epidemiology of stroke in pediatric cardiac surgical patients supported with extracorporeal membrane oxygenation. *Ann Thorac Surg*

Hemostatic Balance



CONTACT ACTIVATION AND CARDIOPULMONARY BYPASS

Contact activation and CPB



Activation

Generation of free thrombin :

- Activation Tissue Factor
- **Activation FXII**
- Activation Fibrinolysis (contact, thrombin)

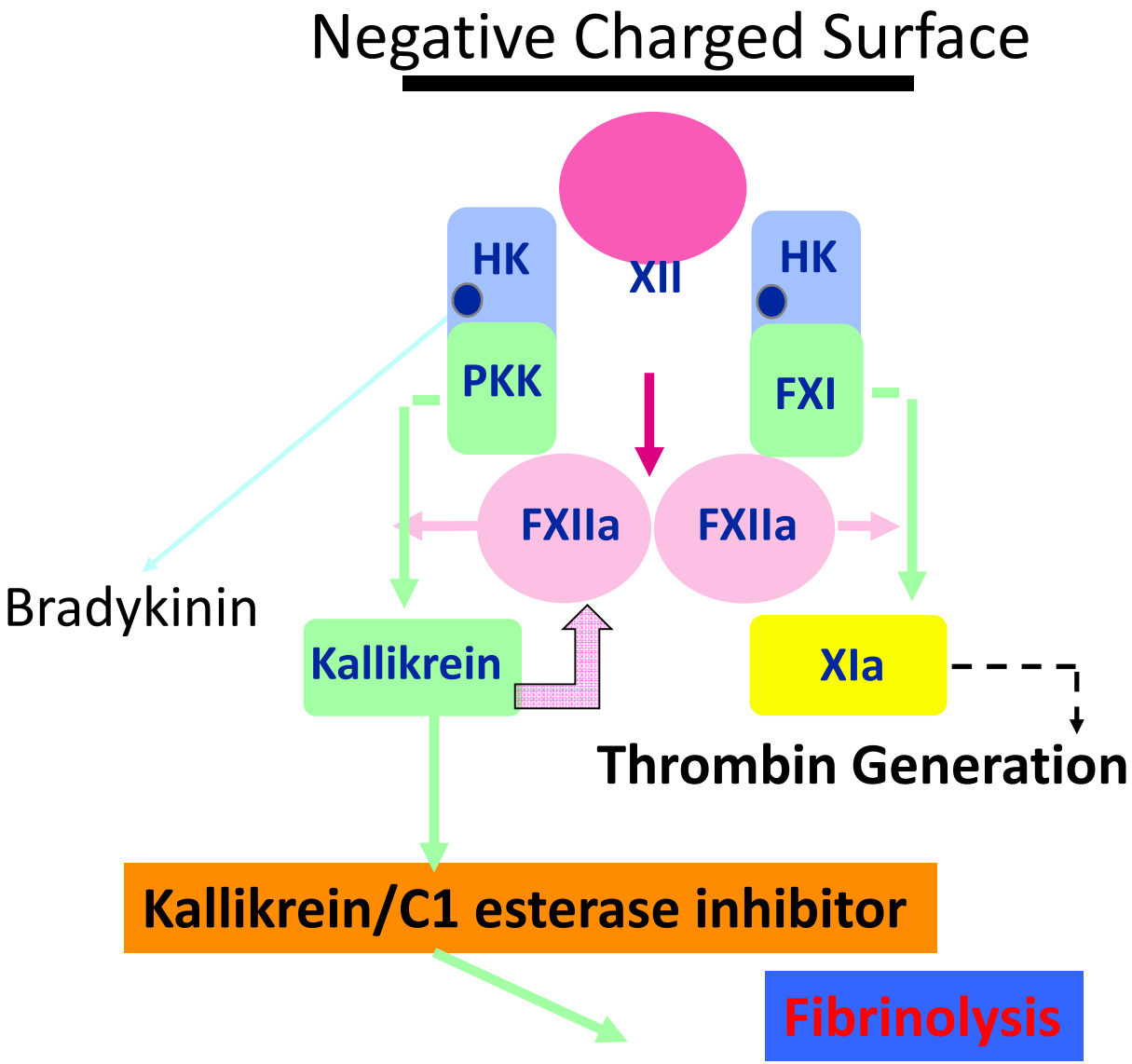
Consumption

Factors level
AT level
Platelets

Hemodilution

- decrease in circulating coagulation factors and AT levels.
- reduction of platelet count

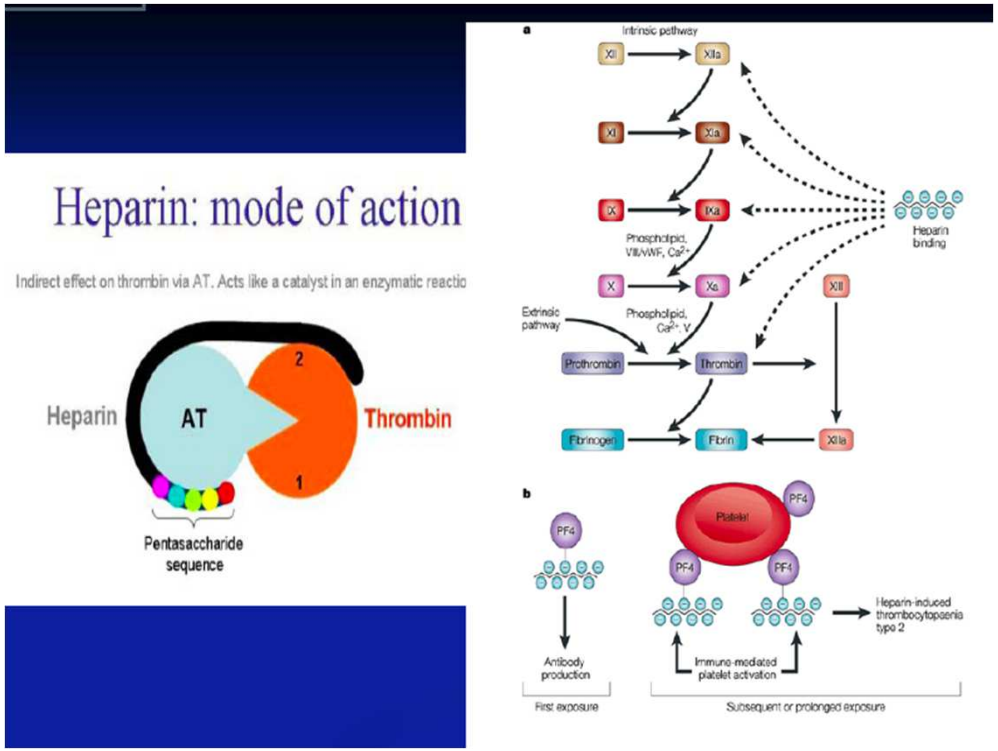
Contact activation – the role of kallikrein



Heparin

UFH: heterogenenous mix of branched GAGs

- 1/3 UFH binds to AT ⇧ anticoag 1000 x
- UFH-AT ⇨ inactivates FIIa, FXa,FIXa, FXIa,FXIIa



Neutralization Protamine 0,8 à 1 U/UI

Anti coagulation

- HNF 250-350 UI/kg

  => ACT > 400 sec

- Corrélation ACT – antiXa imparfaite et.. : anti-Xa plus spécifique, mais pb de rapidité d'exécution. Délais inadaptés à la CEC

Owings J.T.et al. *Arch Surg. 2000*

- Impossibilité utiliser antiXa pendant la CEC car niveau = 1 à 3 U/ml

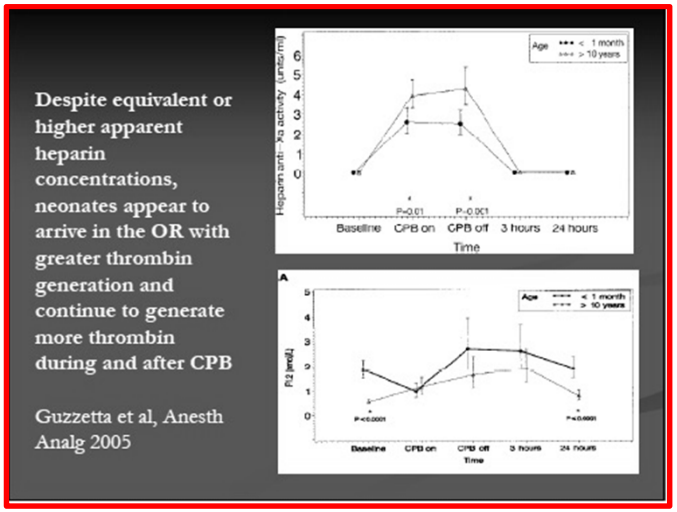
Chez les nouveaux nés et les enfants .. effet résistance

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

Kremers RM et al. Thrombosis and Haemostasis 2016

Moindre sensibilité à l'héparine ou relation dose effet moins fiable (prot fétales, > concentration F 1+2, thrombine, hémodilution, hypotermie,maturation hépatique, polyglobulie)

Owings J.T.et al. *Arch Surg. 2000*



- More inflammation
- Less AT

Guzzetta NA et al. Anesth Analg 2005

And.. shortened R on TEG in healthy newborns suggesting hypercoagulability

Edwards RM et al. Am J Clin Path 2008

"Résistance aussi pour.."

- Rôle ACT pré op +++
- Injection d' héparine oubliée
- Injection d' héparine extravasculaire
- Dose insuffisante
- Déficit en AT congénital ou acquis (HBPM et HNF pré op, consommation)
- TIH

ACT puis dosage antiXa et AT
PFC lors de CEC de longue durée.

TIH TYPE II

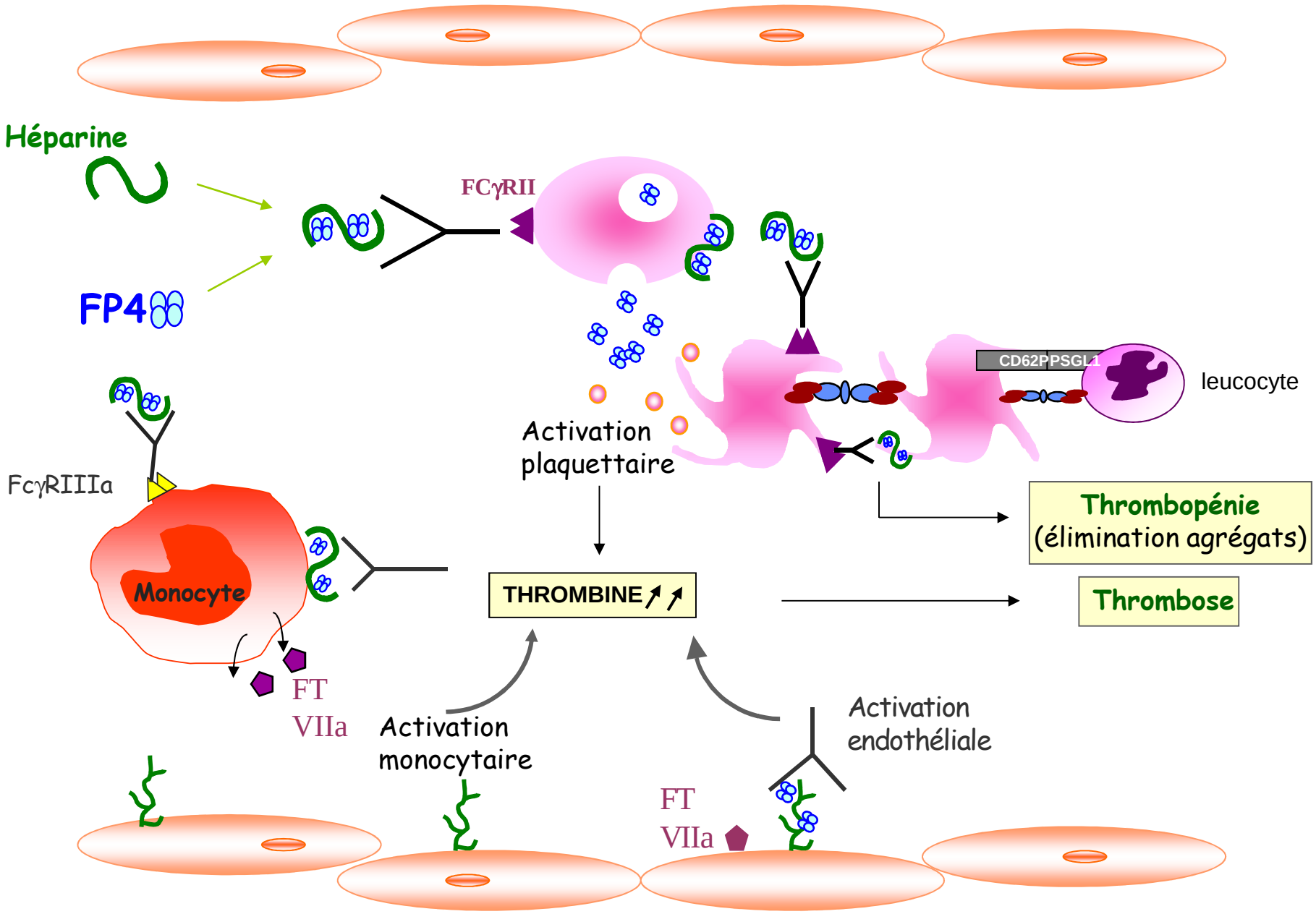
- Fall of ≥ 30- 50% in the platelet count between 5 to 10 days
- Moderate in severity (the lowest value about 50 to 60 x100 G/L)
- Antibodies (Ig-G) against complexes Heparin-PF4

In pediatrics : 1 à 2% HIT without clinical signs (thrombosis or skin lesions)

> bleeding complications in the cases reported

In post-CPB : specificity of anti H-PF4 is low, few DATA in pediatric cardiac surgery

Greinacher A et al. Progress in Ped Cardiology 2005
Boning A et al. Ann Thorac Surg 2005
Mullen MP et al. Anesthesia Analg 2008

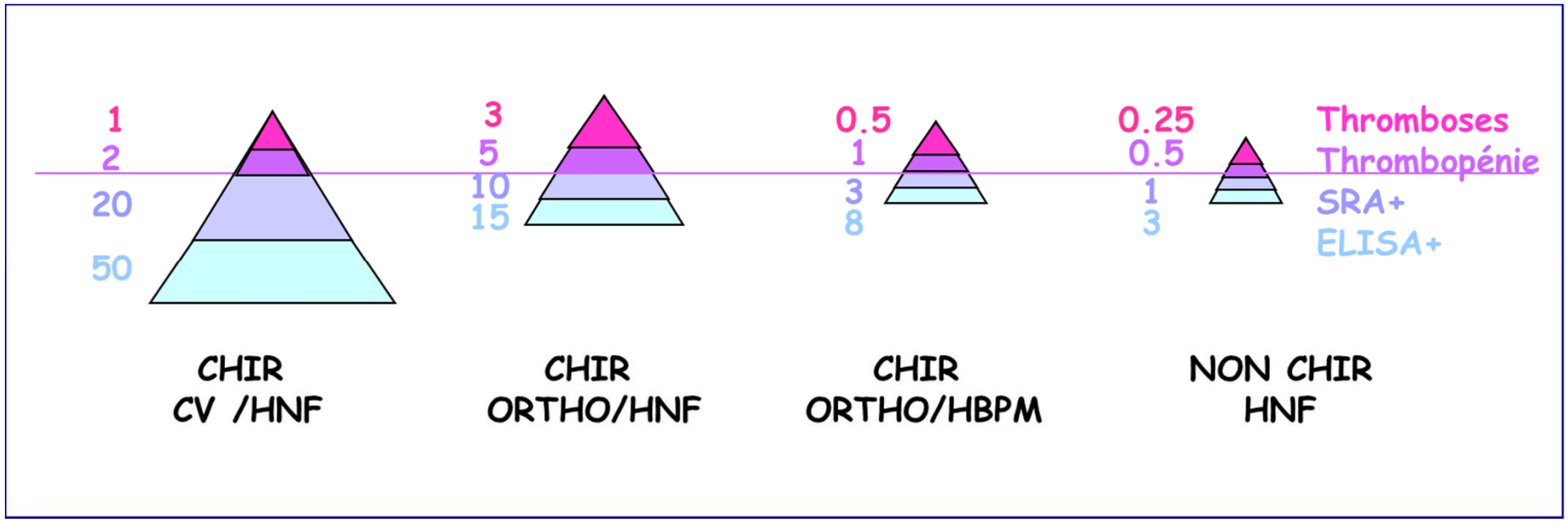


Dominique Lasne

- Type d'héparine : HNF >>> HBPM

- Traitements curatifs > préventifs

- Contexte clinique (incidence 0,5 à 5%) : chirurgical > médical



Etudes adultes

Warkentin T et al. Blood 2000

Pré requis pour une hémostase correcte

- **Hémostase chirurgicale rigoureuse**
- **Température normale**
- pH 7,40
- Calcémie** > 1,30
- Neutralisation de l'héparine correcte
- Facteurs de l'hémostase en quantité suffisante
- Importance de l'hématocrite

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

Facteurs corrélés à la thrombose

Survenue thrombose possible malgré la fibrinolyse, la trombopénie et l'activation du tPA pour:

- **Consommation et activation pendant la CEC (AT, plaquettes…)**
- Plus :

Reconcentration

SD inflammatoire

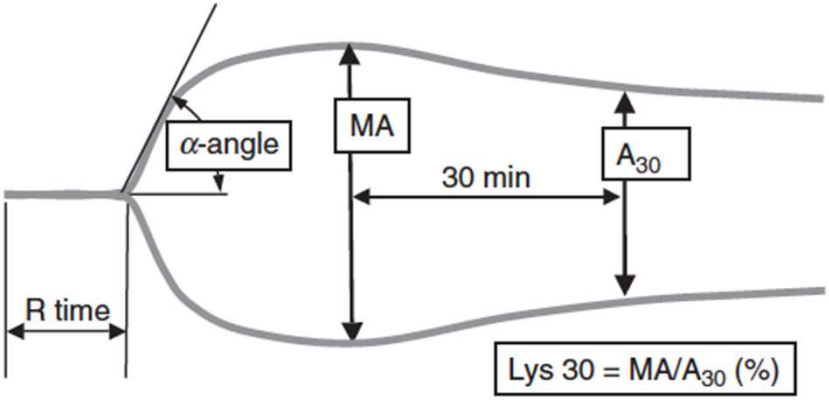
KTC

Bas debit, hypoxie

Risques génétiques : F V Leiden, mutation G20210 du gène de la prothrombine

Type d'intervention : ASP, DCPP& **DCPT**

Existe-t-il des examens prédictifs du saignement ?



Integration of monitoring into clinical care: ability of TEG to follow changes in coagulation

-Rapid diagnostic information about clotting abnormalities
-Inadequate reversal of heparin
-Reduced transfusion prevalence

Pediatric Anesthesia
Pediatric Anesthesia ISSN 1155-5645

REVIEW ARTICLE

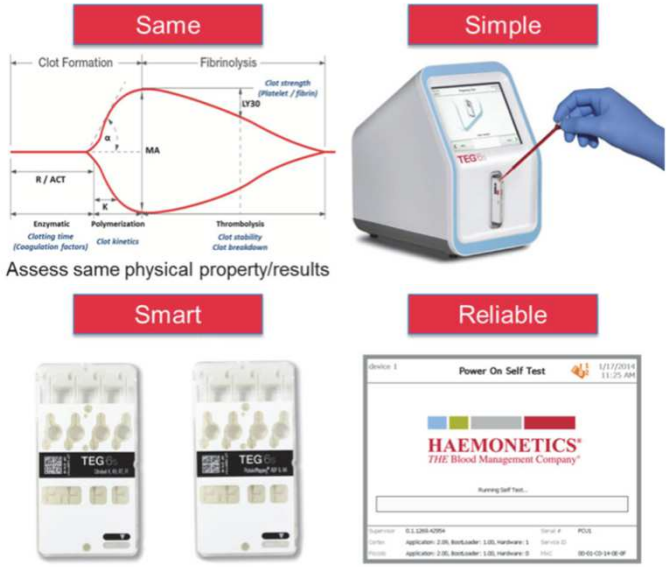
Treatment and monitoring of coagulation abnormalities in children undergoing heart surgery

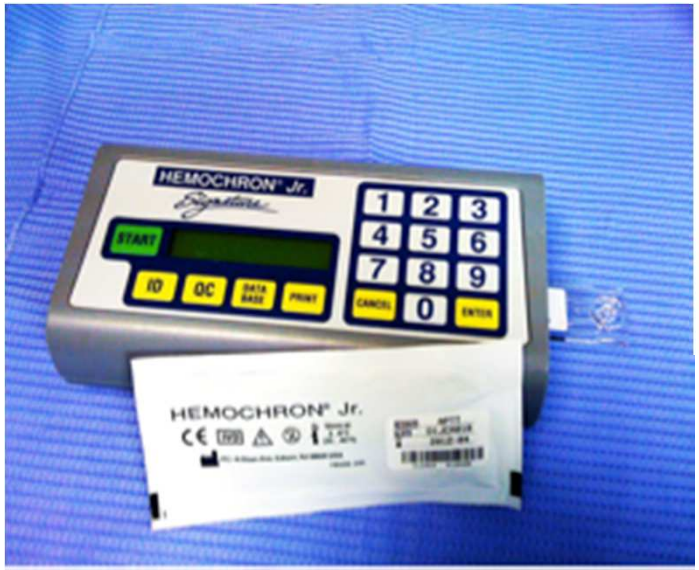
Philip Arnold

Romlin BS, Anesth Analg 2011

Coagulation assessment, multimodal monitoring

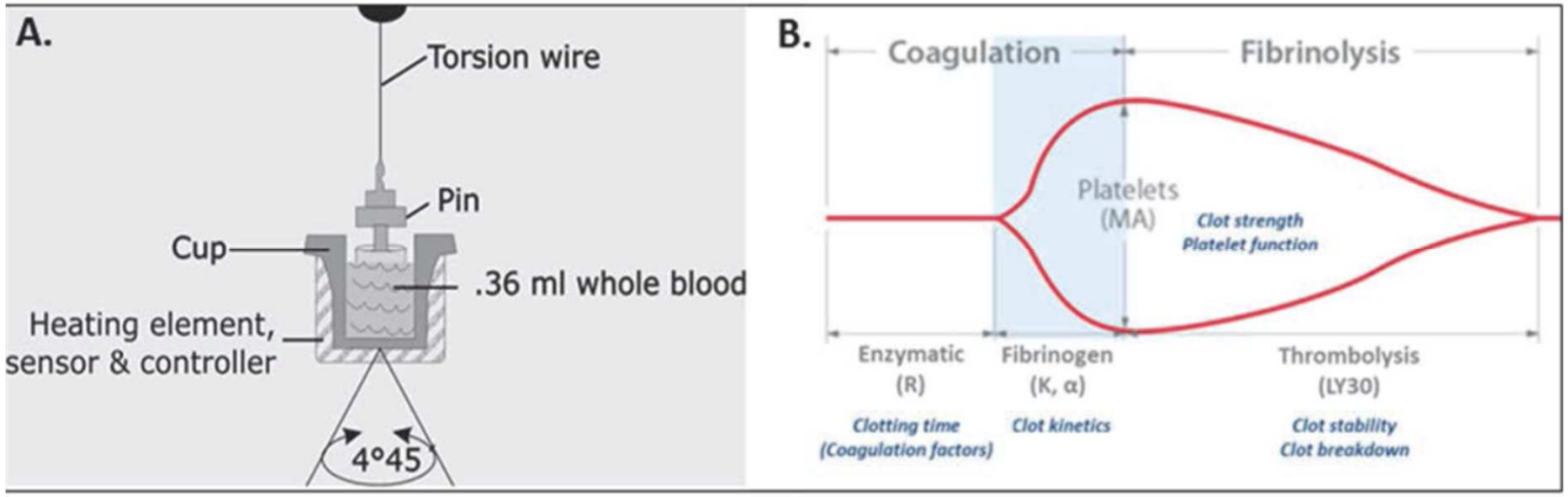
NEW..

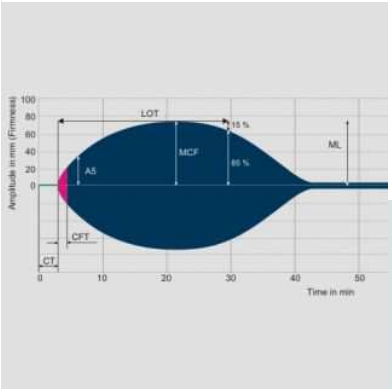




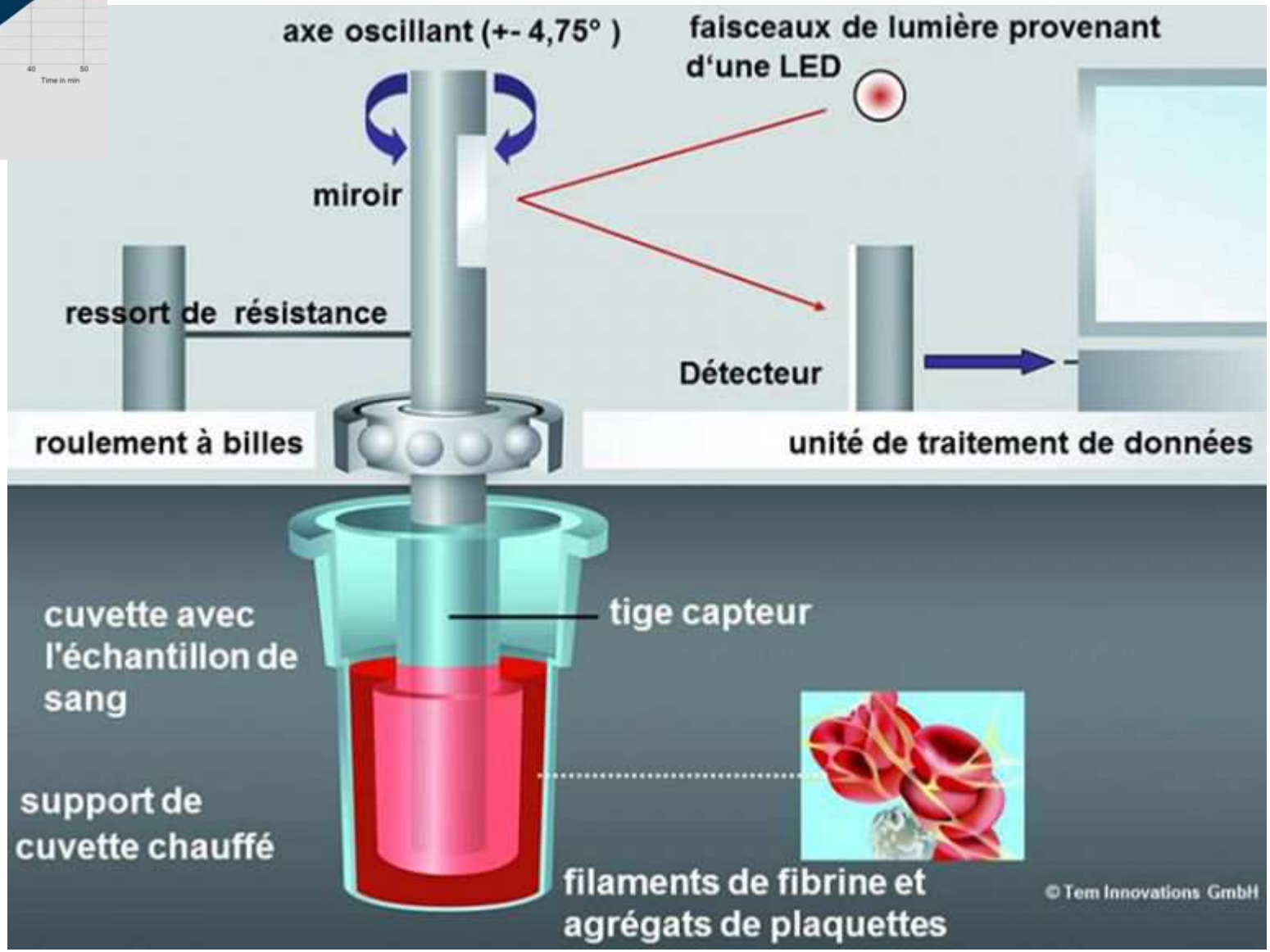
Niveau de fibrinogéne et plaquettes sur citrate pendant la CEC

TEG 5000
Haemonetics®



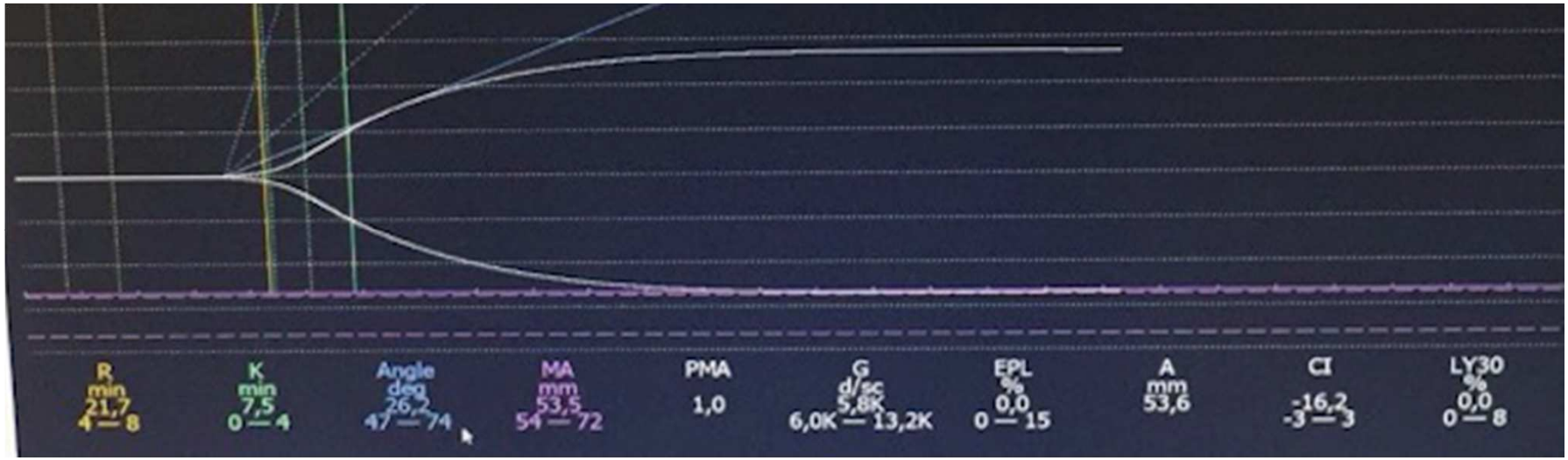

LOT
MCF
A5
CFT
CT
ML
Time in min

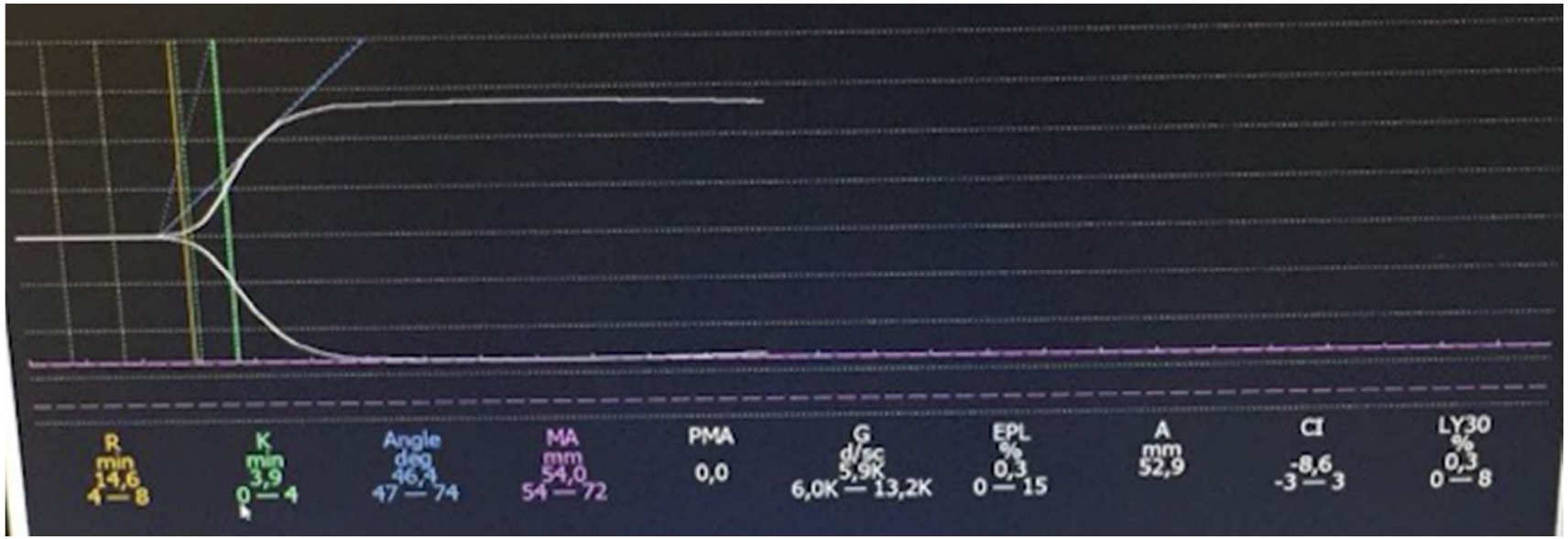
ROTEM®


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

TEG 6 S
Haemonetics®

TEG KAOLIN

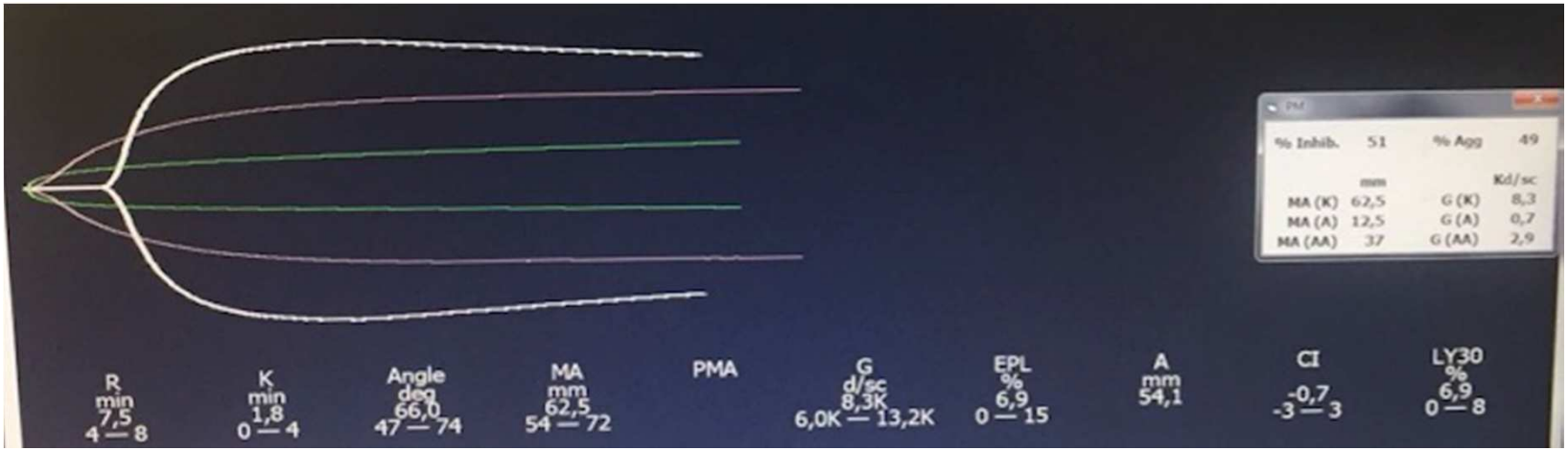




TEG KH

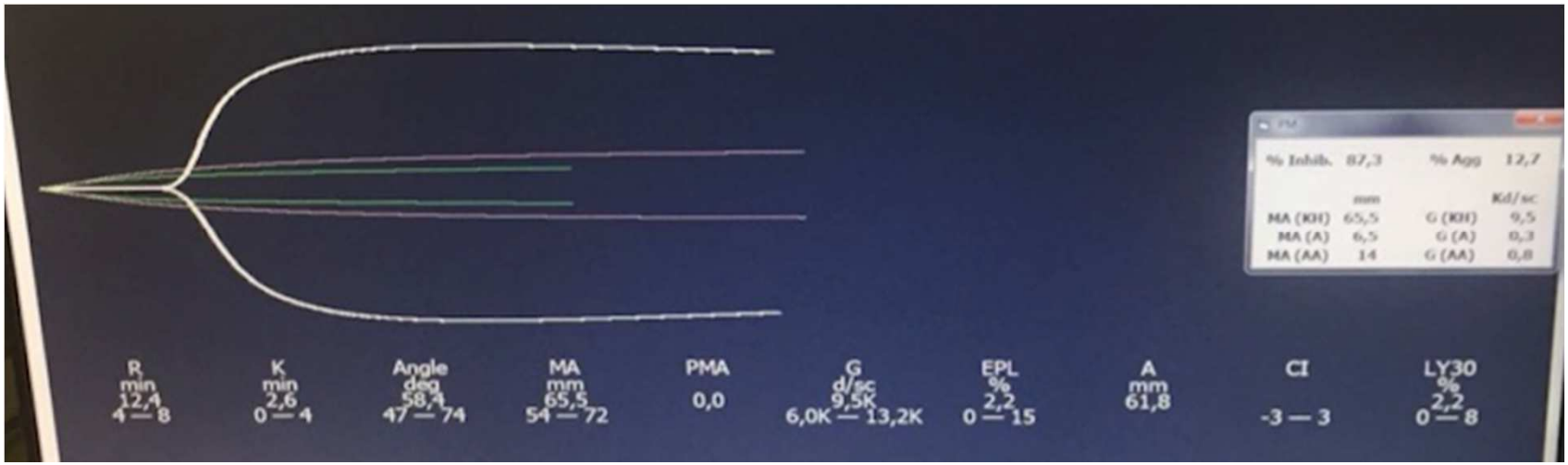
% inhib AA

Aspirine 2 mg/Kg



% inhib AA

Aspirine 3 mg/Kg



TEG 6 S
Test pour calcule % inhib ADP

Trouver l'équilibre pour :

- Eviter de favoriser l'hémorragie post CEC, assurer un monitoring rigoureux per CEC
    - Activation: HNF + CEC
    - Dilution: Priming CEC+ Monitoring Hb
    - Consommation: Monitoring HNF+ CEC
- Eviter la thrombose per et post opératoire

Contrôle de l' hémostase ± inadapté

=> transfusion

Pourquoi éviter la transfusion?

- Réaction allergique
- Transmission virale
- Transmission bactérienne
- Incompatibilité ABO
- Immunisation
- TRALI
- Stimulation pro inflammatoire : bradykinine et IL

Pourquoi faut il transfuser ?

- Incapacité de compenser une réduction du transport d' O_2 par une aug de débit

- Myocarde travail à la performance max sans réserve
- Myocarde nné plus sensible au < transport d' O_2

=> Nécessité d'Hb entre 14 et 20 g/dl à la naissance

Actions pour normaliser l'hémostase et diminuer le saignement et la transfusion :

- Préopératoires: consultation d'anesthésie ± hémostase
- Per opératoires :
  - Pour diminuer l'hémodilution:
  - Pour diminuer les pertes sanguines
- Post opératoires

Pouard P TATM 2005

Predictive Factors for Red Blood Cell Transfusion in Children Undergoing Noncomplex Cardiac Surgery

Muj Mulaj, MD, David Faraoni, MD, FCCP, Ariane Willems, MD, MS, Cristel Sanchez Torres, MD, and Philippe Van der Linden, MD, PhD

Department of Anesthesiology, Centre Hospitalier Universitaire Brugmann and Queen Fabiola Children's University Hospital, and Pediatric Intensive Care Unit, Queen Fabiola Children's University Hospital, Brussels, Belgium

Background. Red blood cell (RBC) transfusion is frequently required in pediatric cardiac surgery and is associated with altered outcome and increased costs. Determining which factors predict transfusion in this context will enable clinicians to adopt strategies that will reduce the risk of RBC transfusion. This study aimed to assess predictive factors associated with RBC transfusion in children undergoing low-risk cardiac surgery with cardiopulmonary bypass (CPB).

Methods. Children undergoing surgery to repair ventricular septal defect or atrioventricular septal defect from 2006 to 2011 were included in this retrospective study. Demography, preoperative laboratory testing, intraoperative data, and RBC transfusion were reviewed. Univariate and multivariate logistic regression analysis were used to define factors that were able to predict RBC transfusion. Then, we employed receiver operating characteristic analysis to design a predictive score.

Results. Among the 334 children included, 261 (78%) were transfused. Age (< 18 months), priming volume of the CPB (> 43 mL/kg), type of oxygenator used, minimal temperature reached during CPB (< 32°C), and preoperative hematocrit (< 34%) were independently associated with RBC transfusion in the studied population. A predictive score 2 or greater was the best predictor of RBC transfusion.

Conclusions. The present study identified several factors that were significantly associated with perioperative RBC transfusion. Based on these factors, we designed a predictive score that can be used to develop a patient-based blood management program with the aim of reducing the incidence of RBC transfusion.

(Ann Thorac Surg 2014;98:662–7)

and process-related factors that can interfere between each other [4]. In a recent study of more than 2,000 consecutive children undergoing cardiac surgery with CPB, Richmond and colleagues [8] observed that CPB prime volume, preoperative hemoglobin value, minimal temperature during CPB, and operative risk (defined by the RACHS) were independently associated with RBC transfusion. These results demonstrated that the complexity of the congenital repair according to the RACHS must be taken into account when assessing predictors of blood transfusion in the global pediatric cardiac surgery population. Our study focused on children undergoing VSD or AVSD repair surgery, 2 procedures with relatively low risk of severe intraoperative complications, which in turn reduces the risk of increased RBC transfusion due to procedure-related factors. However, our population was considered at high risk for perioperative RBC transfusion because of

Actions pré opératoires

- **Consultation**

  Anesthésie => Recherche d'ATCD de saignements et des anomalies de l'hémostase

  Hémostase => identifie les anomalies de l'hémostase + conseils et Tt

- **Erythropoiétine : 100 à 150 units s.c. 3x/sem pdt 3 semaine or une dose de rEPO avant la chirurgie.**

  Ootaki Y et al. Heart Surg Forum 2007

  Few cases report, the effectiveness for avoiding transfusion is not clear

- **Auto Transfusion Différée : > 20kg, 10 à 40 ml/kg, fonction cardiopathie**

  Not really an usual practice for current pediatric cardiac surgery

Actions per opératoires pour diminuer l' hémodilution

- **Rétro priming au sang autologue** :
  - >10kg, pour les cardiopathies sans risque d'instabilité hémodynamique

- Canulations caves correctes

- **Rétrocession immédiate du sang médiastinal**

Rôle du priming

- Pas de solutions cristalloïdes: meta-analysis of controlled trials

Russell JA et al. Cardiothorac Vasc Anesth. 2004

- Albumine/sang pour les patients de poids < 15 Kg
- Utilisation de sang possiblement frais

keidan I et al. JTCVS 2004

Schroederer TH et al.Perfusion 2005

- Utilisation de sang reconstitué (globules rouges +PFC):

Réa plus courte

Moins d'oedèmes

Mou SS et al. N Engl J Med 2004

Hématocrite pré CEC et volume du priming et l'hémodilution au démarrage de la CEC

Hte en CEC = volémie patient*Hte patient / Volémie pt + priming

Pour un Nné de 3kg:

		hématocrite pré CEC (%)		
		44	40	35
Volume priming (ml)	400	18	17	15
	300	22	20	17,5
	200	26	24	21
	150	29	26	23
	100	33	30	26

Hte en CEC

Soit en volume de culot globulaire :

RBCs (ml)= (BV pt+ TPrV) (Hct desired)- (BVpt) (Hct pt)

Albumine vs PFC

1.

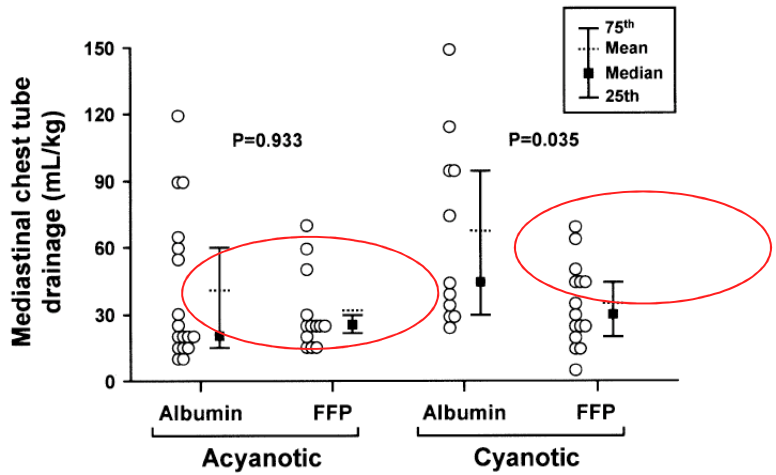


Fig 2. Mediastinal chest tube drainage (mL/kg) during the initial 24 hours in the intensive care unit according to prime type (albumin 5% versus fresh-frozen plasma [FFP]) for patients who are either acyanotic or cyanotic.

PFC in the prime results in less blood loss than albumin 5% in cyanotic pts and for complex operations ...

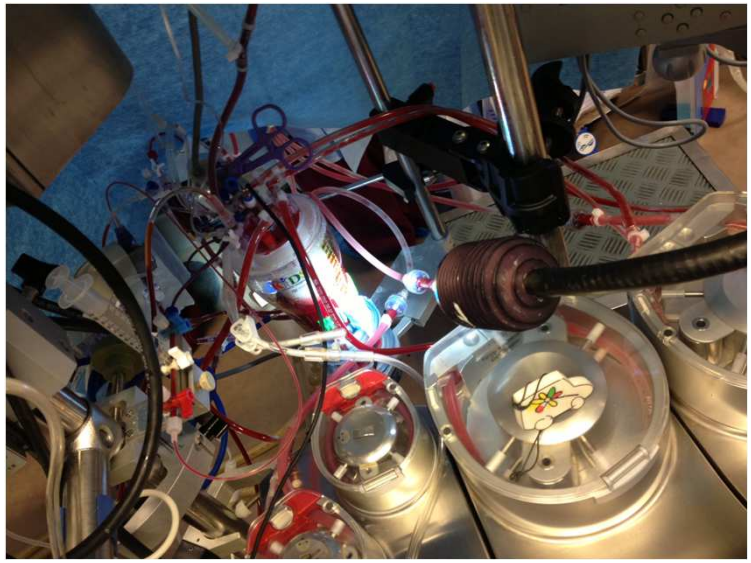
Oliver WC et al. Ann Thorac Surg 2003

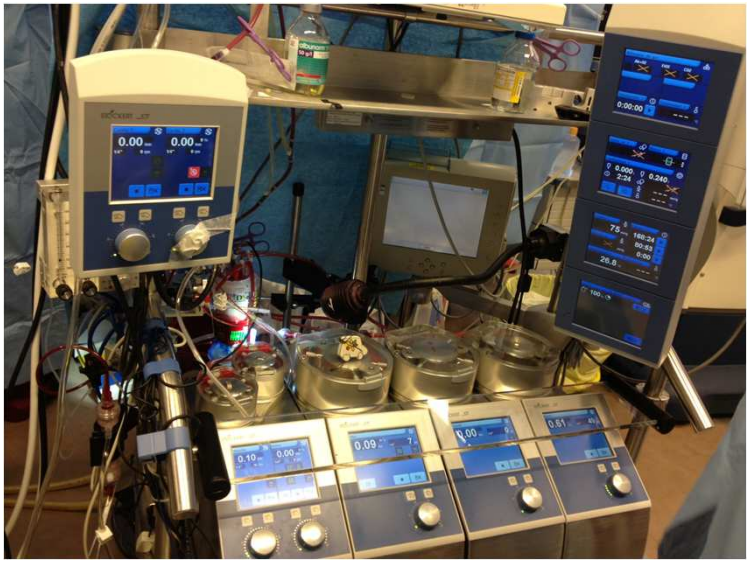
2. Prophylactic use of FFP in the priming solution does not have obvious clinical benefits in cyanotic congenital heart disease (CCHD)

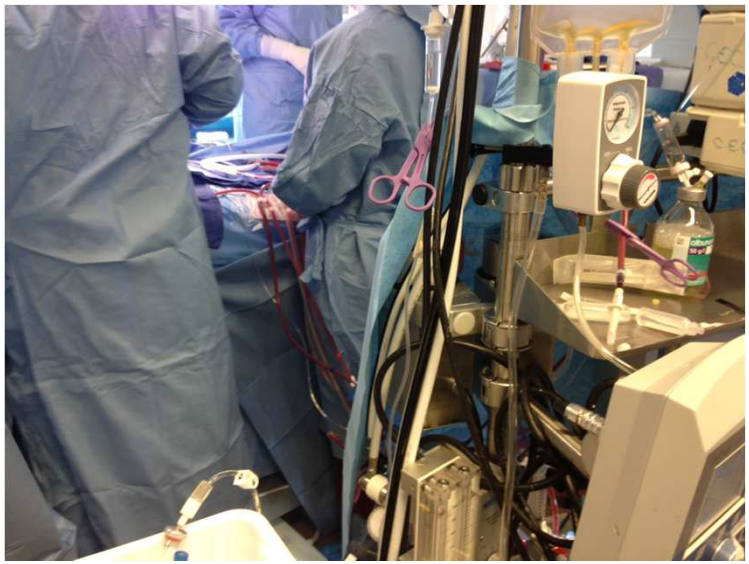
Miao X et al. Eur J Pediatr 2014

Actions per opératoires non pharmacologique pour diminuer les pertes sanguines

- Ultrafiltration conventionnelle ou modifiée
- Récupérateur laveurs d' hématies
- Modificateurs de surfaces
    - Héparine
    - Poly méthyl pentène
    - Poly(2-methoxyethylacrylate) PMEA
    - Phosphorylcholine.







Ultrafiltration

Deux effets
- Hémoconcentration
- Anti inflammatoire

A prospective randomized study:
Conventional vs modified UF:
No statistical differences when standardized volume of fluid is removed

Thompson LD et al. JTCVS 2001

Meta-analysis: même paramètres en terme de outcome

Kuratani N et al. JTCVS 2011

Objectifs peropératoires

- Chirurgie = **bonne hémostase chirurgicale**

- Hb > 12 g/dl, culot globulaire 10-20 ml/Kg
- Fibrinogène > 1g (dose 25-50 mg/Kg en pédiatrie)
- PFC 10-20 ml/Kg ou confidex 1-2 ml/Kg
- Rebound héparine = protamine dose a refaire (modulation par l'anti-Xa)
- Plaquettes > 50 000 (1 U/10 Kg si transfusion nécessaire)

Anti fibrinolytiques pour le redux

protocole a Necker: 20 mg/Kg après l'induction, 20 mg/Kg per CEC

Données de la littérature hétérogène en pédiatrie

RECEMENT:

•Concentrations plasmatiques efficaces plus faibles (20-30 µg/ml) avec doses plus faibles **(in vivo)**

Grassin-Delyle S et al. Anesthesiology 2013

•Comparaison **in vitro** avec la population volontaire adulte: concentration plasmatique efficace plus basses pour les enfants avec cardiopathies congénitales entre 1 et 10 ans (8.6 µg/ml vs 11.3 µg/ml)

Rozen L et al.EJA 2015

•Comparaison **in vitro** nouveau-né- la population volontaire adulte: concentration plasmatique efficace plus basses pour les nouveaux- nés

Yee BE et al. Anesth Analg 2013

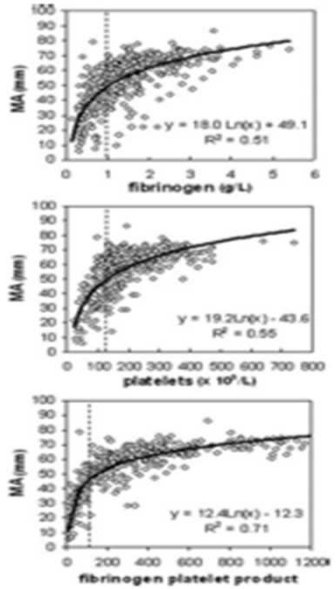
Fibrinogen replacement

The Relationship Among Thromboelastography, Hemostatic Variables, and Bleeding After Cardiopulmonary Bypass Surgery in Children

Shyamala Moganasundram, FRCA,* Beverley J. Hunt, MD,† Kim Sykes, MRCP,*
Fiona Holton, MRCPCH,* Kiran Parmar, MSc,† Andrew Durward, FCP,* Ian A. Murdoch, MRCP,*
Conal Austin, MRCS,‡ David Anderson, FRCS,‡ and Shane M. Tibby, MRCP*

Anesth Analg 2010

Rapid decrease in MA when fibrinogen concentration < 1 g/L, platelet value < 120 x 10*9/L , platelet – fibrinogen product < 100



Protrombin complex concentrate

Dose utilisée = 1-2 ml/Kg IVL

Confidex for infants undergoing cardiac surgery is safe and effective. It reduces postoperative bleeding and allows fewer units of packed red blood cells to be infused in the postoperative phase without major side effects

Giorni C et al. Pediatr Cardiol 2013

Ex vivo: 3F-PCC exerts potent procoagulant activity compared withr FVIIa : importance in restoring thrombin generation

Guzzetta NA et al. Br J Anaesth 2014

CME

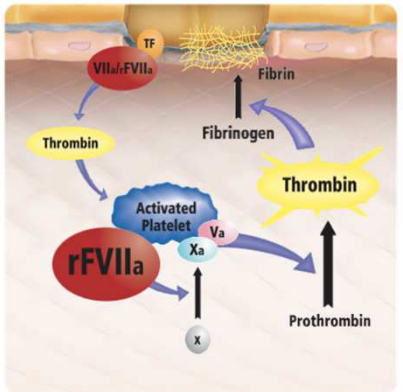
Review of the Off-Label Use of Recombinant Activated Factor VII in Pediatric Cardiac Surgery Patients

Nina A. Guzzetta, MD, FAAP,* Isobel A. Russell, MD, PhD, FACC,† and Glyn D. Williams, MBChB, FFA†

There are insufficient data to make evidence-based recommendations. Randomized controlled trials are needed to assess the efficacy of rFVIIa as prophylactic, routine, or rescue therapy and **to determine the drug's safety profile particularly with regard to thrombosis.**

Anesth Analg 2012

NovoSeven® Mode of Action
Eptacog alfa (activated)



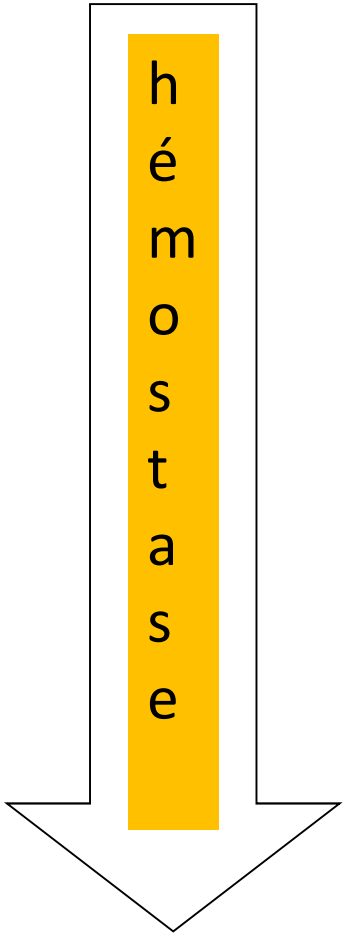
Tissue factor (TF)/FVIIa, or TF/rFVIIa interaction, is necessary to initiatiate haemostasis

At pharmacological concentrations rFVIIa directly activates FX on the surface of locally activated platelets.
This activation will initiate the "thrombin burst" independently of FVIII and FIX.
This step is independent of TF.

The thrombin burst leads to the formation of a stable clot

Take home message

- Miniaturized circuit
- Coated circuits
- Perfect surgical set up
- Multimodal monitoring
  - APPC administration, Fibrinogen replacement on hemostatic variables or thromboelastography results
- Pay attention to recombinant activated Fact VII administration



Grazie…