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Primary hyperfibrinolysis as a cause of bleeding: myth or reality?

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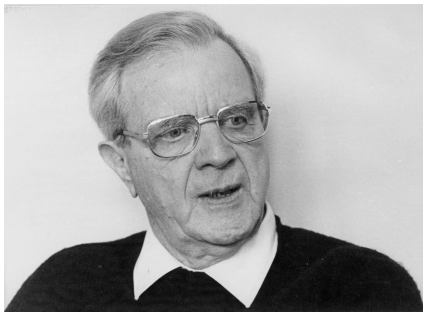


Tage Astrup, 1908-2006

A Pioneer the study of Fibrinolysis

"… it is amazing to see how early some important, fundamental concepts were developed by capable investigators on the basis of incomplete experiments, that remained forgotten being out of the trends of the time…"

(T. Astrup, 1991)

Fundamental concepts introduced by Astrup (years 1950 to 1995)

- **Existence and function of a tissue bound activator of fibrinolysis (the tissue Plasminogen Activator, t-PA) with inequal distribution in different tissues and organs**
- **Existence of a "Haemostatic Balance" between pro-coagulant and pro-fibrinolytic mechanisms, including respective activators and inhibitors, and interconnected in tissues/organs and circulating blood**

Astrup T. Nature 1952, Lancet 1956

The tissue contribution
Content in plasminogen tissue activator (t-PA) in different organs and tissues
(the Astrup-Albrechtsen map)

Organ or tissue	t-PA in units/g fresh tissue
Uterus	720
Prostate	334
Thyroid	325
Urinary tracts	280
Lung	223
Brain (except meninges)	35
Spleen	20
Liver	0

From Albrechtsen OK. Acta Physiol Scand, 1959

Thrombus (fibrin) based fibrinolysis

- **Fibrin surface of thrombus is the main activation site for Plasminogen (PLG) activation to plasmin (PLM)**
- **Fibrin bound tPA is massively activated on the fibrin surface and acquires much higher catalytic efficiency (x 500-fold) than in blood**
- **PAI I is also adsorbed to thrombus, and may impair fibrinolysis activation. Alfa 2 antiplasmin has low affinity for fibrin, and acts mainly in circulating blood.**

Urano et al, JTH 2018; Chapin JC et al, Blood Rev, 2015

Cell surface based fibrinolysis

- **Vascular Endothelial Cells (VECs) but also leukocytes (traps), monocytes, platelets, cancer cells, produce, bind and potentiate Plasminogen (PLG) and tPA.**
- **Urinary epithelial cells produce uPA**
- **Blast cells of Acute Promyelocytic leukemia (APC) produce high Annexin 2 complexed with protein S100-A10, is act as a potent profibrinolytic agent.**
- **Fibrinolysis inhibitors also active on cell surfaces. PAI1 can detach tPA from cell surface thus inhibiting cell based fibrinolysis. Similarly: TAFI (on platelets) and F XIII dependent inhibitor.**

Urano et al, JTH 2018; Chapin JC et al, Blood Rev, 2015

Microparticles and Fibrinolysis

- Microparticles (MPs) are sub-microscopic vesicles springing off from membranes of cells after various types of activation, or apoptosis
- As vectors of a multitude of substances, they may also show pro-coagulant and/or profibrinolytic activity
- In fact they may contain uPA/tPA and may harbour plasmin thus protecting it from circulating α2 anti-plasmin
- Role of MPs is especially important if they originate from cancer cells

Vallier L. , and H.C. Kwaan. Sem Thromb Hemostasis 2016

Coagulation vs fibrinolysis a coordinated self-regulated complex system

- Thrombin, complexed with thrombomodulin, looses pro-coagulant activities and produces anticoagulant (Protein C) and antifibrinolytic properties (TAFI)
- Activated protein C impairs the activity of PAI I
- Plasmin can inactivate Factors Va and VIIIa independently of the similar effects of protein C
- Plasmin can also affect platelet receptors for Fg and FVIII (glycoproteins IIb – IIIa), thus modulating platelet function

Chapin JC et al, Blood Rev, 2015; Kolev K et al, BJH 2016

Bleeding due to primary or secondary hyperfibrinolysis

- **"Primary Hyperfibrinolysis" should indicate an inherited or acquired haemorrhagic state entirely due to strong activation of fibrinolytic mechanisms, without previous or concomitant clinical and laboratory signs of massive activation of coagulation and/or consumption coagulopathy**
- **"Secondary Hyperfibrinolysis" should indicate an inherited or acquired haemorrhagic state in which fibrinolytic activation is associated with clinical and laboratory signs of massive activation of coagulation (DIC)**

But, in consequence of the said interconnections:

- **Massive activation of blood coagulation is not the unique mechanisms for triggering fibrinolysis**
- **The distinction between primary and secondary hyperfibrinolysis remains therefore rather weak in mechanistic terms, although useful in clinical practice**

Example I

Bleeding due to Primary Hyperfibrinolysis

INHERITED

- **α2-plasmin inhibitor deficiency, rare: autosomal recessive transmission.**
  - **Exists as quantitative or only qualitative variant**
  - **Slightly potentiated by adhesion to fibrin**
  - **Clinics: severe hematomas only in homozygotes; heterozygotes need bleeding cofactors or are asymptomatic**
- **PAI I deficiency: rare, even homozygotes have only moderate and concausual bleeding**
- **Quebec Platelet Syndrome: rare, autosomal platelet disorder due to Urokinase Plasminogen Activator (u-PA) bound to platelets: delayed, concausal, moderate bleeding**

Blavignac J et al, Sem Thr Hemost 2011; Franchini M, Mannucci PM, 2018

Example II

Liver cirrhosis: secondary acquired hyperfibrinolysis

- **Severe Liver cirrhosis (50% of cases):**

Activation of blood coagulation (elevated fibrin monomer and FPA). Consumption coagulopathy and related bleeding is described (with secondary fibrinolysis). The fibrinolytic system is also activated (decreased production of TAFI, PAI I and α2 APL (re-adjustement of the haemostatic balance).

However, prevalent hyperactivation of fibrinolysis with massive bleeding can also occur especially in end-stage cirrhosis.

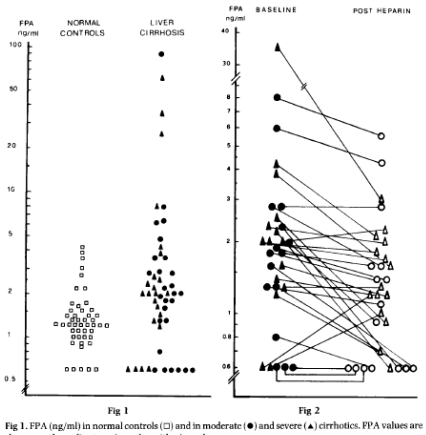


Fig 1

Fig 2

Fig 1. FPA (ng/ml) in normal controls (□) and in moderate (●) and severe (▲) cirrhotics. FPA values are shown on the ordinate, using a logarithmic scale.

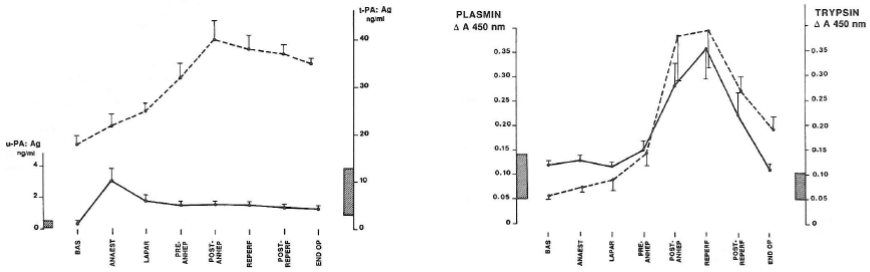
Fig 2. FPA (ng/ml) in cirrhotics (moderate cirrhotics, circles; severe cirrhotics, triangles) before and after heparin administration (see text). FPA values are shown on the ordinate, using a logarithmic scale.

Values of FPA in patients with liver cirrhosis of different degree.
A considerable number (but not all) patients have high FPA values (Fig. 1), reduced by a single heparin dose (fig.2).
Values of fibrinogen/fibrin soluble complexes were also high.

Coccheri S, Mannucci PM et al., Brit J Hematol, 1982

Example III

Liver transplantation and primary hyperfibrinolysis



Left curves: “explosive” increase in t-PA antigen with peak at the anhepatic phase, maintained at reperfusion phases. Weak response of u-PA

Right curves: massive increase in plasmin, but also trypsin and other proteolytic enzymes peaking at reperfusion phases.

Legnani C, Palareti G, Coccheri S et al, Transplantation 1993

Example IV

Acquired condition with primary fibrinolysis

Acute bleeding in severe trauma

- **Early bleeding complications cause 50% of trauma deaths** (*Gall SS. Sem Thromb Haemost 2017*)
- **Trauma induced coagulopathy (TIC) has been tentatively explained in different ways:**
  - **Primary hyperfibrinolysis attributed to Protein C inactivation of PAI I,** (*White NJ, 2013*)
  - **However, a large systematic review recently denied any role of Protein C in hyperfibrinolysis of trauma** (*Gando S, Thrombosis Jour 2018*)
- **The largest study on TIC with Tranexamic Acid showed reduction in mortality only if given before 3 hours** (*Shakur H et al The CRASH2 study, Lancet 2010 and 2011. Gayet Ageon A et al, Lancet 2018*)

Bleeding in Acute Promielocytic Leukemia (APL)

- **A unique hemostatic dysfunction** (*Kwaan HC, Semin Thr Haemost 2014*)
- **Fusion of gene for APL and the retinoic acid receptor gene (RARA). The fusion protein is the responsible oncogenic agent** (*Breen KA et al, Br J Hematol 2012*)
- **This agent expresses the S100 protein that potentiates annexin2, a promoter of t-PA activation** (*O'Connel PA et al, Blood 2011*)
- **The result is strong primary activation of cellular fibrinolysis with severe bleeding and high mortality**
- **Treatment with trans-retinoic acid induces benefits and reduces death. Association with antifibrinolytics is discussed** (*Wassenaar T et al, Hematol Oncol 2008. Brown JE, Br J Hematol 2000*)

Abnormal uterine bleeding (AUB)

- **Any utero-vaginal bleeding exceeding in amount, rythm, frequency the normal cyclic bleeding, and significantly affecting quality of life.**
- **AUB is multifactorial: hormonal causes, many gynecological conditions, coagulation defects (platelets, von Willebrandt), etc.**
- **A considerable number of cases of AUB remain undiagnosed**
- **Tissue hyperfibrinolysis (local) should be considered and investigated.**

Cheong Y et al. Br Med Bull 2017

Possible role of hyperfibrinolysis in AUB (acquired, primary or secondary)

- **Heavy menstrual bleeding coupled with fibrinolytic hyperactivation, or unrestrained angio-proliferation (***Lockwood CJ, Menopause 2011***)**
- **Thus, estrogenic activity and t-PA increase induce abnormal bleeding (***Ying Cheong, Brit Med Bull 2017***)**
- **In baseline conditions, women in "high estrogen status" show much lower PAI 1 activity in blood (increased fibrinolytic potential) than those in "low estrogen status"(***Gebara OG et al, Framingham Offspring Study, Circulation 1995***)**
- **In women with AUB, good results are obtained with Tranexamic Acid** *(Leminen H et al, Int J Women Health 2012***)**

Gonadal hormones and fibrinolysis

- **EARLY OBSERVATIONS: the incoagulability of menstrual blood (MB) is known from early times. Formation of a "fibrinolysin" in MB was postulated (*HB Whitehouse, Lancet 1914*)**
- **The endometrium contains vast amounts of t-PA exceeding that in other tissues (*Albrechtsen OK, 1956*)**

CURRENT KNOWLEDGE:

- **Formation of endometrial t-PA is under the control of VEGF and other Endothelial Growth Factors, thus coupling cell proliferation with massive t-PA production.**
- **Increased t-PA enters the bloodstream first by spiral arteries. Later at estrogenic fall, necrosis of endothelial cells massively pours t-PA into the blood *(Smith SK, Repr Update, 1998)***

Severe post-partum hemorrhage

Primary hyperfibrinolysis?

- **A leading cause of maternal mortality (*Hibbs SP et al, Br J Hematol 2018*)**
- **Hyperfibrinolysis probably triggered by massive t-PA production and PAI 1 inhibition through activation of protein C. (*Ducloy-Bouthors AL. Br J Anaesth 2016*)**
- **In a large study (20,000 cases of bleeding), early administrated Tranexamic Acid reduced bleeding by ~ 20% (*WOMAN trial, Lancet 2017*)**

Bleeding due to hyperfibrinolysis

Other conditions

- **Prostate surgery, esp for cancer**
- **Other cancer surgery**
- **Amiloidosis (u-PA increase)**
- **Cardiopulmonary by pass**

Hyperfibrinolysis as a cause of bleeding: myth or reality?

- **"Or something in between?"** *(Walsh M et al, 2017)*
- **Hyperfibrinolysis certainly exists "per se" as a distinct clinical cause of bleeding**
- **Regarding acquired conditions, primary or secondary hyperfibrinolysis may occur**
- **Activation mechanisms different from DIC (APL, trauma, potentiation by fibrin) have been proposed but are still under discussion**
- **The role of distribution and control of t-PA and PAI 1 in different tissues needs further research**
- **The distinction "Primary vs Secondary" Hyperfibrinolysis is therefore not a mechanistic but rather a clinical classification**

Bleeding due to hyperfibrinolysis

Proposed classification

Primary Hyperfibrinolysis

- *Inherited conditions*: deficiency in inhibitors: α2 PI, PAI 1, Quebec platelet disease
- *Acquired conditions*: acute promyelocytic leukemia, severe hepatic resection, orthotopic liver transplantation, severe trauma*, abnormal uterine bleeding*

Secondary Hyperfibrinolysis

- *Inherited conditions*: Hemophilia, Factor XIII deficiency, Disfibrinogenemia
- *Acquired conditions*: severe liver cirrhosis, post- partum hemorrhage*, abnormal uterine bleeding*, prostate surgery for cancer, other cancers, cardiopulmonary by-pass*, sepsis, amyloidosis (u-PA)

* Could belong to primary or secondary to DIC