New Trends in Diagnosis and Management of Acquired Coagulation Factor Disorders

Essay

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List of Abbreviation

A2-AP	Alpha-2-antiplasmin
ab2GPI	Anti-b2 glycoprotein-i antibodies
ACCP	American college of chest physicians
aCL	Anticardiolipin antibodies
ACTION	Antiphospholipid syndrome alliance for clinical trials and international networking
ADAMTS 13	A disintegrin and metalloprotease with thrombospondin 1 motif, member 13
ADP	Adenosine diphosphate
AHA	Acquired hemophilia a
APACHE	Acute physiology and chronic evaluation
APCC	Activated prothrombin complex concentrate
aPL	Antiphospholipid antibodies
APS	Antiphospholipid syndrome
APTT	Activated partial thromboplastin time
AT	Antithrombin
ATP	Adenosine triphosphate
AVWS	Acquired von willebrand syndrome
BT	Bleeding time
BU	Bethesda units
cAMP	Cyclic adenosine monophosphate
CBC	Complete blood cell count
CDC	Center for disease control and prevention
CLD	Chronic liver disease
CML	Chronic myeloid leukemia
COX-1	Cyclooxygenase-1
CR	Complete remission
CTLA	Cytotoxic t-lymphocyte antigen
CVADs	Central venous access devices

DDAVP	**1-deamino-8-d-arginine-vasopressin**
DIC	**Disseminated intravascular coagulation**
DVT	**Deep vein thrombosis**
EACH2	**European acquired hemophilia registry**
EBV	**Epstein–barr virus**
ECs	**Endothelial cells**
ELISA	**Enzyme-linked immunosorbent assay**
ELT	**Euglobulin clot lysis time**
EPI	**Epinephrine**
ER	**Endoplasmic reticulum**
ET	**Essential thrombocythemia**
FDA	**Food and drug administration**
FDPs	**Fibrinogen degradation products**
FFP	**Fresh frozen plasma**
FSAP	**Factor vii-activating protein**
GGCX	**Gamma glutamyl carboxylase gene**
HA	**Hemophilia a**
HB	**Hemophilia b**
HES	**Hydroxyethyl starch**
HLA	**Human leucocyte antigen**
HMWM	**High molecular weight multimers**
ICH	**Intracranial hemorrhage**
Igs	**Immunoglobulins**
IL-1	**Interleukin-1**
INR	**International normalization ratio**
ISI	**International sensitivity index**
IST	**Immunosuppressive treatment**
ISTH	**International society on thrombosis and haemostasis**
IT	**Immunotherapy**
IVIG	**Intravenous immunoglobulin**

LA	**Lupus anticoagulants**
LAHS	**Lupus anticoagulant hypoprothrombinemia syndrome**
LMAN1	**Lectin mannose binding protein gene**
LMWHs	**Low molecular weight heparins**
LVAD	**Left ventricular assist devices**
MCFD2	**Multiple coagulation factor deficiency 2 gene**
MGUS	**Monoclonal gammopathy of undetermined significance**
MI	**Myocardial infarction**
MIBS	**Malmö inhibitor brother pair study**
MPD	**Myeloproliferative disorders**
MPN	**Myeloproliferative neoplasia**
NOACs	**New oral anticoagulants**
NSAID	**Non steroidal anti-inflammatory drugs**
PAI-1	**Plasminogen activator inhibitor**
PCC	**Prothrombin complex concentrates**
pdFVIII	**Plasma-derived fviii**
PFA-100	**Platelet function analyzer**
PRP	**Platelet-rich plasma**
PT	**Prothrombin time**
PV	**Polycythemia vera**
rFVIIa	**Recombinant activated factor vii**
RICD	**Rare inherited coagulation disorders**
RIPA	**Ristocetin-induced platelet aggregation**
RR	**Relative risk**
rt-PA	**Recombinant human tissue plasminogen activator**
SLE	**Systematic lupus erythematosus**
SSRIs	**Serotonin reuptake inhibitors**
TAFI	**Thrombin activatable fibrinolytic inhibitor**
TEG	**Thromboelastogram**
TF	**Tissue factor**

TFPI	**Tissue factor pathway inhibitor**
TNF	**Tumour necrosis factor**
tPA	**Tissue plasminogen activator**
TT	**Thrombin time**
TXA2	**Thromboxane a2**
UFH	**Unfractionated heparin**
UKHCDO	**United kingdom hemophilia centre director organization**
uPA	**Urokinase plasminogen activator**
VKORC	**Vitamin k epoxide reductase complex**
VWD	**Von willebrand disease**
VWF	**Von willebrand factor**
VWF:RCo	**Von willebrand ristocetin cofactor assay**
WBC	**White blood cell**

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Haemostasis and blood coagulation

Haemostasis (from the Greek: aima, blood + stasis, halting) is the termination of bleeding. It requires the rapid interaction of a number of closely regulated processes to produce a localized clot at the site of vessel injury. Two millennia ago, the Greek philosopher Plato already described that the blood forms fibers once it leaves the heat of the body. He was also the first one to coin the term fibrin, which nowadays refers to a key blood clotting protein composing those fiber structures. Interestingly, Plato’s view on blood clotting, which was shared by other early philosophers, such as Aristotle and Galen, remained the leading concept until the end of the 18th century. In the course of the 19th century, groundbreaking discoveries were made on the biological mechanism of coagulation. Around 1865, platelets were discovered as well as their critical function in hemostasis. **(Versteeg et al., 2013).**

It was proposed that a hypothetical protein termed “thrombin” could induce the formation of fibrin. The majority of the key players in coagulation were discovered during the course of the 20th century. In 1905, Morawitz constructed the first coagulation model in which thromboplastin, now known as (TF), was released by damaged vessels to convert prothrombin into thrombin in the presence of calcium. Thrombin then convert fibrinogen into fibrin resulting in the formation of a blood clot. However, this four-clotting factor model could not fully explain the complex process of coagulation. Around the 1950s, many of the remaining factors had been characterized, such as (VWF) and factors V, VII, VIII, IX, and XI. **(Riddle et al., 2007).**

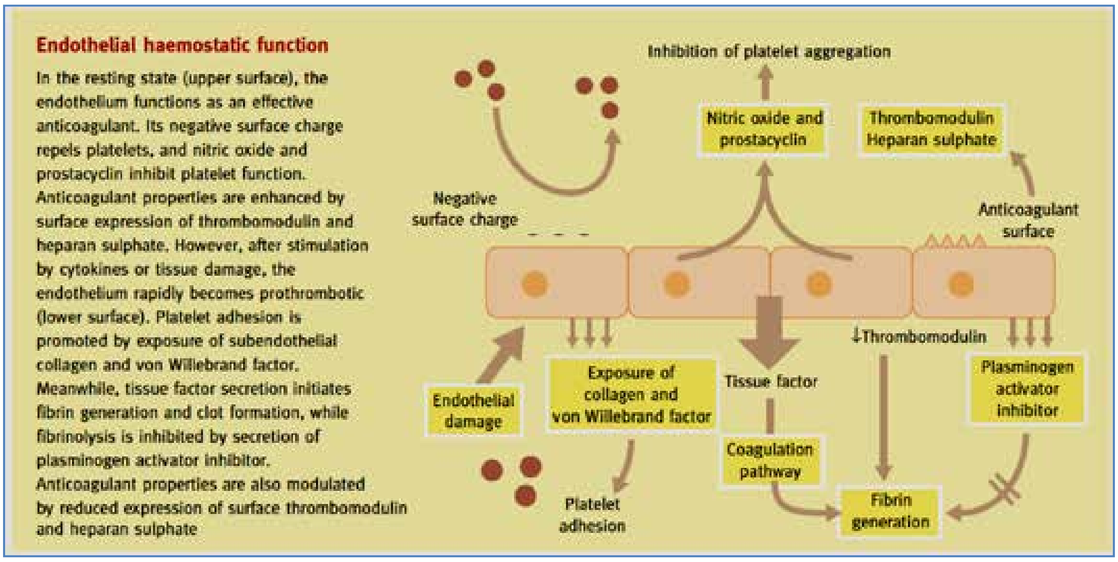
Haemostasis is an essential protective mechanism that depends on a balance of procoagulant and anticoagulant processes. It is controlled by an intricate interplay of four key components: the vascular endothelium, platelets, the coagulation pathway and fibrinolysis. The process of coagulation is divided into primary and secondary phases. Primary haemostasis occurs rapidly following vascular injury with platelet plug formation and vasoconstriction. Secondary haemostasis follows with the exposure of tissue factor expressing cells and formation of insoluble fibrin fibers through the action of the serine protease coagulation factors. There is a great degree of overlap between these phases with tight regulation to limit clot formation only to sites of injury. **(Kemball-Cook et al., 2011).**

Primary haemostasis

Endothelium

All blood vessels have a single layer of endothelial cells (ECs) that are in constant contact with blood flowing through the vessel lumen. ECs, underlying collagen and elastin fibrils make up the tunica intima. The tunica media consists of smooth muscle cells (which regulate vascular tone), further collagen fibrils and an elastic layer. The outer tunica adventitia has a protective and structural role, being made up of collagen and fibroblasts. **(Hoffbrand et al., 2011).**

The role of the endothelium is multifaceted. Primarily, it acts as a physical barrier separating haemostatic blood components from reactive sub-endothelial structures. It modulates vascular tone and permeability. In addition, endothelial cells also produce inhibitors of coagulation and platelet aggregation. (Figure 1.1). **(Van Hinsbergh, 2012).**



(Figure 1.1) Endothelial haemostatic functions **(Van Hinsbergh, 2012).**

In the resting state, the endothelium functions as an effective anticoagulant. Expression of specific proteins (thrombomodulin) and mucopolysaccharides (heparan sulphate, dermatan sulphate) promote an anticoagulant effect by accelerating the action of circulating natural anticoagulants. Platelet aggregation is inhibited by production of prostacyclin and nitric oxide and endogenous synthesis of ectoenzymes, which degrade ADP (platelet agonist). Lastly, the endothelium modulates fibrinolysis, by producing activators and inhibitors of clot lysis. **(Van Hinsbergh, 2012).**

Tissue damage disrupts the integrity of the endothelial basement membrane exposing the underlying extracellular matrix and prothrombotic haemostatic factors, including collagen, (VWF), fibronectin (promotes platelet adhesion) and (TF). Additionally, anti-thrombotic endothelial properties are lost by thrombin, shear stress, oxidants, endotoxin or cytokines interleukin-1 (IL-1), tumour necrosis factor (TNF) and interferon-γ. Activated endothelial cells express TF, which initiates the coagulation pathway, impairs fibrinolysis by secretion of plasminogen activator inhibitor (PAI-1), and reduces the surface expression of the anticoagulant, thrombomodulin. Furthermore, stimulated endothelial cell attract leucocytes by synthesizing chemokines, and expressing intracellular adhesion molecules (leucocyte integrins). **(Van Hinsbergh, 2012).**

These procoagulant events are themselves regulated, limiting intravascular extension of the thrombus. Proposed mechanisms include the negative charge of intact endothelium (repels platelets), adjacent prostacyclin release (inhibits platelet activation), heparan inhibition of thrombin, thrombomodulin enhancement of thrombin anticoagulant effects, and secretion of tissue plasminogen activator (tPA), which can initiate fibrinolysis. The fine balance between procoagulant and anticoagulant phenotype varies and led to the concept of vascular bed-specific haemostasis. Responsible mechanisms include growth factors, cytokines, mechanical forces, circulating lipoproteins, coagulation factors and components of extracellular matrix. Hence the prevalence of pathological thrombosis varies at different vascular sites, and may be associated with different acquired factors or disease states. **(Van Hinsbergh, 2012).**

Platelets

The circulating platelet is an anuclear discoid cell produced from megakaryocytes. It functions as a vehicle for transportation of regulatory factors, prothrombotic proteins, growth factors and other molecules inside platelet granules to the endothelium. The platelet membrane functions as a template for promotion/acceleration of haemostasis and wound healing. Also it facilitates rapid recognition of disruption or injury. The reduction in the number of platelets results in a bleeding tendency. The normal platelet count is 150- 450 $\times10^9$/L, and below 80 $\times10^9$/L, haemostasis may be impaired. The risk of bleeding correlates with the severity of the platelet reduction. **(Michelson, 2007).**

Internally, they contain mitochondria, glycogen particles, lysosomes, and different secretory granules, which are essential for normal platelet function:

· The α-granules containing large polypeptides that contributes to haemostasis, such as VWF and fibrinogen, and platelet factor 4, FV, and other factors.

· The d-granules (dense granules) rich in low molecular weight compounds that potentiate platelet activation, such as ADP, ATP, GTP, serotonin, and calcium

The cytoskeleton, containing tubulin, actin, and filamin, is responsible for the shape of the resting platelets and for the contractile events, such as the secretion of granules and clot retraction. Despite the lack of genomic DNA, platelets contain more than traces of messenger RNA and the translational machinery necessary for protein synthesis. **(Healy et al., 2009).**

A wide variety of mobile transmembrane receptors is displayed on the surface and work synergistically in platelet adhesion, activation, and aggregation. The subendothelial components involved in the interactions with platelets include VWF, different types of collagen, fibronectin, thrombospondin, and laminin. Fibrin and fibrinogen, which are not produced by endothelial cells, are immobilized onto extracellular matrix at the site of vascular damage and also bind to platelets. Although several tissue components are able to interact with platelets, only a few may have an essential role in initiating thrombus formation. (Table 1.1) summarizes the characteristics of the main platelet receptors. **(Rivera et al., 2009).**