



International Journal of Current Research in Biosciences and Plant Biology

ISSN: 2349-8080 Volume 2 Number 10 (October-2015) pp. 68-77

www.ijcrbp.com



Review Article

Haemostasis and Aging: A Review

Emmanuel Ifeanyi Obeagu^{1*}, Babatunde Nnamdi Nwachukwu² and Gloria Daniel-Igwe³

¹Diagnostic Laboratory Unit, University Health Services, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria

²Laboratory Department, Gwarzo General hospital, Kano, Nigeria

³Department of Veterinary Pathology, College of Veterinary Medicine, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria

**Corresponding author.*

Abstract	Keywords
<p>Haemostasis is very important because it arrests bleeding (clot formation) when blood vessels are damaged which if the bleeding is not arrested (sudden and severe loss of blood) can lead to shock and death. Haemostasis is the instinctive response for the body to stop bleeding and loss of blood. During haemostasis three steps occur in a rapid sequence. Vascular spasm is the first response as the blood vessels constricts to allow less blood to be lost. In the second step, platelet plug formation, platelet stick together to form a temporary seal to cover the break in the vessel wall. The third and last step is called coagulation or blood clotting. Coagulation reinforces the platelets plug with fibrin threads that act as a “molecular glue. With advancing age, many individuals who are otherwise normal show laboratory evidence of heightened coagulation enzyme activity.</p>	<p>Aging Coagulation factors Haemostasis Platelet plug Vascular spasm</p>

Introduction

Haemostasis as a word is taken from the Greek word, Haem meaning blood and stasis meaning standing. It is a process which causes bleeding to stop thereby stopping blood from escaping through damaged blood vessel. It is the first stage of wound healing, most of the time this includes blood changing from a liquid to solid state. Intact blood vessels are central to moderating blood’s tendency to clot. The endothelial cells of intact vessels prevent blood clotting with a heparin like molecule and thrombomodulin which prevents platelet aggregation with nitric oxide and prostacyclin (Marieb and Haelin,

2010). When endothelia injury occurs, the endothelial cells stops secretion of coagulation and aggregation inhibitors and instead secrete Von Willebrand factors which initiate the maintenance of haemostasis after injury.

Haemostasis is very important because it arrests bleeding (clot formation) when blood vessels are damaged which if the bleeding is not arrested (sudden and severe loss of blood) can lead to shock and death.

Haemostasis is the instinctive response for the body to stop bleeding and loss of blood. During haemostasis

three steps occur in a rapid sequence. Vascular spasm is the first response as the blood vessels constricts to allow less blood to be lost. In the second step, platelet plug formation, platelet stick together to form a temporary seal to cover the break in the vessel wall. The third and last step is called coagulation or blood clotting. Coagulation reinforces the platelets plug with fibrin threads that act as a “molecular glue” (Marieb and Haelin, 2010). Platelets are large factors in the haemostatic process. They allow for the creation of the “Platelet plug” that forms almost directly after a blood vessel has been ruptured. Within seconds of a blood vessel’s epithelial wall being disrupted, platelets begin to adhere to the sub-endothelium surface. It takes approximately sixty seconds until the first fibrin strands begin to intersperse among the wound. After severe minutes the platelet plug is completely formed (Boon, 1993). Haemostasis is maintained in the body via three mechanisms.

- (1) Vascular spasm is the blood vessels first response to injury. The damaged vessels will constrict (vasoconstriction) which reduces the amount of blood flow through the area and limit the amount of blood loss. This response is triggered by factor such as a direct injury to vascular smooth muscle, chemicals released by endothelial cells and platelet, and reflexes initiated by local pain receptors. The spasm response becomes more effective as the amount of damage is increased.
- (2) Platelet plug formation, when the vessel wall is damaged, the endothelial structures, including basement membrane, collagen and microfibrils are exposed. Surface bound Von Willebrand factor binds to glycoprotein 1b on circulating. Platelets resulting in an initial monolayer of adhering platelets. Being the second step in the sequence they stick together (aggregation) to form a plug that temporarily seals the break in the vessel wall. As platelets adhere to the collagen fibers of a wound they become spiked and much stickier. They then release chemical messenger such as adenosine disphosphate (ADP). These chemicals are released to cause more platelets to stick to the area and release their contents and enhance vascular spasm. Platelets alone are responsible for stopping the bleeding Of unnoticed wears and tears of our skin on a daily basis (Clemetson, 2012) platelet

plug formation is activated by glycoprotein called the Von Willebrand factor which are found in the blood plasma. When platelets in the blood are activated they then become very sticky so allowing them to stick to other platelets and adhere to the injured area (Lassila, 2012; Springer, 2011).

- (3) Blood coagulation- Clots form upon the conversion of fibrinogen to fibrin, and its addition to the platelet plug (secondary hemostasis). Coagulation which is the third and final step in its rapid response reinforces the platelet plug. Coagulation uses fibrin threads that act as a glue for the sticky platelets. As the fibrin mesh begins to form the blood is also transformed from a liquid to a gel like substance through involvement of clotting factors and pro-coagulates.

Haemostatic factors and aging

With advancing age, many individuals who are otherwise normal show laboratory evidence of heightened coagulation enzyme activity.

The lecture of D-Maris on haemostasis and aging held on (March 19, 2008) says, physiological aging is associated with increased plasma levels of many protein of blood coagulation with fibrinolysis impairment. This may be of great concern in view of the known association between vascular and thromboembolic diseases and aging. Prothrombotic clotting factor; the plasma concentration of several clotting factors namely fibrinogen factor vii, factor viii, Von Willebrand factor (VWF) factor ix, factor xii increase with progressing age in healthy individuals (Maris et al., 2008). A study by Meade et al. (1977) in a population study of subjects aged 53-64years had shown significantly higher level of fibrinogen (300mg/dl) than those found in younger subjects aged 20 (250mg/dl).As 10mg/dl for each decade can be expected in healthy subjects. Fibrinogen moreover is a molecule that plays a role in acute phase inflammation and fibrinogen level increases in reference to interleukin in 6 and both are strongly connected with aging (Balleisen et al., 1985). Factor vii plasma levels progressively increase with age from a mean of 95 units/dl in subjects of 20 years old to over 110 units/dl in subjects over 50 years old. Thrombotic disorders have shown to be more frequent in subjects with higher plasma levels of factor vii (Ershler, 1983) acting as a

cofactor in the activation of factor X promoted by factor IXa, progressively increase with age reaching a mean of over 200 units/dl in the healthy subjects over sixty of age, the level of factor ix and factor X activation peptide also increase with advancing age (Bauer et al., 1990). The mean physiological inhibitors of blood coagulation are natural anticoagulants produced by the liver and circulating in the plasma, anti thrombin iii heparin cofactor ii. The protein C, protein S system and tissue factor pathway inhibitors (T.F.P.I). The increase activation of the related coagulation is not the tissue factors pathway, which increase with increase in age, the behavior pattern of TFPI is gender dependent, in women statistically significant increase in plasma concentration of TFPI with age have been observed paralleling the rise in factor VII. No significant age-related change in TFPI has been found in men (Ariensm et al., 1995).

Normal haemostasis pathways

Normal haemostasis is achieved by a close interaction of numerous dynamic processes or mechanisms which include:

- Vascular spasm
- Platelet formation
- Blood coagulation

Vascular spasm

Damaged blood vessels constrict vascular spasm is the blood vessel's first response to injury. The damaged vessels will constrict which reduces the amount of blood flow through the area and limits the amount of blood loss. This response is triggered by factor such as a direct injury to vascular smooth muscle, chemicals released by endothelia cells and platelets and reflexes initiated by local pain receptors. The spasm response becomes more effective as the amount of damage is increased (Marie and Haelin, 2010).

Platelet plug formation

Platelets are cellular elements, found in the blood of mammals that are important for the initiation of blood clotting (Laki, 1972). Platelets are small fragments of cytoplasm derived from megakaryocytes in the bone marrow which bud off into the circulation (Machlus et al., 2014). On a stained blood smear, platelets appear as dark purple spots. The smear is used to examine platelets for size, shape, qualitative number and clumping.

The main function of platelets is to contribute to haemostasis. The process of stopping bleeding at the site of interrupted endothelium. They gather at the site and physically plug the hole. First platelets stick to substances outside the interrupted endothelium adhesion. Second they change shape, turn on receptors and secrete chemical messengers activation. Third, the stick to each other aggregation formation of this platelet plug (primary haemostasis) is followed by activation of the coagulation cascade with resultant fibrin deposition linking (secondary haemostasis). These process may overlap the spectrum is from a predominantly platelet plug, or "white clot" to a predominantly fibrin clot, or "red clot" or the more typical mixture, the final result is the clot. Low platelet concentration is thrombocytopenia and is due to either decreased production or increased destruction.

Elevated platelet concentration is thrombocytosis and is either congenital, reactive (to cytokines), or due to unregulated production. The central cytoplasm is dominated by three types of platelet granules. The δ granules, ∞ granules and lysosomal granules. The platelet membrane is the site of interaction with the plasma environment and with the damaged vessel wall. It consists of phospholipid, cholesterol, glycolipids and at least nine glycoproteins named GPI, to GPIx. The membrane phospholipids are asymmetrically distributed, with sphingomyeline and phosphatidylcholine predominating in the outer leaflet and phosphatidylethanolamine,-inositol and serine in the inner leaflet.

Platelet aggregation

Platelet aggregation may occur by at least two independent but closely linked pathways. The first pathway involves arachidonic acid metabolism. Activation of phospholipids (phosphatidyl choline). About 50% of free arachidonic acid is converted by a lipo-oxygenase enzyme to a series of products including leucotrienes, which are important chemoattractants of white cells. The remaining 50% of arachidonic acid is converted by the enzyme cyclooxygenase into labile cyclic endoperoxides, most of which are in turn converted by thromboxane synthetase into TxA₂. TxA₂ has profound biological effects and local vaso contribution, as well as further local platelet aggregation via the second pathway it exerts these effects by raising intracellular cytoplasmic free calcium concentration and binding to specific granule receptors. TxA₂ is very labile with a half-life of <1min before it is degraded into

the inactive thromboxane B₂ (TxB₂) and malonyldialdehyde. The aggregation of platelets join together into loose reversible aggregates, but after the release reaction of the platelet granule larger, firmer aggregates form changes in the platelet membrane configuration now occur flip-flop rearrangement of the surface brings the negativity charged phosphatidylserine and inositol on the outer leaflet, thus generating platelet factor 3 (procoagulant) activity. At the same time specific receptors for various coagulation factors are exposed on the platelet surface and help coordinate the assembly of the enzymatic complexes of the coagulation system. Local generation of thrombin will then further activate platelets.

Platelets are not activated if in contact with healthy endothelial cells. Platelets have at least three roles in haemostasis.

1. Adhension and aggregation forming the primary haemostatic plug.
2. Release of platelet activating and procoagulant molecules.
3. Provision of a procoagulant surface for the reactions of the coagulation system.

Blood coagulation

The central event in the coagulation pathway (Mann, 1999) is the production of thrombin which acts upon fibrinogen to produce fibrin and thus the fibrin clot. This clot is further strengthened by the cross linking action of factor XIII, which itself is activated by thrombin. The two commonly used coagulation test, the activated partial thromboplastin time (APTT) and the prothrombin time (PT), have been used historically to define two pathway of coagulation activation, the intrinsic and extrinsic pathway, respectively. However, this bears only a limited relationship to the way coagulation is activated in vivo for example, deficiencies of factor XII or of factor VIII both produce marked prolongation of the APTT, but only deficiency of the latter is associated with a haemorrhagic tendency. Moreover, there is considerable evidence that activation of factor IX (intrinsic pathway) by factor VIIa (extrinsic pathway) is crucial to establishing coagulation after an initial stimulus has been provided by factor VIIa –tissue factor (Tf) activation of factor X (Mann, 1999) (Table 1).

Investigation of the coagulation system centers on the coagulation factors, but the activity of these proteins is

also greatly dependent on specific surface receptors of platelets and also by activated endothelium. The necessity for calcium in many of these reactions is frequently used to control their activity *in vitro*.

The contact activation system

The contact activation system (Colman and Schmaier, 1997) comprises factor XII (Hageman factor), high molecular weight kininogen (HMWK) (Fitzgerald factor) and prekallikrein/Kallikrein (Fletcher factor). Important activities of these factors are to activate the fibrinolytic system, to activate the complement system and to generate vaso active peptides in particular, bradykinin is released from HMWK by prekallikrein or FXIIIa also function as chemoattractants for neutrophils. The contact activation system also has some inhibitory effect on thrombin activation of platelets and prevents cell binding to endothelium. Recent evidence implicates the contact system in thrombosis via activation by polyphosphate released from platelets (Multer et al., 2009).

When bound to a negatively charged surface *in vitro*, factor XII and prekallikrein are able to reciprocally activate one another by limited proteolysis, but the initiating event is not clear. It may be that a conformational change in factor XII on binding results in limited autoactivation that triggers the process. HMWK acts as a (zinc-dependent) cofactor by facilitating the attachment of prekallikrein and factor XI, with which it circulates in a complex to the negatively charged surface. It has been shown in *in vitro* studies that platelet or endothelial cells can provide the necessary negatively charged surface for this mechanisms and also process specific receptors for factor XI. The contact system can activate fibrinolysis by a number of mechanisms plasminogen cleavage, urokinase plasminogen activator (UPA) activation and tissue plasminogen activator (EPA) release most importantly from the laboratory point of view, the contact activation system results in the generation of factor XIIIa, which is able to activate factor XI, thus initiating the coagulation cascade of the intrinsic pathway.

Tissue factor

Tf is the cofactor for the extrinsic pathways and the physiological initiator of coagulation. It is a transmembrane protein and constitutively present in many tissues outside the vasculature and on the surface of stimulated inflammatory cells such as monocytes and under some conditions, endothelial cells factor VIIa binds to Tf in the presence of calcium ions and then becomes

enzymatically active. Some amounts of factor viia are present in the circulation but bound to Tf. The factor viia-Tf complex can activate both factor X and therefore two routes to thrombin production are stimulated factor xa subsequently binds to Tfpl and then to factor vlla to form an inactive quaternary (xa-Tf-vlla-Tfpl) complex. This mechanism therefore functions to short off the extrinsic pathway after an initial stimulus to coagulation has been provided.

Cofactors

Factors VIII and V are the two most labile of the coagulation factors and they are rapidly lost from stored blood or heated plasma. They share considerable structural homology and are cofactors for the serine proteases fix and fx, respectively, the both require proteolytic activation by factor IIa or xa to function factor VIII circulates in combination with vwf, which is present in the form of large milltimers of a basic 200 KDa monomer. One function of vwf is to stabilize factor VIII and protect it from degradation. In the absence of vwf, the survival of factor VIII in the circulation is extremely short. VWF may also serve to deliver factor VIII to platelets adherent to a site of vascular injury once factor VIII has been cleaved and activated by throbin, it no longer binds to vwf.

The vitamin K-dependent factors

The vitamin k-dependent factors group includes coagulation factor II, VII, IX and X. however, it is important to remember that the anticoagulant protein s, c and z are also vitamin k-dependent. Each of these proteins contains a number of glutamic acid residues at

its amino terminus that are y-carboxylated by a vitamin K-dependent mechanism. This results in a novel amino acid, y-carboxyglutamic acid, which by binding calcium is essential in promoting a conformational change in the protein and binding of the factor to negatively charged phospholipid. Because this binding is crucial for coordinating the interaction of the viral factor, the proteins produced in the absence of vitamin K (PIVKA) that are not y-caroxylated are essentially functionless. The vitamin k-dependent factors are proenzymes or zymogens which require cleavage, sometimes with release of a small peptide (activation peptide) to become functional.

Conversion of fibrinogen to fibrin

Fibrinogen is a large dimeric protein consisting of three polypeptides, it has a high molecular weight of 340,000 plasma glycoprotein. Fibrin is formed from fibrinogen by thrombin cleavage releasing the A and B peptides from fibrinogen, this result in fibrin monomers that then associate and precipitate forming a polymer that is the visible clot (Lord, 2007).

Conversion of prothrombin to thrombin

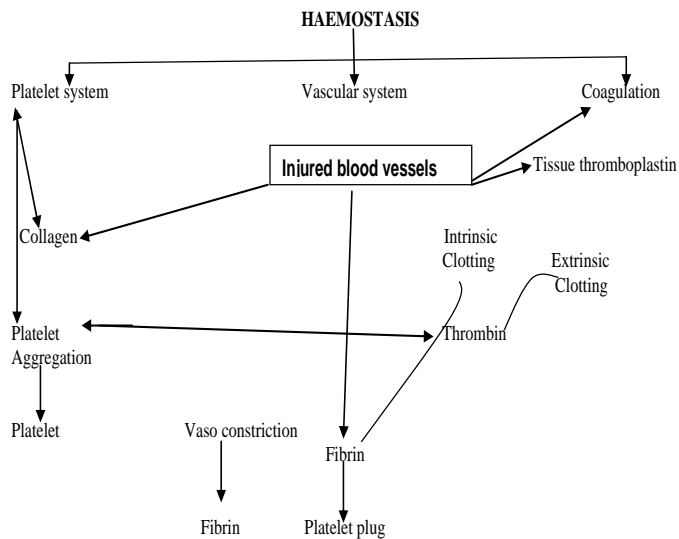
Prothrombin has a molecular weight of 72,000, it is a plasma protein. It is press in normal concentrations of blood 130mg/dl. The prothrombinase complex catalyzes the conversion of prothrombin (factor II) and inactive zymogen to thrombin (factor IIa) an active serine protease. The activation of thrombin is a critical reaction in the coagulation cascade, which functions to regulate haemostasis in the body. Prothrombin is converted to thrombin in the presence of thromboplastin and calcium ion during blood clotting.

Table 1. Some properties of coagulation factors

No.	Factor	RMM (Daltons)	Half-life	Concentration in plasma (mg/dl)
I	Fibrinogen	340 000	90 h	150.0 – 400.0
II	Prothrombin	70 000	60 h	10.0 – 15.0
V	-	330 000	12-36 h	0.5 – 1.0
VII	-	48 000	6 h	1.0
VIII	-	200 000	12 h	< 0.01
VWF	-	800 000-140 000000	10-24 h ^a	0.5 -1.0
IX	-	57 000	24 h	0.01
X	-	58 000	40 h	0.75
XI	-	158 000	60 h	1.2
XII	-	80 000	48-52	0.4
Prekallikrein	-	85 000	48 h	0.3
HMWK	-	120 000	6.5 days	2.5
XIII	-	32 000	3-5 days	2.5

RMM, relative molecular mass (molecular weight); h, hours; HMWK, high molecular weight Kininogen; VWF, Von Willebrand factor.

Fig. 1: Haemostasis and the balance between the coagulation factors, platelets and fibrinolytic system.



Fibrinolytic enzyme in the elderly

During aging, fibrinolytic activity in plasma increase markedly (Manucci and Maris, 1995) in the elderly. There is secondary hyper fibrinolysis which results to an increased D-dimer and plasmin antiplasmin complex.

Plasma antigenic markers of fibrinolysis V, Z, plasminogen activator inhibitor (PAI-1) fibrin fragment d-dimer and plasmin antiplasmin complex (PAP) for the prediction of arterial thrombosis in healthy elderly persons over the age 65. They found out that there was increasing quartile of D-dimer and PAP levels but not of PAI-1, there was no independent risk of myocardial infarction or coronary death, but not of angina (Cushman et al., 1999).

In older persons, increase in plasma antigenic markers of fibrinolysis predict arterial thrombosis and these markers play in major role in identifying a high risk of arterial disease in this age group.

Clotting factors

The clotting factors are the group of chemicals that are constantly circulating in the blood or present in tissues of the blood vessels. These compounds are responsible for the formation of a blood clot. Clotting factors are usually inactive but once there is tissue injury to the wall of the blood vessel, the first factor is activated. This has a cyclical effect with each factor activating the next.

Functions of clotting factors

Haemostasis is the body's mechanism to stop blood loss (Fig. 1). It is made up of several mechanisms with the coagulation phase involving the clotting factors and the formation of a blood clot. The series of clotting factor whereby one clotting factor activates the next is known as the coagulation cascade. The clotting factors eventually convert fibrinogen to fibrin which then forms a mesh network at the site of injury. This traps blood cells and other components to form a firm blood clot and thereby completely stop blood loss. Therefore the functions of clotting factors are to trigger the formation of a blood clot and stabilize it for as long as necessary. Clotting factors are therefore known as procoagulants.

List of clotting factors

Factor I

Name: fibrinogen
 Source: liver
 Pathway: Both extrinsic and intrinsic
 Activator: Thrombin
 Actions: when fibrinogen is converted into fibrin by thrombin, it forms long strands that compose the mesh network for clot formation.

Factor II

Name: prothrombin
 Source: liver
 Pathway: Both extrinsic and intrinsic
 Activator: prothrombin activator
 Actions: prothrombin is converted into thrombin which then activates fibrinogen into fibrin.

Factor III

Name: thromboplastin/Tissue factor
 Source: platelets (intrinsic) and damaged endothelium (cells) living the blood vessel.
 Pathway: Both intrinsic and extrinsic.
 Activator: Injury to blood vessel.
 Action: activates factor VII (VIIa).

Factor IV

Name: Calcium
 Source: Bone and absorption from food in gastrointestinal tract.

Pathway: Both extrinsic and intrinsic.
Action: works with many clotting factors for activation of the other clotting factors.

Factor V

Name: Proaccerin/Labile factor
Source: Liver and platelets
Pathway: both extrinsic and intrinsic
Activator: Thrombin
Action: Works with factor X to activate.
Thromprombin (prothrombin activator).

Factor VII

Name: Proconvertin/serum prothrombin conversion accelerator (SPCA) stable factor.
Source: Liver
Pathway: Extrinsic
Activator: Factor III (Tissue factor).
Actions: Activates factor X which works with other factors to convert prothrombin into thrombin.

Factor VIII

Name: Anti-hemophilic factor (AHF).
Source: Endothelium living blood vessel and platelets (plug).
Pathway: Intrinsic
Activator: Thrombin
Actions: Works with factor IX and calcium to activate factor X.

Factor IX

Name: Christmas factor / plasma thromboplastin component (PTC)/ Antihemophilic factor B.
Source: Liver
Liver
Activator: Factor XI and calcium
Actions: works with factor VIII and calcium to activate factor X.

Factor X

Name: Stuart Prower factor/Stuart factor.
Source: Liver
Pathway: Extrinsic and intrinsic
Activator: Factor VII (extrinsic) / factor IX + factor VIII + calcium (intrinsic).

Actions: Works with platelet phospholipids to convert prothrombin into thrombin. This reaction is made faster by activated factor V.

Factor XI

Name: Plasma thromboplastin antecedent (PTA)/ antihemophilic factor c.
Source: Liver
Pathway: Intrinsic
Activator: factor XII + prekallikrein and kininogen.
Actions: works with calcium to activate factor IX.

Factor XII

Name: Hageman factor
Source: Liver
Pathway: Intrinsic
Activator: contact with collagen in the torn wall of blood vessels.
Action: works with prekallikrein and kininogen to activate factor xi. Also activates plasmin which degrades clots.

Factor XIII

Name: Fibrin stabilizing factor
Source: Liver
Activator: thrombin calcium
Actions: stabilizes the fibrin mesh network of a blood clot by helping fibrin strands to link to each other.
Prekallikrein
Source: Liver
Pathway: Intrinsic
Action: works with Kininogen and factor XII to activate factor XI.
Kininogen
Source: Liver
Pathway: Intrinsic
Action: works with Prekallikrein and factor XII to activate factor XI.

Natural anticoagulants aging and thromboembolism

The normal aging process alters blood coagulation system in humans with an associated vascular disease with advancing age. The plasma concentration of several coagulation factor namely fibrinogen, factor VII, factor VIII, factor IX, high molecular weight kininogen and prekallikrein, decrease in healthy individuals paralleling the physiological aging process. Plasma parameters of

clotting activate *in vivo* such as prothrombin fragment 1+2 fibrinopeptide A, thrombin antithrombin III complex and D-dimer are positively related with age.

Natural anticoagulants including antithrombin III heparin cofactor II, protein C, protein S and tissue factor pathway inhibitor can modulate the reactions of blood coagulation system. The occurrence of menopause is accompanied by a significant increase in antithrombin III plasma level, the mean antithrombin III level in older women exceeds the level in male counterparts (Sapripanti and Carpi, 1999).

In healthy elderly subjects, heparin cofactor II plasma concentration is lower than in younger subjects independently of gender. In women, statistically significant increases in the plasma concentration of the tissue factor inhibitor have been observed protein C level rise with age in both sexes as well as free protein S level. In healthy elderly individuals, an increase in natural anticoagulants can balance the age-related increase to clotting mechanism are antibodies that neutralize specific clotting proteins, thereby interfering with their normal function.

Thromboembolism in the elderly

The aging process is associated with increased and fibrinolysis parameter resulting in an overall prothrombotic state (Van-Gorp and Branddies, 1998).

In the elderly, unregulated clotting will result in the conversion of the blood vessels and thrombosis (Kalfalis et al., 1997). This probably explains the development of thromboembolic disease. Additional factor such as major surgery or malignant disease multiply the risk of thromboembolism in this population.

Platelet function during aging

In recent study of platelet life span during aging, Kotze and his colleagues isolated platelet from blood of baboons and treated them with neuraminidase to remove platelet membrane sialic acid, a process which artificially ages the platelets. The platelet were then labeled with ¹²⁵I and their mean life span *in vivo* distribution and sites of removal of sialic acid on the attachment of immunoglobulin to platelet were investigated and related to the sequestration of the platelets by the spleen, liver and bone marrow. The research showed that the removal of sialic acid by

neuraminidase did not affect the aggregation of platelets by agonists *in vitro*, nor their sites of sequestration but shortened their life span. And there was an exponential correlation between the shortening of the mean platelet life span and the amount of sialic acid removed (Kotze et al., 1993).

Also Merlo-Pich and his colleagues assayed NADH-coenzyme Q reductase in platelet mitochondrial membranes obtained from 17 pools of two venous blood samples from female young (19-30 years) individuals and 18 pools from aged ones (66-107 years). The research showed that the enzyme activities were not significantly changed in the two group, but a decrease of sensitivity to the specific inhibitor, rotenone, occurred in a substantial number of aged individuals (Merlo-Pich et al., 1996). Therefore the effect of aging is shorten the mean platelet life span which in turn affects the mean platelet count (Kotze et al., 1993).

Metabolism of vitamin K

Vitamin K is required for the biological activity of several coagulation factors. It plays a vital role in blood coagulation especially in vitamin K dependent factor X. Vitamin K is continuously being synthesized in the intestinal tract by bacterial flora. The metabolic role of vitamin K is act as a cofactor in the carboxylation of glutamyl to gamma-carboxyglutamyl residues.

Besides the hepatic tissues, in which the clotting factors are produced, gamma-carboxyglutamyl containing proteins are also abundantly available in bone tissue. Evidence from observational studies and first intervention trials indicate that vitamin K intakes much higher than current recommendations improve biochemical markers of bone formation as well as bone density. Activated partial thromboplastin time (APTT) is moderately increased in the presence of a vitamin K deficiency.

Clinical significance of prothrombin time

The prothrombin time test is used for controlling anticoagulant therapy and ideal prothrombin time range for this therapy is 20-25 seconds. Decreased prothrombin time is associated with increased level of factor VII. The first is prolonged as a result of liver disease since the physiology of blood coagulation closely linked to liver function, synthesis of some coagulation factors occur in the liver. The conversion of

fibrinogen to fibrin is facilitated by the reticuloendothelial system. Prothrombin time is also decreased in disseminated intravascular coagulation (DIC). In normal aging, prothrombin time is increased in both men and women and in a study by Hamilton et al. (1974) in 61 subjects. The prothrombin time increased in both sexes.

Clinical significance of activated partial thromboplastin time (APTT)

APTT is prolonged in disseminated intravascular coagulation DIC, in liver cirrhoses. Also liver disease is developed as massive transfusion with stored prolonged APTT. It is also moderately increased in the presence of a vitamin K deficiency. Also patients with previously undiagnosed haemophilia (though it has not been thought to be a problem in old age) or congenital coagulation disorder present with prolonged APTT.

Clinical significance of platelet counts

Thrombocytopenia is the disease in platelet numbers and this may result in either an internal or external haemorrhage when the count is less than 50,000 platelets per mm³ purpura (sensil) seen in elderly people is a haemorrhagic disorder due to defects in vascular reaction in reduced number of platelets. An increased platelet production (thrombocytosis) may follow haemorrhage, surgery.

Conclusion

Haemostasis is the instinctive response for the body to stop bleeding and loss of blood. During haemostasis three steps occur in a rapid sequence. Vascular spasm is the first response as the blood vessels constricts to allow less blood to be lost. In the second step, platelet plug formation, platelet stick together to form a temporary seal to cover the break in the vessel wall. The third and last step is called coagulation or blood clotting. Coagulation reinforces the platelets plug with fibrin threads that act as a "molecular glue". Platelets are large factors in the haemostatic process. They allow for the creation of the "Platelet plug" that forms almost directly after a blood vessel has been ruptured. Within seconds of a blood vessel's epithelial wall being disrupted, platelets begin to adhere to the sub-endothelium surface. It takes approximately sixty seconds until the first fibrin strands begin to intersperse among the wound. After severe minutes

the platelet plug is completely formed. With advancing age, many individuals who are otherwise normal show laboratory evidence of heightened coagulation enzyme activity. The aging process is associated with increased and fibrinolysis parameter resulting in an overall prothrombic state. In the elderly, unregulated clotting will result in the conversion of the blood vessels and thrombosis

References

- Ariensm, R., Coppola, R., Potenza, I., Mannucci, P., 1995. The Increase with age of the components of the tissue Factor coagulation pathway is dependent. *Blood Coag. Fibrinol.* 6, 433-37.
- Balleisen, L., Bailey, J., Epping, P.H., Schulte, H., Loo, J., 1985. Epidemiological study on factor VII, factor viii and fibrinogen in industrial population. Baseline data on the relation to age, gender, body-weight, smoking, alcohol, pill using and menopause. *Throm. Haemost.* 45, 475-79.
- Bauer, K.A., Kass, B.L., Cate, H.C., Hawiger, J.J., 1990. Rosenberg RD: factor ix is activated *in vivo* by the tissue factor mechanism. *Blood.* 76, 731-36.
- Boon, E.D., 1993. An overview of hemostasis. *Toxicol. Pathol.* 21(2), 170-79.
- Clemetson, K.J., 2012. Platelets and primary haemostasis. *Thromb. Res.* 129(3), 220-224.
- Colman, R., Schmaier, A., 1997. Contact system, a vascular biology modulator with anticoagulant, profibrinolytic, antiadhesive and proinflammatory attributes. *Blood.* 90(10), 3819-43.
- Cushman, M., Lemaintre, R.N., Kuller, L.H., 1999. Fibrinolytic activation markers. Predict myocardial infarction in lytic activation markers. Predict myocardial infarction in the elderly. *Arterioscler Thromb. Vasc. Biol.* 19(3), 493-498.
- Ershler, W.B., 1983. Intetleukin-6, a cytokine for gerontologist. *J.A.M. Geriatr Soc.* 41, 179 – 181.
- Hamilton, P.J., Allardyce, M., Ogston, D., Dawson, A.A., Douglas, A.S., 1974. The effect of age upon the coagulation system. *J. Clin. Pathol.* 27, 980-82.
- Kalfalis, M., Egan, J.O., Cawthem, K.M., 1997. The regulation of clotting factors. *Crit. Rev. Eukaryot. Gene Expr.* 7(3), 241-80.
- Kotze, H.F., Van-Wyk, V. Lotter, M.G., 1993. Influence of platelet sialic acid on aging. *Throm. Haemostasis.* 70(4), 676 -80.
- Laki, K., 1972. Our ancient heritage in blood clotting and some of its consequences. *Ann. New York Acad. Sci.* 202, 297-307.

- Lassila, R., 2012. New Insights into Von Willebrand Disease and Platelet function. *Sem. Thrombosis Res.* 38(1), 55-63.
- Lord, S.T., 2007. Fibrinogen and fibrin. Scaffold protein in hemostasis. *Curr. Opin. Hematol.* 14(3), 236-241.
- Machlus, K.R., Thon, J.N., Hliano, J.E., 2014. Interpreting the developmental dance of the megakaryocyte. A review of the cellular and molecular processes mediating platelet formation. *Brit. J. Haematol.* 165(2), 227.
- Mann, K.G., 1999. Biochemistry and physiology of blood coagulation. *Throm. Haemostasis.* 82(2), 165-74.
- Manucci, P.M., Maris, D., 1995. Hypercoagulability in centenarians. The paradox of successful aging. *85(11)*, 3144-49.
- Marieb, E., Haelin, K., 2010. Human Anatomy and physiology 8th Edn.). Benjamin Cummings, San Francisco. pp.649-650.
- Maris, D., Coppola, R., Provenzano, R., 2008. Hemostasis factors and aging. *Exp. Gerontol.* 43, 66-73.
- Meade, T.W., North, W.R.S., Chakrabarti, R., Itaines, A.P., Stirling, Y., 1977. Population-based distributions of haemostatic variables. *Br. Med. Bull.* 33, 283-288.
- Merlo Pich, V., Schmaier, A., James, G.E., 1996. Population study of platelet and aging. *Br. Med. Bull.* 22, 180-85
- Multer, F., Mutch, N.J., Schenk, W.A., 2009. Platelet polyphosphates are pro inflammatory and procoagulant mediators *in vivo*. *Cell* 139(6), 1143-1156.
- Springer, T.A., 2011. Biology and physics of Von Willebrand factor concatamers. *J. Thromb. Haemostasis.* 9(7), 130-143.
- Van-Gorp, E.C., Brandtjes, D.P., 1998. Rational antithrombotic therapy and prophylaxis in the elderly. *Drugs-Aging* 13(2), 144-157.