Coagulation System in Various Diseases

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ABSTRACT

Recent advancements in anesthetic practice have led to a deeper understanding of the blood coagulation system. It is important to recognize that coagulation is a dynamic process. While the traditional categorization into extrinsic and intrinsic pathways remains relevant, recent insights provide a more precise depiction. The pro-coagulant pathway, responsible for initiating clot formation, is intricately balanced by mechanisms that restrict its spread beyond the site of injury in the normal coagulation process. Critical illness or the perioperative phase can disrupt this balance, potentially resulting from various underlying conditions that heighten the risk of either bleeding or thrombosis. Through a comprehensive search of the different literature using MeSH terms such as "coagulation system, haemostasis, and anesthesia," twenty-eight interconnected clinical trials and review articles from the past decade were identified. It is imperative for clinicians to grasp the physiological underpinnings of hemostasis in order to effectively diagnose and address coagulation abnormalities. This understanding is also crucial for interpreting diagnostic tests related to coagulation, as the equilibrium of the coagulation system can tip towards bleeding or thrombosis in various clinical scenarios.

Keywords: Thrombohaemorrhagic syndrome, cascade theories, anaesthesia, coagulation system, haemostasis system,.

Introduction

In the 1960s, Davie, Ratnoff, and Macfarlane introduced the "waterfall" and "cascade" theories, outlining the concept of a sequence where proenzymes activate downstream enzymes. The term "haemostasis," signifying "arrest of bleeding," stems from the Greek words "haeme" for "blood" and "stasis" for "to stop." Complex interactions between the coagulation and fibrinolytic systems, along with platelets and the arterial wall, maintain this delicate balance between clotting and hemorrhage in the body.

The coagulation process is regulated by various inhibitors that curb clot formation and prevent thrombi from spreading. Any elevation in the procoagulant activity of coagulation factors or a decrease in the activity of natural inhibitors disrupts this equilibrium. For a perioperative physician, understanding the intricate interplay between these systems that collaborate to maintain blood circulation in a fluid state is crucial, especially in the presence of preexisting hematological issues.

Pathological situations necessitating surgery, anesthesia, or other invasive procedures activate the hemostatic system. Trauma, cytokines, or pathogenic agents can also disturb this balance. Consequently, both bleeding and clotting abnormalities are highly likely to occur during the perioperative phase. Factors like hypoxia, hypothermia, metabolic acidosis, and extracorporeal circulation could exacerbate the condition.The intensivist may encounter coagulopathy due to physiological changes, primary hemostasis issues, blood or plasma anomalies, or as a consequence of disseminated intravascular coagulation (DIC).

This study aims to elucidate the comprehensive understanding of the coagulation system and highlight various abnormalities that can impact both the perioperative and intensive care unit (ICU) settings. These anomalies can be classified into those affecting the fibrinolytic system, coagulation pathways, and primary hemostasis.

Primary haemostasis

The intricate interactions between platelets, vessel walls, and adhesive proteins that culminate in the creation of the first "platelet plug" are the cause of primary haemostasis. Numerous variables, including negatively charged heparin-like glycosaminoglycans, neutral phospholipids, the creation and release of platelet inhibitors, coagulation inhibitors, and fibrinolysis activators, contribute to the antithrombotic capabilities of the endothelial cells lining the arterial wall. In contrast, the subendothelial layer is very thrombogenic and includes proteins including laminin, thrombospondin, and vitronectin that are important for platelet adherence in addition to collagen and von Willebrand factor (vWF). Any vascular injury causes arteriolar vasospasm, which is caused by reflex neurogenic processes and the release of regional mediators including endothelin and thromboxane A2 (TxA2), which is produced by platelets.

Megakaryocytes give rise to platelets, which are disc-shaped, anucleate cellular pieces. By generating the first haemostatic plug, which serves as a surface for the assembly of active coagulation components leading to the creation of fibrin stabilized platelet aggregates and ensuing clot retraction, they play a crucial role in haemostasis. Granules in platelets come in two varieties:

- P-selectin, fibrinogen, fibronectin, factors V and VIII, platelet factor IV, platelet-derived growth factor, and tumour growth factor (TGF) are all present in the granules [9].
- Adenosine triphosphate (ATP), adenosine diphosphate (ADP), calcium (Ca), serotonin, histamine, and epinephrine are all present as granules or dense granules [9].

Normally, undamaged vascular endothelium does not allow platelets to adhere. Following vascular injury, platelets bind to collagen and vWF in the subendothelial tissue, undergo morphological change, take on an irregular surface, and create numerous pseudopods, greatly increasing their surface area.[10] A series of processes lead to the formation of the platelet plug.

Platlet adherence

The platelet glycoprotein complex I (GP-Ib) is the main receptor for vWF. After vascular damage, vWf functions as a bridge between endothelial collagen and platelet surface receptors GpIb and increases platelet adhesion.

Platelet release

Following adhesion, both types of granules degranulate, releasing a number of variables. Here, calcium is released. Following platelet activation, phospholipids that are present in the body bind to calcium, creating a surface on which different coagulation components can be assembled.

Aggregation of platelets

Platelet activation results in the production of thromboxane A2, which stimulates more platelet aggregation. This platelet aggregation is enlarged by TxA2 and ADP, which results in the creation of the platelet plug that momentarily shuts off vascular damage. Additionally, GpIIb/IIIa receptors located on the surface of platelets undergo a conformational shift in response to ADP, which results in the deposition of fibrinogen. Secondary haemostasis, which increases the stability of the platelet plug and is catalyzed by the production of thrombin, is the process by which this fibrinogen is converted to fibrin [9].

The balance between TxA2 and prostacyclin causes localized platelet aggregation, which prevents the clot from spreading and maintains the patency of the vascular lumen. Prostacyclin suppresses platelet aggregation (platelet anti aggregating function) [6,11].

Coagulation Disorders Involving Primary Hemostasis

Primary haemostasis deficiencies can result from anomalies in the vascular wall or qualitative or quantitative platelet defects, which can lead to bleeding of varied severity.

Rare hereditary platelet diseases must be treated with platelet concentrates both before and after surgery. If present, these illnesses are often discovered in childhood.

High platelet counts can happen during the perioperative phase following significant bleeding, splenectomy, major reconstructive surgery, or they might simply be an indicator of an inflammatory reaction.

Some inherited bleeding disorders with platelet glycoprotein deficiencies, such as Glanzmann thromboasthenia (deficiency of IIb/IIIa) and Bernard-Soulier syndrome (deficiency of platelet glycoprotein Ib), can develop as a result of viral infections and are linked to an immediate failure of hemostasis [12,13].

Massive blood transfusions include replacing one volume of whole blood over the course of 24 hours with banked blood that is lacking in both functional platelets and coagulation factors. Red cell transfusions also reduce the patient's natural coagulation reserve. Fluid infusion, particularly colloids, exacerbates all of these effects. Because of this, a large blood transfusion may cause a coagulopathy with dilution.

Coagulation Pathways

The coagulation system's essential components, the coagulation proteins, are responsible for converting soluble fibrinogen into insoluble fibrin threads through a complicated interplay of events.

Clotting Factors (Coagulation Proteins)

The majority of clotting factors are zymogens, inactive proteolytic enzyme precursors that circulate in the body. Each zymogen's activation is indicated by adding the letter "a" to the Roman number designating that specific zymogen. With the exception of factors III, IV, and VIII, the liver produces the majority of the procoagulants and anticoagulants. These proteins go through a post-translational change that allows them to bind calcium and other divalent cations and take part in the clotting cascade (vitamin K dependent carboxylation of glutamic acid residues) [14]. Anticoagulation results from vitamin K deficiency or from using vitamin K antagonists like warfarin.

Coagulation proteins have a complicated nomenclature [Table 1]. The first four of the twelve factors that were initially found are referred to by their common names, i.e., fibrinogen, prothrombin, tissue factor (TF), and calcium, and are not given any Roman numerals. FVI is no longer around. Roman numbers have not been allocated to the more modern clotting factors (such as prekallikrein and high-molecular-weight kininogen). Some factors go under multiple names. Because their coagulant activity is not stable in preserved blood, factors V and VIII are also known as labile factors.

The liver produces the plasma protein prothrombin (MW 68700). It is an unstable protein that breaks down into smaller proteins, thrombin (MW33700) being one of them. The pro-inflammatory effects of thrombin, which is produced from prothrombin, are also mediated through protease activating receptors found on monocytes, lymphocytes, endothelium, and dendritic cells [15].

Blood plasma contains the glycoprotein known as von Willebrand factor, which is also generated naturally by the endothelium, megakaryocytes, and subendothelial connective tissue as ultra-large vWf. It facilitates the adherence of platelets to subendothelial surfaces. It also serves as a carrier protein for Factor VIII's coagulant action, where it is known as VIII: C [16,17]

Disorders Of Coagulation

In a healthy physiological state, the body consistently regulates a equilibrium between clotting and bleeding. However, any pathological condition can disrupt this balance, leading to either hemorrhagic or thrombotic outcomes. Consequently, disorders of hemostasis can be categorized into those causing unusual bleeding and those resulting in abnormal clotting.

Table 1.

Bleeding disorders	Thrombotic disorders (thrombophilia)
Hereditary	Hereditary
Von Willebrand disease	Hereditary thrombophillia
Haemophilia A	Antithrombin III deficiency
Haemophilia B	Protein C deficiency
Haemophilia C	Protein S deficiency
Factor V deficiency	Factor V Leiden (factor V mutation)
Factor X deficiency	Prothrombin mutation (Gene 20210A mutation)
Factor VII deficiency	
Factor XIII deficiency	
Prothrombin deficiency	
Afibrinogenemia	
Acquired	Acquired
Consumptive coagulopathies	Antiphospholipid antibody syndrome
DIC	Increased levels of factors VIII, IX, XI, or fibrinogen
Microangiopathic haemolytic anemias	Fibrinolysis defects
Vitamin K deficiency	Homozygous homocystinuria
Liver disease	

DIC – Disseminated intravascular coagulation

Conclusion

Hemostasis, a complex physiological process, maintains the fluidity of blood and is regulated by a delicate equilibrium between the body's thrombogenic and antithrombogenic systems. When this balance is disrupted, it can lead to an increased risk of bleeding or thrombosis in a patient. Hence, before administering any pharmacological interventions, it is imperative to have a thorough grasp of its physiology to anticipate the potential pathological and clinical consequences.

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