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Platelet Hyperactivity and Thrombosis: Biochemical Mechanisms in Critical Conditions

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Abstract

Background: Platelet hyperactivity has a central role in the process of thrombosis during important stages like injury, sepsis, and cardiovascular events. Platelets are required for hemostatic plug formation, but the activation of platelets can also result in formation of pathological thrombi and life threatening events.

Aim: The goal of the present research is to examine the metabolic background of platelet hyperactivity and its implication in thrombosis in severe medical conditions.

Methods: A literature review was performed and the findings based on the biochemical processes accounting for platelet activation and aggregation during trauma, sepsis and cardiovascular diseases have been reported.

Results: The review identified that inflammation, oxidative stress and endothelial dysfunction are main factors that influence the platelet activation and thereby enhancing the thrombus formation and corresponding risks of stroke, myocardial infarction and pulmonary embolism.

Conclusion: Hyperactivity of platelets is essential during thrombosis in critical conditions. Knowledge of such biochemical pathways displays practical approaches on how the thrombotic risks that are so characteristic of individual critically endangered can be controlled.

Keywords: Hyperactivity, Thrombosis, Critical illness, activated platelets, inflammation, platelet, oxidant stress.

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1. Introduction

Platelet hyperactivity and thrombosis are dangerous events in critically ill patients, especially in cases of trauma, sepsis, and cardiovascular related emergencies. Hemostatic platelet play a critical role in wound healing; however, when over activated by the upstream events such as invading pathogens, SPS, Oxidative stress and endothelial dysfunction can provoke pathological thrombus. This brings more life threatening complications such as stroke, myocardial infarction, and pulmonary embolism. Knowledge of the biochemical processes that contribute to platelet hyper reactivity in these essential states is important to enhance patient prognosis and control thromboembolism. This work investigates the role played by platelet hyperactivity in thrombosis during critical situations and the biochemical pathways underlying thrombus formation in traumatic and emergency conditions. Studying the causes for platelet activation and congregation in their pathophysiological context will help to understand possible approaches for prevention of thromboembolic complications in critically ill patients.[1,2]

Platelet Structure and Function: A Biochemical Perspective

Platelets or Thrombocytes are relatively small, enucleate cell fragments in the blood formed in the processes of the fragmentation of mega-karyotypes in the bone marrow. Although they are ace nucleated they are highly active metabolically, packed with organelles, receptors For coagulation and with a highly organized cytoskeleton these cells play a important role in hemostasis. Human platelets are enucleate and assume a discoid shape in their quiescent state, the shape of which is preserved by a marginal band of micro tubules. The photocatalytic properties of this shape also affords optimal circulation throughout the bloodstream or within a desired specific area of the body. A human platelet membrane has a structure with glycoprotein receptors on the platelet membrane surface in the form of a dense network which includes direct interactions with the platelet surface membrane lipids and proteins, other cells, including leukocytes, endothelial cells and almost all soluble proteins of the blood. These receptors therefore serve as important signal-transducing machinery for detecting clues of vascular injury that elicits platelet activation and clotting.[3,4] The plasma membrane of platelets also has glycoprotein complexes: GPIb-IXV complex, which anchors the platelets to vWF and GPVI which binds platelets to exposed collagen at the site of the lesion. This activation leads to an astonishing reorganization of the platelets tending towards thexa high degree of activation reflects the aggregation of multireceptor signals, which causes a range of morphological, biochemical and functional changes at the platelet level. ChromAFF-positive platelets contain three types of granules : alpha granules

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containing coagulation factors, dense granules containing adenosine derivatives and lysosomal granules. These are the largest and most numerous and are involved in storage of adhesive proteins such as von Willebrand factor, fibrinogen and thrombospondin as well as growth factors including platelet derived growth factor, PDGF. Small dense granules on the other hand contain ongoing particles such as ADP ATP, calcium ions and serotonin which are released immediately upon platelet activation to enhance platelet congregation and congregation. Lysosomes provide enzymes which have an involvement in tissue repair and also in those processes which cause inflammation.[3,4]

Platelet cytoskeleton is a structural element that is important in determining how these cells are capable of reacting to sites of vascular damage. In combination with microtubules and myosin, actin filaments force the shape change from the adopted smooth discoid to a spiky. low over-arching organization upon activation and high spread-out morphology. This reorganization of the cytoskeleton enables these platelets to stick well to the damaged endothelial lining and connect to other platelets when they begin to aggregate. Apart from shape change, there is a rearrangement on platelet surface whereby phosphatidylserine moves from the inner membrane to the outer surface in a pro-coagulant state. PS exposure lay the platform upon which coagulation factors assemble as a result enhancing thrombin production and ensuing fibrin clot over the platelet plug.[5,6,7]

Biochemically, platelets have the ability to react to numerous agonists indicating tissue damage or damaged blood vessels. These agonists include; thrombin, adenosine diphosphate (ADP), collagen, and thromboxane A2 (TXA2). As is derived from coagulation factors , thrombin is one of the most potent activators of the platelets. This substance activates protease-activated receptors (PARs) and links to intracellular calcium signaling that triggers granule release and increases the function of integrins. Likewise, the stored in dense granules ADP binds to P2Y12 and P2Y1 receptors and enhances platelet aggregation and the desired coagulation effect. TXA2 prepared from arachidonic acid through cyclooxygenase-1 (COX-1) is both a cofactor and a vasoconstrictor in the hemostatic process.[8,9]

Platelet activation and aggregation, inferred from the pathways in Figures 1–4, will be briefly described below.

Platelet activation and aggregation are central pathophysiological events during hemostasis, which prevents blood loss after vascular damage. These processes occur through an orderly series of reactions that act on cell surface receptors and signaling pathways as well as the secretion of diverse bioactive products. Whenever the endothelium is damaged, one comes across such sub endothelial components as collagen and von Willebrand factor, or vWF, which binds and activates platelets. This first step represents the first in a cascade of very orderly biochemical reactions leading to platelet aggregation and the formation of a stable platelet plug.[10,11] In the first instance of platelet contact, exposure of GP receptors on the platelet surface is most prominent. Glycoprotein Ib-IX-V complex interacts with vWF and attaches the platelets to the exposed extracellular matrix during high shear stress. At the same time with that, the GPVI receptor connects to collagen and triggers intracellular signaling pathways. This results in the activation of phospholipase C (PLC) which further cleaves phosphatidylinositol 4,5- bisphosphate (PIP2) to generate inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 mobilizes calcium ions (Ca^{2+}) from dense tubular stores and this activity is central to platelet activation. High intracellular concentrations stimulate the activity of protein kinase C (PKC) and calcium-dependent enzymes as representative components of the platelet activation response. PKC, in particular, modulates secretion of granules, activation of integrin, and other rounds of activation signals.[12,13] Perhaps the best characterized event associated with platelet activation is the change in conformation of the integrin αIIbβ3 (also referred to as the glycoprotein IIb/IIIa receptor). αIIbβ3 in its basal conformation is not active and is unable to bind fibrinogen. But in activated platelets, intracellular signaling pathways mainly involving talin and kindlin proteins cause a change in conformation of the integrin. The αIIbβ3 in their active state binds to fibrinogen which link two adjacent platelets putting a push towards aggregation. This fibrinogen-mediated platelet-platelet aggregation is the basis of consolidation of the primary hemostatic plug.[14,15]

The activation of platelets is again augmented by the release of granule content and the formation of thromboxane A2 an important contributors to platelet aggregation. Platelet is laden with granules concentrated with ADP capable of working as strong agonist through P2Y1 and P2Y12 receptors available on the platelet membrane. Binding of ADP to these receptors produce more intracellular calcium signaling and increase αIIbβ3 activation to encourage more aggregation. On the other hand TXA2 produced through the cyclooxygenase-1 (COX-1) pathway from arachidonic acid is a platelet activator and a vasoconstrictor. TXA2 binds the TP receptor on the neighboring platelets in a positive feedback mechanism that increases platelet recruitment as well as agglutination.[16,17] At the same time thrombin the enzyme that plays a crucial role in the clotting process is one of the most effective activators of platelets. Thrombin acting on PAR-1 and PAR-4 receptors cleaves a site resulting in the formation of a tethered ligand that stimulates intracellular signal transducers. These lead to an additional rise in intracellular calcium, granules release and activation of integrin and greatly enhances the formation of the platelet plug. Also, reversible expression of phosphatidylserine (PS) on the platelet membrane provides the site for the fixation of coagulation factors that enhance thrombin formation and the subsequent deposition of fibrin that stabilizes the platelet aggregate into a clot.[18,19]

Top biomolecules involved in blood clotting process

Blood clot formation is called hemostasis which is a dramatic change of the blood biomolecules therein such as proteins, lipids, ions and cells. These biomolecules act in concert to stop bleeding after injury to the blood vessels, while at the same time ensuring that there is no excessive clotting. The principle ingredients in this process are platelets and plasma proteins, members of the coagulation factor family. Altogether, they contribute to the formation of a platelet-fibrin clot – the formation of a thrombus' body, which is made of platelets and fibrin. Components that form clot can be grouped as platelet activators, coagulation factors, adhesive proteins, and signaling molecules; all of which have a specific role in the entire process of hemostasis.[20,21] Closely associated with

clotting products, platelets require biomolecules hence the essence of this section to highlight the key biomolecules involved in the shape change, activation, and aggregation of the platelets. Membrane receptors on the platelet surface including Glycoprotein Ibs-IX-V and Glycoprotein VI that interacts with von Willebrand factor (vWF) and collagen, respectively, are key to platelet adhesion. Von Willebrand factor is a large adhesive glycoprotein that allows platelet adhesion to the sub endothelial matrix in response to vessel injury to aggregate at the site of injury. After adhesion, platelets acquire full activation and express on their surface biomolecules stored in their granules such as ADP, serotonin and calcium ions. ADP takes part of an applied signal amplifier interacting with P2Y1 and P2Y12 receptors on platelets surface to amplify the activation and strengthen platelet aggregation. Likewise to that, the thromboxane A _{2} (TXA _{2}) derived from arachidonic acid through, cyclooxygenase- 1 (COX-1) increases aggregation of the platelets and vasoconstriction hence contributing to the platelet plug.[22,23]

The coagulation cascade is another vulnerable factor and is actually a series of proteolytic reactions that comprise clotting factors. Clotting factors are for the most part zymogens or inactive derivatives of enzymes and each clotting factor is brought about in a consecutive fashion. Whereas the extrinsic pathway is founded on factor VII, tissue factor (TF) and calcium ions the intrinsic pathway involves factors XII, XI, IX and VIII. The final step in these pathways is the generation of Factor X to active Factor Xa form which complex with Factor Va, to form prothrombinase complex. This complex fosters the activation of prothrombin to thrombin; which is the special REQUIREMENT enzyme on the formation of a blood clot. Thrombin plays a dual role in hemostasis: that splits fibrinogen into fibrin monomers that then polymerize into stable fibrin meshwork and it activates platelets and other coagulation factors including factors V, VIII as well as XIII . Factor XIII or known as fibrin-stabilizing factor ties the fibrin filaments to covalent bonds, at the same time making the clot firm and more susceptible to mechanical and enzymatic breakdown. One more biomolecule necessary for blood clot formation as well as a soluble plasma protein is fibrinogen. It functions as the precursor to fibrin and also as a central player in platelet aggregation by interacting with activated platelet's – GPIIb/IIIa integrin receptors. After the thrombin cleaves the fibrinogen it forms fibrin monomers which then deposit by processes of further polymerization to form insoluble fibrin strands. Elements here form a network, which strengthens the platelet plug and also help to fan red blood cells thus reinforcing the clot. One of the less recognized, but very important biomolecules is Calcium ions (Ca^{2+}) who act as a cofactor for several enzymatic reactions As a co-factor it is involved in the activation of Factors II, VII, IX and X and stabilizes coagulation complexes of negatively charged phospholipid surface of platelets.[24,25]

Signaling molecules along with structural biomolecules must not only form clot but regulatory biomolecules ensure that this clot stays localized and the process is controlled. About antithrombin, protein C and S which works as agents to resist blood clotting. Heparin neutralizes both thrombin and Factor Xa and Protein C system inactivates Factors Va and VIIIa to check extension of clot. tPA and plasmin are implicated in the dissolution of clot through the dissolution of the fibrin in the blood vessel which is formed by the coagulation of platelets, once vessel repair work is over.[26,27]

The Coagulation Cascade: Interregistration with Platelet Biochemistry

The coagulation cascade and platelet biochemistry are major processes which work hand in hand to promote hemostasis, which is the body's way of ceasing to bleed, following vessel damage. Whether from platelets, being the cellular components responsible for the clot formation or the coagulation cascade that produces fibrin, a structural protein need for the firmed up clot. Each of these alliances between platelet biochemistry and the coagulation cascade show the cellular biochemical interdependence and coherence of the cellular parts and biochemistry of platelets –with particular focus on their localized and global maintenance of vascular integrity.[28] Coagulation factor reactions are organized into two principal pathways: intrinsic factor and extrinsic factor that combine at a similar point in the clotting process to produce thrombin, an essential ingredient in the clotting process. The extrinsic pathway is triggered by tissue factor (TF), a transmembrane cycler protein derived from the injured endothelial cells and sub endothelial tissues. TF binds to FVII and, after the cleavage of FVII to FVIIa, the complex TF-FVIIa converts FX to FXa. At the same time the intrinsic pathway is activated if collagen, basement membrane or other negative surface expose Factor XII and activates it starting up the chain of activation of Factors XI, IX and VIII. In both pathways, calcium ions (Ca^{2+}) and phospholipids are cofactors which drive the assembly of enzymatic complexes on the activated platelet surface, and hence guarantee the appropriate continuation of the cascade.[28,29] Platelets have an important function of linking the coagulation cascade because they offer a surface on which the enzymes act. W hen stimulated, platelets alter their shape and express anionic phospholipid phosphatidylserine at the outer surface. This exposure provides a favorable condition for the formation of coagulation complexes, the tenase complex [Factor IXa, Factor VIIIa and Ca^{2+}] and the prothrombinase complex [Factor Xa, Factor Va and Ca^{2+}]. These complexes increase the formation of thrombin and push the production of fibrin and strengthening the clot. More importantly, activated platelets release calcium ions and procoagulant granule contents that subsequently amplify the coagulation reactions of the coagulation factors establishing a direct biochemical relationship between platelet and clotting factor activation.[30,31] Thrombin the main function being the last enzyme in the coagulation cascade ties the efforts of this process with the activation of platelets. The thrombin formed then binds to protease-activated receptors (PAR-1 and PAR-4) on the exterior surface of the platelet, this activates intracellular signalling pathways that encourage the platelet to change shape and to secrete granules. Thrombin also stimulates receptors GPIIb/IIIa the fibrinogen in plates and plays a central role in platelet aggregation. In addition, thrombin cleaves fibrinogen, a soluble plasma protein into individual fibrin monomers that immediately react with one another to form a fibrous meshwork which reinforces the platelet plug. Besides from augmenting the strength of the clot, fibrin strands present a supportive stroma onto which additional platelet aggregates, red blood cells, and plasma proteins can be immobilized and integrate the final coagulative process.[32,33]

This interaction between platelets and coagulation cascade is regulated in a reciprocal manner to give a high of hemostasis. Web of activated platelet discharged bioactive substances, including adenosine diphosphate (ADP), thromboxane A2 (TXA2), and serotonin that will attract extra platelets and accelerates thrombin production. At the same time, platelets also promote the amplification of coagulation through supply of a phospholipid canvas for enzymatic reactions. Positivity of these feedbacks makes sure that only high rate of thrombin production and fibrin formation is achieved at the site of injury. On the other hand, coagulation cascade, especially by means of thrombin, thereby promoted platelets activation, aggregation, and granules release and, thus, further confirm clotting.[34]] Coinciding with the processes of clot formation, platelets and the coagulation cascade interfaced with the anticoagulant and fibrinolytic to control size of the clot formed and to prevent excessive formation of blood clots or thrombi. Antithrombin, protein C and Tissue factor pathway inhibitor works to counter activate coagulation factors and make sure that clot formation only occur at the site of vessel damage. At the same time, other enzymes, e.g., plasmin, solubilizes fibrin, and promotes its clearance from the site of vascular repair once complete. On the one hand, activated platelets stimulate coagulation, on the other – they bear thrombin-sensitive molecules, such as thrombomodulin, that can turn on the protein C pathway to prevent excessive clotting. [34]

Emergency Situations and the Role of Platelet Biochemistry in Hemostasis

Blood clotting is most critical in disaster or occurrences like traumatic injuries, surgery, or vascular rupture when a rapid response is needed to avoid much bloodshed. This response called hemostasis involves platelet biochemistry and coagulation series to create blood clot that is stable. Among the blood cells, platelets, those that define as small blood cells, are the first one engaged in the [hemostasis]. Because of their biochemical characteristics they are capable of binding to and recognizing vascular injury, attaching themselves to the site of damage, activating, and actualizing to form a clot that stops blood loss. This initial wielding of the platelets is supported by the biochemical coagulation cascade which forms fibrin a supporting protein that constructs the platelet plug stronger and durable enough to take Mechanical stress in emergency conditions.[35] Specifically, regarding biochemistry of platelets and their participation in emergency hemostasis, adhesion of the platelets to the extracellular matrix, including collagen and von Willebrand factor (vWF). Damage of endothelium and its subsequent exposure to extracellular matrix initiates activation of platelets in a trauma situation. This integrated network rearrangement and the surface receptors present on the platelet membrane, particularly the glycoprotein Ib-IX-V, attaches to vWF for platelet adhesion to the site of injury. At the same time, another receptor of platelet membrane – GPVI – can adhere to the surface and flank collagen fibers, and activate the signaling processes inside the platelet. It results in some micro morphological changes, changes in the platelet form and function such as shape change, release reaction and opening of the glycoprotein IIb/IIIa receptors. These activated receptors are central to platelet aggregation since after binding to fibrinogen, the receptors hook adjacent platelets together and form a stable plug via interaction.[36] This biochemical signaling within activated platelets is especially important under emergent conditions because it increases the amplitude of the hemostatic response. The contents of dense granules which include ADP, calcium ions and serotonin are released and amplify platelet activation more platelets are drawn into the site of injury.[37]

The biochemical signaling within activated platelets is specially required in emergency situations because it enhances the hemostatic response. Bound platelets release substances stored in dens granules that include ADP, Calcium ions and serotonin which act to amplify the activation of other platelets to the site of injury. Thromboxane A2(TXA2) acting probably through the cyclooxygenase (COX) pathway is another potent mediator responsible for platelets activation along with vasoconstriction, which in turn decrease the blood flow to the injured site. This biochemical interplay has the effect of provoking a fast and localized platelet activation, which is vital in haemostasty since a bleeding has to be stopped immediately in order to avert shock and sometimes death.[38] Initiation of coagulation is by platelets but distinct from platelets, the coagulation cascade plays enhances and supports the clot integrity. Able to form a procoagulant surface exhibiting negative phosphatidylserine on its surface which is required for the assembly of enzymatic complexes that are essential for thrombin formation. Thrombin, the central enzyme in the coagulation cascade, serves multiple functions: the activation of which converts soluble fibrinogen into fibrin, enhances platelet activation by binding to protease-activated receptors (PARs) and supports the clotting process through the activation of factors V, VIII, and XIII. In emergency situations, the formation of thrombin is higher and fibrin ensures that the platelet plug formed rapidly conforms to a robust fibrin mesh that denies further bleeding at the site of injury.[39] Particularly, one must emphasize the importance of abovementioned biomolecules as supply of only analysed biomolecules to platelet biochemistry for the process of efficient emergency hemostasis will be insufficient for signal transduction in case all factors are not functional. Calcium ions for instance takes part in both platelet activation and coagulation. They are needed for granule release, cytoskeletal reorganization, and the binding of coagulation proteins to the platelet surface. Also, vWF, fibrinogen, and thrombin are also important for platelet adhesion, aggregation and fibrin then formation, respectively. Consequently, any defects or disorders in these biochemical constituents affect coagulation, resulting in excessive bleeding in even the simplest types of injury. In more extensive injury or extensive hemorrhagic states, the capacity for platelet response in challenged even more, especially if the patient loses significant amount of blood or has developed coagulopathy. Potentially relevant diseases that include hypothermia, acidosis and hemodilution which are normal in emergent trauma cases affect the functionality of platelets and coagulation cascade. For instance hypothermia effects enzymatic reactions that are needed to form thrombin While acidosis affects the responses of platelets. In such important situations where complication may arise, treatment like platelet transfusion, fibrinogen products and coagulation factors are called for to enhance proper coagulation.[40] It remains critical to change the fact that platelet biochemistry is the primary and essential for emergency hemostasis action to prevent blood loss.

Regarding initiation, the diverse relationships among the platelets entail the formation of an initial plug by platelets adhesion, activation, and aggregation. This process is efficient in terms of its own function and needs a proper combination of signaling molecules, receptors and biochemical mediators. Knowledge of these mechanisms is of particular concern not only for the treatment of trauma and surgical events but also for the possibility of creating specific therapies for bleeding disorders and situations where platelet function is impaired.

Assays of Biochemical Clotting Abnormalities in Trauma and Emergency Situations

Disorders in platelets are the leading causes of coagulopathy and hemorrhagic conditions, when trauma patients develop various adverse emergency scenarios. It is essential for diagnosis, management, and monitoring of recalcitrance of these life threatening situations that biochemical markers of platelet dysfunction are determined. Disorders of hemostasis such as TIC, platelet consumption, and platelet signaling defects are common in severe trauma, hence the need for biochemical data on which to base management efforts. Several biochemical markers can indicate platelet function and activation status and overall hemostatic efficiency and serve as the basis for the investigation of the pathophysiology of platelet abnormality in emergency conditions.

Among all biochemical markers of platelet pathophysiologic state, perhaps the most extensively investigated marker correlates with platelet dysfunction and mobilization is P-selectin (CD62P), which belongs with platelet membrane glycoproteins and is stored in platelet alpha granules. P-selectin is carried from 600 to the platelet surface during the process of activation and consequently serves as an indicator of degranulation and activation of platelets. However, in trauma and emergency, as we saw, platelets can be activated and remain active for a relatively long period, after which it starts to shed P-selectin making it unavailable on the surface of the platelets. These results also reveal that increased concentrations of plasma sP-selectin can present a sign of erroneous platelet activation or the disturbance of hemostasis. Unfortunately in severe trauma patients, over-release of P-selectin reflects platelet overload and coagulopathy formation, which makes them more prone to postoperative bleeding. Therefore, the determination of serum P-selectin concentrations is an important way to access the platelet activity in traumatic coagulopathies.[41]

Another important biochemical marker are thromboxane A2 (TXA2) and their stable metabolite thromboxane B2 (TXB2). TXA2 in a metabolite of arachidonic acid through the COX route to promote platelet aggregation and vasoconstriction during hemostasis. In the trauma patients, low thromboxane levels might be due to depression of platelet biosynthetic activity or disorder in COX pathway caused by hypothermia or acidosis. On the other hand, over-production of TXA2 may leads to platelet hyper activation and microvascular thrombosis, that superimposes on systemic inflammation and organ dysfunction. Therefore in order to evaluate the biochemical activity of platelets and identify their dysfunction in emergency conditions, it is necessary to use quantitative evaluation of TXA2 and its metabolites.[42]Other crucial undesirable changes that reflect platelet dysfunction can also be seen in the markers of platelet granule secretion. Semi-lattices secrete adenosine diphosphate (ADP), serotonin to promote platelet retention and cohesion. For example, in the trauma patients, if granule secretion is defective, ADP release may be inadequate to platelet signaling and aggregation. Biochemical indicators of disharmonious platelet functioning include low concentrations of plasma-ADP or serotonin. Likewise, disorders that affect the secretion of alpha granule can correspondingly manifest in the reduction of PF4 and β-TG – proteins which are secreted during platelet activation. Lower plasma concentrations of these granule markers might be expressing platelet consumption or impaired functionality in severe trauma and severe hemorrhage.[42,43]

The other biochemical abnormality is the reduction in platelet surface receptor expression and abnormalities in signaling molecules. Based in part on this premise the glycoprotein IIb/IIIa is arguably the most important marker, the integrin receptor among platelets which is directly involved in fibrinogen binding and platelet aggregation. Trauma and emergency-related dysfunction may cause low GPIIb/IIIa activation or platelet receptor shedding affecting platelets aggregation. Other test to diagnose defective platelet function include flow cytometry or biochemical assays that are used to measure activated GPIIb/IIIa. Such omissions or dysfunctions in receptors as GPVI (collagen receptor) or GP Ib-IX-V (von Willebrand factor receptor) can prevent platelet adhesion and activation and, therefore, impaired hemostasis. Calcium ions (Ca^{2+}) are main bioactive elements in platelets and are involved into various reactions as secondary messengers of platelet activation and coagulation. Abnormalities in calcium homeostasis are known to affect platelet cytoskeletal rearrangement, dense/alpha-granule release, and expression of the procoagulant surface. Acidosis or hypocalcemia as seen in the traumatized patient for instance, can deny the platelets the correct mobilization of calcium, which generates faulty response to platelet activation . Also, changes in phosphatidylserine (PS) exposure that delivers a procoagulant surface for coagulation cascade can also be used as a biochemical index of platelet dysfunction. Lower PS exerts a detrimental effect on thrombin production and synthesis of fibrins thus enhances bleeding complications in the trauma patients.[44] In addition, platelet mitochondrial dysfunctions have been described as a novel biochemical marker of platelet pathophysiology in emergencies. Platelets have provisions that show that mitochondria are involved in energetic modifications and generation of reactive oxidant species. Mitochondrial damage in the patient who has sustained a trauma can compromise ATP production, results in energy level deficiency that affect the ability of platelets to clot. They may also enhance ROS production which also leads to oxidative stress and platelet apoptosis and dysfunction. Mitochondrial membrane potential, ATP levels and ROS generation are thus potential biomarkers of platelet quality and function in trauma. Platelet Hyperactivity and Thrombosis: Risks from Critical Conditions[45]

Increased platelet reactivity is considered the central pathophysiological event in thermogenesis, especially in the setting of critical illness, including the trauma, infection, or acute cardiovascular catastrophe. In steady state, the platelets are beneficial components of the blood since they form plugs where there is any form of vascular damage to check bleeding. However, during critical conditions, platelets agitated inadvisedly and formed pathological thrombi which in some way occlude blood vessels and can lead to conditions such as stroke,

myocardial infarction, or pulmonary embolism. It is therefore important to elucidate the factors that lead to platelet hyperactivity and its involvement in thrombosis with a view of helping clinicians recognizing potential patients at risk and in the development of strategies of dealing with the same in critical care settings. [46,47]

Conclusion

Hyperactive platelet is one of the most important contributors to favorable thrombosis during critically ill situations through inflammation, oxidative stress, and endothelial dysfunction that enhance thermogenesis. Inflammatory mediators like Thromboxane A2, cytokines and endothelial impairments predetermine hyperactivity of platelets and promote pathologic coagulation and thermogenesis in trauma, septicemia, cardiovascular etc. The following study uncovers multifactorial biochemical mechanisms of hyperactive platelet, which is beneficial for understanding the increased thrombotic threat in emergencies. Since platelet dysfunction involves the control of the clotting process, its management ought to be extremely sensitive to encourage clot formation while suppressing clot formation that is dangerous to the body. Thus, knowing these mechanisms, clinicians can more effectively use therapeutic approaches to decrease the thrombotic risks in the critically ill population. Lastly, selective tackles for the biochemistry of platelet over activity may translate to preventing the catastrophic effects of thrombosis in critical care situations.

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