# Thrombopoietic singularity of some acquired coagulopathies (hypothesis)

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***Abstract.*** *Fundamentally different etiology, pathogenesis and clinical manifestations of acute massive blood loss and viral infection COVID-19 differ most of all in the rate of replacement of hypercoagulation with hypocoagulation: in acute massive blood loss, this occurs almost instantly and ends in bleeding, with infection, hypercoagulation is prolonged, and although active platelet cells are removed, macrophage cells are removed spleen and immune complexes, thrombocytopoiesis is constantly stimulated by thrombopoietin (TPO) synthesized in the liver, which leads to the formation of blood clots and thromboembolism. In this regard, when compared with each other, both models of coagolopathy can shed light on the "grimaces" of hypercoagulation and provide information on how the physiological response closes in a vicious pathological circle.*

***Keywords:*** *coagulopathy, acute massive blood loss, COVID-19, thrombopoietic activity, young platelets, hypercoagulability.*

## Introduction

In creating man, nature did not invent anything specifically for health or illness; in a particular case, the disease may differ from the norm by an individually excessive adaptive response of the organism to the pathogenic factors of the internal or external environment [7]. Acquired coagulopathies, the fatal consequences of which begin with hypercoagulation - in essence, the body's adaptive response to damage to the vascular endothelium.

**Coagulopathy** — diseases caused by disorders of the blood coagulation system, hemostasis. Acquired coagulopathy associated with another pathology, posing a mortal threat, will not be understood without assessing the body's ability to protect itself, for example, from blood loss or from infection, i.e., hemostatic reactions.

**Hemostasis** — body reactions aimed at preventing and stopping bleeding, i.e. complex interaction of platelets, plasma coagulation cascades, fibrinolytic proteins, blood vessels and cytokines to limit blood loss by maintaining the integrity of the vascular wall and the formation of blood clots while maintaining the liquid state of the blood: "System of regulation of the aggregate state of blood" (RASB) [2].

***Thrombocytes*** or platelets - this "dust of blood", until now, from the moment of their first description, attract the attention of practitioners and researchers [18]. The functions of these cells still cannot be considered uncovered, but it is clear that membrane complexes of glycoproteins (GP) play a leading role in them. It is also clear that the formation of a thrombus at the site of damage to the vessel - **primary hemostasis**, begins with the adhesion, secretion and aggregation of these cells. In addition, circulating usually in large numbers, platelets are the first to get on the path of viral infection, meeting with which accelerates the renewal of their population [28]. In the bone marrow of an adult weighing 70 kg, $175x10^9$ platelets should be produced daily. The process of their production controlled by TPO, interleukins (IL-3, IL-6, IL-11) and transcription factors (GATA-1, FOG-1, NF-E-2) is conventionally divided into maturation of megakaryocytes (megakartocytopoiesis) and platelet biogenesis (thrombocytopoiesis) [41]. An important stage is the formation of young (immature or reticular) cells containing mRNA residues [25]. Informational RNA (mRNA) of newly formed platelets during their circulation in the blood rapidly degrades: within 24 hours in dogs and mice (the life cycle of mature platelets in dogs is 7 days, in humans - 10 days); usually about 10% of platelets contain residues of mRNA (staining with fluorochromes), corresponding to the number of young cells, on the determination of which non-invasive monitoring of thrombocytopoiesis is based [20, 46, 49]. The number of platelets usually falls within the range from $150x\ 10^9$/l. to $400x\ 10^9$/l., their number from $100x\ 10^9$/l. to $150\ x\ 10^9$/l. is considered borderline, and bleeding usually does not occur until it falls below $50\ x\ 10^9$/l. [40]. With a platelet count of $100\ -149\ x\ 10^9$/l. thrombocytopenia is considered mild, less than $100\ x\ 10^9$/l. –moderate to severe [43]. In thrombocytopenia, megakaryocytes migrating from the bone marrow are responsible for 50% of platelet biogenesis in the lungs [31].

Interacting with GP receptors with von Willebrand factor (vWF) and collagen, platelets adhere to vascular lesions, release granules, change their shape, and, aggregating, bind to plasma ligands, forming a platelet clot [48]. Having a high density of GP-receptors, in particular, the fibrinogen receptor (integrin αIIb αIIb/$\beta_3$), hemostatically active young platelets in vivo during thrombus growth are the first to attach to the subendothelial matrix, activate and activate mature cells and blood coagulation cascades [17, 36, 37]. The proportion of immature cells in the total platelet population (IPF,%), as well as their daily biogenesis (aIPF) [12], even with relative thrombocytopenia, increases within a short period of time, and the growth of these cells in platelet donors lasts for two weeks [6].

Violations of the mechanisms of primary hemostasis cause almost 80% of cases of bleeding and 95% of cases of blood clots [2].

**Acute massive blood loss**

A catastrophic decrease in the volume of circulating blood, a prolonged decrease in the efficiency of blood flow, a drop in the oxygen capacity of the blood, and hypovolemic shock are the main consequences of massive blood loss. Severe arterial hypotension, slowing of blood flow in microvessels (stasis) and ongoing bleeding at the same time contribute to the development of hypercoagulation, and then - hypercoagulative and hypocoagulant phases of disseminated intravascular coagulation (DIC) [5], which is characterized by multiple microthrombosis, primarily of capillaries and venules, consumption of thrombocytes and plasma blood factors [4].

It is believed that acute massive blood loss is a traumatic coagulopathy with a hemorrhagic phenotype and microthrombosis of blood vessels due to activation/suppression of blood coagulation [32, 45]. Acute blood loss with concomitant shock, impaired clot formation and, in severe cases, hyperfibrinolysis predominates at the early stage of traumatic coagulopathy, however, the state of systemic endogenous hypercoagulation observed in the immediate post-traumatic period (within 1 hour after injury) quickly turns into consumption coagulopathy [38, 44]. Perhaps due to the accelerated selective removal of young platelets.

**Its genesis in this case can be hypothetically represented as follows:**

1. Tissue factor (TF) is the primary cellular initiator of blood coagulation; after a vascular injury, it activates the coagulation protease cascade, which leads to the deposition of fibrin and "revitalization" of platelets [34].
2. The "revitalization" of platelets adhered to the endothelium through PAR receptors, apparently, begins with their young forms, since they are the first to interact with the damaged endothelium [36].
3. The duration of circulation in the peripheral blood of young platelets is 24 hours [20], but with thrombocytopenia, their composition is rapidly renewed [6].
4. Active platelets lose sialic acid residues (glycans) and are recognized by Ashwell-Morrell receptors (AMR) of hepatocytes, which is combined with their apoptosis through the "JAK2-STAT3" signaling pathway [19].
5. AMR-mediated selective removal of desialylated platelets by regulating the synthesis of thrombopoietin in the liver, forcing thrombocytopoiesis [22].
6. Primary hemostasis after selective clearance of young platelets and depletion of blood coagulation factors becomes a pathogenetic link in coagulopathy.
7. In conditions of ongoing bleeding, this mechanism contributes to the transition of hypercoagulation to hypocoagulation.

The mortal danger of acute blood loss, as well as the need for blood replacement, were realized in antiquity: the alchemist Libavius in 1615 described in detail the rules for blood transfusion [27]. Today, transfusion aid for acute massive blood loss is correction by means of

modern transfusion medicine: saline and colloidal solutions, components and preparations of donor blood, including plasma, blood gas carriers, platelet concentrates and hemostasis correctors [5].

**Coagulopathy COVID-19** (CAC)

The 2020 pandemic caused by a new β-coronovirus or coronavirus of severe acute respiratory syndrome CoV-2 (SARS-CoV-2) and called "COVID-19" manifested itself in a number of organ-specific and systemic phenotypes, some of which were observed in viral infections earlier, and many others are unique [13].

Considering the pathogenesis of infection, Domingo et al. (2020), identified four interconnected vicious circles: viral infection, dysfunction of the renin-angiotensin-aldosterone (RAS) system, inflammation, and coagulation defects - the four riders of the viral apocalypse [16].

With regard to coagulation defects, Chinese doctors were the first to note the efficacy of low molecular weight heparin in CAC: a decrease in mortality after 28 days of observation, even in patients with more than four points for sepsis severity or in patients with a distinct rise in D-dimer. In general, coagulation disorders in COVID-19 are characterized by a distinct rise in procoagulant factors such as fibrinogen and D-dimers, combined with a poor prognosis: in patients in intensive care units (ICU), the frequency of venous thromboembolism increases (25% -36%) with primary localization in the lungs. In 7.7% of them, the standard prophylaxis of venous thromboembolism is not effective.

Infection of endothelial cells, cell infiltration and exposure to cytokines/chemokines cause dysfunction and apoptosis of these cells, contributes to the development of microcirculatory prothrombotic effects: hyperinflammation leads to hypercoagulation. Inflammation involves both the intrinsic and extrinsic coagulation pathways: TF activates endothelial cells and macrophages through the extrinsic pathway, and the intrinsic pathway can be activated by extracellular neutrophil traps (NETs) in the process of so-called NETs, triggered by endothelial cells, platelets and the complement system, after whereby proteases inactivate endogenous anticoagulants.

The role of platelets in CAC is dual. First, the secretion of α-granules recruits polymorphonuclear neutrophils and macrophages, the main source of interleukin IL-1b. In addition, platelets, stimulating NETs, are activated secondarily (feedback). Second, the assembly of the "enzyme-cofactor-substrate" complex on the platelet surface "triggers" coagulation.

The mechanisms of coagulation and acquired thrombophilia in COVID-19, in most cases leading to venous, arterial and microvascular thrombosis, require careful thought, reflection and research [3, 9, 11, 13].

The data accumulated during 2020 suggests that a consequence of severe COVID-19 infection is a virus-associated CAC with an imbalance in platelet consumption and production [11, 29, 35, 47, 50].

**Perhaps SARS-Cov-2 generates fatal hypercoagulability** either by attracting more and more hemostatically superactive platelets to the damaged endothelium, or by acting directly on hematopoiesis:

1. CAC – hypercoagulability: high clot strength, low rate of lysis (decreased fibrinolysis), and rapid formation of fibrin with a greater effect of inflammation on fibrinogen, vWF and platelets than on blood clotting factors [21].
2. The daily increase in young platelets in severe patients only increases [15, 24, 33].

CAC is fundamentally different not only from acute massive blood loss, but also from bacterial sepsis:

1. The absolute number of young platelets in septic coagulopathy, reflecting the forcing of thrombocytopoiesis, increases in the initial stage, but with an increase in the severity of the process, it decreases: on the third day of being in intensive care in patients with severe sepsis, the production of immature platelets falls dramatically [23, 29, 30, 39 ].

Possibly, like the "neocytolysis" that frees the body from young erythrocytes [10, 42], a kind of "neoclerance" (our definition) removes hyperactive young platelets, simultaneously forcing thrombocytopoiesis, but with massive blood loss or with severe sepsis, platelet production for some reason suppressed.

There are no means of etiotropic therapy for COVID-19 with proven efficacy [8], just as there are no indications for the transfusion of blood components and blood products to patients with COVID-19 ... except for anticoid plasma. The experience of past epidemics has shown that in the absence of specific treatment, transfusion of blood plasma of convalescents can be an effective approach [1]. Passive immunization by administering antibodies to an infectious agent using such plasma has also found applications in patients with COVID-19 [14]. Disaggregant correction of COVID-19 is a controversial issue, even though a high level of young platelet production (aIPF) is associated with the severity of infection and in the long term may help in the individualization of the antithrombotic regimen in COVID-19 [15, 24, 26].

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