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HAEMOSTASIS AND HAEMORRHAGE

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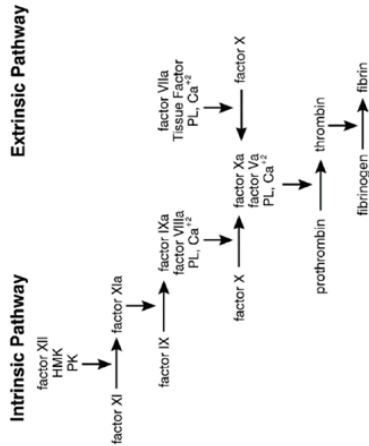
1. Haemostasis

Normal haemostasis practically incorporates interaction of two processes that are traditionally known as primary and secondary haemostasis. The final outcome of these complex and interdependent processes, is the formation of solid haemostatic (fibrin) cloth and stop of further bleeding. Simultaneously with the activation of the haemostatic cascade, the natural control mechanisms in the form of fibrinolytic system and antifibrinolytic cascade processes, are being activated as well. The end result of the complex haemostatic cascade reactions is the control of the ongoing haemorrhage, but also at the same time, prevention of excessive intravascular coagulation and prevention of uncontrolled fibrinolysis. The complete resolution of the formed cloth and re-establishment of the adequate blood circulation represents the final stage of haemostasis.

The primary haemostasis represents the initial response of the system upon the injury of blood vessel wall, and incorporates interaction of the nearby present platelets (Plt) with the endothelium of injured wall of the blood vessel. The first response of the blood vessel is local vasoconstriction as an attempt to limit the blood loss. Although the nerve reflexes play some role, it is accepted that local vasoconstriction response primarily is the result of the local myogenic spasm (1). Depending on the severity of the injury of the vessel wall, this reflex vasoconstriction can last from few minutes to several hours. The second component of the primary haemostasis is the formation of the initial platelet thrombus. Platelet primarily adhere to the collagen in the vessel wall that is being exposed after the endothelium injury. The next step in the cascade process is the activation and subsequently aggregation of the surrounding Plt to the site of injury. The formation of the platelet thrombus (initial cloth) usually takes from 3-7 minutes.

Secondary haemostasis incorporates the sequence of processes that ends with the formation of fibrin cloth. The coagulation factors (CF) are activated either through the intrinsic or the extrinsic pathway of the activation of coagulation cascade. According to the traditional understanding of the coagulation, the two pathways merge together into common pathway. The end result of this phase of coagulation, is the conversion of circulating fibrinogen into active fibrin. This process is usually completed in 3-10 minutes.

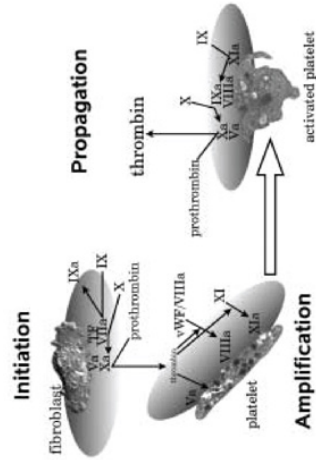
Figure 1. The cascade model of coagulation (From Hoffman et al. [2])



The final stage of coagulation is contraction of the components of the formed fibrin cloth (platelet thrombus, fibrin and trapped Erythrocytes (Er)) and formation of solid haemostatic cloth, also known as final cloth. In normal circumstances this final phase is finished within one hour. Platelets (Plt) are playing vital role in the haemostatic process. The initial adhesion of Plt to the sub endothelial collagen fibers, is followed by the activation phase, which triggers the degranulation of the α granules and dense granules of the surrounding Plt.(3) Many active substances that are being released during the process, have the effect of expression of until then, inactive receptors on the Plt surface. This enzymatic activity will rapidly increase the adhesion and aggregation properties of the surrounding Plt. Alongside with their role in the primary haemostasis, Plt also acts as catalysts in the cascade activation processes between different CF, promoting the conversion of prothrombin into active thrombin. Plt also have influence on the final retraction of the haemostatic cloth (3).

Besides the traditional understanding of the coagulation cascade some authors recently are increasingly accepting the novel cell-based model of coagulation (2).

Figure 2. The cell-based model of coagulation (From Hoffman et al. [2])



2. Tests of Coagulation

Bleeding Time

Bleeding time is evaluating the effects of the primary haemostasis, which is referring to the initial interaction of Plt with the blood vessel wall and the formation of the Plt thrombus. The predictive value of this test is considered to be relatively low and the test shouldn't be performed if the Plt count is $<100 \times 10^9/L$. (4) Also the results of this test shouldn't be taken into consideration during clinical decision making, if the patient was taking aspirin in the previous 7-10 days or NSAID's in the period of 1-4 days (5). The bleeding time can have abnormal values in isolated acquired or inherited disorders of the Plt function and in other minimal disorders of the coagulation process. Accordingly, this test is not recommended as secure predictor of surgical bleeding and shouldn't be routinely performed pre operatively (3, 5).

Activated Partial Thromboplastin Time – APTT

APTT reflects the activity of the CF that are participating in the intrinsic and common pathways of the activation of coagulation cascade. Prolonged APTT is the most commonly considered to be, the result of: deficit of circulating CF, excess of CF inhibitor or the influence of heparin (5). This test is less sensitive, as compared to Prothrombin time (PT), on the effects of warfarin, as well as the effects that the liver disease and vitamin K deficiency have on haemostasis. The greatest clinical applicability of APTT is in the following areas: monitoring of the therapy with heparin (but it doesn't have great diagnostic value when the patient is on therapy with LMWH – clexane), detection of CF deficiency, detection of lupus inhibitor, CF inhibitors and their antibodies (4, 5).

Prothrombin Time – PT and International Normalized Ratio – INR

PT reflects the activity of the extrinsic and common pathway of the activation of coagulation cascade. This test is performed by the addition of thromboplastin to the patient's plasma, which then activates the tissue activating factor. Compared to APTT, PT is significantly more sensitive in detection of coagulation defects caused by the effects of oral anticoagulant therapy, and less sensitive to the effects of therapy with heparin (5, 6). In clinical practice, PT is the most commonly used as a monitoring tool in the follow up and control of oral anticoagulant therapy. For the purpose of standardized approach in the treatment of this group of patients, another test in the form of the International normalized ratio (INR) was introduced. The INR value provides the clinicians with the reproducible and standardized result in accordance to the local reagents and the methodology of work in the different laboratories (4). PT is also used for the detection of vitamin K deficiency, as well as follow up and treatment of the patients with hepatocellular diseases. On the other hand, PT has only limited value in establishing diagnosis in patients with hereditary disturbances of coagulation (5).

Thrombin Time – TT

TT is performed by the addition of thrombin in the patient's blood sample and is the most commonly used to assess the process of conversion of fibrinogen to fibrin. It is considered that TT can solely detect the abnormalities of the fibrinogen and fibrin formation (4,6). In everyday clinical practice, the main uses of this test are: detection of heparin in the sample of patient's blood (especially if the patient has prolonged APTT), as a complementary test in establishing the diagnosis of Disseminated Intravascular Coagulation (DIC), detection of low levels of fibrinogen and detection of rare inherited anomalies of fibrinogen and dysfibrinogenemia (4,7).

3. Bleeding and Massive Transfusion

After major trauma and especially in polytraumatized patients that have sustained injuries on multiple tissues and organs, one of the main complications is uncontrolled massive haemorrhage and haemorrhagic shock. Although less frequent in the operation theatre (OT), massive bleedings is also one of the most alarming emergencies, both during elective or urgent surgical procedures. The sub sequential massive transfusion of blood and blood components (MT), although inevitable part of treatment protocol, can also be cause of complications and further deterioration of patients clinical condition. The most common definition of MT is the transfusion of an approximately one circulating volume of blood during the period of 24 hours (8). In this population of patients in which MT was inevitable therapeutic intervention, we can expect that a certain form of coagulopathy will develop in relatively high percentage (9). The literature shows that abnormal values of both PT and APTT can be measured after the transfusion of 12 units of packed red blood cells (PRBC's), while reduced Plt count can be seen after the transfusion of 20 PRBC's (8, 9).

3.1 Pathophysiology of Coagulopathy in MT

The first therapeutic intervention during massive bleeding is the introduction of the wide bore intravenous (i.v.) cannula and administration of high volume of fluids (crystalloids and colloids if needed). In the early phases of the reanimation of these patients, it is also necessary to take active measures to control the body temperature and to warm up the shocked patient. It is recommended to start the warming process of the bleeding patients as soon as possible (10,11). This is of course much more difficult to achieve in traumatized patients outside the hospital, than during major surgery in the OT. When the initial i.v. substitution of the lost circulating volume of blood with fluids is not enough, and when the bleeding cannot be immediately controlled, the next step is the transfusion of PRBC's, Plt, and accordingly to the latest recommendations, early administration of fibrinogen and CF (12). The experiences shows that during elective surgery, rapid haemodilution which is the result of administration of large volumes of crystalloids over a short period of time, can result in significant changes in the haemostatic balance of the patient. In the clinical perspective, the consequences will be presented in some form of clinical

coagulopathy and either further bleeding or excessive intravascular coagulation (11, 13). These changes can be detected and followed by using thromboelastometry (TEG/ROTEM) (14). The shift in the balance of the complex coagulation system, is suggesting increased generation of thrombin and hypercoagulable state, even in the absence of continuous active bleeding. On the other hand during infusion of high volume of colloids (especially high molecular starch – HES), we can often detect abnormal Plt function. In general, we can summarize that, administration of high volumes of i.v. fluids during a short period of time (especially colloids), will result in significant haemodilution and reduction in the CF concentration.

The evidence from the literature shows that, a group of patients where active measures to maintain normal body temperature (normothermia) were undertaken during the whole perioperative period, had significantly less blood loss compared to other patients. It is accepted that by avoiding excessive hypothermia, we can help in preserving both the normal haemostatic processes, as well as their control mechanisms (10). The main negative effect of hypothermia (core body temperature <35°C) is the slowing down of the initiation and activation phase of the coagulation cascade, which is consequently disturbing the balance of the coagulation system. The science data also confirms that hypothermia can also have negative effects, such as: decreased enzymatic activation of the Plt, slowing down of the synthesis of CF in the liver and increased fibrinolysis (11). This is the reason why the results of multiple research studies are showing that patients who were acidotic and hypothermic for certain period of time, either during major trauma or in the perioperative period, had significantly larger bleeding, despite timely substitution of blood components, PRBC's, Plt and fresh frozen plasma (FFP) (10, 11, 13).

Frequent control of the haemoglobin level (Hb) and timely correction of anemia in the actively bleeding and shocked patient, have great contribution in the preservation of normal haemostatic function. According to the currently available data, there are two scientific explanations regarding the level of Hb during the reanimation process of the patient in hemorrhagic shock that are incorporated in the latest recommendations. Erythrocytes (Er) are playing important role in the control of biochemical responses of activated Plt at the site of injury of the blood vessel wall. (11) This is confirmation of the hypothesis about multi cellular nature of initial phase of coagulation and the formation of initial Plt cloth. Er contain adenosine diphosphate (ADP) that plays important role in the process of activation of Plt. (9, 10). At the same time Er are also indirectly involved in the activation of the surrounding circulating Plt by activation of platelet cyclooxygenase and production of thromboxane A₂. The second mechanism, through which Er are influencing the haemostatic potential of the patient, is their rheological effect on the rest of circulating components of the blood. In normal circumstances, the Er flow is highest near the center of blood vessel and they have natural tendency to push out the circulating pool of Plt, towards the wall of the blood vessel. In this setting, Plt normally flow near the endothelium layer, the place where they usually exert their action. It is accepted that in this way, Er are acting in indirect fashion by creating ideal conditions for interaction between Plt and damaged endothelium

and thus promoting the initial haemostatic response to injury. During active bleeding on the other hand, the circulating pool of Er is decreasing, which causes unopposed Plt to start circulating near the center of the blood vessel. In this setting, as Plt in the absence of force that is pushing them outwards, starts circulating away from the endothelium, they are at the same time losing their haemostatic potential (11, 13). Considering the effect that Er are having in maintaining the potential and balance of the haemostatic system of the blood, the latest recommendations suggest that the level of Hb must be frequently checked and maintained $>8\text{gr/dl}$ during the acute phase of the resuscitation process of the patient that is actively bleeding (12).

3.2 Level of Platelets (Plt)

During the acute phase of resuscitation of massively bleeding patient, it is mandatory to regularly check: the level of Plt, the level of fibrinogen and the activity of CF. It is accepted that during MT, the deficit in the level of fibrinogen is the first anomaly that develops in the course of the development of coagulopathy (8). Consequently, the current recommendations are suggesting that in the early stages of resuscitation, the level of fibrinogen must be measured, and the deficit must be substituted as soon as it is diagnosed (4). The first line of choice for the substitution of fibrinogen, is the use of fibrinogen concentrate, and if not available cryoprecipitate. Due to small and relatively variable concentration of fibrinogen, the use of FFP is not recommended for rapid substitution (4, 12). One of the main consequences of MT is the decrease of the level of Plt. The first reason for the drop in the Plt count, is the consumption of the circulating pool of Plt at the place of injury of the blood vessel wall. The second reason is rapid haemodilution that develops early in the resuscitation process, mainly because of rapid administration of crystalloids, as well as transfusion of Er and FFP that are relatively poor with Plt.

One of the key emphasis in the latest recommendations is the importance of correct anamnesis of pharmacological history of the bleeding patient (where it is possible) or heteroanamnesis from the patient relatives (4). We should insist on receiving correct information about the patients' therapy with anticoagulant drugs that are influencing different stages of the coagulation process. Acutely bleeding patients, which were on therapy with drugs that are reducing the Plt's ability for activation and aggregation, will inevitably need Plt transfusion, even if the Plt count is normal. According to the recommendations, in the patients with ongoing bleeding, absolutely critical level of Plt is $50 \times 10^9/\text{l}$ (4). The literature review shows that the drop of Plt count below this critical level, will compromise the normal haemostatic potential of the blood (3, 9). This is the reason why the recommendations suggest that the trigger value for Plt transfusion in bleeding patient, should be $75 \times 10^9/\text{l}$ (4,12). This practice enables safe margin for the clinicians in the treatment protocol, which guarantees that Plt count will not drop below the critical level of $50 \times 10^9/\text{l}$ at all stages of the resuscitation. In the population of bleeding patients that has suffered brain trauma or has been polytraumatized, it is recommended to keep higher trigger value of Plt, $100 \times 10^9/\text{l}$ (4,12).

We should always keep in mind that depending on the cause of bleeding, there are some key differences in the treatment of the different populations of massively bleeding patients. Unlike during massive bleeding associated to major trauma, in the patients that are bleeding during operations and invasive procedures, the pathogenesis of coagulopathy is different. In the operation theatre (OT) during major operations (especially during elective surgery), regardless of the extensity of the procedure, the trauma to the tissues and organs is easier to be controlled and is more limited to the operation site, as compared to the traumatized patients. Also even in the situation of unexpected massive blood loss, in the OT there are ideal conditions, for timely intervention with administrations of adequate volume of crystalloids and/ or colloids. In these patients, if needed, transfusion of Er and other blood components, can be started significantly sooner, than in traumatized patients outside the hospital. This gives the clinicians opportunity to establish normovolemia in a timelier manner, and also to engage rapid substitution of the decreasing levels of Hb, Plt, fibrinogen and CF. We should never underestimate, the great significance that maintaining the normal body temperature and correction of acidosis has on the normal haemostatic potential of the patient. All this taken into consideration, we can conclude that, acquired coagulopathy that is developing during massive bleeding and MT in the OT, is mainly associated to the secondary deficit of fibrinogen and decreased activity and/ or low levels of CF (7, 8).

4. Treatment of the Coagulopathy associated to MT

Numerous attempts have been made over the years, for the discovery of the ideal way to monitor the changes of complex coagulation system during major trauma and surgery. Unfortunately, according to the current evidence, we don't have a single, reliable and fast diagnostic test, that will enable clinicians with continuous monitoring of dynamic changes in the coagulation profile during hemorrhagic shock in the critical ill patients. Currently available tests attempt to measure the potential of coagulation by quantifying certain segments of the haemostatic cascade. Regarding the traditional tests of haemostasis, current recommendations suggest that, in the bleeding patient when the measured level of fibrinogen is normal, only marked elevations in the values of APTT and PT (1.5-1.8 times above control/ standard values) can be considered significant in the clinical decision making process (4). This population of patients can be considered at high risk of developing clinically significant coagulopathy.

In the latest literature reviews, the current knowledge in this field puts a great emphasis on the implementation of "the point of care" principle in the algorithms for treatment of acquired coagulopathy (4, 12, 13). This implies the inclusion of diagnostic tools such as TEG/ ROTEM, which are examining the quality of different segments of haemostasis and fibrinolysis, by using the thromboelastographic principle. By measuring the viscoelastic properties of the patient's blood, TEG/ ROTEM within a short time interval (5-10 minutes), are capable of producing real-time image about the in vivo ability for the formation of firm haemostatic cloth and his subsequent

lysis (14, 15). On this way the clinicians are provided with a quick estimate of the action of both coagulation regulatory mechanisms and anticoagulation pathways. The most importantly, this practice offers a reliable and reproducible data that can help in prompt decision making.

The golden rule during the prevention and treatment of the coagulopathy associated to massive bleeding and MT, is rapid intervention specifically directed towards the deficit of the elements of coagulation. This is so called **“deficit-directed” principle** in the resuscitation of these patients (10, 11). The clinical decision whether to administer Plt and when, depends on the measured Plt count, tests of coagulation, but also on the clinical evaluation of the patient's clinical condition. The recommendations suggest that administration of Plt is allowed only for correction of clinically manifested coagulopathy that is clearly associated to low Plt count and/or decreased functional ability of the circulating pool of Plt (4, 12).

We should always keep in mind that during massive bleeding and MT, the first negative change that is affecting the balance of the coagulation system, is the decrease in the circulating level of fibrinogen (7, 8, 10). Current knowledge suggests that during major bleeding, the alteration of the level of fibrinogen is happening before the decrease in the level of Plt and CF, all of which are promoting the development of the coagulopathy associated to MT. This is why the level of fibrinogen must be measured early in the resuscitation process, especially if we know that a low concentration of fibrinogen will impair the final phase of coagulation and the formation of solid haemostatic cloth. Regular measurement of the fibrinogen level will give us chance to timely correct the decrease in the fibrinogen concentration in the acutely bleeding patient. In a patient where we are suspecting the development of acquired coagulopathy, the measured concentration of fibrinogen $<1.5\text{--}2.0$ gr/l must be considered as hypofibrinogenaemia (4). This patient carries a significant risk of further bleeding. According to the current recommendations, the first line of choice is the administration of fibrinogen concentrate in the initial dose of $25\text{--}50$ mg/kg. Only when fibrinogen concentrate is not available, the recommendations suggest the use of cryoprecipitate in the dose of $4\text{--}6$ ml/kg (4). FFP according to the current clinical evidence, is not recommended as a secure source of fibrinogen, mostly because of a small and variable concentration of fibrinogen. Cryoprecipitate on the other hand, is considered to have a relatively constant concentration of: fibrinogen, CF VIII, CF XIII and von Willebrand factor. However, during the administration of Cryoprecipitate, we need to be aware that there are individual variations in the content, and also of the danger (although minimal) of transmission of infectious agents.

When the patient has significantly prolonged values of APTT and PT (>1.5 / normal values), and no other coagulation abnormality can be detected, we can conclude that the patient has a deficiency of CF in the circulation or their low activity. If the patient also has normal level of fibrinogen, these results should trigger the substitution of CF. There are specific tests of coagulation that are measuring the concentration of specific CF in the patient's blood sample. Still we need to know that these tests are not available in every laboratory, and even if they are available, it takes several hours for the results to be ready. When a patient is confirmed to have deficit of CF,

we need to start the substitution process. The recommended way is the administration of fabric CF preparations. Preparations that contain single CF are the most commonly used for treatment of patients that have inherited CF deficiency. Currently on the market there are also preparations that are containing several CF. Good example of these preparations is Prothrombin Complex Concentrate (PCC). These formulations are containing all the vitamin K dependent CF, as well as Protein C and Protein S, that play active role in the anticoagulation regulation processes. Special attention should be paid to the bleeding patients (during operation or trauma) that are on therapy with some of the oral anticoagulants. These drugs have the pharmacological action to antagonize vitamin K dependent synthesis of CF in the liver, and are decreasing the activity of CF in the patient's blood. Before surgery or other invasive procedure, it is recommended that these patients receive i.v. dose of vitamin K and also substitution of CF deficiency by administration of PCC preparation (11). This preparations are recommended as a first line of choice for CF substitution, mainly because they have a relatively constant and balanced concentration of CF in the final solution. This is making the whole resuscitation process much more controllable in comparison to FFP (2, 9). Also they have superior security profile in the field of possible transmission of infectious agent to the recipient's blood. Only when PCC preparations are not available, substitution can be done by administration of adequate volumes of FFP (4, 12). However regarding the clinical use of FFP, we need to emphasize this facts: 1) concentration of CF in one unit of FFP is small and variable and also highly dependent on the characteristics of every single donor; 2) large volume of FFP is needed to achieve satisfactory concentration of CF in the recipient's circulation. This practice brings significant danger of volume overload and rapid haemodilution; 3) administration of FFP carries significant risk of transmission of infectious agents; 4) probably the most dangerous complication is the development of acute immune reaction in the recipient, caused by the presence in the FFP, of active immune elements from the donor. This can lead to potentially fatal complications, such as acute lung injury ALI/ TRALI (4, 11).

Excessive fibrinolysis and premature decomposition of the already formed haemostatic cloth, plays significant role in the development of acquired coagulopathy that accompanies major bleeding and MT. The main clinical manifestation in this setting will be prolonged and persistent bleeding, even when the deficiency of other elements of coagulation has been corrected. This is the reason why administration of tranexamic acid must be included as mandatory part of the treatment protocols for hemorrhagic shock (8, 12). Currently in clinical practice, tranexamic acid is the most commonly used for the treatment of the ongoing bleeding in OT after major trauma and for prevention of major bleeding during surgery and other invasive procedures (4, 12). In the current data from the literature, there is a strong suggestion that tranexamic acid, if administered early and in an adequate dose ($20\text{--}25$ mg/kg), will have positive role in the limitation of further bleeding and the development of acquired coagulopathy (4).

Alongside with the standard therapeutic methods in the treatment of acquired coagulopathy, there are some very important additional interventions that can significantly improve the final

outcome. Lately a number of so called **“additional factors”** in the development of acquired coagulopathy have been identified. Data from many research studies are showing that if clinicians fail to correct these conditions in a timely manner, it can promote further misbalance of the coagulation system (8, 9). This is the reason why the latest recommendations are strongly suggesting: early treatment of the hypothermia, correction of clinical acidosis and correction of hypocalcaemia (4, 12). It is recommended that in traumatized patient with massive bleeding, and especially in the OT, active measures to warm up the patients must be undertaken as soon as possible (12). The available data are clearly showing that, the group of patients where normal body temperature was successfully preserved during resuscitation process, had significantly lower blood loss and decreased need for transfusion of blood components (10, 11). It is also recommended that during active bleeding, we need to perform strict control of the patient's acid-base balance and timely correct the clinical acidosis (3). Despite the fact that the correction of the Ph value alone, cannot control the developing coagulopathy, still this intervention will surely help in the easier recovery of the coagulation system.

The treatment algorithm during MT, must also incorporate regular measurements of the level of calcium. Hypocalcaemia that can frequently be seen in these patients, must be promptly corrected with adequate i.v. calcium infusion (4). The preservation of normocalcaemia is very important for normal functioning of coagulation mechanisms, especially because calcium plays a vital role as a cofactor in the activation of certain CF in the coagulation cascade. The evidence from the literature is suggesting that during acute bleeding and MT, until the complete cessation of bleeding, the level of calcium needs to be maintained above 0.9 mmol/l (4, 12). This will help in preservation of the normal balance of haemostasis in critically ill patient.

At the end we can conclude that acquired coagulopathy is relatively frequent complication of massive bleeding and MT. The clinicians need to be aware of the fact that patients that develop this complication, will have higher rate of prolonged bleeding and higher possibility of potentially lethal complications during the resuscitation process. This is the reason why it is mandatory that current recommendations from this field must be incorporated in the local treatment protocols for acute bleeding during major trauma or during surgery.

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