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Prevention of bleeding and thrombosis in patients with liver disease

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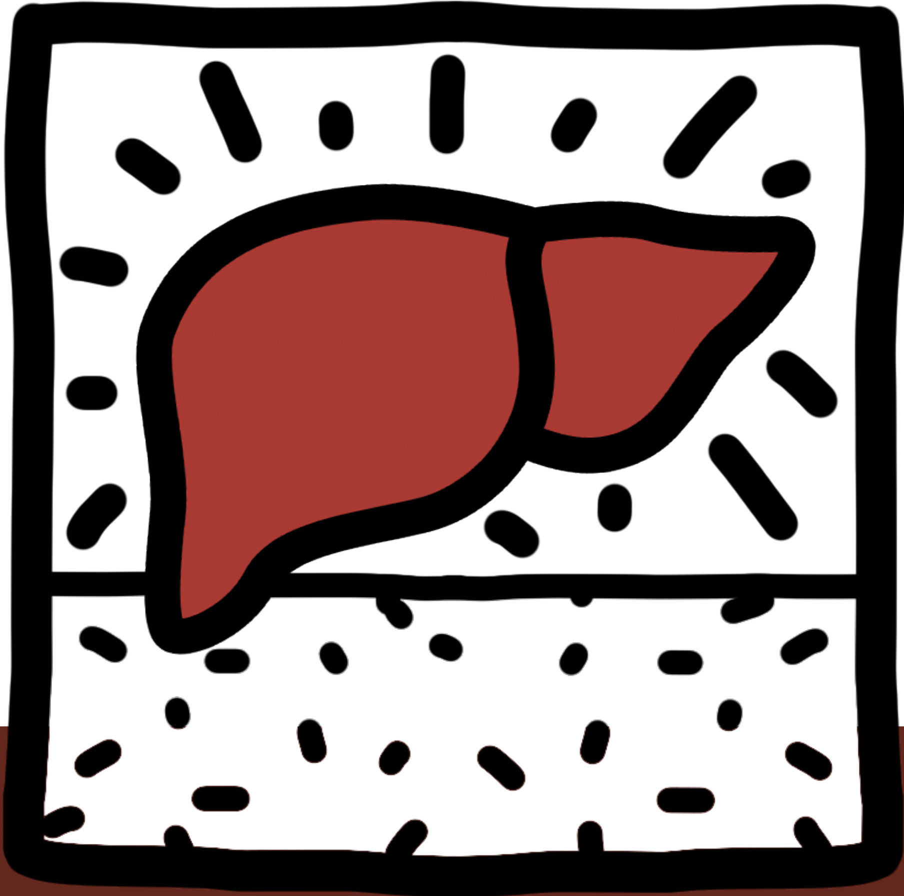

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General introduction

The physiological process of haemostasis, in which endothelial damage is restored while normal blood flow throughout the circulation is maintained, consists of multiple mechanistically intertwined interactions between the vessel wall and platelets, the coagulation cascade, and the fibrinolytic system.

Primary haemostasis

Initial interaction between platelets and injured vessel wall is the first step in the process of platelet plug formation (**Figure 1**)[1,2]. A breach of the endothelial layer of the vessel wall exposes the subendothelial matrix, triggering a series of events to repair the defect[3]. A key initial step to this repair mechanism is the presence of multimeric protein von Willebrand factor (VWF) at the site of injury, either due to the adhesion of circulating VWF to the exposed collagen, or to the release of VWF from endothelial cell-specific Weibel-Palade bodies[4]. Circulating platelets adhere to VWF through interactions with platelet glycoprotein (GP) Iba and present on the platelet membrane[4–6]. Platelet activation due to GPVI interaction with collagen further induces activation of integrins including αIIbβ3, which binds to fibrinogen and VWF (or other ligands such as vitronectin and fibronectin)[7] and enhances aggregation through platelet-platelet connections. The responsiveness of VWF to platelets is determined by its multimeric size, with higher reactivity associated with larger multimers. Endothelial cells release "ultra-large" VWF multimers that are highly reactive to platelets. This responsiveness is however regulated by the protease ADAMTS13, which rapidly cleaves VWF into smaller multimers and thus reduces the reactivity to platelets [8]. For further progression of platelet plug formation, the platelets that initially adhere release agonists, such as ADP and thromboxane A_2, which activate additional platelets recruited from circulation[9]. Platelet plug stability is additionally provided by deposition of insoluble fibrin, generated by the coagulation cascade that is further explained below.

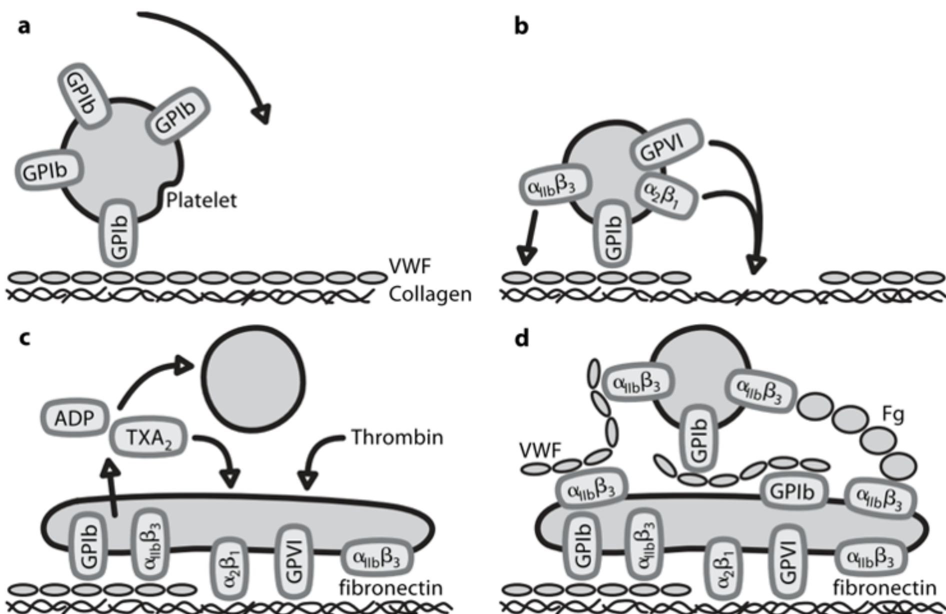

Figure 1. Schematic presentation of the process of adhesion (panel A and B) and aggregation (panel C and D) of platelets in physiological conditions. Abbreviations: GP, glycoprotein; VWF, von Willebrand factor; TXA_2, thromboxane A_2; Fg, fibrinogen. ***Reprinted from Lisman et al.*** [10]

Coagulation

Secondary haemostasis, better known as coagulation, is a complex interplay between pro- and anti-haemostatic proteins that ultimately leads to the generation of fibrin strands. The cascade model of coagulation, proposed in 1964[11,12], describes coagulation as a sequential activation of coagulation factors through an intrinsic (initiated by factor XII) and an extrinsic pathway (initiated by the tissue factor-VIIa complex). Although this cascade model was a great advance in our understanding of coagulation, it failed to accurately incorporate the effect the complex feedback systems within the process. The cell-based model[13,14], on the other hand, proposes that coagulation is not a cascade but consists of overlapping stages, and is thus a more accurate representation of in vivo coagulation. The coagulation process is initiated when factor VII comes into contact with tissue factor through exposed extravascular tissues (**Figure 2)**. The tissue factor-VIIa complex further activates factors IX and X, connecting the classical intrinsic and extrinsic pathways as proposed in the cascade model of coagulation. Factor Xa activates and binds to factor V(a), forming the prothrombinase complex responsible for activating prothrombin to thrombin. Through a positive feedback loop consisting of thrombin-mediated activation of factor XI (**Figure 2**), even a small amount of thrombin is enough to generate the burst of thrombin needed to generate a stable haemostatic plug. Thrombin generation initially results in conversion of fibrinogen to fibrin. Insoluble fibrin polymers are subsequently reinforced by factor XIIIa-mediated crosslinking. This cross-linked fibrin mesh formed at the site of injury stabilises the initial platelet plug. In addition to its central role in fibrin formation and further enhancement of thrombin generation by activation of factor XI, thrombin also plays an essential role in down-regulation of coagulation by binding to thrombomodulin on endothelial cells and activating protein C[15]. In a reaction requiring co-factor protein S, protein C inactivates factors VIIIa and Va, limiting further thrombin formation. Other down-regulators of the coagulation cascade include antithrombin and tissue factor pathway inhibitor, which inactivate thrombin, and the ternary tissue factor-VIIa-Xa complex[16].

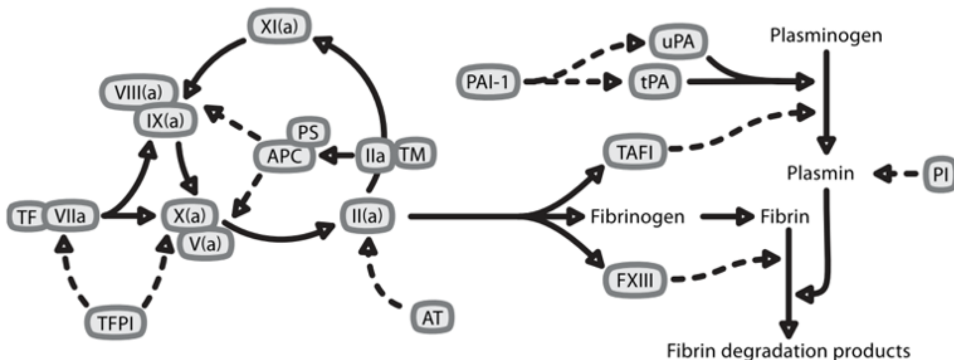

Figure 2. Schematic representation of the processes that result in the formation and degradation of fibrin. Uninterrupted lines indicate activation, interrupted lines indicate inhibition. Abbreviations: APC, activated protein C; AT, antithrombin; PAI-1, plasminogen activator inhibitor-1; PI, plasmin inhibitor; PS, protein S; TAFI, thrombin-activatable fibrinolysis inhibitor; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TM, thrombomodulin; tPA, tissue-type plasminogen activator; uPA, urokinase-type plasminogen activator. *Reprinted from Lisman et al.* [10]

Fibrinolysis

The fibrinolytic system (**Figure 2**) is responsible for degradation of blood clots in healthy blood vessels and the breakdown of fibrin clots after the vasculature is repaired. This system involves several proteases and protease inhibitors that regulate the conversion of plasminogen into plasmin, which is the primary fibrinolytic protease[17,18]. The conversion of plasminogen into plasmin can be initiated by either tissue-type or urokinase-type plasminogen activator[19]. Once formed, plasmin cleaves fibrin into soluble fibrin degradation products, leading to dissolution of the fibrin clot. The two most significant inhibitors involved in fibrin dissolution are plasminogen activator inhibitor-1 and plasmin inhibitor[20], inactivating plasminogen activator and plasmin, respectively. Other proteins that down-regulate the fibrinolytic system include thrombin-activatable fibrinolysis inhibitor, which reduces the binding of tissue-type plasminogen activator and plasminogen to fibrin, and factor XIII, which cross-links and thus further strengthens the fibrin clot[20].

Haemostatic status in patients with chronic liver disease

The liver plays a fundamental role in the activation and regulation of the haemostatic system, not only because of its role in the synthesis of the majority of haemostatic proteins, but also because of its role in the clearance of these proteins. Understandably, the development of liver disease may thus affect the haemostatic system significantly. The second chapter of this thesis therefore extensively reviews the specific haemostatic alterations that occur in patients with liver disease.

In short, advanced liver disease is characterised by complex changes in primary haemostasis, coagulation and fibrinolysis[21–23]. Thrombocytopaenia is one of the most common haemostatic abnormalities found in patients with liver disease[24], and is thought to be caused by platelet sequestration in the spleen due to spenomegaly[25], reduced thrombopoietin synthesis[26,27] and bone marrow suppression[28]. Additionally, there is an ongoing debate whether platelet function is altered in patients with liver disease, and whether this potentially altered platelet function is of clinical relevance[28,29]. The antithrombotic effects of these changes in platelet count and/or function are however at least in part compensated by prothrombotic changes, such as increased plasma levels of VWF and decreased plasma levels of ADAMTS13[30,31].

As the synthetic function of the liver is impaired, plasma levels of nearly all proteins involved in coagulation and fibrinolysis are decreased in patients with advanced liver disease[22]. Exceptions to this rule include coagulation factor VIII, tissue-type plasminogen activator and plasminogen activator inhibitor-1, which are not synthesised by the liver and of which plasma levels are often increased in these patients[22,32]. The deficiency of coagulation factors is at least in part compensated for by a similar decrease in the anticoagulant factors synthesised by the liver, such as protein C, protein S and antithrombin[22]. Similarly, the altered levels of pro- and antifibrinolytic proteins result in a net rebalance of the fibrinolytic system[33].

The net result of these changes is a “rebalanced” but fragile haemostatic status (**Figure 3**), which may be easily tipped over to either thrombotic or haemorrhagic side, for example triggered by infection or decompensation of disease. Although patients with liver disease may thus be at increased risk of both bleeding and thrombosis, not all haemostatic complications can be directly attributed to the haemostatic changes. For a more in-depth understanding of the pathophysiology behind these complications, however, please refer to Chapter 2.

Anti- and prothrombotic strategies in liver disease

Patients with chronic liver disease are at twofold increased risk of venous thromboembolism compared to patients without liver disease[35]. Moreover, patients with specific aetiologies of liver disease (e.g. metabolic dysfunction-associated fatty liver disease) have an increased risk of cardiovascular events, including stroke

and myocardial infarction[36]. The risk of thrombosis may be proportional to disease severity[37], but little is known about specific risk factors for thrombosis in this patient group. Despite the increased risk of thrombosis however, patients with advanced liver disease have been excluded from major randomised clinical trials of drugs that are used to prevent or treat thrombosis, such as anticoagulant and antiplatelet drugs. Previous studies demonstrate an altered anticoagulant effect of heparins and direct oral anticoagulants when added to plasma of patients with chronic liver disease[38–40], but limited data is available on the in vivo anticoagulant potency of anticoagulant drugs in these patients. Data on the potency of antiplatelet drugs – such as aspirin and $P2Y_{12}$ inhibitors – is even more scarce, despite increasing evidence that demonstrates benefits of these agents in the prevention of cardiovascular disease[41,42] and of progression to advanced fibrosis[43,44].

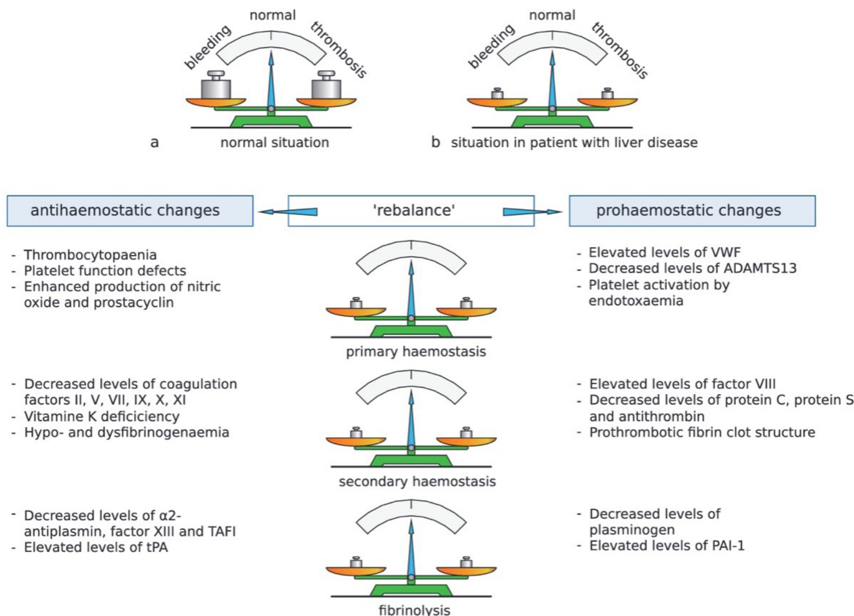

Figure 3. Schematic presentation of the rebalanced haemostasis in patients with liver disease. In healthy individuals (a), haemostasis is in solid balance. In patients with liver disease (b and table) both pro- and antihaemostatic changes result in a 'rebalance' of the haemostatic system. This new balance is however more fragile, and may therefore more easily tip toward bleeding or thrombosis. Abbreviations: TAFI, thrombin activatable fibrinolysis inhibitor; tPA, Tissue plasminogen activator; VWF, von Willebrand factor; ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PAI-1, plasminogen activator inhibitor-1. *Modified from Warnaar et al.*[34]

Conversely, clinicians frequently prescribe prophylactic transfusions of prohaemostatic blood products (e.g. platelets, fresh frozen plasma) prior to invasive procedures in patients with liver disease. Current protocols for the prophylactic transfusion of these blood products are based on the general population and often recommend correction for elevated INR or severe thrombocytopenia[45,46]. These laboratory measures do however not take the complex alterations of the haemostatic system of patients with liver disease into account, and thus may falsely reflect a high risk of bleeding. In addition, little is known about the efficacy of these transfusions, and the risk of adverse events (such as allergic reactions, transfusion-related circulatory overload and graft vs host-disease) may not outweigh the benefits[47].

Aim of this thesis

The overall aim of the work presented in this thesis is to gain a better insight in the haemostatic status and its predictive value in patients with liver disease, and the efficacy of haemostatic interventions within this patient group. The first part of this thesis will focus on the haemostatic status in patients with liver disease, in which the pathophysiology and management of haemostatic complications are further highlighted. The second part of this thesis will focus on interventions that affect the haemostatic status in patients with liver disease. Here, the effects of heparins, blood product transfusions and antiplatelet drugs on the haemostatic status of patients with liver disease are further demonstrated using observational clinical studies. The work presented in this thesis may contribute to the understanding of the complex alterations of the haemostatic system in patients with liver disease, and may contribute to the development of evidence-based guidelines regarding anti- and prothrombotic strategies for this specific patient group.

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