

Plenary Lectures

PL1 Hemostatic Balance in 2009

PL1-1

Blood coagulation dynamics in hemostasis

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Our studies involve mathematical (computer) simulations, a reconstructed plasma/platelet proteome, whole blood *in vitro* and blood exuding from microvascular wounds. All studies indicate that in normal hemostasis, tissue factor (Tf) in combination with plasma FVIIa provides an INITIATION PHASE through the extrinsic fXase (Tf-fVIIa) which is largely controlled by tissue factor pathway inhibitor (TFPI) in combination with antithrombin (AT) and the protein C (PC) pathway. The synergy between these inhibitors provides a threshold-limited reaction in which a stimulus of sufficient magnitude must be provided for continuation of the reaction. With sufficient stimulus, the fXa produced activates some prothrombin. This initial thrombin activates the procofactors and platelets required for presentation of the intrinsic fXase (fVIIIa-fIXa) and prothrombinase (fVa-fXa) which drive the subsequent PROPAGATION PHASE: continuous downregulation of which is provided by AT and the thrombin-thrombomodulin-PC complex. FXa generation during the PROPAGATION PHASE is largely (>90%) provided by the intrinsic fXase. Tf is required for the INITIATION PHASE of the reaction but becomes non-essential once the PROPAGATION PHASE has been achieved. The PROPAGATION PHASE catalysts (fVIIIa-fIXa and fVa-fXa) continue to drive the reaction as blood is resupplied to the wound site by flow. Ultimately, the control of the reaction is governed by the pro- and anticoagulant dynamics and the supply of blood reactants to the site of a perforating injury. Our systems have been utilized to examine the qualities of hypothetical and novel antihemorrhagic and anticoagulation agents in epidemiologic studies of venous and arterial thrombosis and the hemorrhagic pathology.

PL1-2

Players of the inhibitory system

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During coagulation, thrombin formation is down-regulated by natural anticoagulant proteins which include antithrombin, tissue factor pathway inhibitor (TFPI) and activated protein C (APC) and protein S. Hereditary or acquired deficiencies of anticoagulant proteins are associated with an increased risk of venous thrombosis. However, impaired anticoagulant pathways diminish bleeding problems of haemophiliacs. Antithrombin is a serine protease inhibitor that inhibits activated coagulation factors. It acts as a 'suicide substrate' which traps the target protease in an intermediate of catalysis. TFPI is a Kunitz-type inhibitor that inhibits tissue factor (TF)-induced coagulation via a two-step mechanism. In the first step, a bimolecular FXa/TFPI complex is formed that subsequently inhibits TF/FVIIa by formation of an inactive quaternary complex. APC down-regulates thrombin formation via inactivation of FVa and FVIIIa. Protein S is a non-enzymatic cofactor of APC that enhances its anticoagulant activity ~20-fold. Thrombin generation experiments in normal plasma and in plasmas deficient in TFPI and/or protein S demonstrated that protein S not only acts as a cofactor of APC but also stimulates the down-regulation of coagulation by TFPI by enhancing the formation of the binary FXa-TFPI complex ~8-fold. Thrombin generation assays further show that functional TFPI levels are greatly decreased in protein S-deficient individuals and also in FV-deficient individuals. The low TFPI levels in plasma likely contribute to the increased thrombosis risk of protein S-deficient individuals and protect FV-deficient patients against bleeding.

PL2 ACCP 2008 and Beyond

PL2-1

ACCP 2008: VTE treatment and prophylaxis – what's new?

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New developments in the prevention and treatment of VTE will be presented, emphasizing the results of recently published studies and new recommendations of the American College of Chest Physician (ACCP) guidelines. These will include: 1) Primary prophylaxis: Change in emphasis from identifying the subgroup of hos-

pitalized patients who need prophylaxis to identifying the subgroup who do not need prophylaxis. A strong recommendation that patients who have hip surgery should receive greater than 10 day and up to 35 days of prophylaxis. Identification of patients who should not routinely receive prophylaxis, such as patients having same-day laparoscopic or arthroscopic surgery, and with indwelling intravenous catheters. Review of studies that have evaluated apixaban and dabigatran for prophylaxis. 2) Acute Treatment of DVT and PE Recommendations for the use of fondaparinux and subcutaneous unfractionated heparin in the acute treatment of VTE. Reconsideration of the role of catheter-directed thrombolysis for the acute treatment of DVT (no longer strongly discouraged). Expansion of the role of thrombolytic therapy in patients with PE that is associated with hemodynamic compromise, and for selected high-risk patients without hypotension. Indications for inferior vena caval filter insertion and recommendation for anticoagulation after insertion of a filter. 3) Long-term treatment of DVT and PE Identification that the presence or absence of a reversible provoking risk factor is the most important determinant of the risk of recurrent VTE and the optimal duration of anticoagulation. Rationale for recommending that VTE should generally be treated for 3 months or long-term. Recommendation for indefinite treatment of patients with unprovoked proximal DVT or PE if: a) there is a low risk of bleeding, b) good anticoagulation is achievable; and c) this is acceptable to patients.

PL2-2

Thromboprophylaxis: ACCP 2008 and the new anticoagulants

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New anticoagulants have been developed in an attempt to overcome the shortcomings of existing agents. They are classified according to their targets, mainly FXa and FIIa. Among these two families of drugs some are oral and other parenteral. The anti-Xa agents include Fondaparinux and biotinylated-Idraparinux which are parenteral and indirectly active as well as Rivaroxaban (Xarelto®), Apixaban and DU-176b which are oral and directly active. The anti-FIIa drugs include Lepirudin, Bivalirudin and Argatroban which are parenteral and directly active while Dabigatran etexilate (prodrug) is taken orally and acts directly. Dabigatran and Rivaroxaban have recently been both recently approved by European health authorities for the prevention of VTE in major orthopedic surgery in adults.

These drugs differ regarding their mechanism of action their pharmacokinetics and pharmacodynamics. The common denominator for all of these new drugs is the inhibition of thrombin generation – but they accomplish this by different mechanisms of action. New anticoagulants could replace VKA in the treatment and the secondary prevention of VTE, atrial fibrillation and coronary syndromes. Coagulation monitoring and dose adjustment of these new drugs do not seem to be required. However, well standardized coagulation assays should be available for testing patient compliance and anticoagulant action of the treatment in some particular groups of patients. The use of orally active new anticoagulants is very attractive in hip surgery since thromboprophylaxis has to be continued for 35 days according to 2008 ACCP recommendations. Secondary, prevention of VTE without laboratory monitoring and without influence of concomitant drugs will improve patients safety and their quality of life. Finally, the new anticoagulants are expected to be prescribed for the treatment of patients with atrial fibrillation, who should receive a VKA, but don't use it for fear of bleeding and remain exposed to stroke.

With the plethora of new anticoagulants, we are in the beginning of a new era in antithrombotic therapy. Every general hospital should have an appropriate committee to assist physicians in selecting the most ideal anticoagulant and dose for each related medical problem. This committee will use the guidelines established by appropriate experts in the field.

Weitz JI, Hirsh J, Samama MM. Chest Suppl 2008; 133/6/234S-256S New antithrombotic drugs.

PL3 Hemophilia Treatment of the Future

PL3-1

The improved factor concentrate

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The current treatment of hemophilia with coagulation protein replacement therapy is both effective and safe. Nevertheless, this therapy requires frequent, repeated intravenous infusions and approximately 25% of treated hemophilia A patients develop antibodies to the replacement protein. Furthermore, the cost and limited availability of current concentrates has restricted access to therapy to less than 30%



of the global hemophilia population. With this background, efforts are now underway to develop coagulation concentrates with enhanced biological properties that further improve the quality of care for hemophiliacs. The specific areas of enhancement that are being explored include improved biosynthetic processes, prolonging the circulating half-life and reducing concentrate immunogenicity. Coincident with these approaches, it is hoped that there will be more widespread availability of these concentrates and that their cost will be contained.

PL4 Platelets: Physiology and Diseases

PL4-2

Cross-talk of inhibitory and stimulatory signalling pathways of human platelets

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The major (but not only) roles of the hemostatic system are to maintain blood in a fluid state under physiologic conditions and to seal a vessel wall defect in order to prevent blood loss. Pathologically, bleeding or thrombosis may occur if the hemostatic stimulus is unregulated, either at the level of stimulatory or inhibitory pathways. The balance of stimulatory and inhibitory pathways is also well established for platelets. These specialized adhesive cells play a key role in normal and pathological hemostasis through their ability to rapidly adhere to subendothelial matrix proteins and to other activated platelets. Such platelet functions are strongly inhibited by endothelium-derived prostacyclin and NO and their cAMP/PKA- and cGMP/PKG-regulated pathways including kinase targets such as VASP, IRAG, LASP and others (1). It is also well established that both stimulatory and inhibitory platelet pathways interact at various levels representing significant functional cross-talk. Recently, we re-addressed one of the controversially discussed pathways, the platelets NOS system. We discovered that human and murine platelets do not express functional NOS proteins and that platelet soluble guanylyl cyclase (sGC) is NOS-independently activated by von Willebrand factor (VWF) which may represent a new mechanism of feedback inhibition (2). The underlying mechanisms are currently studied using a recently established quantitative phosphoproteomic approach. As long-term goal, it is hoped that such studies will establish new diagnostic and therapeutic approaches with respect to platelet function and dysfunction. 1. Munzel et al (2003) *Circulation* 108, 2172–2183 2. Gambaryans et al (2008) *J Thromb Haemost* 6, 1376–1384