



Symposia

SY1 Venous Thromboembolism

SY1-1

Thrombophilic risk factors for venous thromboembolism – too many and too minor?

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Venous thromboembolism (VTE) is a multicausal disease. The risk of VTE is dependent upon the number and severity of risk factors present in an individual person. The most important circumstantial risk factors are advancing age, surgery and trauma, oestrogen intake, pregnancy, and certain medical illnesses including heart failure and cancer. Gain of function mutations (factor V Leiden or the prothrombin mutation) and natural coagulation inhibitor (antithrombin, protein C and protein S) deficiencies are the most important inherited risk factors for a first VTE. Risk factors for a first VTE are not necessarily associated with a high risk of recurrence. We were the first to demonstrate that the heterozygous carrier state of either the factor V Leiden mutation or the prothrombin mutation does not confer an increased risk of recurrent VTE. Conversely, patients with high factor VIII or hyperhomocysteinemia have an increased risk of recurrence. Nevertheless, thrombophilia screening, i.e. measurement of laboratory risk factors of VTE, has a low predictability with regard to the likelihood of recurrence in an individual patient and has therefore been widely abandoned. The risk of recurrence is increased among patients with more than one episode of VTE, unprovoked VTE, proximal VTE, pulmonary embolism at manifestation or cancer. For instance, patients with proximal deep-vein thrombosis and/or pulmonary embolism have a recurrence risk as high as 30 % after 5 years. Hence, these patients are good candidates for indefinite anticoagulation regardless of the presence or absence of laboratory risk factors of VTE.

SY1-3

Consequences of thrombophilia screening for life quality in women before prescription of oral contraceptives and family members of VTE patients

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A large number of hereditary and acquired alterations in the coagulation system that are associated with an increased risk of venous thrombosis have been described. Screening for these thrombophilic defects has become particularly popular in women before the prescription of oral contraceptives. The relevance of the results with regard to the management of the patients remains, however, to be questioned. In a recent review of six articles that were aimed to determine the nature and extent of psychological impact of thrombophilia screening, no valid conclusions could be drawn about the psychological impact due to heterogeneity of the data and lack of methodological accuracy. We performed a questionnaire-based study in 247 women with and in 132 women without factor V Leiden who were referred for factor V Leiden testing before oral contraceptive intake. A large proportion (76 %) of the women reported being emotionally disturbed by genetic testing. 16 % of women with wildtype factor V were discouraged from OC use, while 3 % of women with factor V Leiden were encouraged to take OC. This indicates that recommendations after testing are not consistently driven by the test result, which compromises the quality of patient care. Given the large number of women who are taking oral contraceptives unequivocal guidelines for counselling prior to their prescription are urgently needed. These guidelines should integrate the risks and benefits of oral contraceptives but also the impact of screening on quality of life and aspects of counselling.

SY2 Biology and Functions of Platelets

SY2-1

Do platelet receptors communicate?

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Inter-receptor communication has recently received significant attention. It helps in understanding the increasingly complex signalling networks. Cross-talk between different receptors allows the integration of a great diversity of stimuli that the platelet receives under different physiological situations. There are different ways for cell membrane receptors to interact. One way is the simultaneous binding of multivalent ligands to several receptors. These receptors can be identical, as high multimers of one von Willebrand factor protein can bind to several GPIb molecules, or different, as one von Willebrand factor molecule can bind GPIb and GPIIb/IIIa proteins. Of vital importance for platelet function are the polyvalent ligands collagen, von Willebrand factor and thrombospondin-1. Use of multivalent ligands allows high sensitivity to low ligand concentration (significant amplification of signal) as well as better fine tuning of platelet activation control. Another way to communicate is signal transactivation. This leads to the phenomenon of synergism between the actions of different agonists. Activation of the thrombin receptors for example causes an increase in ligand affinity of the thromboxane A₂ receptors. Among the receptors which communicate are: the collagen receptors, GPIIb-FcRIIa, GPIb-gpVI, GPIb-PAR-1/PAR-4, P2Y₁-P2Y₁₂, CD36-CD47, PAR-4-alpha (2A) adrenergic receptor. A third way to communicate is direct posttranslational modification of receptors by other membrane proteins, which controls ligand binding. Ecto-kinases, ecto-phosphatases and protein thiol-oxidoreductases modify platelet receptors on the platelet extracellular surface, and in that way regulate their function. The understanding of communication between receptors is essential for intervention of platelet function.

SY2-2

Platelet function under high shear conditions

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Blood platelets are the first line of defense against bleeding and as such involved in the hemostatic repair of damaged vasculature. Their true prowess seems to be displayed under high shear conditions where platelets interact with a variety of plasma proteins, all of which are tightly regulated to close the leak but at the same time prevent lumen occlusion and thromboembolism. The first task is to arrest fast flowing platelets on exposed collagen of the damaged subendothelial surface. Although platelets are endowed with several collagen receptors, most notably integrin $\alpha 2\beta 1$ and the immunoglobulin superfamily member GPVI, they can not arrest platelets at high shear rates. The latter requires binding of the platelet receptor GPIIb/IIIa to the A1-binding domain of von Willebrand factor (VWF), which first has to be immo-

bilized from the flowing blood onto the site of injury. Under high shear conditions further accrual of newly arriving platelets again requires VWF, which has to bridge platelets not only to the exposed collagen but also to each other by being sandwiched between the multiple platelet layers of the hemostatic plug. Signaling processes and engagement of further receptors secures firm adhesion and formation of a hemostatic plug or thrombus.

SY2-3

Assessment of platelet function in the laboratory

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Platelet function testing is essential for the diagnosis of congenital/acquired bleeding disorders and may be useful for the prediction of surgical bleeding. Nowadays there is also much interest in monitoring the efficacy of anti-platelet therapy and measuring platelet hyper-function. However, this often presents clinical laboratories with significant challenges as platelet function tests are complex, poorly standardized, time consuming and quality assurance is not straightforward. There are also few comprehensive modern guidelines available and many recent published surveys have revealed poor standardization between laboratories. Up until the late 1980's the traditional clinical platelet function tests that were available were the bleeding time (BT), light transmission (LTA) and whole blood aggregometry (WBA) and various biochemical assays. These were also usually performed within specialized research and clinical laboratories. Since the last BCSH guidelines were published in 1988 a variety of new platelet function tests have become available. These include flow cytometry and an ever increasing choice of new commercial instruments. Although the potential clinical utility of the new assays is emerging some have not yet entered into routine clinical practice. It is encouraging that a number of standardization committees (e.g. CLSI, BCSH and ISTH Platelet Physiology SSC) are now beginning to produce new platelet function testing guidelines and this will hopefully improve clinical practice, quality assurance and result in less variability between different laboratories.

SY3 Mechanisms of Vascular Disease

SY3-1

Role of von Willebrand Factor in vascular disease

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Plasma levels of von Willebrand factor (VWF) are increased in patients with cardiovascular risk factors. Various studies were aimed to elucidate the relation of vWF with thromboembolic cardiovascular events, ischemic stroke as well as with peripheral arterial occlusive disease. In the general population, there is only a weak association between VWF levels and future cardiovascular events or stroke. In contrast, VWF levels are predictive in patients with documented vascular disease. Those patients with increased VWF suffer a higher incidence of major adverse cardiac events including death. The extent of the VWF release and its levels independently predict clinical outcome in patients with acute coronary syndromes. Elevated VWF levels have also been observed in patients with atrial fibrillation compared to controls and predict outcome. This may at least in part be attributable to the association of VWF with underlying cardiovascular risk factors. Hence, VWF correlates with Framingham and CHADS stroke risk stratification score and can be used as a biological marker in patients with AF. However, VWF is not only a predictor; it also plays a crucial role in thrombogenesis. This fact has made VWF a promising target for research into new anti-platelet therapies that specifically inhibit VWF. This review focuses on the role of VWF in ACS, ischemic stroke and peripheral arterial disease and outlines the relevance of therapeutic interventions targeting VWF for ACS patients.

SY4 Inflammation in the Vessel Wall

SY4-2

Key transcriptional regulators of the vasoprotective effects of shear stress

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Atherosclerotic plaque rupture and subsequent thrombosis is the main cause of sudden coronary death. Remarkably, atherosclerosis only develops in certain pre-disposed areas of the vasculature. Endothelial cells in these pre-disposed areas experience low or oscillatory shear stress, which activates the pro-inflammatory and pro-coagulant transcription factors activator protein 1 (AP-1) and nuclear factor

κ B (NF κ B), thus inducing a pro-inflammatory, pro-coagulant surface. In contrast, healthy endothelial cells that are exposed to prolonged high laminar shear stress, express anti-inflammatory and anti-coagulant genes. The key shear stress-induced transcription factors that govern the expression of these genes are Krüppel-like factor 2 (KLF2) and nuclear factor erythroid 2-like 2 (Nrf2). Together KLF2 and Nrf2 govern ~70% of the shear stress-elicited gene sets. Nrf2 potently induces anti-inflammatory/antioxidant enzymes, while KLF2 induces anti-inflammatory and anti-coagulant proteins, most specifically endothelial Nitric Oxide Synthase (eNOS), and Thrombomodulin (TM). KLF2 also inhibits pro-inflammatory and anti-fibrinolytic genes through inhibition of proinflammatory transcription factors AP-1 and NF κ B. The wide-spread beneficial effects of the key transcription factors KLF2 and NRF2 on endothelial phenotype, holds the promise that their targeted modulation might lead to a whole new class of cardiovascular drugs.

SY4-3

Immune modulation by natural antibodies to prevent vessel wall inflammation

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Atherosclerosis is a chronic inflammatory disease, characterized by the accumulation of oxidized lipoproteins and apoptotic cells, which both contain various oxidation-specific neoepitopes. Adaptive immune responses to these have been shown to play an important role in atherogenesis. In addition, these epitopes are also recognized by innate receptors, including natural antibodies (NABs) that are selected by evolution and constitute the humoral arm of innate immunity. We previously showed that the specific stimulation of the natural IgM antibody T15/EO6, which binds to phosphorylcholine (PC) of oxidized phospholipids, decreases atherogenesis in mice. We now provide multiple lines of evidence that oxidation-specific epitopes in general constitute a dominant, previously unrecognized target of NABs in both mice and humans. Using reconstituted mice expressing solely IgM NABs, we found that ~30% of all NABs bind to model oxidation epitopes. Moreover, a large percentage of IgM antibodies in human umbilical cord blood, which are predominantly NABs, bind these epitopes. Importantly, this set of NABs was found to recognize epitopes in atherosclerotic lesions, on apoptotic cells and circulating microparticles. Because oxidative processes are ubiquitous, we hypothesize that these epitopes exert selective pressure to expand NABs, which in turn play an important role in mediating homeostatic, protective functions consequent to inflammation and cell death as demonstrated by their ability to facilitate clearance of apoptotic cells and cellular debris. These findings provide novel insights into the functions of NABs in mediating host homeostasis, and into their roles in health and diseases, such as chronic inflammatory diseases and atherosclerosis.

SY/FC5 Pediatric Session

SY/FC5-1

Diagnosis and treatment of bleeding disorders in term and preterm infants

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Haemostasis is a dynamic process, which begins in-utero. Coagulation factors are synthesised by foetuses by 10 weeks' gestational age and their concentrations gradually increase, being physiologically lower in premature infants as compared to full-term babies or healthy children. In the neonate, plasma concentrations of vitamin-K dependant coagulation factors (II, VII, IX, X) and contact factors (XI, XII, prekallikrein and high molecular weight kininogen) are about 50% of adult values. Furthermore, the capacity of new-borns to generate thrombin, dependant upon plasma concentrations of procoagulants, is reduced. These facts, theoretically increasing the risk of severe bleeding, are balanced by the protective effects of physiologic deficiencies of the inhibitors of coagulation, as well as by the decreased fibrinolytic capacity in infants. Laboratory variations of hemostatic tests may render any diagnosis of bleeding disorder in infants difficult to establish. Diagnostic problems of special concern are the need to adapt all coagulation assays for small amounts of blood and the age-related interpretation required for tests' results. The prolonged PT in neonates reflects decreased plasma concentrations of vitamin-K dependant factors, whereas the prolonged PTT stems from decreased plasma levels of contact factors as well. Platelet function is often impaired in term neonates, however high levels of Von Willebrand's protein and its large multimers render them less susceptible of bleeding. Bleeding disorders may sometimes present in infancy, with acute various symptoms and even severe intra cranial hemorrhage. Therapy of bleeding episodes is mandatory, and relies upon proper replacement and repeated hemostatic evaluations of patients' status, while dealing with underlying etiological causes. Potential use of off-label hemostatics (eg rFVIIa) may be discussed under special conditions.



SY6 Hot Topics in Vascular Biology

SY6-1

Obesity and vascular risk

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Objective: To study the role of the fibrinolytic and matrix metalloproteinase (MMP) systems in development of adipose tissue and to evaluate obesity as a pro-thrombotic risk.

Methods: A nutritionally induced obesity model was used in transgenic mice with deficiency or overexpression of components of both proteolytic systems. Venous and arterial thrombosis models were applied to lean and obese mice.

Results: Tissue-type plasminogen activator (t-PA) deficient mice, kept on high fat diet, had higher body weight and adipose tissue mass than wild-type controls. However, development of obesity was impaired in plasminogen deficient mice. The role of plasminogen activator inhibitor-1 (PAI-1) in development of obesity remains controversial. Stromelysin-1 (MMP-3) deficiency promoted adipose tissue development, whereas deficiency of tissue inhibitor of metalloproteinases-1 (TIMP-1) induced impaired adipose tissue development associated with adipocyte hypotrophy. Administration to wild-type mice kept on a high fat diet of broad-spectrum or relatively gelatinase-specific MMP inhibitors resulted in moderate to significant reduction of adipose tissue weight. In an inferior caval vein thrombosis model obese mice showed an increased thrombus weight as compared to lean controls. In a femoral arterial thrombosis model obese mice showed a shorter occlusion time and lower total blood flow.

Conclusion: Studies in transgenic mice support a role of the fibrinolytic and MMP systems in development of obesity. Studies in venous and arterial thrombosis models confirm a prothrombotic risk associated with obesity.

SY6-3

Fibrin in angiogenesis and wound healing

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Fibrinogen and fibrin play an important role in blood clotting, fibrinolysis, cellular and matrix interactions, inflammation, wound healing, angiogenesis, and neoplasia. The contribution of fibrin(ogen) to these processes largely depends not only on the characteristics of the fibrin(ogen) itself, but also on interactions between specific-binding sites on fibrin(ogen), pro-enzymes, clotting factors, enzyme inhibitors, and cell receptors. Fibrin(ogen) contributes to cutaneous wound repair via these molecular and cellular mechanisms. More specifically, the outcome of wound healing depends largely on the fibrin structure, such as the thickness of the fibers, the number of branch points, the porosity, and the permeability. Furthermore, the binding of fibrin(ogen) to hemostasis proteins and platelets as well as to several different cells such as endothelial cells, smooth muscle cells, fibroblasts, leukocytes, and keratinocytes is indispensable during the process of wound repair. High-molecular-weight and low-molecular-weight fibrinogen, two naturally occurring variants of fibrin, are important determinants of angiogenesis and differ in their cell growth stimulation, clotting rate, and fibrin polymerization characteristics. Fibrin sealants have been investigated as matrices to promote wound healing. These sealants may also be an ideal delivery vehicle to deliver extra cells for the treatment of chronic wounds.

SY7 Hemostasis in Major Surgery

SY7-2

How much blood transfusion is needed in major surgery?

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Objectives: The goal of the Austrian benchmark study was to measure and to compare the current transfusion practice and to identify predictors of transfusion.

Study Design and Methods: This was a prospective observational study in 18 randomly selected public hospitals from April 2004 to February 2005. Primary outcome measures were the amount of intra- and postoperative blood components transfused and intercenter variability of transfusion rate. Secondary outcome measures were prevalence of preoperative anemia, calculated perioperative blood loss, and lowest measured perioperative hemoglobin (Hb) level.

Results: Adult patients undergoing primary unilateral total hip replacement (THR, n = 1401), primary unilateral knee replacement (TKR, n = 1296), and coronary

artery bypass graft (CABG) surgery (n = 777) were enrolled. There was a large intercenter variability in the percentage of patients who received transfusions: THR 16 to 85 percent, TKR 12 to 87 percent, and CABG 37 to 63 percent. In the patients who received transfusions, the number of red blood cells (RBC) units transfused varied significantly. There was also a considerable intercenter variability in RBC loss. The prevalence of preoperative anemia was 19 percent and identical in both sexes. The incidence of preoperatively untreated anemia was three times higher in patients who received transfusions compared to those who did not.

Conclusion: This study demonstrates a high intercenter variability in RBC transfusions and RBC loss in standard procedures. Whereas the variability in blood loss remains largely unexplained, the main predictors for allogeneic RBC transfusions are preoperative and nadir Hb and surgical RBC loss.

SY7-3

Use of recombinant factor VIIa in the perioperative period

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Recombinant activated factor VII (factor VIIa) is a pro-hemostatic agent that can be used for patients with hemophilia and inhibiting antibodies towards a coagulation factor. Recombinant factor VIIa is, however, increasingly used for several other indications, including patients who experience serious and life-threatening bleeding. In addition, recombinant factor VIIa has been evaluated for the prevention of major blood loss in patients undergoing surgical procedures that are known to be associated with major blood loss. In this manuscript we review the available data on efficacy and safety of recombinant factor VIIa in the prevention of excessive blood loss and transfusion requirements in the perioperative period. We conclude that recombinant factor VIIa is a promising agent for perioperative prevention of major blood loss but that its efficacy will probably vary between specific clinical settings. The exact place of recombinant factor VIIa in surgery warrants further clinical trials in various situations that will also more precisely determine the safety of this intervention.

SY8 Chemotherapy Induced Thrombosis

SY8-1

Pathophysiology of chemotherapy-associated thrombosis

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Epidemiological studies revealed that most antineoplastic agents and regimes enhance the risk of venous and arterial thromboembolic events in cancer patients. The purpose of this article is to review clinical and pathophysiological data related to chemotherapy-associated thromboembolism under special consideration of newer treatment strategies, such as angiogenesis inhibitors and immunomodulatory agents. Despite numerous clinical and experimental studies it has to be concluded that we are far from a comprehensive understanding of the pathogenesis of chemotherapy-associated thrombosis.

SY8-2

Identifying cancer patients at risk for venous thromboembolism

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Venous thromboembolism (VTE) is a known complication of cancer which impacts on patient mortality and quality of life. Despite the known deleterious effects of VTE, the benefits of thromboprophylaxis have not been fully established. Identification of patients at highest risk of VTE could lead to better targeting of thromboprophylaxis. Several risk factors have been identified as contributing to VTE such as site and stage of cancer, age, comorbidities, obesity, and acquired prothrombotic states. Anti-cancer agents as well as the use of growth factor support have also been implicated in VTE. Recent data have identified biomarkers such as blood counts, tissue factor and P-selectin. In this review, we briefly summarize the risk factors for VTE as well as candidate biomarkers for VTE in cancer patients. We also review a validated risk score that can identify cancer patients at high risk for VTE. Risk stratification of cancer patients will allow clinicians to identify those patients at highest risk for VTE, who may derive the most benefit from thromboprophylaxis.

SY8-3

Cancer-associated thrombosis: predictive parameters, data from the Cancer and Thrombosis Study (CATS)

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Patients with cancer have a high risk to develop venous thromboembolism (VTE), which leads to additional morbidity and increased mortality of cancer patients. The management of cancer patients could be improved, if VTE could be reliably predicted by clinical or laboratory parameters. A high platelet count was reported to be associated with cancer-associated VTE. Recently a risk scoring model for chemotherapy-associated thrombosis incorporating known clinical and laboratory parameters was developed by Khorana et al to define high-risk patients and predict VTE in the ambulatory setting. In 2003 we have initiated the Vienna Cancer and Thrombosis Study (CATS) to define predictive parameters for occurrence of VTE in cancer patients. Over 1000 patients have been included in the ongoing CATS. The cumulative probability of developing VTE in the whole study population was 5.7% after six months and 7.9% after one year. At present, four laboratory parameters were identified to significantly increase the risk for VTE in cancer patients. A high platelet count (>95th percentile of the total study population) was associated with an increased hazard ratio (HR) of 5.5 (95% CI: 2–13.5) for VTE. Elevated soluble P-selectin (>75th percentile of the total study population) increased the VTE risk with an HR of 2.6 (1.4–4.9). Furthermore, the multivariable HR of VTE in patients elevated D-Dimer (1.8 [1.0–3.2]) and elevated F1+2 (2.0 [1.2–3.6]) were statistically significantly associated with VTE. Strong predictive risk factors for VTE were also surgery and radiotherapy, whereas chemotherapy could not be shown to increase the risk. In conclusion, certain clinical and laboratory parameters would help identify cancer patients at increased risk for VTE. The benefit of prophylactic anticoagulant treatment needs to be evaluated in appropriately designed randomized interventional studies considering these new laboratory risk factors.

still unclear, but a number of studies suggest involvement of MV-cell fusion or ligand-receptor interactions. More importantly, MV have been shown implicated in horizontal transfer of genetic material. This review focuses on the role of MV in the context of cancer, and their possible part in cancer associated thrombosis.

SY9 Microparticles in Hemostasis and Thrombosis

SY9-1

Microparticles and female issues

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Emerging evidence suggests that circulating, cell-derived microparticles (MP) play a role in various physiological and pathophysiological processes. MP are involved in coagulation, inflammation and transportation. The role of circulating MP in the field of obstetrics and gynaecology has been investigated only recently. Healthy women show menstrual cycle-specific differences in circulating MPs which differ significantly from age-matched men. With regard to obstetrics, MP were elevated in subgroups of patients with miscarriage or preeclampsia. Whether MP contribute to the pathogenesis of the diseases themselves is part of ongoing research. Moreover, recent studies indicate MP levels parallel tumor invasiveness in breast cancer patients and show similar sensitivity-specificity profiles than established biomarkers.

SY9-2

Pathophysiologic significance of procoagulant microvesicles in cancer disease and progression

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Microvesicles (MV) are submicrometric membrane fragments (0.1 to 1 µm), released from the plasma membrane of activated or apoptotic cells. They are characterized by most of the antigenic profile of the cells they originate from, and by the presence of procoagulant phospholipids at their surface. MV are detectable in the peripheral blood of mammals and considered as efficient effectors in the haemostatic or thrombotic responses, able to remotely initiate or amplify beneficial or deleterious processes, depending on the circumstances. Variations in their level and phenotype make them relevant pathogenic markers of thrombotic disorders and vascular damage. To date, MV are recognized as mediators of communication allowing cells to influence a target present in the local microenvironment as well as to distant sites. The mechanisms by which MV interact with target cells are