Vascular Haematology: The Growing Discipline at the Interface of Cardiology and Haematology

Kalman RAK

Medical Center, Debrecen of University, Debrecen, HUNGARY

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Since the eighties of the last century a new, growing and promising discipline at the interface between two once separate specialties, cardiology and haematology is witnessed. Questions concerning research, biology and clinical practice of the cardiovascular system and haemostaseology are closely related. The proposed terminology which is linked with the name of Caen and Castaldi covers considerable parts of these basic disciplines. The new conception may help the better knowledge, prevention and management of cardiovascular disorders by researching physiological and pathological relations and interpreting experimental and clinical experiences.

Prof. Orhan N. Ulutin, the Editor in Chief of the Turkish Journal of Haematology since 1962 is an outstanding personality of international haematology. The clinical and experimental studies and observations made on the topic of vascular biology and medicine or - using the proposed terminology- on the new specialty of vascular haematology are widely known and highly appreciated. He and his group had during the former years and decades definitive influence on the research of several teams belonging to the European haematological societies. He was especially active in helping, promoting and personally organizing the meetings of the Danubian League against Thrombosis and Haemorrhagic Diseases. As the president of the XIIIth ISH Meeting 1995 in Istanbul he was who generously invited us to participate in the programme and organize a symposium under the title "new approaches of vascular haematology" providing the good opportunity to present some of our clinical and experimental results concerning this fascinating topic. It is a great pleasure and honest to say sincere thanks to him at every given occasion.

Some of the appropriate data concerning the normal and altered functions of endothelium, platelets and plasmatic factors as the main participants of vessel-blood interactions, together with the today's diagnostic and therapeutic options are very briefly reviewed.

What is the main subject of vascular haematology? The interaction of the cellular (platelets, white cells) and the plasmatic (fibrinogen, von Willebrand and several other factors) components of blood and the endothelium of vessels in physiological and pathological conditions under the variable relations of circulation, i. e. the blood flow. Briefly: Connection of the blood and

the vessel wall in normal and disordered states. The vascular system is a dispersed and integrated organ of significant mass which includes the contents (blood cells, plasma) and the container (blood vessels). Blood fills the vast vascular reservoir preserved in a fluid state by the endothelium that together with the blood cells and some plasmatic factors actively maintains an anticoagulant state with several biological functions. Vascular haematology covers the wide topic of the major life-threatening human diseases: Thrombosis, haemorrhage and atherosclerosis.

Endothelium, an active organ, located at a strategic position between the circulating blood and tissues, modulates vascular smooth-muscle tone and mediates haemostasis, cellular proliferation, inflammatory and immune mechanism in the vessel wall. A crucial mediator of proper function is nitric oxid (NO), the molecule of year 1992. Cardiovascular risk factors (dyslipidaemia, hypertension, smoking, diabetes) result in a deminished NO bioavailability, and enhanced production of endothelial vasoconstrictors, such as endothelin-1 and oxigen free radicals. Endothelial dysfunction is characterized by the imbalance between vasodilators, particularly NO, and vasoconstrictors such as ET-1, angiotensin II and reactive oxygen species, between anti and procoagulant mediators or growth-inhibiting and growth-promoting factors. Various factors (endotoxin, cytokines, growth factors, "injury") can induce changes in endothelial cell structure and function by a process termed endothelial cell activation leading to specific functional changes. They become activated also by the binding of leukocytes, monocytes and lymphocytes by via adhaesion molecules (Rubanyi and many others). Prostacyclin (PGI_2), NO and the ecto-ADPase (endothelial cell CD39) are mainly responsible for "thromboregulation" by endothelial cells. A novel soluble form of recombinant human ecto-ADPase (solCD39) may indicate a new class of antithrombotic agents acting by metabolism of ADP (Marcus et al). Only recently was shown the qualitatively unique nature of each vascular segments (vascular-bed specific hemostasis). "The theory that the hypercoagulable state represents a systemic disorder is no longer tenable" (Rosenberg et al.). The concept of multiple tissue-specific networks of procoagulants and anticoagulants probably serves as an important model for understanding the other homeostatic processes, too. The anticoagulant activity of endothelial cells is mediated via heparin sulfate (with antithrombin), thrombomodulin (with protein C), tissue factor pathway inhibitor, and tissue-type plasminogen activator. The growth of smooth-muscle cells and the adhaesion of blood cells are also well balanced. The mechanism and pathophysiological importance of the hyperlipidaemia caused endothelial dysfunction was thoroughly studied.

The dominant role of platelets in thrombo-and atherogenesis is widely accepted. The steps of primary haemostasis (adhaesion, release, aggregation, providing procoagulant surface for activated coagulation protein complexes) are well known and routinely measured. The "platelet-activation" is not so clearly defined and its assessment and quantification need more sophisticated laboratory methods. Platelets are the distinguished components of "white thrombus" in unstable coronary syndromes and have crucial role in the clinical manifestations of atherosclerosis. The so-called risk factors act chiefly through the haemostatic system, first via platelets. The rational use of antiplatelet agents and drugs is certainly well based. A lot of data on atherosclerosis-research was coming from Ulutin's laboratory.

Endothelial dysfunction promotes atherogenesis, therefore modern treatment strategies are aimed its reversing:

1. Protective substances (L-arginine, stable PGI_2, vasodilators, solCD39, therapeutical vasculogenesis, e.g. cytokines with angiogenic activity, antisense agents for angioplasty or stent restenosis).

2. Inhibitors of contracting factors (ACE inhibitors, angiotensin II receptor antagonists, TXA2-synthase inhibitors and receptor antagonists).

3. Cytoprotective agents (antioxidants, free-radical production inhibitors).

4. Lipid lowering drugs (statins).

5. Others: Lifestyle, diet, anticoagulants (indirect and direct thrombin inhibitors), hormones, several forms of cobined treatment are more or less accepted, under studies or even questioned. "Strategy for ensuring a better future for the vessel wall" (Fuster et al.) remains the primary goal of vascular haematology.

Antiplatelet therapy has now been shown to reduce the risk of serious vascular events by about one-quarter

among patients with coronary, cerebral and peripheral arterial diseases. The aspirin or even clopidogrel "dilemma" "till and already exists. The platelet glycoprotein IIb/IIIa integrin blockade, the use of several PG IIb/IIIa antagonists are continuously studied in different clinical situations. The return of these drugs "from bench to bedside" proved to be very successful. The GP Ib blockers to inhibit adhaesion, the very first step of platelet-surface interaction, could be theoretically even more promising (perhaps used as complimentary drug), but the present options are poor. A hybrid peptide capable of inhibiting aggregation and promoting fibrinolysis is worth for further study (Udvardy et al).

Vascular haematology is a growing specialty between cardiology (mainly angiology) and haematology (mostly haemostaseology) and represent a significant part of vascular biology and medicine. Atherosclerotic cardiovascular and cerebrovascular diseases are still the list leaders of morbidity and mortality statistics. Common effort is justified in its future research and adoption.

Address for Correspondence:

Kalman RAK, MD

Debrecen University, Medical Centre
H-4012 Debrecen, HUNGARY

e-mail: *krak@jaguar.dote.hu*