LXI JCET LECTURE, 24.04.2015, 9.00

Thrombin generation and blood platelets

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Thrombin is the key biologically active product of the haemostatic mechanism, as is apparent from its many functions, including pro- and anticoagulant activities and pro-inflammatory effects. Thrombin generation analysis therefore is a physiological function test of the haemostatic capacity of the isolated organ blood (-plasma). Unlike clotting times (PT, aPTT, WBCT) it also detects hyper-function, i.e. a tendency to thrombosis, which is clinically much more relevant than bleeding tendency is.
The capacity of a plasma to generate thrombin is reflected in the thrombin generation curve (Thrombogram) and notably in the endogenous thrombin potential (ETP), which is the area under the thrombin generation curve and is a direct measure of the amount of "enzymatic work" that thrombin can do. The currently available thrombin generation assay (Calibrated Automated Thrombogram, CAT) allows routine; quantitatively correct (imprecision 2.5 – 4%) measurement of the thrombin generation curve at low cost and high throughput. Alternative devices are semi-quantitative and/or require addition of polymerisation inhibitors that strongly influence normal thrombin generation.
Monitoring of the thrombogram allows *(i)* to detect ongoing thrombosis; *(ii)* to detect increased risk of thrombosis *(iii)* to install and monitor antithrombotic treatment; *(iv)* to detect bleeding disorders and monitor their prophylaxis and therapy. Although arterial and venous thrombosis show important differences it seems likely that thrombin generation can cover all these indications; notably when thrombin generation is not only carried out in platelet poor plasma but also in platelet rich plasma. Recently we developed a method to determine thrombin generation from a drop of whole blood.

Curriculum vitae

Professor Hendrik Coenraad Hemker

Main present positions

- Professor and Senior Councilor Cardiovascular Research Institute Maastricht (CARIM)
- Scientific Director of “Synapse BV, Research, Development and Consultation in Haemostasis and Thrombosis”, a research company.

Career

- MD University of Amsterdam 1959
- Ph. D in Biochemistry, Univ. of Amsterdam 1962 (Prof. Dr. E.C. Slater)
- Head of the research laboratory of the Division of Haemostasis and Thrombosis, Department of Internal Medicine, University of Leyden, 1962 - 1968.
- Professor of Internal Medicine, for the biochemistry of heart - and vessel diseases, University of Leyden, 1968-1975 continued on a part time basis until 1996.
- Professor of Biochemistry, Chairman of the Department, University of Maastricht 1975 - 1999.
- Rector Magnificus (Vice Chancellor) University of Maastricht 1982 - 1985.
- Professeur Étranger Université René Descartes (Paris V) Hôpital Necker - Enfants Malades and Université Pierre et Marie Curie (Paris VI), Hôpital Lariboisière 1984 - 1987.
- Professeur Étranger Collège de France 1988
- Affiliate professor of Internal Medicine, Mount Sinai Medical School, New York. 1995 - 2005

Main Distinctions and Awards

- Prix Européen Ganassini (Milano) 1967
- Boerhaave Medal (Leyden) 1974
- Ernst Jung Price (Hamburg) 1985
- Commandeur de l'Ordre des Palmes Académiques (France) 1987
- Member of the Royal Dutch Academy of Arts and Sciences 1987
- Career Award for contributions to Haemostasis and Thrombosis (International Society of Thrombosis and Haemostasis) 1987
- Medal of Honor Dutch Federation of Thrombosis Services 1989
- Member of the Academia Europaea 1990
- Chevalier de la Légion d'Honneur (France) 1990
- Honorary member of the Royal Flemisch Academy 1991
- Christiaan Huygens Lecture, Académie des Sciences, Paris 1992
- Dutch Science Foundation, 8 year program grant 1993
- Honorary Doctorate Xi’An Medical Faculty 1996
- Honorary member of the Dutch Society of Thrombosis and Haemostasis 1997
- Medal of the Medical Faculty Maastricht 1999
- Knight of the order of "Nederlandse Leeuw" (Royal distinction, The Netherlands) 2000
- Foreign member of the “Académie Nationale de Médecine” (France) 2001
- Opening of the “Coen Hemker” lecture theatre University of Maastricht 2009
- Establishment “Hemker Fund” for fostering the Haemostasis and Thrombosis

Research at the University of Maastricht. 2010

- Officier de la Légion d'Honneur (France) 2012
- Medal of Merit of the City of Maastricht 2012
- Honorary Member of the Russian National Hematological Society 2014

General

- Author of over 500 scientific articles and several books.
- Supervisor of over 70 Ph.D. theses.
- Numerous editorial boards; among others 1980 – 2002 Haemostasis (Editor in Chief)

Main Scientific Achievements

- Discovery of uncarboxylated clotting factors (PIVKAs) in vitamin K deficiency (Nature, 1963)
- Discovery of the prothrombin converting enzyme as a complex of factors Xa, Va and phospholipid (Nature 1968)
- Discovery of the role of the antihaemophilic factors A and B as constituents of the factor X activating enzyme complex (Nature 1968)
- With J.Rosing: Discovery of the enzyme mechanistic role of factor Va and phospholipid in prothrombinase (JBC 1980)
- With Chr.Reutelingsberger: Discovery of Annexin V (Vascular AntiCoagulant, Eur J Biochem. 1985)
- With W.Hermens: Development of ellipsometry as a tool in biochemistry of surface-bound reactions.(JBC, 1992 - 1999)
- With S.Béguin: Clarification of the mode of action of heparins in plasma, rationalisation of heparin determinations, development of standard-independent units for heparin activity. (Thrombosis and Haemostasis, 1987 - ongoing).
- With T.Lindhout and W.Hermens: Thrombin formation at macroscopic surfaces (JBC, 1992 - 1999)
- With S.Béguin: Discovery and development of the Endogenous Thrombin Potential (ETP) as a universal laboratory probe for hypercoagulability and the effect of anticoagulant drugs (European and USA Patents. Thrombosis and Haemostasis, 1987 - 1993).
- With S.Béguin: Development of methods to determine the Thrombin Generation Curve in defibrinated platelet poor plasma automatically by conversion of special chromogenic substrates. (Thrombosis and Haemostasis 1993 - 1998)
- With S.Béguin: Discovery that fibrin can activate and provokes procoagulant activity in platelets (Thrombosis and Haemostasis 1995 - ongoing)
- With S.Béguin: Discovery that von Willebrand factor plays a compulsory role in thrombin generation in platelet rich plasma, together with the receptors GPIIb/IIIa and GPIb (Thrombosis and Haemostasis 1997 - 1999)
- With J.Rosing: Discovery the biological variable in the clotting system that correlates with pill thrombosis (British Journal of Haematology, 1997 - ongoing).
- With S.Béguin and P.Giesen: Development of Calibrated Automated Thrombinography (CAT) a method to measure thrombin generation in real time in platelet poor or platelet rich plasma. (Thrombosis and Haemostasis 2000 - ongoing).
- Simulation of the clotting system. With R. Wagenvoor, P.W. Hemker and others (J. Thromb. Haemost. 2006 - ongoing)
- With R. Wagenvoord: The molecular mechanism behind the action of heparins (Thromb.Research. 2008).

- With P.W. Hemker and R.AlDieri: Mathematical techniques for compensation for substrate consumption (Thromb.Haemost. 2009)
- With R.Apitz-Castro, S.Béguin, M,Ninivaggio and others: Development of thrombin generation measurement in whole blood (J. Clin.Chem. 2012).

With R.Al Dieri : A new regulatory function of factor V (J. Thromb. Haemost. 2013)