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Fahraeus lecture

From hyperviscosity to endothelial dysfunction: a return trip?

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Sandro Forconi
Department of Internal, Cardiovascular and Geriatric Medicine, School of Medicine, University of Siena, Italy
E-mail: forconi@unisi.it

Dear friends, colleagues, ladies and gentlemen,

I don't know if I'm able to hide the great emotion of being here as a Fahraeus Awardee. The medal represents an important milestone for me and to have reached it fills me with joy. I thank all those who voted for me and all those who have collaborated with me in my haemorheological studies. A particular thought goes to my mentor Tullio Di Perri, also a Fahraeus Awardee in 1989 at Frankfurt, together with whom I have shared these many years of research. Tullio Di Perri should have been here today (I asked him to do the Laudatio) but he did not feel up to making such a long trip: however, he asked me to pass on his warm greetings to all of you.

This is the Twelfth European Conference.

Table 1
European Conferences on Clinical Haemorheology and Fahraeus Medal Awardees

	Year	Seat	President	Fahraeus Medal
1st	1979	Nancy	Jean-François Stoltz	
2nd	1981	London	John Dormandy	Shu Chien
3rd	1983	Baden-Baden	Holger Schmid-Schönbein	John Dormandy
4th	1985	Siena	Tullio Di Perri	Holger Schmid-Schönbein
5th	1987	Bordeaux	Michel Boisseau	Jean-François Stoltz
6th	1989	Frankfurt	Albrecht Ehrly	Tullio Di Perri
7th	1991	Southampton	Stuart Roath	John Stuart
8th	1993	Vienna	Edgar Ernst	Herbert Meiselman
9th	1995	Siena	Tullio Di Perri	Albrecht Ehrly
10th	1997	Lisbon	Joao Martins e Silva	Siegfried Witte
11th	2000	Rouen	Gerard Potron	Gustav Born
12th	2003	Sofia	Nadia Antonova	Sandro Forconi

Clinical haemorheology was born in the 1970s when a small group of friends and scholars began to meet and formed a Study Group on filtration methods and then a Coordinating Committee which, until the Vienna Congress in 1993, organized the various European Conferences. 1993 was the year in which these friends quarrelled, and in consequence two Societies were born, the International one and the European one. Unfortunately, in those years the interest of the pharmaceutical industry, which had supported our research, fuelling our laboratories but also gaining economic advantages, began to decrease until it almost died out completely. However, I must say that, instead of destroying haemorheological science, these difficulties contributed to its rebirth, with the entry of new young researchers, new scenarios and new fields of interest. Moreover, as often happens in good families, the difficulties created a selection among researchers, whose quality returned to past levels, and in a great spirit of friendship the two societies have begun discussing ways to overcome their past misunderstandings in order to re-unite under a single banner all the forces throughout the world interested in Clinical Haemorheology.

At Siena, we began to deal with this topic in a research laboratory that was part of a clinical department interested in cardiovasculopathies. As clinicians, we approached haemorheology by studying heart failure and then the pathophysiology of the peripheral circulation (particularly the microcirculation), after which we moved on to study the properties of blood flow in humans, considering first the vessels and then the blood.

It was natural that the first studies were strongly focused on methodology. Even now, methodology is one of the most frustrating problems because, even though theoretically the viscosity of the blood represents the gold standard, in practice the ideal viscometer has still not been manufactured. For a long time, we argued about the methods of filtration used throughout the world, divided into two groups that fiercely praised or denigrated the various techniques. Personally, although aware of the limits of these techniques, we have forcefully supported the concepts that could derive from the application of rigorous methodological standards, such as the use of whole, unstored blood, evaluated at 37°C immediately after sampling. We now apply this method to morphological studies, carried out with the Zipursky technique, having eliminated the error made by this Canadian friend who failed to consider the rigidification of the erythrocytes due to blood storage. However, the haemorheological methods, beyond the specific significance given to them concerning the deformability or aggregability of blood cells, have provided us with information about macro- and microcirculatory haemodynamics, leading to the creation of new physiopathological entities (blood hyperviscosity syndromes) which can be followed in the clinic even without evaluating these sophisticated parameters. They are fundamental in our research laboratories and have allowed us to spread the haemorheological word, but in clinical practice, current parameters, like the haemochromocytometric test, ESR, haematocrit, fibrinogenemia, immunoglobulins, etc., are sufficient.

What has haemorheological research brought to clinical practice? First of all, evidence of the peculiarity of blood which is a fluid able to flow even in extreme physical conditions with a fluidity that can vary according to the flow characteristics and vice versa.

This is due to:

- the presence of circulating cells (red, white, platelets);
- their number (htc, ltc, ptc) and characteristics (deformability, aggregability);
- the plasmatic components;
- the influence on flow conditions of the output (shear stress), velocity (shear rate) and vessel bore in the macro- and microcirculation.

The main concepts in clinical haemorheology are:

- blood fluidity can change in a short time and can be modified, with consequences for tissue perfusion;
- there is evidence of true clinical syndromes, with definite signs and symptoms, due to impairment of blood fluidity (Blood Hyperviscosity Syndromes);
- it is possible to modify blood fluidity with procedures like haemodilution and/or plasmapheresis and also with drugs acting on the plasmatic components or on the properties of circulating cells.

Of all these characteristics/concepts, allow me to focus on the concept of hyperviscosity syndrome. It was Wells in 1970 who identified three situations due either to an increased number of red cells (polycythemic hyperviscosity) or to their decreased deformability (sclerocythemic hyperviscosity) or to the presence of pathological elements in the plasma (plasmatic hyperviscosity), all of which strongly influence erythrocyte aggregability. Therefore, the red cells are viewed as both protagonist and victim of the modifications of blood flow.

The blood hyperviscosity syndromes described by Wells were clinical syndromes in which a primary disturbance of the blood caused a reduction of blood flow, leading to poorer tissue perfusion. The rheological disturbance preceded the disease, thus it was Primary. Very briefly, the Primary Hyperviscosity Syndromes are those of the polycythemias, myelomas (particularly Waldenstrom disease) and haemolytic anaemias (particularly Sickle Cell Disease). In Waldenstrom and in SCD, the classical symptoms regress after treatment to reduce the viscosity.

Therefore, unlike in the first approach, looking at the flow conditions of Primary Hyperviscosity Syndromes, we consider firstly the blood and then the vessel as the cause of hindered tissue perfusion.

In our studies, we have dealt with other situations in which the rheological disturbance appears to accompany instead of cause the disease. Together with other authors, we have identified many situations in which this occurs, in various pathologies from inflammatory and neoplastic diseases to vascular diseases.

We have studied vascular diseases for many years and, anticipating our conclusions, which in fact are already known because they have been published, we are convinced of the existence of Secondary Hyperviscosity Syndromes. While in the Primary Hyperviscosity Syndromes, the rheological disturbance precedes the flow reduction and appears as the cause of the disease, in the Secondary Hyperviscosity Syndromes the rheological disturbance follows the flow reduction and appears dependent on, in association with, or a risk factor for, or a marker of, the disease itself (Fig. 1).

How did we arrive at these conclusions? I will try to list some concepts based on published studies.

(a) In vascular diseases associated in some way with tissue ischemia, many authors have demonstrated a disturbance, or better a rheological impairment. I cite among others the work by Dormandy, Ehrly, Dintenfass, Lowe, Le Devehat, as well as many present in this auditorium.
(b) The rheological disturbance tends to be related to the degree of ischemia and it is more evident in the acute phase than in the chronic stage of the disease.
(c) When one has rheological data from before an episode of acute ischemia, one notes that the increase follows the ischemic episode. In our experience, this has been observed in myocardial infarction and in angina pectoris.
(d) After a myocardial infarction or a stroke, the viscosity tends to increase in the first few days and then decrease in the following days.
(e) Ischemia-provoking tests show increased viscosity after the stress test.
(f) The arterial blood appears more fluid than the venous blood. The arterial-venous difference increases after the stress test.

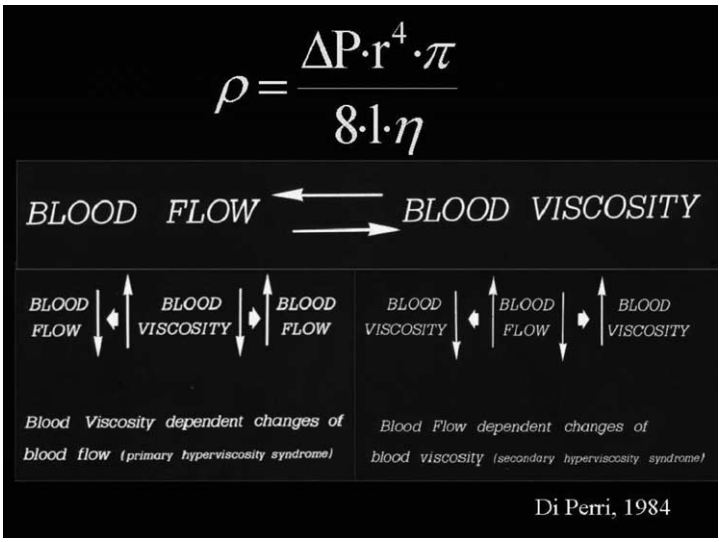

Fig. 1.

(g) Sampling of venous blood from the regions subjected to the stress test show abnormal increases of the viscosity values. This has been observed not only in the limbs but also in the coronary circulation.

All these results convinced us that during peripheral ischemia a series of phenomena is triggered in the ischemic tissue, characterized by:

- the release of substances that interfere with the coagulative and fibrinolytic processes and with the state of the circulating cells,
- activation of leukocytes and platelets,
- modifications of the membrane and internal component of the red cell, in which we have identified an increased concentration of cytosolic calcium in parallel with decreased erythrocyte deformability.

The participation of the coagulative-fibrinolytic system logically leads the researcher's attention to the vascular endothelium. In recent years, our view of endothelium has changed from a simple border between blood and vessel to a complex factory producing substances that profoundly affect the circulatory homeostasis, particularly vasomotility. The endothelium produces vasoconstrictors (endothelin) and vasodilators, basically nitric oxide whose secretion and synthesis occur via nitric oxide synthetase. The main stimulus for increased activity of the enzyme NOS is vessel wall shear stress which, through the transformation of arginine into citrulline, releases nitric oxide.

For this reason, we have focused our attention on haemorheological–endothelial relationships. We wanted to see if endothelial function is modified in the classical conditions in which haemorheological changes occur.

Unfortunately it is not easy to evaluate this aspect, that is endothelial function. In the clinic, endothelial integrity in humans is assessed by local intra-arterial infusion of acetylcholine and subsequent echocolourdoppler measurement of the induced vasodilation. Alternatively, the activity of nitric oxide synthetase and thus the production of nitric oxide, impossible to measure directly because it is too

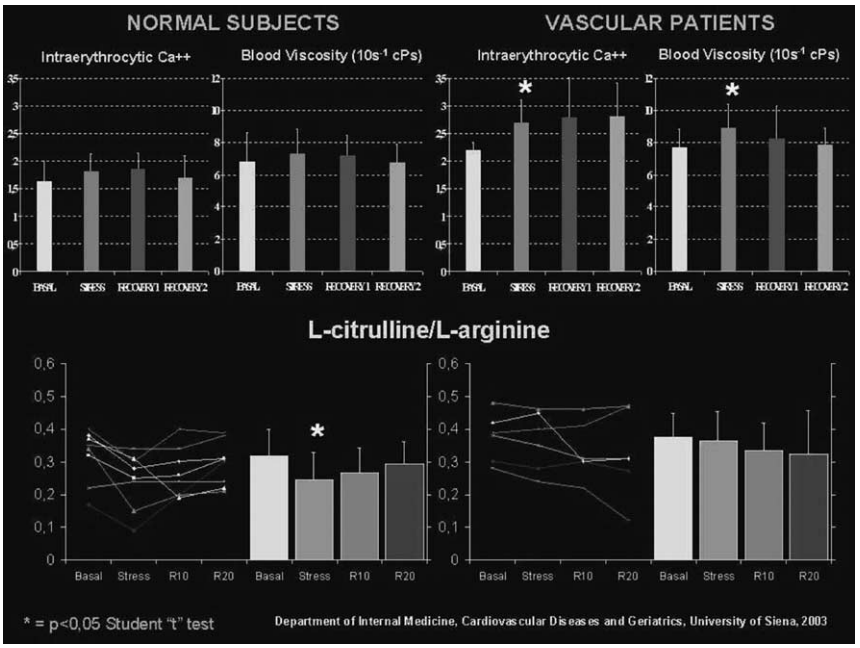

Fig. 2.

ephemeral and rapidly disappears from the circulation, can be indirectly expressed by the arginine and citrulline values, measured by high pressure liquid chromatography. Therefore, we have chosen the value of the citrulline/arginine ratio as an index of endothelial function and we have tried to compare it with the viscosity values in one of our classical study models, that of exercise in the normal and cardiopathic subject.

In Fig. 2 which briefly summarizes the concept (the complete results are in press in *Clinical Hemorheology and Microcirculation* and will be also presented by Dr. Turchetti later this morning), we can see the difference in the response to physical exercise between the normal subject, presumably with healthy endothelium, and the subject with ischemic cardiopathy in which the cycloergometer stress test was positive and thus it is assumed there is an endothelial dysfunction.

In the upper left are the normal subjects, in whom exercise does not cause variations of rheology (viscosity) nor of intraerythrocytic calcium concentration. In the upper right are the vasculopathic subjects, in whom both the viscosity and the intraerythrocytic calcium content are increased by exercise and the increase persists even during the recovery phase.

In the lower part, we see the response of the endothelium: The normal subject, to the left, reacts with a decreased citrulline/arginine ratio, which then returns to basal values during the recovery. In the vasculopathic subject, to the right, this does not occur: there are no significant changes, perhaps a tendency to a slow decrease but in general there is no response by the apparently dysfunctional endothelium.

Are the two phenomena related? If so, we would have to hypothesize that in the peripheral circulatory response to exercise by the normal subject with healthy endothelium, at the level of peripheral resistance there are processes characterised by a lower production of nitric oxide while the viscosity does not change. In the pathological subject, with dysfunctional endothelium, this does not occur and the increased viscosity would mean not so much a hindrance to the circulation but would have the ultimate

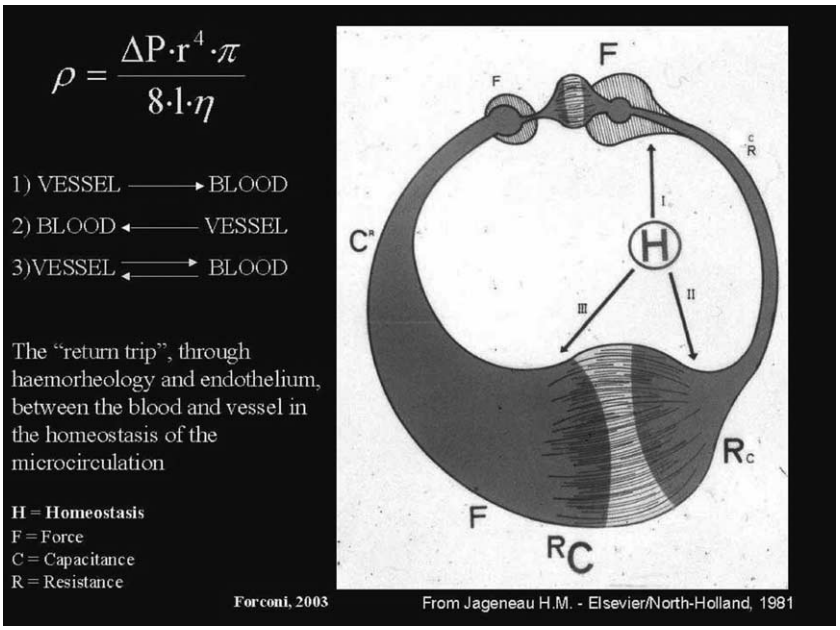

Fig. 3.

purpose of slowing the blood flow in the microcirculation, thus allowing greater extraction of oxygen and substances necessary for tissue metabolism.

And thus the third point (Fig. 3) which explains the title I decided to give to this lecture and the stimulus I want to transmit to you the listener. Our research trip in the field of peripheral blood flow in the normal subject and in the vasculopathic patient started by considering the calibre of the vessel as of primary importance with respect to the viscosity of the blood, then instead we placed blood viscosity in the principal position, now we are brought back through the endothelium to the point of departure, in a kind of "return trip" in the field of circulatory physiopathology.

And now my warm thanks: to the Council and the Advisory Committee of the European Society for Clinical Haemorheology, my family and my research group. See you in Siena in 2005!

Acknowledgements

This lecture summarizes the work done in the laboratories of the Institutes and/or Departments of the University of Siena chaired first by Tullio Di Perri and then by Sandro Forconi. It is not meant to be a comprehensive review, and many important studies from other laboratories are not cited. The author would like to acknowledge the valuable collaboration of all those cited in the reference list.

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