CLINICAL HEMORHEOLOGY, Vol. 10, pp. 581-595, 1990
0271-5198/90 $3.00 + .00 Printed in the USA.


SIXTH EUROPEAN CONFERENCE ON CLINICAL HEMORHEOLOGY
Frankfurt am Main, Germany, 15-17 June 1989

FÅHRÆUS AWARD LECTURE

# THE HYPERVISCOSITY SYNDROMES

Tullio Di Perri
Department of Medicine, University of Siena, Siena, Italy

Let us imagine a long ideal continuity starting two centuries ago and tracing the rheological way until today.

The spirit of Poiseuille and successively that of Womersley, Reynolds and Fåhræus have haunted blood rheology throughout its history and it is to them that almost all the controversies in the subject can be traced.(1,2,3)

They each bequeathed to our world arguments and conceptions of superlative intellectual and scientific power. It is not surprising that whereever they were read, their influence was felt.

I think thatevery body approaching biorheology or hemorheology was aware of the importance and, at the same time, of the intrinsic difficulty to apply the theoretical laws coming from experimental data, based on models or on numerical simulation to mammal physiology and especially to human physiology. As I am a clinician, the subject matter of my presentation is oriented on Clinical Hemorheology.

The term "Hyperviscosity syndromes" was chosen to stress my design to be as close as I could to the clinical problems connected with hemorheological disorders. In this line the criticism which can accompany the word "syndrome" must be accepted, since often blood hyperviscosity is not associated or followed by dependent sign and symptoms. The last assumption is particularly true, if we intend physical signs and symptoms.

Physical signs and symptoms are the key for reading the book of clinicans. But the term of sign must be extended to humoral and

Physical signs and symptoms are the key for reading the book of clinicans. But the term of sign must be extended to humoral and molecular changes if detectable at the point to be transfered in clinical and pathophysiological terms.

Since the clinical observation is enlarging its field to consider biochemical, cellular and molecular changes as signs, I have chosen the term "syndrome" to indicate all the signs, physical, functional, biochemical or molecular dependent on blood hyperviscosity or associated with it. In my opinion it must be considered an actual useful unitary hypothesis for planning a nosographic classification of the hemorheological disorder.

We consider two groups of pathological processes presenting hemorheological disorder. Therefore, we consider two types of blood hyperviscosity, the first one is dependent on structural factors and the second one on functional factors.

In a more comprehensive terminology, the structural blood hyperviscosity conditions are considered as primary syndrome, being the viscosity the determinant and the blood flow the dependent factor. The functional hyperviscosity conditions are considered as secondary syndromes, where the blood flow represents the determinant factor and the viscosity change the dependent one.

It appears obvious, at this point, that the pathophysiological and clinical principal target of hyperviscosity is over the entire microcirculation and the signs and symptoms that can be ascribed in some patients to the chronic irreversible blood hyperviscosity are localized in this vascular tree. In other words, in primary hyperviscosity (hyperviscosity dependent syndromes) the appearance of specific signs and symptoms can be clearly related to the increase of blood viscosity or to a very clear change of a viscosity factor.

On the contrary, in the secondary hyperviscosity (hyperviscosity associated syndromes) the humoral change is the compass on which we can evaluate the appearance of the hemorheological disorder, since its clinical equivalence is confused in a more complex multifactorial pattern in which it is impossible to distinguish how the rheological mechanism is working on a functional disorder yet existing independently and not different in its clinical expressivity, from the qualitative point of view.

On the basis of data, when the pathophysiologist or the clinician is trying to give a functional meaning to increased blood viscosity which is considered the marker of increased viscous forces, the vessels with predominant viscous forces are considered as the target of the

hemorheological disorder. They are the vessels showing a Reynolds number less than one, the microvessels. But besides such physiological way, other experimental evidence supports the view which leads the clinician to turn his attention to the microcirculatory environnement in face of a blood viscosity or viscosity factor increase.

Thus, we know a serum, a polycythemic and a sclerocythemic blood hyperviscosity, all situations marked by an irreversible high blood viscosity, each of which due to a different specific viscosity factor.

The primary serum hyperviscosity is a marker of the plasma cell dyscrasias. It is dependent on the enormous increase of circulating immunoglobulins, which lead to an increase of plasma viscosity. In this situation, there is frequently the appearance of signs and symptoms, which suggested to Fahey and later on to Wells the introduction of the terms "hyperviscosity syndrome".(4,5) The capillary engorgement with a marked slowdown of blood flow is the mechanism leading to the appearance of symptomatology. Its specific treatment is plasmapheresis. The plasmapheresis treatment allowed Fahye to suggest a relationship between a threshold of clinical symptomatology appearance and plasma viscosity level, thus stressing a close dependence of the former on the latter.

The second type of primary structural blood hyperviscosity is the polycythemic one, where the pivotal viscosity factor is the increased hematocrit as index of the circulating cellular mass. It is present in primary erythrocythemia as well as in hypercellular leukemia and sometimes in thrombocytosis. The microcirculatory disorder is always associated with a strong impairment of available oxygen transport.

It was demonstrated that there is a direct relationship between hematocrit and whole blood viscosity which presents a different slope in controls and in polyglobulic patients where it is less vertica, thus inducing Leopold Dintenfass to suggest that such patients can bear very high values of viscosity because of increased deformability of circulating cells.(6)

The actual strategy of therapeutics, besides of every antiproliferative treatment, is to reduce cellular mass by hemodilution, which results are rather successful.

Finally, there is a third homogeneous group of diseases, which share a genetic defect of the metabolic structure of erythrocytes, showing a type of primary blood hyperviscosity, the so-called sclerocythemic hyperviscosity.

In this group several hemolytic diseases, such as sickle cell disease, spherocytosis, purivatokinase deficiency were included.

The irreversibility of the hemoglobin changes was the reason to include such diseases in this group.

From here the microinfarcts, which can critically appear during the course of the disease, and the hemolytic episodes with the consequent anemia. Blood tranfusion, erythrocytopheresis are the usual strategy of treatment. The speculative study of the drug usefulness is an open question. It is my pleasure to quote the studies of John Stuart on this topic.(7)

I will not discuss such primary structural blood hyperviscosity since they were extensively treated in the previous Fåhræus lectures by Shu Chien and John Dormandy.(8,9) I prefere to spend more time for the discussion of secondary functional blood hyperviscosity and particularly of those associated with tissue hypoperfusion, leading to the ischemic picture.

The natural observation of the primary structural hyperviscosity conditions is supporting the fact that the microcirculation is the target of the excessive decrease of blood fluidity.

Until this point a unidirectional relationship was hypothesized, considering primary blood viscosity as determinant factor and blood flow as dependent component.

This kind of relationship was obviously related to the primary structural blood hyperviscosity, marked by very high changes either of viscosity or of viscosity factors, which were relatively steady if not artificially corrected.

Successively many epidemiological and experimental data were collected, emphasizing the presence of a rather constant hemorheological abnormality in different groups of diseases, all presenting a circulatory or, better, microcirculatory impairment. A theoretical approach to this type of hyperviscosity was attempted.

Simplifying the Poiseuille equation, leaving only two opposite terms, flow on one side and viscosity on the other, it was proposed to test wether the equation was still worthwhile working after changing the direction of the determinant influence. In other words, the hypothesis was to give the role of determinant component to blood flow and of dependent factor to viscosity .

Together with the thrombical speculation the first approach was clinical and especially epidemiological to investigate in homogeneous groups of vascular patients, wether or not a hemorheological disorder was present.

The second point was epidemiological consisting in collecting an homogenous group of patients, showing a localized or generalized, either acute or chronic, slowdown of blood flow and evaluating blood viscosity and viscosity factors according to a transversal method of investigation.

Let me focus the attention on this common aspect of blood hyperviscosity associated disease which was the object of our study.

A lot of time was spent in this direction in many laboratories. These researches gave an important contribution to the assessment of such a topic, working either on ischemic heart disease or on cerebrovascular disease or on peripheral artery obstructive disease.

The findings were converging on a similar conclusion, supporting the fact that in such patients, indipendently from the localization of the blood slowdown, blood viscosity was significantly higher than in control subjects. I will spend the remaining time, discussing this topic in some detail.

Let me, therefore, present certain data, collected in our laboratory in selected groups of patients, showing a chronic localized ischemic syndrome.

What kind of blood viscosity disorder was found in such patients ? How was the approach to the problem of its pathophysiological meaning?

The inclusion criteria of each group was the assessed chronic ischemic heart disease, chronic cerebrovascular disease (post ictal stage) and peripheral artery occlusive disease at stage II or III of Fontaine's classification.

The collected data were: Whole blood viscosity and filterability, plasma viscosity, fibrinogen concentration and hematocrit value.

The elaboration of such data showed that in all these patients the chronic ischemic disease, indipendently from its localization, was associated with a hemorheological disorder, involving either blood viscosity or the viscosity factors.

A horizontal investigation of the same type was done on acute vascular disease, evaluating blood viscosity and the viscosity factor levels at the onset of the disease. Here myocardial infarction, angina pectoris, stroke and TIA patients were introduced in the trial. Also in these patients, a significant modification of blood rheology markers was registered. In detail a more or less important change of whole blood viscosity, plasma viscosity, whole blood filterability, fibrinogen and hematocrit was detected.

Since no primary structural changes were detected, all registered data were considered as secondary to the ischemic disease and dependent on functional mechanisms.

This interpretation was supported by the longitudinal observations on acute myocardial infarction or stroke. The ontset of the vascular storm was associated with high levels of whole blood viscosity, especially at low shear rate and with low blood filterability in rats, together with an increase of blood lactoferrin and ß thromboglobulin.

Here, two new actors of this hematic aspect of the drama are introduced. They cannot be considered as hemorheological factors in the strict sense of the word, because lactoferrin is the marker of the in vivo activation of PMN and B is the marker of in vivo activation of platelets.

But these findings, which were constantly associated with ischemia-thrombotic diseases, suggested new enlarged experimental ways in order to correlate several lines of biological activities, other than the hemorheological one with the latter.

Along the natural course of the acute episode, the trend of the hemorheological findings was to return toward the normal range according to the improvement of the clinical state. Such findings suggested a short-time dependence of some blood rheological function at least associated with the development and the course of the ischemic necrotic process.

In acute either spontaneous or provoked ischemia not followed by tissue distruction such as exercise dependent angina pectoris or intermittent claudication, the appearance of pain as clinical sign of local ischemia was associated with a significant impairment of systemic blood viscosity and filterability.

A relationship between local ischemic and increased blood viscosity seemed to be admitted. In this sense the reduction of blood flow can be considered the component leading to the complex circulatory first and metabolic process known as ischemia, the latter being the

intermediate step leading to the induction of the hemorheological abnormality. Which pathways is linking the development of ischemia and the appearance of the hemorheologic disorder?

Is there a mechanism, locally inducing a cascade of metabolic processes which influences the viscosity factors ?

And moreover, which viscosity factor is firstly and specifically more affected by ischemia ?

The induction of an ischemic process due to the absolute or relative reduction of blood flow and the dependent hemorheological disorder was rather regular and easily to be reproduced. To answer such questions, the exercise test in patients with vascular occlusive disease localized either in coronary tree or in the aorto-iliac-femoral axis seemed to be a good experimental dynamic model.

In atrial pacing angina pectoris, for example, the positive patients showed a significant increase of blood viscosity and a contemporary decrease of whole blood filterability more marked in coronary sinus than in venous systemic blood when the pain appeared. In the negative subjects, no change of such hemorheological markers were registered.

Does it mean that ischemia dependent hemorheological changes are developing locally in ischemic tissues ? We think so. May be, it is not the mechanism, but it can be one of the mechanisms.

We collected similar findings in exercise dependent claudication in POAD patients.

This model was employed in our laboratory to study the dynamics of the above mentioned changes, together with the time-course of several selected markers of the metabolic and coagulation pathways as well as the leucocyte functional behaviur.

Such extension of the field of our investigation was suggested by the clinical observation of the frequent association between ischaemic and thrombotic events and by the more and more extended knowledge of the existence of a close relationship among circulatory coagulation and inflammatory phenomena.

The clinical sense which is always directed to the olistic interpretation of the biological processes played a not secondary role in planning such study.

We had the opportunity to study the hemorheological, metabolic and pro-coagulant changes in a group of POAD, submitted to exercise on a treadmill, until the appearance of the claudication. These findings were compared with those registered in a age-sex matched control group, also submitted to maximal exercise

The comparison showed a strong difference of the response to exercise in the two groups.

Regarding blood viscosity in the control subjects , a slight increase of whole blood viscosity (P= 0.5) appeared only at a low shear rate. No change was detected in plasma viscosity, whole blood filterability, washed erythrocyte filterability, hematocrit and fibrinogen concentration.

In POAD patients, the hemorheological markers at the onset of the claudication appearance were dramatically modified with a great increase of whole blood viscosity (P=0.01), of haematocrit (P=0.05) and of fibrinogen (P=0.01)and a reduction of whole blood filterability (P=0.01). No changes in washed red cell filterability and plasma viscosity were detected.

Regarding the metabolic markers, after exercise, the control group showed a strong increase of venous lactate (P=0.01), a decrease of venous standard bicarbonate (P=0.01) and of venous pH (P=0.01) without changes of venous $PCO_2$ and $PO_2$ In POAD patients the increase of venous lactate was higher than in control group, as well as the increase of $PCO_2$ and the reduction of pH and SBS (P=0.01).

Finally, both groups showed a post-exercise increase of B thromboglobulin and of thromboxane $B_2$ levels more marked in the POAD patients (P=0.02) . The post-exercise increase of adenosine and lactoferrin levels was also much higher in the patients group.

What is the meaning of these results ?

I think that we can draw the following conclusions :

1) The pain inducing exercise in vascular patients was associated with a clear hemorheological disorder of rapid outset. Since the painful syndrome indicates an ischemic process, we can correlate it with the appearance of hyperviscosity.

2) Exercise dependent hyperviscosity in POAD patients was associated with a marked change of acid-base balance due to the appearance of lactic acidosis.

3) At the same time, an increase of B thromboglobulin and thromboxane B2 levels indicated the in vivo activation of the platelet system, which can be considered as a preliminary step of a pre-thrombotic state .

4) Simultaneously, an increase of lactoferrin plasmatic concentration in the same patients seemed to indicate also the in vivo activation of polymorphonuclear leucocytes.

Just as the scientific investigation may be pushed back to the point where it becomes possible to design hypotheses for proposing a general law, so may its own method be thrown in question by asking for the reasons for each particular assertion.

Let us consider details.
Erythrocytes seem to play an important role in the development of such a hemorheological imbalance. The decrease of erythrocyte membrane deformability was firstly ascribed to endocellular metabolic changes secondary to the extracellular acidosis, inducing a calcium overloading with increased rigidity of the structure. Succesively, in our laboratory we had the opportunity to demonstrate that the erythrocyte membrane can incur rigidity by the activity of PMN and platelet released substances upon its external surfaces.

There is good experimental evidence that the development of tissue ischemia is associated with intravascular activation of PMN and platelets together with the slowdown of blood flow and with capillary stasis. It is not surprising, therefore, that the erythrocyte loss of fluidity could be ascribed also to extramembrane changes due to interaction with the activated PMN and platelet cytoplasmic factors release.

In vitro experiments support the existence of a correlation between some functions of the coagulation cascade, focused on platelet activation, PMN activation, endothelial EDRF release, erythrocyte lysate and free hemoglobin with blood viscosity and erythrocyte filtration.

The findings of these investigations were presented elsewhere.(10,11,12,13,14,15,16,17,18) We want here only recall what can aid us towards better understanding of the meaning of the experimental data, registered in the exercise test in claudicant patients.

They are as follow:

1) In vitro FMLM or PMA activated PMN release its cytoplasmic content (superoxide anion; enzymes a.s.o.) The supernatant, if incubated with whole blood, induces an increase of its viscosity and a decrease of whole blood filterability and washed erythrocyte filterability.

2) This action of the PMN activated supernatant on the filterability of washed erythrocytes is cancelled by the addition of antiprotease.

3) The platelet activated supernatant induces PMN activation.

4) Free hemoglobin, added to whole blood, increases its viscosity and reduces its filterability.

5) Paf induces a decrease of whole blood viscosity. This activity is cancelled by Pxf.

6) Erythrocyte lysate activates platelet aggregation anion. Such activity is antagonized by pentoxyphillin.

7) Nitroprussiate, which is considered as equivalent to EDRF, inhibits platelet aggregation. Hb does counteract such inhibition.I should like to emphasize that hemoglobin is known to be a specific inhibitor of EDRF.

I hope to have given some reasons for these assumptions, but my principal purpose was to analyze all possible interconnections, starting from the identifications of the single extrapolated biological process. All these experimental data indicate what happens in single models. But they fit with the network of findings, which always mark the spontaneous or provoked ischemia regarding several lines of investigation: the hemorheological, the coagulant, the inflammatory and the metabolic ones.

Therefore, any attempt to give a rational reasoning for the ischemia associated hyperviscosity must be confronted with all these pathways.

In other words, the hemorheological disorder, associated with ischemia in vascular patients is only a face of a very complex network of humoral and cellular interactions, which seems to be associated, from one hand, with evident metabolic imbalance (lactic acidosis).

The hemorheological modification is likely to be an effect, being the metabolic impairment the cause.

On the other hand, leucocyte and platelet activation, as well as endothelial activation, suggest a relationship between the two groups of data opening once again the old question, never completely answered, on the eventual pre-or post-thrombotic meaning of the ischemic associated hemorheological changes.

Clinical and pathophysiological evidence seems to support such a hypothesis and our sense of the clinics suggests further investigations in this direction. A better understanding of the real weight of each component, of its timing in the phenomenological cascade and a confirmed knowledge of the respective role in terms of cause and effect, could give a practical and useful answer to our interest either regarding the clinical or on the physiological point of view.

Therefore, let me conclude with a comprehensive tentative explanation of the whole subject matter.

It goes without saying that the description that I had given now of the nature of hemorheological changes, associated with ischemia will reflect the particular theoretical point of view which I consider to be valid.

Can we try to give a rationate to the hemorheological functions in the regulation of microcirculation in normal and pathological conditions, or more exactly during an acute reduction of blood flow, leading to tissue ischemia ?

We cannot follow the continous dynamic change of viscosity factors in each circulatory segment, but, anyway the rather homogeneous type of collected findings seems to support a guide-line of interpretation.

We are now in a position to make a preliminary distinction of the greatest importance, the distinction between the apparent role, played by the hemorheological mechanisms in normal or in pathological physiology.

We know that in term of hemorheological change, accompanying a strenuous exercise, the difference between the normal subject and the ischemic patient is apparently quantitative.

In the vascular patient, the active as well as the reactive blood hyperviscosity is much higher than in the normal control and it is not followed by an improvement of the circulatory metabolic disorder, which becomes more severe.

We believe that in such patient the active and the reactive hyperviscosities participate in a complex mechanism, which amplifies the ischemic process. There is good evidence that either the circulating cells or the plasmatic systems play a role, converging to increase the vascular shear stress.

In normal controls too, the exercise, inducing a reduction of blood flow, triggers several cascades, leading to an increase of the vascular shear stress.

Well, both sequential cascades, even if differently composed, induce an increase of the vascular shear stress. The latter must be considered, at the end of stimulated intermediate mechanisms, the specific trigger, the same one either for the normal control where it is followed by a negative feed-back, or in ischemic patient, where it induces a positive feed-back.

Besides the quantitative differenceis the degree of viscosity after a strenuous exercise, accompanying a normal subject, and the vascular patient, there is a lesser evident qualitative different hemorheological profile. In the patient, a major role is played by the cellular component and by the activation at a measurable degree of the platelet PMN and plasmatic systems.

The net difference in the kind of reactivity, therefore, must be localized below the vascular shearing in its target mechanism, with the awareness that shearing is much higher in vascular patients.
We suggest, today, two target mechanisms. The first is equally active in both normal and abnormal subjects. We propose to identifiy it within the endothelial cell.

It was clearly demonstrated that vascular shearing is a specific inductor of several endothelial functions as well as of several blood-endothelial cell interplaying mechanisms.

In the normal subject, the shear dependent release of endothelial mediators, leads to the liberation of vasodilating and platelet antiaggregating autacoids such as EDRF, $PGI_2$ and adenosine, which are acting locally .So, these substances rapidly cancel the blood flow reduction, and are immediatly destroyed.

In the patient, perhaps, the potentiality of the endothelial cell to release such factors is strogly reduced or overcome by the liberation of vasocostrictor substances, such as ECRF and Endothelin, which lead to a further reduction of blood flow.

This is the first pathway, inducing a positive feed-back mechanism, since the reduction of blood flow will be further increased.

Moreover, in the ischemic patient, a second strong mechanism is the activation of the neurohumoral loop, which releases several mediators, mainly cathecolamines, which add a receptor dependent mechanism of vasocostriction on resistance vessels. thus leading to its effect in reducing tissue perfusion.

Such schematic view seems to fit with the collected selective information on animal models,numeric simulation and clinical observations. It gives a broad meaning to the role of hemorheological factors, the understanding of which needs a correlative evaluation together with hemodynamic, metabolic and biochemical factors. The pivotal role in the regulation of the microcirculation will be therefore, the vascular shear stress.

Besides of it, new important functions, such as that of the endothelial cell, suggest a balanced mediation, the knowledge of which deserves more attention in the near future.

The pharmacological research, focused on the study and the supply of so-called "hemorheological drugs" may be considered as another sign of how credible is this line of theoretical and practical study.
Finally, the fact that every two years so many students of these problems feel the need to meet, compare and discuss their experiences and their level of knowledge, is the best documentation of how much clinical hemorheology is alive.

## REFERENCES

1. WOMERSLEY J.R. *Oscillatory flow in arteries: the reflection of the pulse wave at junctions and rigid insert in the arterial system.* Phys. in Med. Biol. 2,313-323. 1958.

2. REYNOLDS S.R.M., LIGHT W.F., ARDRAN G.M., RICHARD M.M.L. *The qualitative nature of pulsatile flow in the umbilical vessels with observations on flow in the aorta.* John Hopk. Hosp. Bull. 91,83-104, 1952.

3. FÅHRÆUS R. *The suspension stability of the blood.* Physiol. Reviews 9, 241-274, 1929.

4. FAHEY J.L., BARTH W.F., SOLOMON A. Serum hyperviscosity syndrome. JAMA 192, 464-466, 1965.

5. WELLS R.E., *Syndromes of hyperviscosity.* N.Engl. J. Med. 283, 183-186, 1970.

6. DINTENFASS L. *Hypothesis of viscoreceptors : malfunction of viscoreceptor and viscosity controllers in hypertension and policythemia.* In: Lewis D.H. (ed) Bibliotheca Anatomica 16,478-489, S.Krager 1977.

7. STUART J., ELLORY J.C. *Effects of cation and water on erythrocyte rheology in clinical disorders.* Clinical Hemorheology 7,827-851, 1987.

8. CHIEN SHU . *Hemorheology in Clinical Medicine.* Fåhræus Lecture. 1981 in: Progress in Clinical Hemorheology - Fåhræus Lectures. Hoechst AG Ed p.5-23.

9. DORMANDY J.A. *The dangerous red celll.* Fåhræus Lecture 1983. In: Progress in Clinical Hemorheology. Fåhræus Lectures. Hoechst AG Ed. p.29-87.

10. DI PERRI T. *Rheological factors in circulatory disorders.* Angiology 30, 480-485, 1979.

11. LAGHI-PASINI F.,GUERRINI M.,PASQUI AL.,CECCATELLI L., ACCIAVATTI A.,PIERAGALLI D., DEL BIGO C.,GALIGANI C;, FORCONI S., DIP PERRI T. *Whole blood filterability versus red cell filterability.I In vitro influence of PMN-induced polimorphonuclear leucocyte activation.* Clinical Hemorheology 3,303, 1983.

12. GUERRINI M.,LAGHI-PASINI F., PIERAGALLI D., ACCIAVATTI A., DEL BIGO C.,GALIGANI C.,FORCONI S.,DI PERRI T. *Whole blood filterability versus red blood cell filterability.II In vitro influence of platelet activation.* Clinical Hemorheology 3,304,1983.

13. PASQUI AL,LAGHI-PASINI F,GUERRINI M,PIERAGALLI D.,ACCIAVATTI A., DEL BIGO C., GALIGANI C;, CECCATELLI L.,FORCONI S., DI PERRI T. *Whole blood filterability versus red blood cell filterability. III In vitro influence of FMLP induced polimorphonuclear leucocyte activation. A possible direct role of FMLP.* Clinical Hemorheology 3, 3044, 1983.

14. DI PERRI T, FORCONI S, GUERRINI M,PIERAGALLI D. *Blood viscosity in the different stages of ischaemic heart disease: angina pectoris and myocardial infarction.* International Congress Series 491. Florence Int. Meeting on Myocardial Infarction. Excerpta Med. Amsterdam 1979, 349-355.

15. FORCONI S, PIERAGALLI D, ACCIAVATTI A, GALIGANI C, MATERAZZI M, RALLI L, FRANCHI M, LAGHI-PASINI F, MESSA GL, BIANCIARDI A, RIGATO M, CAPPELLI R, GUERRINI M, DI PERRI T. *Blood hyperviscosity and peripheral ischaemia: the secondary hyperviscosity syndrome of ischaemizing vascular diseases.* Clinical Hemorheology 6,215-227, 1986.

16. LAGHI-PASINIF, ACCIAVATTI A, CAPECCHI PL, DOMINI L, PASQUI A, PIERAGALLI D, GALIGANI C, GUIDERI F, SALETTI M, BLARDI P, DI PERRI T. *Soluble hemoglobin in vitro affects blood rheology and platelet aggregation.* Clinical Hemorheology, 9, 488, 1989.

17. PIERAGALLI D, ACCIAVATTI A, GALIGANI C, GUIDERI F, SALETTI M, LAGHI-PASINI F, DI PERRI T. *In vitro effect of PAF on hemorheological parameters: protective action of iloprost.* Clinical Hemorheology 9, 511, 1989.

18. DI PERRI T, LAGHI-PASINI F, ACCIAVATTI A, PIERAGALLI D, DOMINI L, PECCHI S, MESSA GL, FRIGERIOC, MATERAZZI M, GALIGANI C, PASTORELLI M, BLARDI P, DAMIANI P,GUIDERI F, DE FRANCO F, SALETTI M, MONACI A. *Hemodynamics, rheology and mechanism of action of iloprost in man.* Clinical Hemorheology 10, 171-184, 1990.