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Review

Hemorheological abnormalities in human arterial hypertension

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Blood rheology is impaired in hypertensive patients. The alteration involves blood and plasma viscosity, and the erythrocyte behaviour is often abnormal. The hemorheological pattern appears to be related to some pathophysiological mechanisms of hypertension and to organ damage, in particular left ventricular hypertrophy and myocardial ischemia. Abnormalities have been observed in erythrocyte membrane fluidity, explored by fluorescence spectroscopy and electron spin resonance. This may be relevant for red cell flow in microvessels and oxygen delivery to tissues. Although blood viscosity is not a direct target of antihypertensive therapy, the rheological properties of blood play a role in the pathophysiology of arterial hypertension and its vascular complications.

***Keywords*:** essential hypertension, blood viscosity, erythrocyte deformability, erythrocyte membrane

Introduction

The relationship between arterial hypertension and blood rheology has been investigated for a long time. Despite the bulk of experimental and clinical results accumulated during the last decades, some relevant questions are still open. This paper will review the hemorheological alterations described in hypertensive subjects and their possible link with pathophysiological mechanisms and organ damage. The influence of antihypertensive drugs on the rheological pattern will be briefly discussed, and the results obtained by the authors investigating erythrocyte and leukocyte microrheology will be described.

Arterial blood hypertension can be either 'essential' or 'secondary'. In the first one, also called 'idiopathic' and much more common than the other, there is not an underlying disease causing the rise in blood pressure, which happens in secondary hypertension. The studies described in this paper regard essential hypertension unless it is differently stated.

The hyperviscosity syndrome in arterial hypertension

Applying the Poiseuille's law to blood circulation it is clear that an elevated blood pressure within arteries can be the result of either an increase of cardiac output or an increase of vascular resistance. The latter can be due not only to an abnormal state of vasoconstriction but also to higher blood viscosity.

The pathophysiology of essential hypertension is not definitely clarified. Several complex mechanisms are involved in the regulation of cardiac output, blood volume and composition, vascular tone. Regulatory mechanisms involve renal function, autonomic nervous system and hormones like the renin-angiotensin-aldosterone axis. A main role in the regulation of vascular tone is played by endothelium, which is the cellular layer covering the internal surface of blood vessels, and is able to modulate the underlying smooth muscle cell contractility. A dysfunction of any of these regulatory mechanisms can alter the blood pressure level (Giles *et al.*, 2012).

The rheological properties of blood can interact with many pathophysiological aspects of arterial hypertension. Despite the direct role of blood rheology as a determinant of vascular resistence, the early studies paid much more attention to the vascular component of resistance than to the blood viscosity. Some pioneering observations date back to the early decades of the 20th century, and the paper by Harris and McLoughlin, published in 1930 (Harris and McLoughlin, 1930), is often considered the first, single example of interest in the topic. Only in the 1970s and 1980s a great deal of research was addressed to the blood rheology pattern in hypertensive subjects. In 1990 Chabanel and Chien (Chabanel and Chien, 1990) exhaustively reviewed the results accumulated until then, describing the hyperviscosity syndrome associated with essential hypertension. Untreated patients commonly showed an increase in blood viscosity, hematocrit, plasma viscosity, fibrinogen and erythrocyte aggregability, and a decrease in erythrocyte deformability. Blood hyperviscosity had been detected over a wide range of shear rates and mostly explained by an increase of both hematocrit and plasma viscosity. The latter was due to a high level of fibrinogen and secondarily to an increase in other high molecular weight plasma proteins, while high hematocrit was at least partly caused by a plasma volume contraction. As regards

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erythrocyte deformability, in these early studies it was determined by viscometry or filtration techniques.

The altered rheological pattern accompanying essential hypertension belongs to the 'secondary' hyperviscosity syndromes, according to the classification by Di Perri and Forconi (Di Perri *et al.*, 1983; Forconi *et al.*, 1987). The 'primary' hyperviscosity syndromes are those in which a marked primary alteration of a blood component (circulating cell number, erythrocyte deformability or plasma viscosity) causes an increase in blood viscosity, often directly responsible for symptoms. This mainly happens in hematological diseases and the correction of blood viscosity through apheretic techniques is a useful therapeutic measure. The secondary hyperviscosity syndromes are associated to common diseases including arterial hypertension, diabetes mellitus, vascular atherosclerotic diseases, which share the trend towards ischemia, that is an insufficient blood supply to tissues. In the secondary syndromes hyperviscosity is usually not as great as in the primary ones and is not a primary therapeutic target. The relationship between hyperviscosity and ischemia is not clear, as it is part of a complex interplay between blood and vascular wall components.

Blood rheology and the pathophysiology of hypertension

In the studies surveyed by Chabanel and Chien, the rheological alterations of hypertensive patients showed some variability, the less constant finding being the increase in hematocrit. Here we face a basic problem inherent in this research field. Even excluding secondary hypertension, hypertensive patients are not a homogeneous population as regards pathophysiological mechanisms, such as salt sensitivity, renin-angiotensin system or autonomic balance. So it is not surprising that, since the early phase of research about hypertension and blood rheology, attention was focused on the possible link between some pathophysiological aspects of hypertension and hemorheology.

In the paper by Chien (Chien, 1986), patients were stratified according to the daily renal sodium excretion, which showed a strong, inverse relationship with the plasma activity of renin, a pressure-regulating factor produced by kidneys. Both the hypertensives and the borderline subjects with the highest renin levels had the highest levels of blood viscosity, hematocrit and plasma viscosity. Measurements of plasma proteins indicated an increased level of globulin and fibrinogen in hypertensives. Recent research has provided some new insights into this aspect. Angiotensin II, a component of the regulatory pathway initiated by renin, acts directly as a growth factor through the AT1 receptor, stimulating proliferation of erythroid progenitors in bone marrow and, additionally, it enhances erythropoietin secretion (Vlahakos *et al.,* 2010). This mechanism also explains anaemia that has been described as a side effect of drugs interfering with the renin-angiotensin system (Sica and Mannino, 2007).

Another aspect which is deemed central in the pathophysiology of hypertension is the autonomic imbalance, consisting in a sympathetic overactivity. As Brook and Julius outlined it in 2000 (Brook and Julius, 2000), the sympathetic overdrive may be responsible for metabolic, trophic, hemodynamic and thrombotic consequences; the overal picture largely overlaps what we call metabolic syndrome. In fact it encompasses aspects like cell resistance to insulin action, hyperinsulinemia and obesity, interrelating in a complex way. Among the consequences of sympathetic hyperactivity there is high hematocrit, in the context of a prothrombotic pattern. An increase in hematocrit may not be the only link between sympathetic hyperactivity and thrombotic risk. In 1984 Caimi et al. (Caimi *et al.,* 1984) subdivided a group of hypertensives according to the plasma level of the sympathetic mediator norepinephrine. There was no difference in blood and plasma viscosity between the two subgroups, neither was there any difference in hematocrit, despite what could be expected, but the high-norepinephrine subgroup had a higher fibrinogen level.

Whatever relation there is between haemorheological abnormalities and the pathophysiological mechanisms of hypertension, it is still uncertain whether blood rheology actually contributes to the onset and maintenance of hypertension or not. The study of the secondary forms of arterial hypertension could be useful because in them the mechanisms leading to the raising of blood pressure are more definite. Unfortunately, only a few studies have focused on blood rheology in human cases of secondary arterial hypertension. The studies on different animal models of arterial hypertension have suggested that the hemorheological alterations are not a mere non-specific consequence of high blood pressure (Hacioglu *et al.*, 2002).

A human disease in which a relevant amount of data have been obtained is pre-eclampsia, a condition that complicates the second half of pregnancy and is characterized by arterial hypertension and protein loss through urine. It has been suggested that an altered blood rheology could impair circulation in the placenta vessels, leading to impaired fetal growth and increased risk of perinatal complications. Hemorheological abnormalities such as hyperviscosity and high fibrinogen level during the first trimester of pregnancy have been put forward as markers for the development of pregnancy-induced hypertension (Robins *et al.*, 2005). However, the relationship between blood rheology and complicated pregnancy is not clear. In the largest study available on this issue (von Tempelhoff *et al.*, 2009) pregnant women with pre-eclampsia showed a significantly increased erythrocyte aggregation in com-

parison with normal pregnant women, while plasma viscosity was not significantly altered. As regards the fetal outcome, higher maternal hematocrit and plasma viscosity were related to better results in tests evaluating the newborn's physical condition.

Blood rheology and organ damage in hypertension

Since blood rheology began to be extensively studied in hypertension, a main point was the possibility that hyperviscosity could be the link between high blood pressure and organ damage, in particular cardiac involvement. In hypertensive patients the cardiac left ventricle (LV) suffers from a work overload consequent to the raised pressure in aorta, so it develops a reactive increase in its muscular mass. The degree of the LV hypertrophy is predictive of cardiovascular morbidity and mortality (Levy *et al.,* 1990).

One of the earliest studies dealing with this issue was published by Devereaux *et al*. in 1984 (Devereux *et al.,* 1984). Mean blood pressure was directly correlated to blood viscosity in hypertensive and normotensive subjects, although the correlation was statistically significant only when the two groups were considered together. A similar relation is a common but not constant finding in studies about hypertension and hemorheology. In the study performed by Devereaux et al., when the authors plotted a graph of mean blood pressure against LV mass, the relation was mildly significant in hypertensives. Significantly stronger was the correlation between LV mass and blood viscosity, and hypertensives without LV hypertrophy showed viscosity values overlapping those of the normotensive controls. Even though this research pointed out that in hypertensive subjects LV hypertrophy was better related to blood viscosity than to mean blood pressure, this did not demonstrate any causal relationship. The authors hypothesized that hyperviscosity and LV hypertrophy could have vasoconstriction as a common cause. Whatever the mechanism linking LV hypertrophy and blood viscosity, the latter seemed to be a better indicator of LV hypertrophy incidence than blood pressure itself.

Besides blood viscosity, also other rheological variables, such as red cell aggregation or fibrinogen, were shown to be related to LV mass (Zannad *et al.,* 1988). A similar correlation was observed about 20 years later by Fornal and colleagues (Fornal *et al.,* 2009) between LV mass and erythrocyte deformability and aggregability. The study group included 66 subjects with at least one cardiovascular risk factor and without coronary heart disease. Forty-nine of them (74%) were hypertensive, 20 were under anti-hypertensive treatment. There was a correlation between LV mass and rheological parameters. It is worth noting that, in this very recent study, the techniques employed to evaluate the LV mass and erythrocyte parameters are more accurate than those used in the previous ones, but the results are confirmed.

Leschke *et al*. (Leschke *et al.,* 1990) studied 35 patients with essential hypertension and ischemic heart pain (angina pectoris), whose coronary arteries were not obstructed by atherosclerotic plaques. All antihypertensive medication had been withdrawn at least 48 hours before measuring coronary reserve by dipyridamole test. The control group included normotensive patients with atypical chest pain and normal coronary arteries, who underwent coronary angiography and dipyridamole test to exclude a macroscopic coronary disease and a coronary microangiopathy. Hypertensives had significantly lower coronary reserve and significantly higher hematocrit and plasma viscosity. Fibrinogen and whole blood viscosity were higher in hypertensives although not significantly. When the hypertensive group was subdivided according to the degree of coronary reserve impairment, only those with a severe impairment showed significantly higher hematocrit and plasma viscosity. The authors concluded that blood rheology seemed to have a major role in determining coronary reserve impairment in hypertensives.

Blood rheology and antihypertensive drugs

Given the common hyperviscosity pattern associated with hypertension, it was obvious to look for an effect of the antihypertensive drugs on blood rheology. In particular, agents able to interfere with the sympathetic tone such as beta-blockers, early emerged as perfect candidates. Among the pioneering papers dealing with this issue, it must be cited the article published by Dintenfass in 1976 (Dintenfass and Lake, 1976), which described an improved red cell deformability following therapy with oxprenolol. Some years later, Caimi *et al*. (Caimi *et al.,* 1983) tested three beta blockers, observing a decrease in blood viscosity only with timolol. No variation was present in plasma viscosity, hematocrit or erythrocyte rheology with any of the drugs.

A lot of antihypertensive drugs have been evaluated for their possible influence on blood rheology. The list includes, besides beta-blockers, calcium antagonists, ACE inhibitors, diuretics, but the results as a whole have been rather inconclusive. Some studies observed a hypoviscosemic effect, others no modifications, and even a deterioration of the rheological pattern sometimes emerged. A comprehensive survey is not feasible here (for a review see Bogar, 2002 and Meiselman and Baskurt, 2006).

Microrheological alterations in essential hypertension

Over the last decades we have been investigating what

can be defined the 'microrheological pattern', a rheological property influencing circulation in microvessels, where erythrocytes mainly flow as single cells and thus their deformability plays a pivotal role.

The oldest studies about red cell deformability used to evaluate it by filtering whole blood or suspensions of washed erythrocytes. In the early 1990s we examined erythrocyte filterability in hypertensive patients, employing the Reid and Dormandy method (Caimi *et al.,* 1993) and the Dodds and Dormandy method (unpublished results). We observed a difference between controls and hypertensives only by filtering whole-blood, and not by filtering erythrocytes suspended in plasma. In the hypertensive patients whole-blood filterability was lower, but this method cannot rule out the influence of plasma proteins or other circulating cells. We later studied red cell deformability by diffractometry, under two different shear stresses, in order to evaluate the intrinsic erythrocyte deformability, and diffractometry was not able to discriminate between hypertensives and controls (unpublished data).

We subsequently employed fluorescence spectroscopy techniques to explore red cell membrane dynamics in hypertensives. This is a multi-faceted issue: on the one hand, membrane fluidity is among the components of erythrocyte deformability and among the factors influencing oxygen delivery to tissues, both potential links between hypertension and vascular ischemic diseases; on the other hand, cell membrane fluidity is able to modulate ion transport, signal transduction and other cell functions whose alteration may be involved in the pathogenesis of some forms of hypertension.

One of the fluorescence spectroscopy techniques employed by us used fluorescent fatty acid derivatives: the 2-(9-anthroyloxy)palmitic acid (2-AP) and three stearic acid derivatives (6-AS, 9-AS, 12-AS). These molecules make it possible to evaluate the membrane fluidity at different depth from the lipid-water interface to the hydrophobic core. We observed an increased fluorescence polarization degree of all the fatty acid probes embedded in the erythrocyte membrane (Caimi *et al.,* 1993), which was an index of reduced fluidity throughout the phospholipid bilayer. A different fluorescence spectroscopy technique employed pyrene derivatives. The pyrene molecules tend to form complexes colliding with each other, and the probability of collision is proportional to the lateral mobility of the fluorescent probe. Thus the intensity of pyrene complex fluorescence is an index of how much the molecules carrying the fluorescence probe are free to move within the membrane. We used two probes, pyrene-decanoic acid (PDA), which binds to phospholipids, and pyrene-3-maleimide (3-PM), binding to proteins. We observed a reduced phospholipid lateral mobility, while the protein lateral mobility was not significantly altered (Caimi *et al.,* 1997). Contemporary and more recent research by other authors reported an impairment of erythrocyte membrane fluidity in hypertension, employing either fluorescence methods or electron paramagnetic resonance (Zicha *et al.,* 1999; Tsuda and Nishio, 2003). The latter was recently employed to demonstrate that the antihypertensive drug benidipine was able to improve the erythrocyte membrane dynamics (Tsuda, 2008). The effect seemed to be mediated by a raised level of nitric oxide (NO), which is known to be produced by erythrocyte itself (Kleinbongard *et al.,* 2006) and to enhance erythrocyte deformability (Bor-Kucukatay *et al.,* 2003). Atomic force microscopy recently showed an alteration of the membrane skeleton structure in erythrocytes from patients with essential hypertension, associated with an impaired O_2 membrane permeability (Kaczmarska *et al.,* 2013).

The abnormalities of erythrocyte membrane dynamics suggest an alteration of the membrane lipid pattern. We examined this aspect and observed a significantly decreased cholesterol/phospholipid ratio in hypertensives (Caimi *et al.,* 1993), but no significant variations of the single phospholipid percentages using two-dimensional thin layer chromatography (Caimi *et al.,* 1991). Literature data about cholesterol/phospholipid ratio and single phospholipids are controversial in hypertension (Ronquist *et al.,* 1992; Fu *et al.,* 1992). Rather than abnormalities in concentrations, some studies demonstrated an altered distribution and transbilayer diffusion of cholesterol in the erythrocyte membrane of hypertensive subjects (Muriana *et al.,* 1994; Muriana *et al.,* 1995). Recently, there has been some renewed interest in this topic. In 2012 Pytel and colleagues (Pytel *et al.,* 2012) investigated the erythrocyte membrane cholesterol level, finding no difference between hypertensives and controls. They also explored the erythrocyte membrane dynamics using diphenyl hexatriene (DPH) and trimethylamino-phenyl-hexatriene (TMA-DPH), which are fluorescent probes different from those previously cited, and failed to detect abnormalities in membrane fluidity. But in the same study the authors examined some aspects of oxidative status in erythrocytes of hypertensives, observing a higher lipid peroxidation level and a lower activity of antioxidant enzymes. The impairment of the red cell oxidative status suggests an explanation for intrinsic erythrocyte membrane alterations observed by us as well as by other authors in hypertension.

But the red cell is not the only player in blood rheology. If we extrapolate the erythrocyte role in microcirculation we end up overlooking the whole picture. This prompted investigation into other circulating cells' behaviour in hypertension. We performed some studies about leukocyte rheology in hypertensive patients. We employed the St. George filtrometer to filter leukocytes, as a whole and subdivided into mononuclear and polymorphonuclear

cells (Caimi *et al.,* 1998). Only mononuclear cells showed an impaired filterability, but it was difficult to make sense of this result as they consist of a heterogeneous population, including monocytes and all the lymphocyte subsets. As regards the much more homogeneous population of polymorphonuclear (PMN) leukocytes, the membrane fluidity explored by the fluorescent probe TMA-DPH was unaltered in resting cells, but a different behaviour emerged, in comparison with normotensive controls, when we activated PMNs in vitro with two agents: phorbol myristate acetate (PMA) and N-formyl-methionyl-leucyl-phenylalanine (fMLP). PMNs from hypertensive patients in fact showed a significantly sharper drop in filterability after activation, suggesting an abnormal functional state, further supported by a high cytosolic Ca^{2+} basal concentration (Caimi *et al.,* 1998).

These abnormalities of PMNs are part of the low-grade inflammation recognized in arterial hypertension and likely involved in the pathogenesis of its vascular complications (Hopps *et al.,* 2009; Harrison *et al.,* 2011; Schiffrin, 2013).

Blood viscosity and endothelium

We measure the blood rheological properties in blood freshly drawn from a large systemic vein. The blood behaviour observed during *in vitro* measurements might not be a reliable model of what happens *in vivo*, even if we try to mime the flow conditions typical of different circulatory districts employing a wide range of shear rates. A major limitation of *in vitro* studies is the ruling out of blood-endothelium interactions. It is known that endothelial cells are able to modulate vascular tone producing various chemical agents, such as nitric oxide (NO), a gas that diffuses to the underlying smooth muscular cells inducing relaxation. One of the stimuli for NO release from endothelium is the shear stress produced by blood flow, and there is experimental evidence that an increase in blood viscosity induced by hemoconcentration is followed by a more effective endothelium-dependent vasodilation (Intaglietta, 2008). So the character of harmful factor traditionally attributed to blood hyperviscosity is now questioned.

Almost all the studies cited in this paper considered hyperviscosity as a detrimental deviation from normality and as a possible link between high blood pressure and organ damage. But some doubts have been raised against this statement (Forconi and Gori, 2009; Salazar Vásquez *et al.,* 2011). Hyperviscosity might share the destiny of free radicals, traditionally considered dangerous byproducts of metabolism and more recently seen as mediators in some physiological processes (Altenhöfer *et al.,* 2012). In a similar way, hyperviscosity may act as a homeostatic factor in particular pathophysiological contexts.

Conclusive considerations

Arterial hypertension is associated to hemorheological abnormalities, which are evident at both macrorheological and microrheological level. This is acquired knowledge, but a question still open is what kind of relationship there is exactly between arterial hypertension and hyperviscosity. In fact, blood hyperviscosity may have a pathogenetic role in the establishment of arterial hypertension, or may be a further effect of the same pathogenetic processes leading to hypertension. Moreover, blood hyperviscosity may be a consequence of hypertension. This issue has been properly defined a “chicken or egg” problem (Meiselman, 1999; Bogar, 2002).

Neither hyperviscosity itself nor its determinants have ever gained credibility as faults to be corrected directly, by drugs or otherwise, in hypertensive patients, should such correction be possible. Though, taking into account blood viscosity and its determinants is still relevant in research about pathophysiology of human hypertension, as well as in general circulation research, in order to outline a thorough picture of the factors coming into play.

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