HAEMORHEOLOGICAL DISTURBANCES AND POSSIBILITY OF THEIR CORRECTION IN CEREBROVASCULAR DISEASES

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RéSUMÉ :
Les perturbations hémorhéologiques dans les maladies vasculaires du cerveau et leur possibilité d’amélioration.

La présence de perturbations hémorhéologiques doit être prise en compte en physiopathologie et en thérapie dans l’approche des maladies vasculaires, notamment cérébrales. La diminution de la fluidité du sang peut-être due à l’augmentation de l’hématocrite (hyperviscosité polyglobulaire) ou de la concentration en fibrino-gène (hyperviscosité plasmatique), ou à la rigidité des globules rouges (hyperviscosité scléro-cellulaire). Cette augmentation de la viscosité est communément considérée comme une condition de haut risque pour les maladies cérébrales aiguës et chroniques. De multiples essais ont été tentés pour améliorer la fluidité sanguine dans le but de prévenir les accidents vasculaires cérébraux (AVC) et de retarder la détérioration cérébrale dans l’ischémie chronique. Cette étude présente une révision de la littérature actuelle sur ce sujet et notre expérience personnelle sur l’utilisation de la hémodilution, de la plasmaphérèse et des agents pharmacologiques. A notre avis la correction de l’hyperviscosité est très utile à la prévention des AVC et à la diminution de leurs conséquences sur les ischémies cérébrales chroniques. Durant la phase aiguë, la perturbation hémorhéologique n’est qu’une composante de la situation hémodynamique complexe : en fait l’hyperviscosité primaire favorise l’AVC et l’AVC favorise l’hyperviscosité, qui devient alors secondaire, ceci créer un cercle vicieux. En considérant ce concept, la fluidification du sang pendant la phase aiguë de l’AVC peut-être proposée, tout en sachant que ce n’est pas la seule solution à cette « tempête circulatoire ». (J Mal Vascl 1999; 24: 110-116)

Mots-clés : Maladie cérébrovasculaire — Hémorhéologie

Abstract:
Haemorheological disturbances and possibility of their correction in cerebrovascular diseases.

The presence of a hemorheological disturbance must be considered in the pathophysiological and therapeutical approach to vascular diseases, including cerebral diseases. A reduction of blood fluidity, due either to increase of hematocrit (polycytemic hyperviscosity) or of fibrinogen concentration (plasmatic hyperviscosity) or of red cell rigidity (sclerocytic hyperviscosity) is commonly considered a condition of high risk for acute or chronic brain ischemia. So many attempts have been made for improving blood fluidity with the purpose to prevent stroke and to delay cerebral deterioration in chronic condition. This paper will present a review of the literature on this subject and the personal experience of our research group with the use of hemodilution, plasmapheresis and pharmacological agents. In our opinion the possible correction of hyperviscosity is very helpful in the prevention of acute ischemic attacks and in the reduction of their incidence in chronic cerebral ischemia. During the acute phase of stroke, hemorheological disturbance is only a part of the complex hemodynamic situation: a primary blood hyperviscosity can favor the onset of the disease but, because of its secondary increase after stroke, a vicious circle might be set in motion resulting in a further reduction of blood supply to the brain. Considering this, attempts in improving blood fluidity during stroke could be made, but with the caution that is required in this complicated “circulatory storm”. (J Mal Vascl 1999; 24: 110-116)

Key-words: Cerebrovascular diseases — Haemorheology

The impact of haemorheology in vascular diseases has been variously considered by several authors in the past. In the late seventies and early eighties, after the first papers on peripheral obliterative arterial disease of the limbs, there were other reports on cardiovascular and cerebrovascular diseases underlining the presence of blood hyperviscosity in acute and chronic illnesses (20, 63, 79).

The most important conclusions were that haemorheological disturbances are usually present in vascular diseases, both in acute and in chronic conditions (24, 34, 35).

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considered a condition of high risk for acute or chronic brain ischemia. During acute ischemic attacks [stroke and Transient Ischaemic Attack (TIA)] blood viscosity further increases (21, 64, 68, 69).

Some authors strongly suggested randomised controlled trials of viscosity reduction in the prevention of acute cerebrovascular events and/or in the attempt of somehow improving brain performance (7, 77).

Concerning these concepts, some years ago our group made several studies which showed that the rheological profile (blood viscosity at different shear rates, whole blood filterability, plasma viscosity, haematocrit, fibrinogen concentration) differs in patients with stroke and TIA at the onset compared with controls. The rheological deterioration is particularly evident 8 hours after the onset of stroke and TIA (18, 19, 28). Likewise in myocardial infarction or in critical limb ischemia, this finding was interpreted seeing a vicious circle in which hyperviscosity of chronic cerebral ischemia is considered a risk factor for stroke and TIA and, after the acute event, there is a worsening of blood fluidity capable of a further reduction of the blood supply to the brain (17, 32, 33, 53).

In the latest papers, published in the nineties, these alterations were interpreted in different ways: some authors, comparing acute and chronic conditions, argued that viscos abnormalities simply reflect either elevated haematocrit or an acute phase response to the stroke itself. They found that the severity of hyperviscosity was decreasing gradually in the series: stroke group-TIA group-at risk group-healthy controls (11).

Nevertheless other authors are doubtful and conclude that haemorheological abnormalities in cerebral ischemia are largely non specific findings with the likely exception of patients with severe stroke (21, 24).

Some studies analysing patients in the rehabilitation phase of stroke stated that rheological factors are associated with the prognosis, but further trials concluded that particularly hyperfibrinogenemia is an independent risk factor for cardiovascular events in stroke survivors. It was suggested that intervention trials with fibrinogen lowering agents may be warranted (64).

Also the importance of cell-to-cell interaction was underlined, particularly among flowing cells and endothelium (5).

Subsequently the spontaneous echo contrast in the cardiac chambers, commonly considered a risk factor for cardioembolic stroke, was identified as a marker of haemorheological deterioration due to elevated fibrinogen level and concomitant increases in both plasma and serum viscosity (6, 23). Similarly it was reported that high-dose intravenous immunoglobulins can increase blood viscosity and could be associated with cardiovascular or cerebrovascular thromboembolic events (12).

An association between altered leukocyte aggregation and cerebrovascular ischemia was also reported (65).

Some authors signalled that increased blood viscosity may be a plausible biological mechanism through which increases in haematocrit and fibrinogen may promote ischaemic heart disease and stroke, suggesting controlled trials of viscosity reduction in the prevention of cardiovascular events (53).

Finally, a recent paper reported that even in silent cerebral ischemia, in stroke at risk patients there is an elevation of plasma fibrinogen level, which increases further after the onset of cerebral infarction; such abnormalities persist up to the chronic stage (74).

All these findings and interpretations confirm the central role of rheology in cerebrovascular disease and the importance of rheological disturbances in the pathophysiology of these illnesses (50, 54, 67).

More difficult is to apply the pathophysiological concepts to the therapy. It seems obvious to try to decompose blood fluidity in all its factors, but while it’s easy to see the blood and the vessel in a steady condition with all its components identified as isolated (liquid elements, plasma and serum components, white and red cells, platelets, endothelium), more difficult is to see the complex interferences of the elements that aggregate or deform, even under the influence of mediators released during cell activation processes (9, 36, 62). And in these complex processes must be considered the endothelial cells, which we know can influence the coagulation and the fibrinolysis as well as the vasomotion at a microcirculatory level (30, 70). Not only blood cells, but even vessels deform themselves under the influence of the shear forces acting in the circulation. And also atherosclerotic plaques produce great disturbances in blood flow properties (38, 76).

From a theoretical point of view, surgery is the best way for improving the flow properties of blood in obstructed or stenotic vessels, as well as fibrinolysis with major agents (rTPA), with which thrombus can be removed (16, 22, 46, 58).

Anyway some attempts, based on the classical rheological therapeutic strategies, should be made.

Following the above lines of reasoning, haemodilution can be performed in polycyticemic patients with chronic cerebral ischemia in order to prevent a second stroke or TIA or to restore in some way the reduction of blood supply to the brain (10, 37, 41, 57). Concerning acute condition, as that of a stroke, after the first promising reports, in the recent literature there have been some doubts papers (40). In our opinion the condition of stroke involves too many mechanisms to counterbalance, particularly in the field of fluids therapy, where we might use at the same time osmotic agents (like mannitol or glycerol). So in our opinion this therapy is to be avoided in the case of acute stroke or TIA (8, 15, 51).

The same opinion we have about the use of major fibrinolytic agents. The contrasting reports on this subject lead to the conclusion that in acute cerebrovascular ischemia the therapeutic window is too tight and the haemoragic risk too high for this kind of strategy (38, 49). And the possible improvement of plasma viscosity due to the fibrinogen concentration reduction does not justify this kind of treatment even in the condition of chronic ischemia (74, 77). Besides, in chronic cerebral ischemia, some attempt in this direction, i.e. possible reduction of plasmatic hyperviscosity, could be made with the so-called minor fibrinolytic agents, like fibrates, stanzanolol, ciclandelate, mesoglican or with an appropriate diet regimen (4, 26, 27, 59).
In some special cases plasmapheresis could be done with the purpose of decreasing plasma hyperviscosity. It has been shown that, simultaneously to the reduction of the apparent plasma viscosity following the plasmapheresis, there was a strong effect on symptomatology attributed by the author to the parallel improvement in blood flow (78). An experience of our group determined, in three cases of Waldenstrom macroglobulinemia plasmapheresis, together with an important reduction of blood and plasma viscosity, also a significant increase in cerebral blood flow (44).

In chronic cerebral ischemia some results have been reported with the use of specific drugs acting particularly on the cell deformability and/or aggregability. Many authors, using pentoxifilline or buflomedil have reported improvement of blood supply to the brain, delay in a second ischemic attack, or improvement in symptomatology (3, 31, 43, 52, 70).

A specific kind of drugs in this field is represented by calcium-entry blockers. Many authors (2, 13, 48), our group included, have demonstrated the importance of the increase of the intracellular calcium that accompanies ischaemic vasculopathies: the cytosolic calcium increase is evident in the red cells and is accompanied by a rheological deterioration (blood viscosity increase, red cell rigification demonstrated with the prevalence of red cell with the shape of disk over the red cell with the shape of bowls) (75).

Some years ago we performed several studies using the calcium entry blocker Nimodipine, a drug which has been employed by other authors with the same purpose. It belongs to the dihydropyridines group and is able to improve in a particular way cerebral circulation for its high liposolubility and linking capability with receptor-dependent calcium channels. In this study we measured, in order to assess the calcium-antagonist and rheological activity of Nimodipine, the variations of intra-erythrocytic calcium and blood viscosity in patients with acute stroke, both ischemic and hemorrhagic, before and after treatment for 7 days with this drug and to evaluate these parameters as indices of clinical improvement and of a more favorable prognosis (14, 47, 56, 61).

We studied a group of elderly patients suffering from stroke, divided into three groups: the first one (Group A) was made by patients suffering from cerebral hemorrhage, treated with Nimodipine by continuous intravenous infusion and with anti edemigenics; the second (Group B) was made by patients suffering from cerebral ischemia, treated...
with Nimodipine by 3 oral administrations and with anti-edemigenics; finally, the third one (Group C) was composed by patients suffering from cerebral ischemia, treated only with anti-edemigenics (table I).

Our results demonstrated a reduction in the mean value of intra-erythrocytic calcium in the first and second subgroups. Blood viscosity increased in a not significant way in the first subgroup because there was a significant increase in the fibrinogen, while in the second subgroup blood viscosity decreased in a significant way. In the control group, intra-erythrocytic calcium and blood viscosity increased only slightly after 7 days of treatment. The protection given by this drug is due, in addition to the action in cerebral vasodilation, also to the reduction of calcium overload, to the improvement of metabolism (with a consequent recovery of ATP), to the inhibition of spasmogenic agents release and to the prevention of secondary vasospasm (1, 25, 42). Thus, they act both at a vascular and metabolic level. This rheological action in patients suffering from cerebral ischemia was accompanied also by a significant reduction of blood viscosity; the absence of a reduced viscosity in hemorrhagic patients is probably due to the increase in fibrinogenemia (39, 66, 71-73).

In another clinical study with Nimodipine, already published in Clinical Haemorheology in 1992, we tried to evaluate possible changes of brain perfusion and blood viscosity in patients, suffering from chronic and clinically stable cerebral ischemia, after long term treatment with this drug. Blood flow in the brain was measured ad index of cortical perfusion using Single Photon Emission Computed Tomography SPECT (45, 60). Ten patients suffering from cerebral ischemia in a not-acute phase (at least three months after acute stroke), documented by clinical and/or instrumental examination (TC or RMN), have been studied.


<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>(Ca++)i before therapy</th>
<th>(Ca++)i after therapy</th>
<th>Viscosity before</th>
<th>Viscosity after</th>
<th>Fibrinogen before</th>
<th>Fibrinogen after</th>
<th>Ht before</th>
<th>Ht after</th>
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<tbody>
<tr>
<td>Group A (n=9)</td>
<td>73.4±10,2</td>
<td>335/385</td>
<td>335/385</td>
<td>10s-1cPs</td>
<td>10s-1cPs</td>
<td>374,78±98,36</td>
<td>455,11±106,24*</td>
<td>38,39±6,26*</td>
<td>38,09±5,4</td>
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<tr>
<td>Group B (n=9)</td>
<td>69.78±7,96</td>
<td>2,42±0,73</td>
<td>1,92±0,90</td>
<td>6,52±0,68</td>
<td>6,82±0,93</td>
<td>374,78±98,36</td>
<td>455,11±106,24*</td>
<td>38,39±6,26*</td>
<td>38,09±5,4</td>
</tr>
<tr>
<td>Group C (n=6)</td>
<td>71.33±9,5</td>
<td>2,06±0,64</td>
<td>2,28±0,47</td>
<td>6,35±0,98</td>
<td>6,61±1</td>
<td>349,33±154,58</td>
<td>354,67±88,94</td>
<td>40,8±2,9</td>
<td>38,75±5,1</td>
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</tbody>
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Group A: patients suffering from cerebral hemorrhage, treated with Nimodipine by continuous intravenous infusion (tdi=48mg/24h) and with anti edemigenics.

Group B: patients suffering from cerebral ischemia, treated with Nimodipine by continuous intravenous infusion (tdi=48mg/24h) and with anti edemigenics.

Group C: patients suffering from cerebral ischemia, treated only with anti edemigenics.
The comparison between scintigraphic images in basal condition and after three months of therapy showed an improvement of cerebral blood flow in almost all the patients while the mean values of the Index of Cortical Perfusion were statistically increased in 13 of 18 brain regions we studied. A statistically significant reduction of blood viscosity was also observed (table II). Even this favourable effect of Nimodipine in chronic cerebral ischaemia can be attributed to its calcium-blocker effect, mainly acting on blood vessels and, possibly, on brain tissue (29, 55).

**Références**


<table>
<thead>
<tr>
<th>Left section</th>
<th>Right section</th>
<th>Blood viscosity (cPs 30s⁻¹)</th>
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<tr>
<td>4 cm</td>
<td>5.6 cm</td>
<td>7.2 cm</td>
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<tr>
<td>4 cm</td>
<td>5.6 cm</td>
<td>7.2 cm</td>
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<tr>
<td>Before therapy</td>
<td>0.75 ± 0.14</td>
<td>0.78 ± 0.13</td>
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<td></td>
<td>0.79 ± 0.15</td>
<td>0.74 ± 0.07</td>
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<td></td>
<td>0.80 ± 0.12</td>
<td>0.82 ± 0.10</td>
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<tr>
<td></td>
<td>5.2 ± 0.5</td>
<td></td>
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<tr>
<td>After therapy</td>
<td>0.80 ± 0.12</td>
<td>0.85 ± 0.06**</td>
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<tr>
<td></td>
<td>0.84 ± 0.07*</td>
<td>0.81 ± 0.08</td>
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<tr>
<td></td>
<td>0.84 ± 0.07</td>
<td>0.83 ± 0.08</td>
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<tr>
<td></td>
<td>4.8 ± 0.6**</td>
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*p<0.05 Student’s « t » test; **p<0.01 Student’s « t » test
HAEMORHEOLOGICAL DISTURBANCES AND POSSIBILITY OF THEIR CORRECTION


42. GODEFRAIND T. Cerebrovascular effect of calcium antagonists. Drugs, 1987; 33: 8-22.


