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Exercise-induced central retinal vein thrombosis: Possible involvement of hemorheological disturbances. A case report

A. Gaudard [a,*], E. Varlet-Marie [a,*], J.F. Monnier [b], Ch. Janbon [c], I. Quéré [c], F. Bressolle [a] and J.-F. Brun [b,**]

[a] *Laboratoire de Pharmacocinétique Clinique, Faculté de Pharmacie, Université Montpellier I, France*
[b] *Service Central de Physiologie Clinique, Centre d'Exploration et de Réadaptation des Anomalies du Métabolisme Musculaire (CERAMM), CHU Lapeyronie, Montpellier, France*
[c] *Service de Médecine B Angiologie, CHU Saint Eloi, Montpellier, France*

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Abstract. Exercise-induced impairment in blood fluidity has been supposed to increase cardiovascular risk but there is no data to support this hypothesis. We report the case of a 50 yr old marathon runner who underwent a central retinal vein thrombosis after a marathon run. We investigated his rheological response to exercise compared to control subjects of previous studies. During a standardized sub-maximal exercise-test, the increase in blood viscosity (+28%) and hematocrit (+25%) exceeded the control range but the most striking differences were found for red cell aggregation (Myrenne +47%) and disaggregation thresholds (Affibio +37%). Although some of this post-exercise hyperviscosity pattern may be due to the previous vascular event, these findings may also support the hypothesis of a role for hemorheological alterations during exercise in the pathogenesis of this marathon-induced retinal thrombosis, and indicate that after such an event hemorheological adaptation to exercise remains markedly disturbed.

Keywords: Blood viscosity, plasma viscosity, exercise, hemorheology, retinal vein occlusion, case report, eye injuries, human, male

1. Introduction

Exercise-induced impairment in blood fluidity has been supposed to increase the risk for vascular thrombotic events [1,2] but there is no clinical evidence to support this hypothesis [2]. In this paper, we reported the case of a 50 yr old marathon runner who underwent a central retinal vein thrombosis after a marathon run, and in whom the rheologic response to exercise was measured in comparison with control values.

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*E. V-M. and A.G. have equally contributed to this work and should both be considered as first authors.

**Corresponding author: Dr J.F. Brun, MD, PhD, Service Central de Physiologie Clinique, Centre d'Exploration et de Réadaptation des Anomalies du Métabolisme Musculaire (CERAMM), CHU Lapeyronie 34295 Montpellier-cédex 5, France. Tel.: +33 (0)4 67 33 82 84; Fax: +33 (0)4 67 33 59 23; Telex: CHR MONTP 480 766 F; E-mail: drjfbrun.@aol.com.

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2. Subjects and methods

2.1. Subjects

The case report presented here is a 50 yr old marathon runner with no prior medical history. He was hospitalised in emergency unit with an acute episode of central retinal vein thrombosis after a marathon. The patient was in good health until the morning of this thrombotic event. There was a familial history of isolated hypertriglyceridemia. The patient had previously presented in 1992 signs of hypertriglyceridemia. Thus, it has been recommended to him to follow a diet combined with exercise, that resulted in normalization of triglyceride levels. This patient had followed a progressively increasing training program for marathon running during 4 years until the date of the event. During the marathon, he had not the opportunity to drink as much as he would want, and thus was thirsty and extremely tired. During the weeks following the run, he noticed a blurred vision with an accommodation defect of the right eye. He went to the hospital where the diagnosis of retinal thrombosis was made. A study of common causes of thrombophilia (protein C, protein S, factor V Leiden, ...) was performed and was unable to detect any abnormalities. After treatment by 4 hemodilution sessions, aspirin, acetazolamide, prednisone and pentoxifylline, there was a partial recovery and the subject continued to run for one hour, three or two times every week.

Control subjects were 20 male sportsmen (national level in football, volleyball and karate) and 20 sedentary subjects [3]. They were submitted daily to a physical training program. Their age ranged from 21 to 36 years, their height from 175 to 196 cm, and their weight from 63 to 96.5 kg. Their hemorheological characteristics are shown on Table 1.

2.2. Methods

Six months later, after treatment by hemodilution and rheo-active drugs, we investigated the rheological response of the subject to exercise compared to parameters derived from a population of athletes followed in our outpatient unit. Thus, he underwent a standardized submaximal exercise session on cycloergometer during 25 minutes. He kept pedal speed constant at 60 rpm and his heart rate was under control. The intensity of the exercise was progressively increased during the first 15 minutes. During the last 10 min, we measured a heart rate corresponding to 85% of the theoretical maximal heart rate according the American Heart Association's tables. Physical working capacity W170 was calculated during

Table 1

Hemorheologic parameters performed in 20 healthy male athletes and 20 healthy sedentary subjects before, during and after an exercise test (25 min with 10 min at 85% of the theoretical maximal heart rate)

	Fasting	T-15	Exercise test			Recuperation
			T0	T10	T25	T35
Hematocrit (%)	43 ± 2.97	42.25 ± 3.18	40.75 ± 2.47	40.75 ± 2.47	45.25 ± 3.18	42 ± 2.83
Whole blood viscosity (mPa s)	3 ± 0.26	2.9 ± 0.35	3 ± 0.21	3.25 ± 0.21	3.5 ± 0.35	3.2 ± 0.28
Plasma viscosity (mPa s)	1.38 ± 0.1	1.35 ± 0.14	1.34 ± 0.14	1.4 ± 0.14	1.43 ± 0.13	1.4 ± 0.14
Erythrocyte rigidity 'Tk'	0.62 ± 0.1	0.575 ± 0.11	0.575 ± 0.11	0.63 ± 0.1	0.66 ± 0.13	0.6 ± 0.05
Red cell aggregation 'M'	3.5 ± 0.16	2.87 ± 1.59	4 ± 1.41	6.37 ± 4.77	5.5 ± 4.24	4.37 ± 1.94
Red cell aggregation 'M1'	7.2 ± 2.16	6.5 ± 2.12	8.25 ± 2.83	9.25 ± 3.18	8 ± 4.24	8.25 ± 3.18
RBC disaggregation threshold	39 ± 6.36	44.25 ± 6.7	46.5 ± 6.36	48.25 ± 6.71	48.87 ± 7.25	46.5 ± 6.36

RBC: red blood cell, T: time (minutes).

these 10 minutes as the work in watts that subjects were able to perform at a heart rate of 170 b min^{-1} [4]. $V_{O_2\ max}$ was measured from the sub maximal steps according to Astrand's normograms [5]. Water loss during cycling was evaluated by accurate weighing (Sartorius model F 150-S-F2, France). Changes in plasma (% Δ PV) during exercise were evaluated from hematocrit changes using a formula developed at the NASA-Ames Research Center [6]:

$$\%\Delta PV = 100/(100 - H_0) \times 100[(H_0 - H)/H_0],$$

where H_0 is the hematocrit at rest and H is the hematocrit during exercise.

Body composition was assessed with a multifrequency bioelectrical impedancemeter Dietosystem Human IM Scan [7].

Blood samples for hemorheological measurements (7 ml) were drawn with potassium EDTA as the anticoagulant in a vacuum tube (Vacutainer). Viscometric measurements were done at high shear rate (1000 s^{-1}) with a falling ball viscometer (MT 90 Medicatest, Saint Benoit, France) [8]. With this device, the apparent viscosity of whole blood at native hematocrit, the plasma viscosity, and the blood viscosity at corrected hematocrit (0.45) were determined according to the equation of Quemada [9]. The Dintenfass' 'Tk' index of erythrocyte rigidity was also calculated [10].

Red blood cell (RBC) aggregation was assessed at native hematocrit with the Myrenne aggregometer [11], which gives two indices of RBC aggregation: 'M' (aggregation during stasis after shearing 10 s at 600 s^{-1}) and 'M1' (facilitated aggregation at low shear rate after shearing 10 s at 600 s^{-1}). The shearing time when working aggregometer was 10 s and the hematocrit was 43%. RBC aggregation was also evaluated with the SEFAM aggregometer [12,13] which measures the changes in backscattered light and gives an evaluation of the total disaggregation threshold (γ_S) and the partial disaggregation shear rate (γ_D). γ_S is the shear rate below which the backscattered light intensity starts to decrease, indicating that the shear stress applied to aggregates is no longer sufficient for allowing complete dispersion of RBC aggregates. γ_D is defined as the shear rate corresponding to the intersection point of the two asymptotes drawn from the extremes (maximum and minimum shear rate). Fibrinogen was assayed with the Clauss method.

3. Results

3.1. W_{170} and $V_{O_2\ max}$

During the standardized sub maximal exercise-test aerobic working capacity (W_{170}) was 2.84 watt/kg (i.e., a $V_{O_2\ max}$ from Astrand's charts of 40.5 ml in^{-1} kg^{-1}).

3.2. Bioelectrical impedancemetry

This patient (height 165 cm, weight 65 kg) had the following body composition by bioelectrical impedance: 20% fat, 52 kg of fat free mass (FFM) with 74.8% of this FFM represented by water (62% intracellular, 38% intracellular).

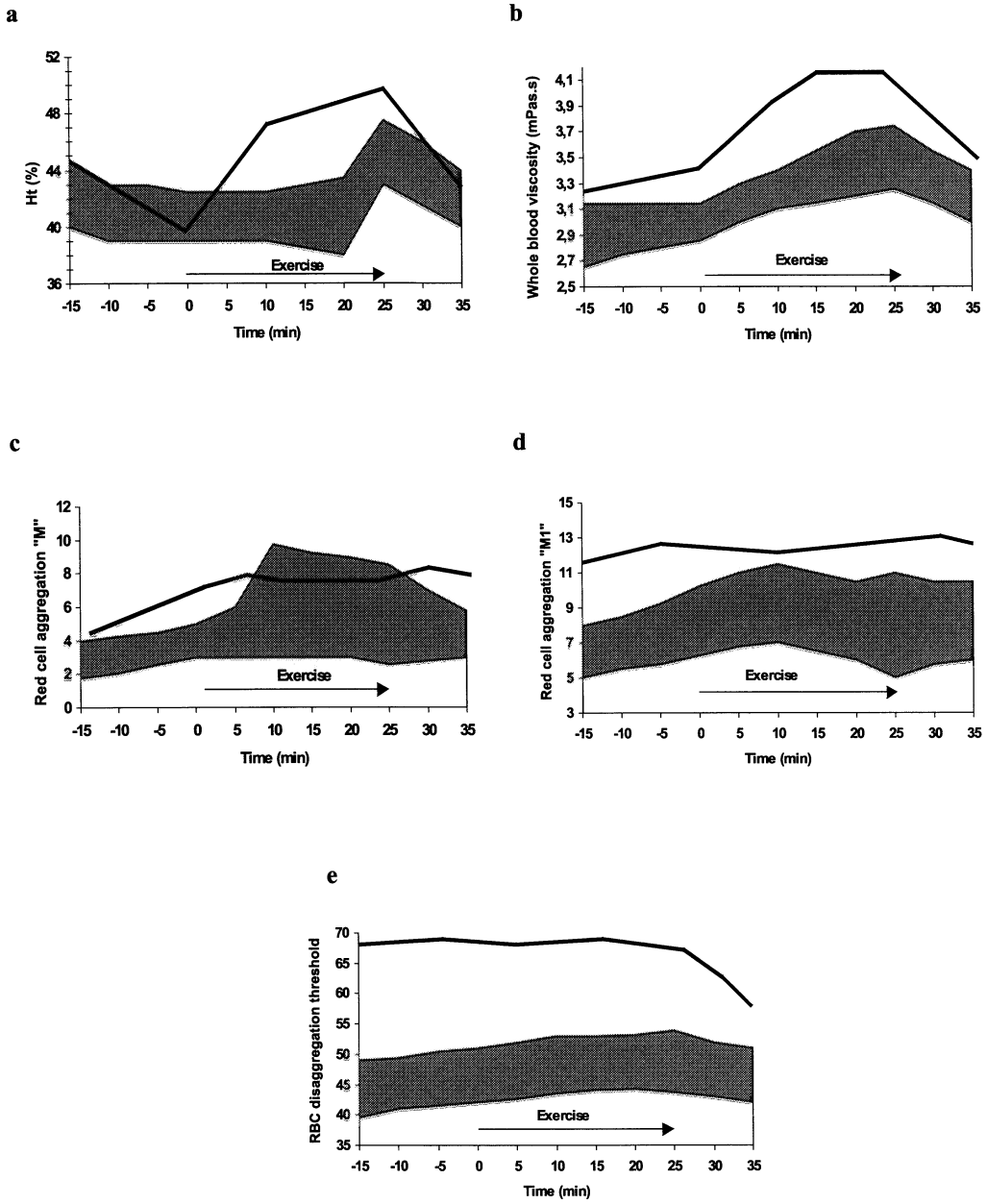

Fig. 1. Hematocrit (a), whole blood viscosity (b), red cell aggregation 'M' (c), red cell aggregation 'M1' (d) and red blood cell disaggregation threshold values after a breakfast (T-15), during an exercise-test, and after the test in control subjects (shaded area) and in a marathon runner (e) who undervent a central retinal vein thrombosis after a marathon run.

3.3. Hemoreology

All the hemorheological results obtained are presented in Table 2. Resting values of fibrinogen were 2.9 $g\,l^{-1}$. The increase in hematocrit (Fig. 1a) and whole blood viscosity (Fig. 1b) exceeded the control range. Ten minutes after the beginning of the exercise-test, the mean value of hematocrit was 40% in

Table 2
Hemorheologic parameters performed in a 50 years old marathon runner before, during and after an exercise test (25 min with 10 min at 85% of the theoretical maximal heart rate)

	Fasting	T-15	Exercise test			Recuperation
			T0	T10	T25	T35
Hematocrit (%)	43	44.5	40	47	50	42
Whole blood viscosity (mPa s)	3.46	3.25	3.41	3.99	4.16	3.41
Plasma viscosity (mPa s)	1.37	1.35	1.43	1.51	1.52	1.45
Erythrocyte rigidity 'Tk'	0.7	0.74	0.64	0.67	0.66	0.69
Red cell aggregation 'M'	5.3	6	7.1	6.7	7.8	6.7
Red cell aggregation 'M1'	11	10.4	12.1	11.3	13.9	12.4
RBC disaggregation threshold	57.5	78.4	78.7	71	72.4	56.3

RBC: red blood cell, T: time (minutes).

control subjects, it reached 49% in the marathon runner (i.e., 22.5% more than in controls). The calculated plasma volume contraction, % Δ PV, was 41.7% after 25 minutes of exercise whereas it was 20.8% in the controls. At the same time, the mean value of plasma viscosity was 1.4 mPas s in controls and 1.53 in the runner (i.e., an increase of 9.3%); the mean value of whole blood viscosity was 3.4 mPa s in controls and reach 4.05 mPa s in the marathon runner (i.e., an increase of 19.2%).

Red cell rigidity index 'Tk' remained constant (near 0.65) during the exercise and corresponded to the sames values observed in the control range.

We observed an increase of both aggregation's parameters – M and M1 – in the marathon runner subject compared to the values obtained in the controls (Fig. 1c and d); the disaggregation threshold was also higher than in controls (Fig. 1e). Twenty minutes after the beginning of the exercise test, the increase of 'M' and 'M1' exceeded the control range of 7.5% and 47%, respectively; the increase of the disaggregation threshold was 36.7% more than in controls.

4. Discussion

Sudden painless visual loss may reflect primary ocular disease or systemic disease [14]. Occlusion of retinal vessels [15] is one of the important diseases causing this symptom but its pathogenesis remains incompletely understood. Among the risk factors, most thrombophilic situations can be found [15,16] including arterial hypertension and a family history of stroke, activated protein C resistance [17], impaired fibrinolysis due to increased PAI activity [18], homozygoty for the methylenetetrahydrofolate reductase MTHFR C677T polymorphism [16]. In the case of the patient studied here, the study of thrombophilic factors gave no explanation and therefore a hemorheologic assessment was undertaken.

Interestingly, impaired blood rheology is also considered as a risk factor for this disease [19], as further supported by the occurrence of venous retinal occlusion after iatrogenic hyperviscosity syndromes [20] and by the efficiency of hemodilution [21,22]. The case presented here is an amateur marathon runner who suffered of a central retinal vein thrombosis after a marathon run. On one hand, it is well known that acute thrombotic events may impair blood rheology [23] and mostly increase erythrocyte aggregation [24]. On the other hand, retinal occlusions are sometimes observed in athletes after endurance run, i.e., a situation where hyperviscosity is likely to occur, with possible prothombotic effects [25,26]. However, although large studies have been performed on baseline blood rheology in patients suffering from retinal occlusion [27,28], we are not aware of any study investigating the hemorheological

adaptation to exercise of such patients. While in a previous study, Neuhaus et al. [29] reported no significant differences in hematocrit, plasma viscosity and red cell aggregation before and after exercise in 8 endurance-trained athletes, it is now well established [2] that all these parameters generally exhibit transient changes at exercise. In some cases, the rapidity of recovery may hide these modifications very soon after exercise discontinuation, explaining Neuhaus's findings. In our study, we measured the following parameters: hematocrit, blood viscosity, aggregation's parameters 'M' and 'M1' and disaggregation thresholds. The values of aggregation parameters and the increase of hematocrit and blood viscosity observed during exercise are unusually high, when compared in standardized conditions to control responses. The runner observed seems to develop an unusual hyperviscosity in the standardized conditions of our exercise test. His pattern of hemorheological response differs from usual findings after exercise tests in healthy volunteers [30,31]. However, two recent studies [27,28] performed on large groups of patients after branch retinal vein occlusion (173 and 292 patients, respectively) did not show any difference in erythrocyte rigidity and aggregation but significant increase in values of hematocrit and plasma viscosity. The difference among studies about aggregability data may have occurred because of relatively high intra-individual variability using the Myrenne aggregometer. Nevertheless, our study is the first to measure disaggregation threshold thanks to the laser backscattering analysis in this context. We observed a markedly elevated disaggregation threshold in our marathon runner compared to controls, indicating that erythrocyte aggregates require a higher shear stress to be dissociated. Therefore, the most prominent modification in RBC aggregability parameters in this case is a low disaggregability, contrasting with quite moderate alterations in the Myrenne aggregation parameters. The value of fibrinogen observed, which was midly elevated 2.9 g/l is not likely to explain this aggregation profile. Such an isolated defect in disaggregability has already been reported in cancer patients [32] and is also found after experimental free radical damage exerted on the red cells [33]. Therefore, it may reflect some degree of red cell damage related to inflammation or thrombosis, or even a pre-existing abnormality involved in the pathogenesis of the thrombotic event. However, this low disaggregability contrasts with a lack of detectable disturbance in red cell deformability as assessed by viscometric indices, while free radical damage to red cells affects both aggregation and deformability parameters [33]. Finally, there is a disproportionate increase in hematocrit, which contrasts with quite normal values of this parameter at rest. When converted into plasma volume changes, these hematocrit modifications become impressive: they indicate a two-fold increased plasma fluid leakage (41.7% vs. 20%), probably related to endothelial disturbances. While, here again, it is difficult to delineate the post-thrombosis syndrome from a pre-existing pathologic state, it is clear that such an excess fluid shift may induce marked circulatory and coagulatory modifications.

To conclude, it remains very difficult to determine if the very unusual parameters observed in the marathon runner are the cause or the consequence of the thrombotic event. Plasma hyperviscosity and high blood viscosity are well known to be important factors in the pathogenesis of veinal occlusion. Both low erythrocyte disaggregability and excess post-exercise plasma volume contraction appear to be less classical findings in this context, and are very likely to reflect an inflammatory reaction resulting in endothelial disturbances, which are probably at least in part secondary to the thrombotic event, but can be considered as least in part as risk factors for further hemocoagulatory disorders.

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