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Editorial Manager(tm) for Medicine & Science in Sports & Exercise
Manuscript Draft

Manuscript Number: MSSE-D-08-00064R2

Title: Central retinal vein occlusion in a sickle cell trait carrier after a cycling race

Short Title:

Article Type: Clinical Investigation/Case Study

Keywords: hemoglobinopathy; exercise; ophthalmologic complications; red blood cell; coagulation

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Case studies

Central retinal vein occlusion in a sickle cell trait carrier after a cycling race

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Running title: SCT and ophthalmologic complications

Abstract

A 26-year-old man with sickle cell trait (SCT) suddenly lost visual acuity in the left eye after a cycling race in hot tropical environment. The cause was massive central retinal vein occlusion (CRVO) with hemorrhaging that rapidly worsened to neovascular glaucoma. Although medically treated, the eye is now marked by total retinal detachment. Cardiovascular function assessment shown no electrocardiographic abnormalities, no anomaly in the supra-aortic tree and no evidence of structural heart disease. Although normal coagulation markers values (i.e. activated partial thromboplastin time, prothrombin time, fibrinogen concentration, antithrombin III, factor V, protein C and S) were observed two and a half months after the clinical event, a trans-esophageal echocardiogram performed few hours after the incident revealed the presence of four thrombi in the left atrium suggesting a post exercise hypercoagulable state at that time. Hemorheological measurements at distance of the events demonstrated high red blood cell rigidity at baseline. Therefore, marked blood rheological impairment and activation of the coagulation pathway in response to the heavy and prolonged cycling race could have promoted CRVO in this cyclist carrying SCT. These data suggest that SCT could be considered as a risk factor for significant ocular complications when severe exercise is performed and support the idea that SCT is a contributing factor in blood rheology and vascular dysfunctions.

Key words: hemoglobinopathy, exercise, ophthalmologic complications, red blood cell, coagulation

Introduction

Paragraph 1: The heterozygous form of sickle cell anemia (sickle cell trait; SCT) is usually considered as a benign disorder by ophthalmologists, as compared with other forms of sickle cell disease known to be associated with ocular complications (38). We report the first case of CRVO (central retinal vein occlusion) coincident with prolonged and intense exercise that rapidly worsened to neovascular glaucoma and painful blindness, in a young athlete with SCT. Since SCT carriers are often marked by coagulation activity imbalance (36), blood rheological disorders (28,35) and abnormalities in vascular adhesion processes (29,34), both at rest and in response to exercise, we propose that blood and vascular dysfunctions might have contributed to the occurrence of this adverse event.

Case report

Paragraph 2: A previously healthy 26-year-old Afro-Caribbean male cyclist was admitted to the Ophthalmology Department of the University Hospital of Pointe-à-Pitre the day after a prolonged and intense cycling race in Guadeloupe, a French West Indies island. The competition consisted of 138 kilometers in mountainous terrain and high ambient temperature (35°C) with 60% of humidity. The patient felt himself particularly thirsty all along the race. At hospital admission, he presented a sudden loss of visual acuity (VA) of the left eye (6/20). VA of the right eye was normal (20/20). Intraocular pressure (IOP) was normal in both eyes (14 mmHg). Ophthalmoscopy and fluorescein angiography of the left eye documented CRVO with massive retinal hemorrhage (Figure 1). The clinical interview revealed that 1) the patient had already experienced a loss of visual acuity of his left eye two months earlier with spontaneous recovery within two days and 2)

he was a SCT carrier. Blood sampled was obtained to confirm the SCT status by isoelectric focusing and high performance liquid chromatography (Table 1). Hematological parameters, inflammatory and biochemical markers were normal (Table 1). The anticardiolipin antibody test was negative (Table 1). Unfortunately, a technical problem occurred during the analysis of the blood coagulation parameters that deprived us of data at that time. An in-depth assessment of cardiovascular function was also performed. The electrocardiographic measurements demonstrated sinusal rhythm, normal QRS and repolarization. Neither anomaly in the supra-aortic tree using arterial echo Doppler, nor evidence of structural heart disease on echocardiography was detected. The trans-thoracic echocardiogram was normal but the trans-esophageal echocardiogram revealed the presence of four thrombi in the left atrium. Medical treatment associating troxerutin (Veinamitol®), a venotonic agent, and acetylsalicylic acid (Kardégic®) was prescribed by the Department of Ophthalmology. Anti-vitamin K medication was also given by the cardiologists to treat the left atrial thrombi. The patient was instructed to avoid physical exercise until the next visit. One month later, because of a severe ischemic form of the disease, panretinal photocoagulation treatment was given in emergency to manage CRVO.

Paragraph 3: The patient returned one month later to the Department of Ophthalmology for headache, nausea and vomiting, blindness and eye pain in the left eye. The interview revealed that the patient had been doing heavy weight lifting, such as 3-5 maximal repetition method, when these medical signs suddenly appeared. Biomicroscopic exam demonstrated important iris rubeosis and neovascular glaucoma with corneal edema. The neovascular glaucoma was confirmed by gonioscopy. The patient was immediately hospitalized and hypotonic medication was given intravenously (acetazolamide, Diamox®) as well as locally (timolol maleate, Ophtim®), which decreased IOP to 20 mmHg. A complement of panretinal photocoagulation was performed in

emergency as soon as the corneal edema was sufficiently reduced. Despite anticoagulation medication, a new trans-esophageal echocardiogram performed three days later revealed two remaining thrombi in the left atrium suggesting that blood coagulation disturbances were still persistent.

Paragraph 4: Two weeks later, the IOP was still high (> 21 mmHg) and the patient complained of eye pain. Cryotherapy was performed on both the ciliary body and retina. One month later, assessment of blood rheology by viscometric method (10,28) demonstrated high red blood cell (RBC) rigidity (Table 2). Blood coagulation parameters (activated partial thromboplastin time, prothrombin time and antithrombin III) were also successfully measured and showed normal values (Table 2).

Paragraph 5: The eye pain disappeared at this time, and the patient has since been chronically medicated with rimexolone (Vexol®), dorzolamide (Trusopt®), brimonidine tartrate (Alphagan®) and latanoprost (Xalatan®) to stabilize the IOP. Medication for platelet anti-aggregation was also prescribed for the patient and exercise is not currently recommended. The patient is followed by the Department of Ophthalmology and the Department of Cardiology every two months to monitor IOP and cardiovascular function. The IOP is now stabilized (12 mmHg) but the left eye is marked by total retinal detachment and very low visual acuity, which is limited to weak luminous perception.

Paragraph 6: Informed consent was obtained from the patient and DNA studies were conduced. Briefly, DNA from blood sample was extracted using standard procedure and detection of the prothrombin A 20210, methyltetrahydrofolate reductase T 677 and factor V Leiden alleles were performed as previously described (15,30,31). DNA analysis revealed that the patient did not carry any of these genetic risk factor for retinal vascular occlusion and thrombotic event (6).

Discussion

Paragraph 7: We report the first identified case of CRVO associated with prolonged and intense exercise in a SCT carrier with no past history of treatment for ocular complication or other disease. The patient was well trained in endurance cycle and performed 3 cyclists outing per week (2 short ones of 60 – 80 km and a longer one of more than 100 km). In addition, he practiced weight lifting twice a week to complete his training regimen. The situation rapidly deteriorated to neovascular glaucoma and blindness of the eye. Several studies have reported ocular complications in SCT but these complications have usually been described as the consequence of traumatic hyphema (19,27,38). Ophthalmologists therefore consider SCT as a benign condition compared with SS or SC hemoglobinopathy (38). However, this issue is still debated since several reports suggest that SCT could be viewed as a potentially dangerous disorder (2,37), particularly in response to prolonged and intense exercise (7,12,20,21,23,24,37).

Paragraph 8: Interestingly, impaired blood rheology was suggested to be a risk factor for CRVO (25). Gaudard et al. (17) recently demonstrated that hemorheological disturbances are likely to be involved in CRVO. SCT carriers usually have impaired RBC deformability in basal conditions (28), as confirmed by the high RBC rigidity found in the present study. Unfortunately, it was not possible to assess RBC rigidity closer to the ocular incident (i.e., the day after the cycling race). Exercise is known to further impair blood rheology in SCT carriers because of the increased sickling of erythrocytes, particularly in hot environment (4), and we recently demonstrated that RBC deformability is further impaired 24 hours after strenuous exercise (35). Therefore, it is conceivable that RBC deformability was also impaired the day after the cycling race and that such abnormality would have been favorable to the occurrence of CRVO. Moreover, the patient

reported that, despite its efforts to drink water, he felt particularly thirsty during and after the race. Sherry (33) hypothesized that dehydration might contribute to the development of sickling and that SCT carriers might be naturally more predisposed to dehydration due to their inability to concentrate their urine when deprived of water (33). This defect might make SCT carriers less able to conserve water than non-carriers and could have played a role in the occurrence of CRVO. Indeed, higher amount of water intake with appropriate amount of electrolytes (notably sodium) (32) may be required for exercising SCT carriers in comparison with control subjects.

Paragraph 9: Abnormal coagulation activities are also among the several risk factors associated with CVRO (16) The role of hemostasis-fibrinolysis balance in CRVO is supported by the recent results of Ghazi et al. (18), who demonstrated that intravitreal tissue plasminogen activator injection may have a beneficial role in the management of CRVO. Westerman et al. (36) reported elevated d-dimers, thrombin-antithrombin complexes and prothrombin fragments 1.2 in SCT carriers at rest, suggesting that they may be prone to a hypercoagulable state in resting conditions (36). In addition Austin et al. (3) recently provided strong evidences of higher risk to develop venous thromboembolism (odds ratio: 1.8) and pulmonary embolism (odds ratio: 3.9) among African Americans with SCT than in non SCT carriers, in agreement with the reported disequilibrium between coagulation and fibrinolytic activities in SCT carriers. Nevertheless, these results contrast with the present finding of no disorder of blood coagulation two and a half months after the incident (Table 2). Our patient did not carry any of the known genetic risk factor for retinal vascular occlusion, namely prothrombin A 20210, methyltetrahydrofolate reductase T 677 and factor V Leiden variants.

Paragraph 10: Due to technical problems, the markers of coagulation could not be obtained at the time of the incident and it is possible that, had we obtained them, the blood coagulation properties would have been different. The presence of four thrombi in the left atrium after the occurrence of CRVO strongly suggested the hypercoagulable state of the patient when the incident occurred. Prolonged exercise usually causes changes in coagulation activity in healthy persons (14). Mandalaki et al. (26) previously reported a decrease in antithrombin III activity after a marathon. Therefore, the stress caused by the cycling race could have disturbed the balance between hemostasis and fibrinolysis (36), leading to increased risk for CRVO. We recently demonstrated no difference in prothrombin time, activated partial thromboplastin time, antithrombin III activity and yield stress between SCT carriers and a control population, before and after a strenuous cycling exercise test conducted in laboratories condition (11). Although large hemostatic dysregulations in SCT carriers following exercise, such as disseminated intravascular coagulation (22), have already been reported, we did not investigate fibrinolytic activity in that study (11). Therefore, no conclusion regarding the coagulation activity of the patient at the time of the incident is possible.

Paragraph 11: Despite the panretinal photocoagulation and the venotonic and platelet anti-aggregating agent treatment, the CRVO rapidly worsened to rubeosis iridis and neovascular glaucoma, which led to a second emergency hospital visit. Interestingly, the signs of ocular complication (blindness, eye pain, headache, nausea and vomiting) appeared immediately after a session of resistance training. Although it may prove difficult to tease out whether it was the intensity or just the type of exercise that contributed to this second incident, resistance training (and particularly heavy weight lifting) is also known to alter blood rheological parameters and blood coagulation (1,13). These alterations could have been involved in the surprising and rapid

ocular complication observed in our patient. Despite anti coagulation medication, two thrombi were present at that time in the left atrium suggesting, again, disequilibrium of the balance between hemostasis and fibrinolytic activity. Despite clear medical recommendations, the patient did not stop practicing intense physical activities, which illustrates the problem of preventing and managing further exercise related medical complication in a sportsman.

Paragraph 12: Although under multiple medical treatments, the patient unfortunately lost his left eye. The exact reasons for this severe ocular incident are not clearly understood, and the most surprising event was the rapid deterioration of CRVO to neovascular glaucoma. Usually, the occurrence of CRVO (whether induced by exercise or not) in young men is well managed, leading to recovery (17) with minimal visual after effects. However, this was not the case in the present study and the poor outcome for our patient could be related to its SCT carrier status. Indeed, the concomitant occurrence of hypoxia, dehydration and acidosis, conditions occurring during excercice, is favorable to the sickling process (5) and coagulopathy (20). The presence of SCT and the associated hemorheological disorders could have played a role in the complications (i.e., retinal detachment and blindness).

Paragraph 13: Altogether, the data presented in this case study suggest that SCT status could be another genetic risk factor for severe ocular complications, particularly when severe exercise is performed in extreme climatic conditions. While SCT carriers often participate in sports and related training, particular attention to preventing dehydration and starting exercise gradually may be warranted. These recommendations have to be applied to the general population; but we do advocate that physicians and trainers should pay a greater attention to people (trained or untrained) carrying SCT. The recommendation on adequate hydration is particularly important for SCT

carriers because they are naturally more predisposed to dehydration due to their inability to concentrate their urine when deprived of water (33). This defect might make SCT carriers less able to conserve water than non-carriers. Blood rheological disorders and coagulation imbalance following intense physical exercise such as heavy and prolonged cycling race could promote CRVO in SCT carriers. This report provides data suggesting that SCT could be considered as a risk factor for severe ocular complications when severe exercise is performed. Several forms of clinical complications related to exercise or not, have already been described in SCT carriers and might be related to different blood and vascular dysfunctions (8,9).

Acknowledgments: This work was supported by our academic funding. The results of the present study do not constitute endorsement by ACSM.

Conflict of interest: We state that there is no conflict of interest**.**

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Figure legends:

Figure 1: Hemorrhagic form of an inferior-predominating central retinal vein occlusion. To be noted: the papillary stasis oedema, the extreme dilation and twisting of the veins and the large retinal bleeding areas are signs of severe ischemia.

Responses to the reviewers and list of changes

Med Sci Sports Exerc – MSSE-D-08-00064R1

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We would like to thank the reviewers for their critical appraisals and interesting comments on our manuscript. We have attempted to fully answer all the questions and to respond with more details where required. The changes introduced in the reviewed manuscript are in red to make the reviewing process easier.

Reviewer 1:

No further comments

Reviewer 2:

First, the authors would like to thank the reviewer for her/his additional comments.

General comments

1) Regarding the "centered" or "middle dot" ("·") character, perhaps this was converted to a "period" in the submission process, and copyediting will take care of this. In any case, the units of measure in the tables should be in a format such as "g·l-1 (superscript)". A few additional specific changes need to be made (indicated below).

We apologize for this mistake. We made the corrections everywhere in the tables.

Specific comments

2) Abstract Line 24: It would be cleaner to change to read "observed two and a half months after the clinical event."

We made the corrections.

3) Abstract Line 38: Change to read "These data suggest that SCT."

We made the changes.

4) Abstract Line 41: Change to read "factor for significant ocular ."

As requested, we replaced “severe” by “significant”.

5) Abstract Line 43: Do the authors mean to say "SCT is a contributing factor in blood rheology and vascular dysfunctions"?

Yes, the reviewer is correct. We replaced our sentence by the sentence proposed by the reviewer.

6) Page 3 Line 14: CRVO needs to be defined here.

Line 24: Change to "we propose."

Line 26: Change to "might have contributed."

Line 36-44: Again, it is a little confusing having the phrase "practicing cycling" and then mention a "race" and "competition" (Was this practice or competition?). Do the authors simply mean to say "Afro-Caribbean male cyclist was admitted."?

As requested, we made all the modifications.

7) Page 7 Line 16: Use the most current position statement on exercise and fluid replacement which replaces the 1996 statement cited here (Sawka et al. Med Sci Sports Exerc. 2007).

We agree with the reviewer and we inserted the proposed reference.

8) Page 9 Line 50-3: Change to read "general population; but we also advocate."

We made the corrections.

9) Table 2 - Use "incident" vs. "accident" in the legend.

We made the changes.

Table

Table 1: Hematological, inflammatory, biochemical parameters measured the day after the cycling race (day of the initial accident)

Parameter	Patient value	Normal value
Red blood cells ($10^{12}\cdot l^{-1}$)	4.9	4.5 – 6.5
Hematocrit (%)	44.1	40 – 54
Hemoglobin ($g\cdot dl^{-1}$)	15.4	13.0 – 17.0
Mean corpuscular volume (fl)	89.5	80 – 100
Mean corpuscular hemoglobin concentration (pg)	31.2	27 – 32
Hemoglobin A (%)	50.8	
Hemoglobin S (%)	38.9	
Hemoglobin F (%)	1.2	
Hemoglobin A2 (%)	3.5	
Platelets ($10^{9}\cdot l^{-1}$)	183	150 – 500
Sedimentation rate ($mm.h^{-1}$)	5	< 15
Leukocytes ($10^{9}\cdot l^{-1}$)	4.4	4.0 – 10.0
Polynuclear neutrophils ($10^{9}\cdot l^{-1}$)	1.7	1.8 – 7.5
Polynuclear eosinophils ($10^{9}\cdot l^{-1}$)	0.05	0.04 – 0.8
Polynuclear basophils ($10^{9}\cdot l^{-1}$)	0.02	0.00 – 0.2
Lymphocytes ($10^{9}\cdot l^{-1}$)	2.4	1.0 – 4.0
Monocytes ($10^{9}\cdot l^{-1}$)	0.25	0.2 – 1.00
C-reactive protein ($mg\cdot l^{-1}$)	3.1	< 5
C3 fraction of complement ($g\cdot l^{-1}$)	1.11	0.75 – 1.4
C4 fraction of complement ($g\cdot l^{-1}$)	0.14	0.1 – 0.34
Anticardiolipin antibody Ig G (GPL units$\cdot ml^{-1}$)	3	< 11
Anticardiolipin antibody Ig M (MPL units$\cdot ml^{-1}$)	10	< 11

No parameter was outside the reference range

Table 2: Red blood cell rigidity, blood coagulation markers measured two and a half months after the initial incident and one month after the end of anti-coagulation treatment.

Parameter	Patient value	Normal value
Red blood cell rigidity (shear rate of 225 s^{-1})*	0.88	< 0.85
Activated partial thromboplastin time (s) Ratio (healthy subject/patient)	31 1.10	< 47 < 1.52
Prothrombin time (%)	90	70 – 100
Fibrinogen ($g \cdot l^{-1}$)	2.50	2.00 – 4.50
Antithrombin III (%)	94	70 - 120
Factor V (%)	104	70 – 120
Protein C (%)	70	70 – 130
Protein S (%)	68	65 – 140
Resistance to activated protein C (normalized ratio)	1.00	> 0.70
C-reactive protein ($mg \cdot l^{-1}$)	3.19	< 5.00

* Except for red blood cell rigidity, no parameter was outside the reference range

Figure

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