



**HAL**  
open science

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

Mona Hedreville, Philippe Connes, Marc Romana, Guillaume Magnaval,  
Thierry David, Marie-Dominique Hardy-Dessources, Marie-Sylvaine Belloy,  
Maryse Etienne-Julan, Olivier Hue

### ► **To cite this version:**

Mona Hedreville, Philippe Connes, Marc Romana, Guillaume Magnaval, Thierry David, et al..  
Central retinal vein occlusion in a sickle cell trait carrier after a cycling race.: SCT and oph-  
thalmologic complications. *Medicine and Science in Sports and Exercise*, 2009, 41 (1), pp.14-8.  
10.1249/MSS.0b013e31818313d0 . hal-00698572

**HAL Id: hal-00698572**

**<https://hal.univ-antilles.fr/hal-00698572>**

Submitted on 16 May 2012

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Corresponding Author: Dr. Philippe Connes, Ph.D.

Corresponding Author's Institution: University of the French West Indies

First Author: Mona Hedreville, M.D.

Order of Authors: Mona Hedreville, M.D.; Philippe Connes, Ph.D.; Marc Romana, Ph.D.; Guillaume Magnaval, M.D.; Thierry David, M.D.; Marie-Dominique Hardy-Dessources, Ph.D.; Marie-Sylvaine Belloy, M.D.; Maryse Etienne-Julan, M.D.; Olivier Hue, Ph.D.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

## Case studies

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

Mona Hedreville<sup>1,2</sup>, Philippe Connes<sup>1</sup>, Marc Romana<sup>3</sup>, Guillaume Magnaval<sup>4</sup>, Thierry David<sup>4</sup>,  
Marie-Dominique Hardy-Dessources<sup>3</sup>, Marie-Sylvaine Belloy<sup>3</sup>, Maryse Etienne-Julan<sup>3,5</sup>, and  
Olivier Hue<sup>1</sup>.

<sup>1</sup>Laboratory ACTES UPRES-EA 3596, Dpt of Physiology, University of the French West Indies,  
Campus of Fouillole, Pointe-a-Pitre, Guadeloupe. <sup>2</sup>Dpt of Cardiology, Academic Hospital, Pointe-  
a-Pitre, Guadeloupe. <sup>3</sup>Inserm, U763, Pointe-a-Pitre, University of the French West Indies, Pointe-  
a-Pitre, F-97159 France. <sup>4</sup>Dpt of Ophtalmology, Academic Hospital, Pointe-a-Pitre, Guadeloupe.  
<sup>5</sup>Carribean Sickle Cell Center, Academic Hospital, Pointe-a-Pitre, Guadeloupe.

**Corresponding author:** Philippe Connes, PhD, Laboratory ACTES UPRES-EA 3596, Dpt of  
Physiology, University of the French West Indies, Campus of Fouillole, Pointe-a-Pitre,  
Guadeloupe

Telephone: 590 590 83 48 99,

Fax : 590 590 83 05 13

Email: [pconnes@yahoo.fr](mailto:pconnes@yahoo.fr),

**Running title:** SCT and ophthalmologic complications

1  
2  
3  
4 **Abstract**  
5

6 A 26-year-old man with sickle cell trait (SCT) suddenly lost visual acuity in the left eye after a  
7 cycling race in hot tropical environment. The cause was massive central retinal vein occlusion  
8 (CRVO) with hemorrhaging that rapidly worsened to neovascular glaucoma. Although medically  
9 treated, the eye is now marked by total retinal detachment. Cardiovascular function assessment  
10 shown no electrocardiographic abnormalities, no anomaly in the supra-aortic tree and no evidence  
11 of structural heart disease. Although normal coagulation markers values (i.e. activated partial  
12 thromboplastin time, prothrombin time, fibrinogen concentration, antithrombin III, factor V,  
13 protein C and S) were observed **two and a half months after the clinical event**, a trans-esophageal  
14 echocardiogram performed few hours after the incident revealed the presence of four thrombi in  
15 the left atrium suggesting a post exercise hypercoagulable state at that time. Hemorheological  
16 measurements at distance of the events demonstrated high red blood cell rigidity at baseline.  
17 Therefore, marked blood rheological impairment and activation of the coagulation pathway in  
18 response to the heavy and prolonged cycling race could have promoted CRVO in this cyclist  
19 carrying SCT. **These data suggest** that SCT could be considered as a risk factor for **significant**  
20 ocular complications when severe exercise is performed and support the idea that **SCT is a**  
21 **contributing factor in blood rheology and vascular dysfunctions.**  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54

55 **Key words:** hemoglobinopathy, exercise, ophthalmologic complications, red blood cell,  
56  
57 coagulation  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 **Introduction**  
5  
6  
7  
8

9 *Paragraph 1:* The heterozygous form of sickle cell anemia (sickle cell trait; SCT) is usually  
10 considered as a benign disorder by ophthalmologists, as compared with other forms of sickle cell  
11 disease known to be associated with ocular complications (38). We report the first case of CRVO  
12 (central retinal vein occlusion) coincident with prolonged and intense exercise that rapidly  
13 worsened to neovascular glaucoma and painful blindness, in a young athlete with SCT. Since SCT  
14 carriers are often marked by coagulation activity imbalance (36), blood rheological disorders  
15 (28,35) and abnormalities in vascular adhesion processes (29,34), both at rest and in response to  
16 exercise, we propose that blood and vascular dysfunctions might have contributed to the  
17 occurrence of this adverse event.  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32

33 **Case report**  
34  
35  
36  
37

38 *Paragraph 2:* A previously healthy 26-year-old Afro-Caribbean male cyclist was admitted to the  
39 Ophthalmology Department of the University Hospital of Pointe-à-Pitre the day after a prolonged  
40 and intense cycling race in Guadeloupe, a French West Indies island. The competition consisted of  
41 138 kilometers in mountainous terrain and high ambient temperature (35°C) with 60% of  
42 humidity. The patient felt himself particularly thirsty all along the race. At hospital admission, he  
43 presented a sudden loss of visual acuity (VA) of the left eye (6/20). VA of the right eye was  
44 normal (20/20). Intraocular pressure (IOP) was normal in both eyes (14 mmHg). Ophthalmoscopy  
45 and fluorescein angiography of the left eye documented CRVO with massive retinal hemorrhage  
46 (Figure 1). The clinical interview revealed that 1) the patient had already experienced a loss of  
47 visual acuity of his left eye two months earlier with spontaneous recovery within two days and 2)  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 he was a SCT carrier. Blood sampled was obtained to confirm the SCT status by isoelectric  
5  
6 focusing and high performance liquid chromatography (Table 1). Hematological parameters,  
7  
8 inflammatory and biochemical markers were normal (Table 1). The anticardiolipin antibody test  
9  
10 was negative (Table 1). Unfortunately, a technical problem occurred during the analysis of the  
11  
12 blood coagulation parameters that deprived us of data at that time. An in-depth assessment of  
13  
14 cardiovascular function was also performed. The electrocardiographic measurements demonstrated  
15  
16 sinus rhythm, normal QRS and repolarization. Neither anomaly in the supra-aortic tree using  
17  
18 arterial echo Doppler, nor evidence of structural heart disease on echocardiography was detected.  
19  
20 The trans-thoracic echocardiogram was normal but the trans-esophageal echocardiogram revealed  
21  
22 the presence of four thrombi in the left atrium. Medical treatment associating troxerutin  
23  
24 (Veinamitol®), a venotonic agent, and acetylsalicylic acid (Kardégic®) was prescribed by the  
25  
26 Department of Ophthalmology. Anti-vitamin K medication was also given by the cardiologists to  
27  
28 treat the left atrial thrombi. The patient was instructed to avoid physical exercise until the next  
29  
30 visit. One month later, because of a severe ischemic form of the disease, panretinal  
31  
32 photocoagulation treatment was given in emergency to manage CRVO.  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42

43 *Paragraph 3:* The patient returned one month later to the Department of Ophthalmology for  
44  
45 headache, nausea and vomiting, blindness and eye pain in the left eye. The interview revealed that  
46  
47 the patient had been doing heavy weight lifting, such as 3-5 maximal repetition method, when  
48  
49 these medical signs suddenly appeared. Biomicroscopic exam demonstrated important iris rubeosis  
50  
51 and neovascular glaucoma with corneal edema. The neovascular glaucoma was confirmed by  
52  
53 gonioscopy. The patient was immediately hospitalized and hypotonic medication was given  
54  
55 intravenously (acetazolamide, Diamox®) as well as locally (timolol maleate, Ophtim®), which  
56  
57 decreased IOP to 20 mmHg. A complement of panretinal photocoagulation was performed in  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 emergency as soon as the corneal edema was sufficiently reduced. Despite anticoagulation  
5  
6 medication, a new trans-esophageal echocardiogram performed three days later revealed two  
7  
8 remaining thrombi in the left atrium suggesting that blood coagulation disturbances were still  
9  
10 persistent.  
11

12  
13  
14  
15  
16 *Paragraph 4:* Two weeks later, the IOP was still high (> 21 mmHg) and the patient complained of  
17  
18 eye pain. Cryotherapy was performed on both the ciliary body and retina. One month later,  
19  
20 assessment of blood rheology by viscometric method (10,28) demonstrated high red blood cell  
21  
22 (RBC) rigidity (Table 2). Blood coagulation parameters (activated partial thromboplastin time,  
23  
24 prothrombin time and antithrombin III) were also successfully measured and showed normal  
25  
26 values (Table 2).  
27  
28  
29

30  
31 *Paragraph 5:* The eye pain disappeared at this time, and the patient has since been chronically  
32  
33 medicated with rimexolone (Vexol®), dorzolamide (Trusopt®), brimonidine tartrate (Alphagan®)  
34  
35 and latanoprost (Xalatan®) to stabilize the IOP. Medication for platelet anti-aggregation was also  
36  
37 prescribed for the patient and exercise is not currently recommended. The patient is followed by  
38  
39 the Department of Ophthalmology and the Department of Cardiology every two months to monitor  
40  
41 IOP and cardiovascular function. The IOP is now stabilized (12 mmHg) but the left eye is marked  
42  
43 by total retinal detachment and very low visual acuity, which is limited to weak luminous  
44  
45 perception.  
46  
47  
48

49  
50 *Paragraph 6:* Informed consent was obtained from the patient and DNA studies were conducted.  
51  
52 Briefly, DNA from blood sample was extracted using standard procedure and detection of the  
53  
54 prothrombin A 20210, methyltetrahydrofolate reductase T 677 and factor V Leiden alleles were  
55  
56 performed as previously described (15,30,31). DNA analysis revealed that the patient did not carry  
57  
58 any of these genetic risk factor for retinal vascular occlusion and thrombotic event (6).  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 **Discussion**  
5  
6  
7  
8

9 *Paragraph 7:* We report the first identified case of CRVO associated with prolonged and intense  
10 exercise in a SCT carrier with no past history of treatment for ocular complication or other disease.  
11  
12 The patient was well trained in endurance cycle and performed 3 cyclists outing per week (2 short  
13 ones of 60 – 80 km and a longer one of more than 100 km). In addition, he practiced weight lifting  
14 twice a week to complete his training regimen. The situation rapidly deteriorated to neovascular  
15 glaucoma and blindness of the eye. Several studies have reported ocular complications in SCT but  
16 these complications have usually been described as the consequence of traumatic hyphema  
17 (19,27,38). Ophthalmologists therefore consider SCT as a benign condition compared with SS or  
18 SC hemoglobinopathy (38). However, this issue is still debated since several reports suggest that  
19 SCT could be viewed as a potentially dangerous disorder (2,37), particularly in response to  
20 prolonged and intense exercise (7,12,20,21,23,24,37).  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37

38 *Paragraph 8:* Interestingly, impaired blood rheology was suggested to be a risk factor for CRVO  
39 (25). Gaudard et al. (17) recently demonstrated that hemorheological disturbances are likely to be  
40 involved in CRVO. SCT carriers usually have impaired RBC deformability in basal conditions  
41 (28), as confirmed by the high RBC rigidity found in the present study. Unfortunately, it was not  
42 possible to assess RBC rigidity closer to the ocular incident (i.e., the day after the cycling race).  
43  
44 Exercise is known to further impair blood rheology in SCT carriers because of the increased  
45 sickling of erythrocytes, particularly in hot environment (4), and we recently demonstrated that  
46 RBC deformability is further impaired 24 hours after strenuous exercise (35). Therefore, it is  
47 conceivable that RBC deformability was also impaired the day after the cycling race and that such  
48 abnormality would have been favorable to the occurrence of CRVO. Moreover, the patient  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65



1  
2  
3  
4 reported that, despite its efforts to drink water, he felt particularly thirsty during and after the race.  
5  
6 Sherry (33) hypothesized that dehydration might contribute to the development of sickling and that  
7  
8 SCT carriers might be naturally more predisposed to dehydration due to their inability to  
9  
10 concentrate their urine when deprived of water (33). This defect might make SCT carriers less able  
11  
12 to conserve water than non-carriers and could have played a role in the occurrence of CRVO.  
13  
14 Indeed, higher amount of water intake with appropriate amount of electrolytes (notably sodium)  
15  
16 (32) may be required for exercising SCT carriers in comparison with control subjects.  
17  
18  
19  
20  
21  
22

23  
24 *Paragraph 9:* Abnormal coagulation activities are also among the several risk factors associated  
25  
26 with CVRO (16) The role of hemostasis-fibrinolysis balance in CRVO is supported by the recent  
27  
28 results of Ghazi et al. (18), who demonstrated that intravitreal tissue plasminogen activator  
29  
30 injection may have a beneficial role in the management of CRVO. Westerman et al. (36) reported  
31  
32 elevated d-dimers, thrombin-antithrombin complexes and prothrombin fragments 1.2 in SCT  
33  
34 carriers at rest, suggesting that they may be prone to a hypercoagulable state in resting conditions  
35  
36 (36). In addition Austin et al. (3) recently provided strong evidences of higher risk to develop  
37  
38 venous thromboembolism (odds ratio: 1.8) and pulmonary embolism (odds ratio: 3.9) among  
39  
40 African Americans with SCT than in non SCT carriers, in agreement with the reported  
41  
42 disequilibrium between coagulation and fibrinolytic activities in SCT carriers. Nevertheless, these  
43  
44 results contrast with the present finding of no disorder of blood coagulation two and a half months  
45  
46 after the incident (Table 2). Our patient did not carry any of the known genetic risk factor for  
47  
48 retinal vascular occlusion, namely prothrombin A 20210, methyltetrahydrofolate reductase T 677  
49  
50 and factor V Leiden variants.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 *Paragraph 10:* Due to technical problems, the markers of coagulation could not be obtained at the  
5  
6 time of the incident and it is possible that, had we obtained them, the blood coagulation properties  
7  
8 would have been different. The presence of four thrombi in the left atrium after the occurrence of  
9  
10 CRVO strongly suggested the hypercoagulable state of the patient when the incident occurred.  
11  
12 Prolonged exercise usually causes changes in coagulation activity in healthy persons (14).  
13  
14 Mandalaki et al. (26) previously reported a decrease in antithrombin III activity after a marathon.  
15  
16 Therefore, the stress caused by the cycling race could have disturbed the balance between  
17  
18 hemostasis and fibrinolysis (36), leading to increased risk for CRVO. We recently demonstrated  
19  
20 no difference in prothrombin time, activated partial thromboplastin time, antithrombin III activity  
21  
22 and yield stress between SCT carriers and a control population, before and after a strenuous  
23  
24 cycling exercise test conducted in laboratories condition (11). Although large hemostatic  
25  
26 dysregulations in SCT carriers following exercise, such as disseminated intravascular coagulation  
27  
28 (22), have already been reported, we did not investigate fibrinolytic activity in that study (11).  
29  
30 Therefore, no conclusion regarding the coagulation activity of the patient at the time of the  
31  
32 incident is possible.  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42

43 *Paragraph 11:* Despite the panretinal photocoagulation and the venotonic and platelet anti-  
44  
45 aggregating agent treatment, the CRVO rapidly worsened to rubeosis iridis and neovascular  
46  
47 glaucoma, which led to a second emergency hospital visit. Interestingly, the signs of ocular  
48  
49 complication (blindness, eye pain, headache, nausea and vomiting) appeared immediately after a  
50  
51 session of resistance training. Although it may prove difficult to tease out whether it was the  
52  
53 intensity or just the type of exercise that contributed to this second incident, resistance training  
54  
55 (and particularly heavy weight lifting) is also known to alter blood rheological parameters and  
56  
57 blood coagulation (1,13). These alterations could have been involved in the surprising and rapid  
58  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4 ocular complication observed in our patient. Despite anti coagulation medication, two thrombi  
5  
6 were present at that time in the left atrium suggesting, again, disequilibrium of the balance  
7  
8 between hemostasis and fibrinolytic activity. Despite clear medical recommendations, the patient  
9  
10 did not stop practicing intense physical activities, which illustrates the problem of preventing and  
11  
12 managing further exercise related medical complication in a sportsman.  
13  
14  
15  
16  
17

18  
19 *Paragraph 12:* Although under multiple medical treatments, the patient unfortunately lost his left  
20  
21 eye. The exact reasons for this severe ocular incident are not clearly understood, and the most  
22  
23 surprising event was the rapid deterioration of CRVO to neovascular glaucoma. Usually, the  
24  
25 occurrence of CRVO (whether induced by exercise or not) in young men is well managed, leading  
26  
27 to recovery (17) with minimal visual after effects. However, this was not the case in the present  
28  
29 study and the poor outcome for our patient could be related to its SCT carrier status. Indeed, the  
30  
31 concomitant occurrence of hypoxia, dehydration and acidosis, conditions occurring during  
32  
33 exercise, is favorable to the sickling process (5) and coagulopathy (20). The presence of SCT and  
34  
35 the associated hemorheological disorders could have played a role in the complications (i.e.,  
36  
37 retinal detachment and blindness).  
38  
39  
40  
41  
42  
43  
44

45  
46 *Paragraph 13:* Altogether, the data presented in this case study suggest that SCT status could be  
47  
48 another genetic risk factor for severe ocular complications, particularly when severe exercise is  
49  
50 performed in extreme climatic conditions. While SCT carriers often participate in sports and  
51  
52 related training, particular attention to preventing dehydration and starting exercise gradually may  
53  
54 be warranted. These recommendations have to be applied to the general population; but we do  
55  
56 advocate that physicians and trainers should pay a greater attention to people (trained or untrained)  
57  
58 carrying SCT. The recommendation on adequate hydration is particularly important for SCT  
59  
60  
61  
62  
63  
64  
65

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

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.

## References

1. Ahmadizad S, El-Sayed MS. The acute effects of resistance exercise on the main determinants of blood rheology. *J Sports Sci.* 2005;23:243-9.
2. Ajayi AA. Should the sickle cell trait be reclassified as a disease state? *Eur J Intern Med.* 2005;16:463.
3. Austin H, Key NS, Benson JM, Lally C, Dowling NF, Whitsett C, et al. Sickle cell trait and the risk of venous thromboembolism among blacks. *Blood.* 2007;110:908-12.
4. Bergeron MF, Cannon JG, Hall EL, Kutlar A. Erythrocyte sickling during exercise and thermal stress. *Clin J Sport Med.* 2004;14:354-6.
5. Bookchin RM, Balazs T, Landau LC. Determinants of red cell sickling. Effects of varying pH and of increasing intracellular hemoglobin concentration by osmotic shrinkage. *J Lab Clin Med.* 1976;87:597-616.
6. Chak M, Wallace G, Graham E, Stanford M. Thrombophilia: genetic polymorphisms and their association with retinal vascular occlusive disease. *Br J Ophthalmol.* 2001;85:883-6.
7. Connes P, Hardy-Dessources MD, Hue O. Counterpoint: Sickle cell trait should not be considered asymptomatic and as a benign condition during physical activity. *J Appl Physiol.* 2007;103:2138-40.
8. Connes P, Hue O, Tripette J, Hardy-Dessources MD. Blood rheology abnormalities and vascular cell adhesions mechanisms in sickle cell trait carriers during exercise. *Clin Hemorheol Microcirc.* In press.
9. Connes P, Reid H, Hardy-Dessources MD, Morrison E, Hue O. Physiological Responses of Sickle Cell Trait Carriers During Exercise. *Sports Med.* In press.

- 1  
2  
3  
4 10. Connes P, Sara F, Hardy-Dessources MD, Etienne-Julan M, Hue O. Does Higher Red  
5  
6 Blood Cell (RBC) Lactate Transporter Activity Explain Impaired RBC Deformability in  
7  
8 Sickle Cell Trait? *Jpn J Physiol.* 2005;55:385-7.  
9
- 10  
11 11. Connes P, Tripette J, Chalabi T, Beltan E, Etienne-Julan M, Chout R, et al. Effects of  
12  
13 strenuous exercise on blood coagulation activity in sickle cell trait carriers. *Clin Hemorheol*  
14  
15 *Microcirc.* 2008;38:13-21.  
16  
17
- 18  
19 12. Dincer HE, Raza T. Compartment syndrome and fatal rhabdomyolysis in sickle cell trait.  
20  
21 *Wmj.* 2005;104:67-71.  
22
- 23  
24 13. el-Sayed MS. Fibrinolytic and hemostatic parameter response after resistance exercise.  
25  
26 *Med Sci Sports Exerc.* 1993;25:597-602.  
27
- 28  
29 14. el-Sayed MS. Effects of exercise on blood coagulation, fibrinolysis and platelet  
30  
31 aggregation. *Sports Med.* 1996;22:282-98.  
32
- 33  
34 15. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, et al. A candidate  
35  
36 genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate  
37  
38 reductase. *Nat Genet.* 1995;10:111-3.  
39
- 40  
41 16. Fruschelli M, Puccetti L, Bruni F, Auteri A. Coagulative, fibrinolytic and metabolic pattern  
42  
43 in patients with central retinal vein occlusion. *Ophthalmologica.* 2002;216:108-12.  
44
- 45  
46 17. Gaudard A, Varlet-Marie E, Monnier JF, Janbon C, Quere I, Bressolle F, et al. Exercise-  
47  
48 induced central retinal vein thrombosis: possible involvement of hemorheological  
49  
50 disturbances. A case report. *Clin Hemorheol Microcirc.* 2002;27:115-22.  
51
- 52  
53 18. Ghazi NG, Noureddine B, Haddad RS, Jurdi FA, Bashshur ZF. Intravitreal tissue  
54  
55 plasminogen activator in the management of central retinal vein occlusion. *Retina.*  
56  
57 2003;23:780-4.  
58  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 19. Goldberg MF. Sickled erythrocytes, hyphema, and secondary glaucoma: I. The diagnosis  
5 and treatment of sickled erythrocytes in human hyphemas. *Ophthalmic Surg.* 1979;10:17-  
6 31.  
7  
8  
9  
10  
11 20. Jones SR, Binder RA, Donowho EM, Jr. Sudden death in sickle-cell trait. *N Engl J Med.*  
12 1970;282:323-5.  
13  
14  
15  
16 21. Kark JA, Ward FT. Exercise and hemoglobin S. *Semin Hematol.* 1994;31:181-225.  
17  
18  
19 22. Koppes GM, Daly JJ, Coltman CA, Jr., Butkus DE. Exertion-induced rhabdomyolysis with  
20 acute renal failure and disseminated intravascular coagulation in sickle cell trait. *Am J Med.*  
21 1977;63:313-7.  
22  
23  
24  
25  
26 23. Le Gallais D, Lonsdorfer J, Bogui J, Fattoum S, versus, Connes P, et al. Point-  
27 Counterpoint: Sickle cell trait should/should not be considered asymptomatic and as a  
28 benign condition during physical activity. *J Appl Physiol.* 2007;In Press.  
29  
30  
31  
32  
33 24. Le Gallais D, Lonsdorfer J, Bogui P, Fattoum S. Point: Sickle cell trait should be  
34 considered asymptomatic and as a benign condition during physical activity. *J Appl*  
35 *Physiol.* 2007;103:2137-8.  
36  
37  
38  
39  
40 25. Lip PL, Blann AD, Jones AF, Lip GY. Abnormalities in haemorheological factors and  
41 lipoprotein (a) in retinal vascular occlusion: implications for increased vascular risk. *Eye.*  
42 1998;12 ( Pt 2):245-51.  
43  
44  
45  
46  
47  
48 26. Mandalaki T, Dessypris A, Louizou C, Panayotopoulou C, Dimitriadou C. Marathon Run  
49 III: effects on coagulation, fibrinolysis, platelet aggregation and serum cortisol levels. A 3-  
50 year study. *Thromb Haemost.* 1980;43:49-52.  
51  
52  
53  
54  
55 27. Michelson PE, Pfaffenbach D. Retinal arterial occlusion following ocular trauma in youths  
56 with sickle-trait hemoglobinopathy. *Am J Ophthalmol.* 1972;74:494-7.  
57  
58  
59  
60  
61  
62  
63  
64  
65

- 1  
2  
3  
4 28. Monchanin G, Connes P, Wouassi D, Francina A, Djoda B, Banga PE, et al.  
5  
6 Hemorheology, sickle cell trait, and alpha-thalassemia in athletes: effects of exercise. *Med*  
7  
8 *Sci Sports Exerc.* 2005;37:1086-92.  
9  
10  
11 29. Monchanin G, Serpero LD, Connes P, Tripette J, Wouassi D, Bezin L, et al. Effects of a  
12  
13 progressive and maximal exercise on plasma levels of adhesion molecules in athletes with  
14  
15 sickle cell trait with or without {alpha}-thalassemia. *J Appl Physiol.* 2007;102:169-73.  
16  
17  
18 30. Nowak-Göttl U, Wermes C, Junker R, Koch HG, Schobess R, Fleischhack G, et al.  
19  
20 Prospective evaluation of the thrombotic risk in children with acute lymphoblastic  
21  
22 leukemia carrying the MTHFR TT 677 genotype, the prothrombin G20210A variant, and  
23  
24 further prothrombotic risk factors. *Blood.* 1999;93:1595-9.  
25  
26  
27  
28 31. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-  
29  
30 untranslated of the prothrombin gene is associated with elevated plasma prothrombin levels  
31  
32 and an increase in venous thrombosis. *Blood.* 1996;88:3698-703.  
33  
34  
35 32. Sawka MN, Burke LM, Eichner ER, Maughan RJ, Montain SJ, Stachenfeld NS. American  
36  
37 College of Sports Medicine position stand. Exercise and fluid replacement. *Med Sci Sports*  
38  
39 *Exerc.* 2007;39:377-90.  
40  
41  
42  
43 33. Sherry P. Sickle cell trait and rhabdomyolysis: case report and review of the literature. *Mil*  
44  
45 *Med.* 1990;155:59-61.  
46  
47  
48 34. Tripette J, Connes P, Hedreville M, Etienne-Julan M, Marlin L, Hue O, et al. Patterns of  
49  
50 exercise related inflammatory response in sickle cell trait carriers. *Brit J Sports Med.* In  
51  
52 press.  
53  
54  
55 35. Tripette J, Hardy-Dessources MD, Sara F, Montout-Hedreville M, Saint-Martin C, Hue O,  
56  
57 et al. Does Repeated and Heavy Exercise Impair Blood Rheology in Carriers of Sickle Cell  
58  
59 Trait? *Clin J Sport Med.* 2007;17:465-70.  
60  
61  
62  
63  
64  
65



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

36. Westerman MP, Green D, Gilman-Sachs A, Beaman K, Freels S, Boggio L, et al. Coagulation changes in individuals with sickle cell trait. *Am J Hematol.* 2002;69:89-94.

37. Wirthwein DP, Spotswood SD, Barnard JJ, Prahlow JA. Death due to microvascular occlusion in sickle-cell trait following physical exertion. *J Forensic Sci.* 2001;46:399-401.

38. Wolf A, Shalem M, Horowitz J, Geyer O. Retinal vascular occlusion following traumatic hyphema and glaucoma, as a presenting sign of sickle cell trait. *Isr Med Assoc J.* 2005;7:476-7.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

**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

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

Mona Hedreville, Philippe Connes, Marc Romana, Guillaume Magnaval, Thierry David, Marie-Dominique Hardy-Dessources, Marie-Sylvaine Belloy, Maryse Etienne-Julan, and Olivier Hue.

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 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 ( $mm \cdot h^{-1}$ )	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.

<b>Parameter</b>	<b>Patient value</b>	<b>Normal value</b>
Red blood cell rigidity (shear rate of 225 s <sup>-1</sup> )*	0.88	< 0.85
Activated partial thromboplastin time (s)	31	< 47
Ratio (healthy subject/patient)	1.10	< 1.52
Prothrombin time (%)	90	70 – 100
Fibrinogen (g·l <sup>-1</sup> )	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·l <sup>-1</sup> )	3.19	< 5.00

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

Figure

[Click here to download high resolution image](#)

