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Exercise-related complications in sickle cell trait

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Abstract. This review presents the epidemiological data regarding the exercise-related complication in exercising sickle cell trait carriers, and focuses on the different potential mechanisms that could be involved in these adverse events, such as hemorheological alterations, inflammation, vascular adhesion of circulating blood cells, oxidative stress and impaired nitric oxide metabolism. We also discuss the effects of different modulating factors such as vascular function, environment (hot temperature), hydration status, physical fitness, exercise intensity and genetic factors.

Keywords: Sickle cell trait, exercise-related sudden death, hemorheology, inflammation, vascular function

1. Introduction

Sickle cell anemia (SCA) is a genetic disease, characterized by the presence of a mutant hemoglobin (Hb), namely HbS, replacing the normal Hb (HbA). The hallmarks of the disease are anemia and recurrent painful vaso-occlusive crises, which result from the physical obstruction of small blood vessels with rigid sickle-shaped red blood cells (RBCs) and involve contributing inflammatory factors and vascular adhesion processes [7, 47]. Recent evidences also suggest that decreased nitric oxide bioavailability, as a consequence of the great amount of cell-free hemoglobin, participates in several chronic complications of sickle cell anemia such as pulmonary hypertension, leg ulcers and priapism [34].

Sickle cell trait (SCT) is the heterozygous form of SCA, which is marked by the presence of both HbS (less than 50%) and HbA. SCT prevalence can reach 8–10% of African-Americans population and

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10% in the Caribbean Islands. In Africa, prevalence can sometimes be even more important in some sub-Saharan area. SCT is usually considered as a benign condition, compared with SCA, which does not affect growth and mental development [1, 2, 14, 17, 36].

However, although debated [27], SCT carriers could be at risk for developing hyposthenuria, hematuria, renal medullary carcinoma and ocular complications following traumatic hyphema, such as retinal vascular occlusions and secondary glaucoma [17]. But larger cohort studies are clearly needed to definitively support those associations [27]. Nevertheless, there is epidemiological evidence of higher risk to develop venous thromboembolism and pulmonary embolism among African Americans with SCT than in non-SCT carriers [4], and this risk could be even more important in women with SCT taking hormonal contraceptive [5]. This higher risk for thromboembolic complications could be related to the greater resting blood viscosity values frequently found in SCT carriers [23, 48, 52]. It seems that almost one third of SCT carriers exhibit greater baseline blood viscosity than the mean value of patients with sickle cell hemoglobin C disease, a disease known to be very exposed to thromboembolic complications [48].

Therefore, even if a direct causal relationship between SCT and the observed medical complications is difficult to prove, evidence suggest that the medical status of this population should not be dismissed and further large epidemiological studies are needed to test the associations between SCT and several medical conditions.

2. Epidemiological studies on Exercise Collapse Associated with Sickle cell Trait (ECAST)

One of the most debated issue for SCT carriers concerns the hypothesis of a greater risk to die unexpectedly in response to exercise compared to the general population [14, 27, 36, 42]. If it is usually admitted that SCT carriers are at risk to develop complications, such as splenic syndrome, when exercising in altitude, the debate is still running regarding exercise at sea level.

Kark et al. [34] were the first to conduct a large cohort study on the exercise-related death among the 2, 087, 600 people who entered the US Armed Forces basic enlisted military training during a five-year period (1977–1981). Forty-one exercise-related deaths occurred. Risk ratios were examined among the black recruits, ignoring the small number of non-blacks with SCT. The relative risk of exercise-related death explained by pre-existing disease (largely silent heart disease) was 2.3 for SCT, but this was not statistically significant. The relative risk of exercise-related death unexplained by pre-existing disease was 28 for SCT. The excess of exercise-related death with SCT was likely caused by the immediate stress of exercise. About 50% of the deaths resulted from heat illness due to over exertion and the remaining cases were idiopathic sudden deaths. Recently, Harmon et al. [29] reviewed the cause of all cases of sudden death in student-athletes from the National Collegiate Athletic Association from January 2004 through December 2008. The authors demonstrated that 72 deaths occurred in football athletes (due to trauma unrelated to sports activities or medical causes). Thirteen of the 20 deaths due to medical causes occurred during exertion; cardiac (6.46%) SCT associated (5.39%), and heat stroke unrelated to SCT (2.15%). All deaths associated with SCT occurred in African-American Division I football athletes. The risk of exertional death in Division I football players with SCT was 1 : 827 which was 37 times higher than in athletes without SCT.

To summarize, although the SCT condition is largely benign, few large epidemiological studies, both in army [32] and civilians [29], suggest that SCT condition is associated with an increased risk for exercise-related complication. The term ECAST has recently been introduced by O'Connor et al. [42],

71 which regroups severe complications occurring in SCT carriers in response to exercise including severe
72 muscle pain and fulminant collapse [24].

73 **3. Blood rheology and inflammatory markers in SCT carriers**

74 Several studies compared the hemorheological properties at rest and during exercise between SCT
75 carriers and subjects without SCT. On the whole, SCT carriers have slightly reduced red blood cell
76 (RBC) deformability [18, 19, 22, 30, 39, 49], increased RBC aggregation [22], increased RBC aggregates
77 strength [49], high blood viscosity [19, 23, 48, 52] and increased plasma level in vascular cell adhesion
78 molecule (VCAM-1) [40, 41]. In addition, a prolonged and strenuous exercise has been demonstrated
79 to cause a greater increase in blood viscosity [51], higher RBC lipid oxidative stress [49] and higher
80 leucocytes and platelets activation [50] in SCT carriers than in a control group. We previously suggested
81 that all these biological abnormalities could be susceptible to increase the risks for microcirculatory blood
82 flow impairment in SCT carriers [13, 15, 17]. However, in a recent study that compared the baseline
83 hemorheological profile between SCT carriers, healthy subjects and patients with either SCA or sickle-
84 cell hemoglobin C disease (SCC), we demonstrated that most of the hemorheological abnormalities found
85 in SCT carriers should be considered subclinical, in comparisons with the abnormalities observed in SCA
86 and SCC patients [48]. This observation is not true for $\frac{1}{4}$ to $\frac{1}{3}$ of SCT carriers who present elevated
87 levels of blood viscosity with possible clinical relevancy [48, 52]. Whether this subpopulation of SCT
88 carriers is at greater risk for ECAST requires further studies. If 25%–33% of the SCT population exhibits
89 elevated blood viscosity values, why do not we observe more frequent complications? The participation
90 of a combination of modulating factors, as discussed below (vascular function, environmental factors,
91 physical fitness, exercise intensity, genetic factors), must be strongly considered.

92 **4. Modulating factors involved in ECAST**

93 *4.1. Vascular function in SCT carriers*

94 Vascular function of SCA patients is impaired. One of the main reasons is the decrease of the nitric
95 oxide (NO) bioavailability caused by the chronic hemolysis and oxidative stress [34]. The plasma free
96 hemoglobin and the release of RBC arginase scavenge NO and consumes L-arginine, respectively. This
97 decrease in NO bioavailability results in endothelial dysfunction and a loss of vasomotor reserve. In
98 addition, the mechanic aggression of endothelium by the flowing rigids sickle RBCs causes endothelial
99 dysfunction [37]. However, while vascular function has been described in the context of SCA [8, 21,
100 56], no research protocol specifically focused on SCT population. Few studies compared the plasma NO
101 levels between SCT carriers and healthy subjects and show very slightly decreased NO concentration in
102 SCT carriers [49], mainly in sedentary people [12]. In contrast, the presence of α -thalassemia in SCT
103 carriers seems to normalize the plasma NO level [25]. These studies have been conducted in small groups
104 in a descriptive fashion; it is therefore difficult to draw definitive conclusions on NO status in SCT
105 carriers. In addition, while some studies reported increased VCAM-1 level in SCT carriers (at rest and
106 during exercise) compared to healthy subjects [40, 41], others reported no difference between the two
107 populations [49, 50]. Here again, the small amount of available data does not allow a clear understanding
108 of specific vascular mechanisms in SCT carriers.

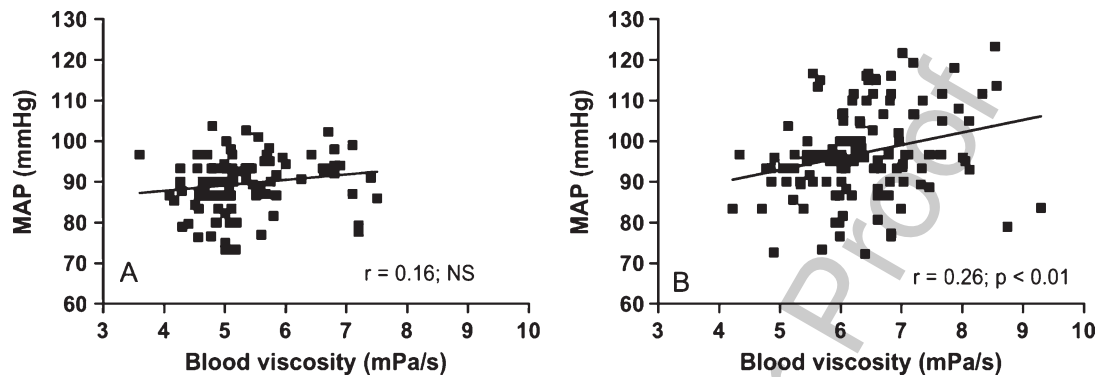


Fig. 1. Relationships between mean arterial pressure (MAP) and blood viscosity in 94 healthy non-SCT carriers (Fig. 1A) and 118 healthy SCT carriers (Fig. 1B). These data have been collected in Senegal and Guadeloupe using the same equipment (cone-plate viscometer, Brookfield DVII+, CPE-40 spindle) at high shear rate (225 s^{-1}). The relationship was not significant in non-SCT carriers while it was positive and significant in the SCT group.

109 Increased blood viscosity has classically been viewed as a risk factor for cardiovascular diseases. How-
 110 ever, counterintuitive data have been recently reported in animal models demonstrating that increment in
 111 blood viscosity resulted in a paradoxical decrease of vascular resistance [53]. This observation demon-
 112 strates that vascular function, if not impaired, is able to adapt to increased blood viscosity, until a certain
 113 threshold, and thus modulating vascular resistance [26, 28, 31]. A rise in blood viscosity has been shown
 114 to increase the wall shear stress applied to the endothelium level, which produces more vasodilators,
 115 such as NO, leading to compensatory vasodilation [16, 20, 44, 45, 53, 54]. Vazquez et al. [54] demon-
 116 strated that, in healthy controls, blood pressure and blood viscosity were not correlated which strongly
 117 supports the concept that vascular function may easily compensate for the increase in blood viscosity
 118 in healthy individuals. In contrast, blood viscosity and blood pressure (or systemic vascular resistance)
 119 are positively correlated in type 1 diabetes [54] and in SCA [35], suggesting impaired vascular function
 120 in these diseases. We looked at the relationships between blood pressure and blood viscosity in a group
 121 of healthy non-SCT carriers and in SCT carriers (Fig. 1A and 1B, respectively). The results obtained in
 122 non-SCT carriers show no relationship between blood viscosity and blood pressure, which confirms the
 123 findings from Vazquez et al. [54]. In contrast, we observed a positive relationship in our group of healthy
 124 SCT carriers without cardiovascular disease, suggesting that the vascular function of SCT carriers may
 125 be less able to compensate for the high blood viscosity described in this population [48, 52]. Further
 126 studies using vascular function exploratory techniques (e.g. flow-mediated dilation) must now be done
 127 to confirm and strengthen these results.

128 4.2. Role of the environmental factors

129 Exercise at high altitude exposure increases the risks for splenic infarction in SCT carriers due to massive
 130 sickling into this organ [46]. But, other environmental factors, such as hot environment exposure, have
 131 been hypothesized to play a role in the occurrence of ECAST [13, 30, 33, 42]. Bergeron et al. [9] tested the
 132 effect of a brisk walking of 45 min duration performed in hot environment on the sickling rate in few SCT
 133 carriers. They demonstrated that sickling rate remained low and unchanged by the mild exercise when
 134 subjects were adequately hydrated. In contrast, when water intake was not provided, the percentage of

sickle RBCs increased above baseline values. Hydration has been demonstrated to be beneficial on blood rheology too. For instance, we demonstrated that hydration was able to normalize the blood viscosity of the SCT carriers to the same level of healthy subjects during a prolonged submaximal cycling exercise and a 90 min soccer game [23, 52]. Indeed, although hot exposure may further impair the rheology of blood and promote RBC sickling in SCT carriers, adequate hydration is able to normalize these abnormalities. Whether greater hemorheological alterations induced by hot exposure and dehydration is sufficient to trigger ECAST is unknown, but Hedreville et al. [30] reported the case of a cyclist with SCT who participated to a prolonged race (140 km) in hot environment (35°C). The cyclist felt very thirsty all along and after the race. The following day, he developed a massive central retinal vein occlusion, which rapidly worsen into neovascular glaucoma. The patient had no cardiovascular risk factor and no genetic mutation involved in hypercoagulation diseases, but he had very rigid RBCs [30]. Authors hypothesized that hemorheological alterations caused by the presence of SCT, the prolonged effort and the dehydration could have precipitated the occurrence of this complication. Adequate hydration should therefore be strongly promoted in exercising SCT carriers, particularly when exercising under hot exposure [13], to limit the risks for vascular complications.

4.3. *Physical fitness and exercise intensity*

Pre-exercise fatigue due to illness (viral infection for example) or lack of sleep [42], and poor conditioning [3] seem to play a role in the occurrence of adverse events in exercising SCT carriers. Aufradet et al. [3] demonstrated that the inflammatory response of exercising sedentary SCT carriers was greater than that seen in exercising subjects without SCT or exercising physically trained SCT carriers. They concluded that regular physical training could decrease endothelial activation and vascular adhesion responses in SCT carriers [3]. More recently, Chirico et al. [12] reported that oxidative stress response to exercise was attenuated in trained compared to untrained SCT carriers. In addition, plasma NO level during exercise was greater in trained than in untrained SCT carriers. Indeed, physical fitness would presumably limit the risk for ECAST.

On the other hand, no study specifically looked at the effect of various exercise intensities on biological markers in a given group of SCT carriers. Yet, some authors [24] suggested that it might be a key factor involved in ECAST. The greater amount of lactic acid produced by active muscles and the subsequent metabolic acidosis could promote the polymerization of hemoglobin S, hence precipitating the sickling of RBCs [18] and microcirculatory dysfunction. Muscle microvascular occlusions could then trigger rhabdomyolysis [24]. Messonnier et al. [38] recently looked at the effects of a moderate and prolonged cycling exercise on biochemical markers reflecting rhabdomyolysis in SCT carriers but no difference with a control group was observed, demonstrating that such an exercise is probably not intense enough to impair muscle microcirculation and function in SCT carriers. Well-designed exercise protocols of various intensities are needed to test the effects of exercise intensity on biological parameters and muscle microcirculatory function in a given group of SCT carriers.

4.4. *Genetic factors*

α -thalassemia is a major modulator of the clinical severity in SCA patients with the presence of α -thalassemia increasing the risks of vaso-occlusive crisis and osteonecrosis [34] but decreasing the risks of stroke [10]. The increased risk of vaso-occlusive like complications in SCA patients with α -thalassemia events is due to the reduction of HbS percent resulting in a decrease of the hemolytic rate leading to the

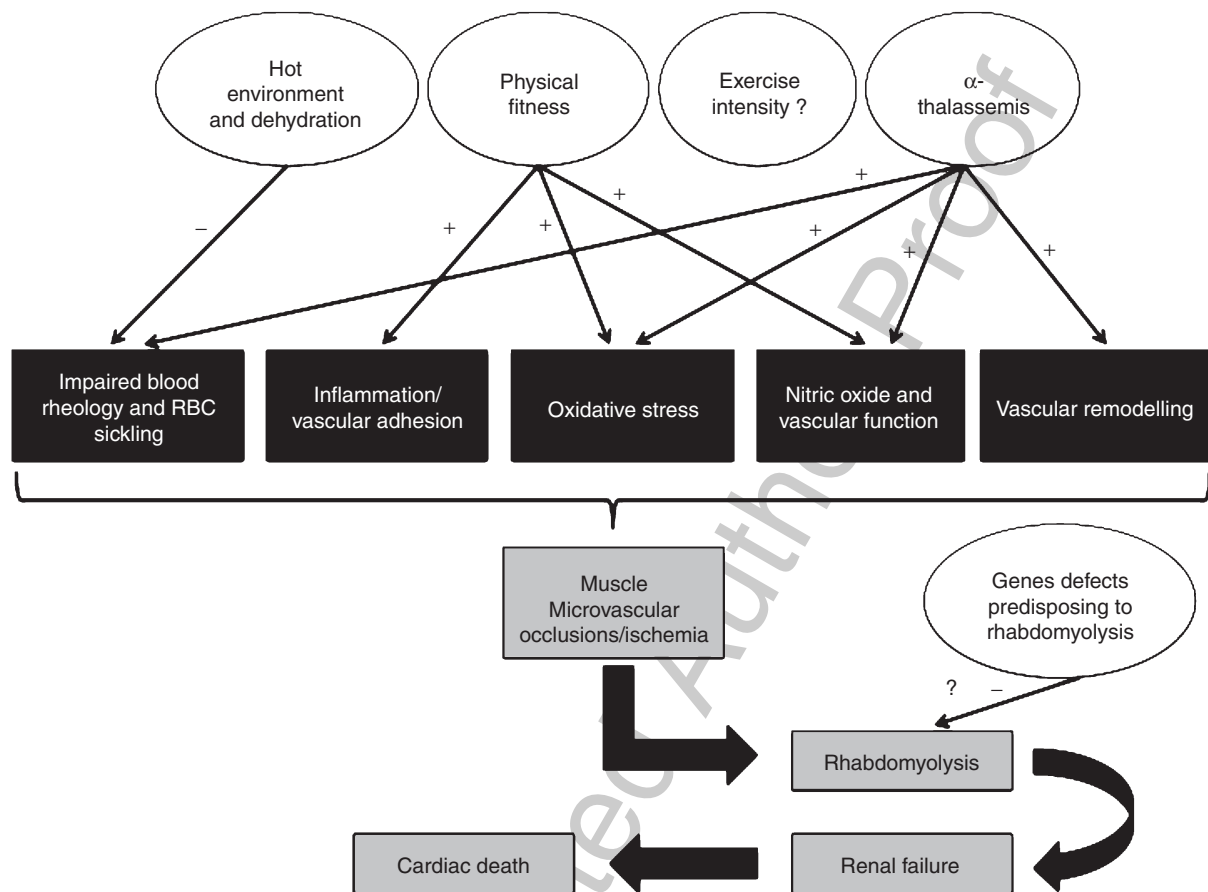


Fig. 2. Proposal of putative mechanisms that could be involved in the cases of rhabdomyolysis, renal failure and death reported in few SCT carriers in response to exercise. Exercise may cause greater hemorheological alterations (mainly blood viscosity and RBC sickling) and promote higher inflammatory and oxidative stress responses in SCT carriers compared to healthy controls. In addition, plasma nitric oxide content is slightly decreased in some SCT carriers that could lead to altered vascular function in this population, but this needs to be confirmed in larger studies using accurate techniques. SCT carriers are characterized by vascular remodeling. All these abnormalities seem to be modulated by several factors. Exposure to hot environment and dehydration further impaired the blood rheology of SCT carriers. Physical fitness and regular training has been shown to normalize the inflammatory, oxidative stress and nitric oxide responses of SCT carriers. Exercise intensity is thought to play a key role in the modulation of these abnormalities but it has never been experimentally tested. The presence of α -thalassemia in SCT carriers limits the vascular remodeling of SCT carriers, blunts the oxidative stress responses during exercise, normalizes the nitric oxide level and improves blood rheology (mainly RBC deformability). All the biological abnormalities, if present in a same subject, could impair microcirculatory blood flow in exercising muscles, hence causing local ischemia. This local ischemia, if exaggerated, could lead to rhabdomyolysis. Recently, it has been suggested that other genes defect could predispose SCT carriers to rhabdomyolysis but this hypothesis needs to be tested. Then, the delivery of toxic by-products occurring during rhabdomyolysis could cause renal failure. Finally, the loss of K^+ could ultimately lead to cardiac arrest. One should be noted that this cascade of events is hypothetical and further longitudinal and basic science studies need to be done to confirm or not these mechanisms. + = protective effect; - = deleterious effect.

176 increase of hemoglobin level and blood viscosity [34]. In contrast, the reduction of hemolysis in these
177 patients protects them from the development of cerebral vasculopathy [10]. In addition, α -thalassemia
178 by improving the deformability of the RBCs [6], may be an advantage in certain tissues, such as the
179 brain [10]. Few studies also look at the effects of α -thalassemia in SCT carriers. The first one was the
180 study of Monchanin et al. [39] and they demonstrated that SCT carriers with α -thalassemia had greater
181 RBC deformability than SCT carriers without. Then, Faes et al. [25] demonstrated that the presence of
182 α -thalassaemia may blunt the higher level of oxidative stress and the impaired bioavailability of NO
183 observed in SCT carriers at rest and during exercise. Vincent et al. [55] performed muscle biopsies in
184 SCT carriers with and without α -thalassemia. Probably as a consequence of the greater hemorheological
185 impairment [39, 49, 52], SCT carriers without α -thalassemia are marked by lower capillary density, lower
186 capillary tortuosity and enlarged microvessels compared to non-SCT carriers. However, the presence of
187 α -thalassemia normalized these abnormalities. It seems that α -thalassemia improves the biological and
188 microcirculatory profiles of SCT carriers and this could be a way to decrease the risk for ECAST.
189 Nevertheless, further epidemiological studies are needed to comfort this hypothesis.

190 An alternative hypothesis is that HbS is a marker for other gene variants that worsen the outcome of
191 severe exercise complications [42]. One such category might be metabolic susceptibility to exertional
192 rhabdomyolysis. Gene variants associated with β^S gene polymorphisms could account for some of the
193 excess risk, especially if these variants mainly act to decrease the chance of surviving severe ECAST.
194 Several gene defects may predispose to rhabdomyolysis [11, 43]. Further studies should screen for the
195 presence of genetic defects that could explain the exercise-related events, improve the understanding of
196 ECAST pathophysiology and ultimately allow an answer as to whether SCT is or is not an independent
197 risk factor of exercise-related sudden death [42].

198 5. Conclusion

199 The present review focused on the different potential mechanisms that could be involved in the exercise-
200 related complications reported in SCT carriers. The Fig. 2 summarizes the main findings collected in
201 the last two decades. This review emphasizes the need to 1) perform further systematic epidemiological
202 studies to really assess the burden of SCT in the society, and 2) continue explorative protocols investigating
203 the SCT-related microcirculatory and endothelial specificities that influence the vascular function.

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